LifeExtension

Print This

Chemotherapy

Contents

References

Introduction

Cancer chemotherapy involves treating cancer with drugs that impair the ability of malignant cells to grow and divide (Galmarini 2012; ASCO 2014; Mayo Clinic 2015). However, similarities between cancer cells and healthy cells make it challenging to kill only malignant cells while sparing normal cells (Keyomarsi 2003; Galmarini 2012; Mihlon 2010; Chabner 2013a).

Cancer cells are mutated, dysfunctional versions of healthy cells. They are well adapted for survival and propagation in the human body. Cancer cells usually divide rapidly and thus are more vulnerable to chemotherapy than healthy cells, most of which divide more slowly. This is because chemotherapy drugs typically damage cells during cellular division (Beck 2004; Xian 2003; Kamil 2010; Mouser 2014; Lin 1999; Beer 2001; Galmarini 2012; Baszkowsky 2012).

Unfortunately, several normal cell types *do* divide rapidly under healthy conditions and *are* susceptible to the toxic effects of chemotherapy. This is the basis for the many well-known side effects of chemotherapy, such as hair loss, gastrointestinal problems, anemia, and immune system suppression (Beck 2004; Xian 2003; Kamil 2010; Mouser 2014; Lin 1999; Beer 2001; Galmarini 2012; Baszkowsky 2012).

This fine line between killing cancer cells and sparing normal, healthy cells has been a major focus of chemotherapy drug development for years (Galmarini 2012).

Another challenge in the treatment of cancer is that malignant cells are often naturally resistant to chemotherapeutic drugs, or develop resistance to them during early rounds of chemotherapy. This is called *chemoresistance* (Marin 2012; Galmarini 2012; Mihlon 2010; Chabner 2013a; Abdullah 2013; Baszkowsky 2012).

The good news is that emerging technologies such as **chemosensitivity testing** and **genetic profiling** are helping to better match patients with treatments that are more likely to effectively treat their specific cancer (Grigsby 2013; Geng 2013; Herzog 2010; Smith 1990; Kalia 2013; Cobo 2007; Goncalves 2013). Moreover, studies have shown that certain drugs and integrative interventions, such as the staple antidiabetic medication **metformin** and the natural phytochemical **curcumin** (found in the spice turmeric), may help overcome chemoresistance and sensitize some cancers to the toxic effects of chemotherapy (Soritau 2011; Tan 2011; Jiralerspong 2009; Lee, Kim 2012; Honjo 2014; Dhandapani 2007; Howells 2011; Sung 2009; Yu 2011).

Other novel strategies, such as **intermittent fasting**, may also protect against chemotherapy side effects and sensitize cancer cells to the effects of chemotherapy (Lee, Raffaghello 2012; Lee 2011; Raffaghello 2010; Naveed 2014; Safdie 2012).

These developments, along with other advancements in the science of oncology, mean that cancer patients have a better chance of positive outcomes than ever before.

This protocol aims to empower cancer patients with knowledge about strategies to lessen chemotherapy side effects and potentially enhance the efficacy of chemotherapeutic drugs through the novel utilization of pharmaceuticals, integrative interventions, and healthy dietary and lifestyle approaches.

Note: this protocol should be consulted in conjunction with Cancer Treatment: The Critical Factors (/Protocols/Cancer/Cancer-Critical-Factors/Page-01). Other protocols potentially of interest include Cancer Radiation Therapy (/Protocols/Cancer/Radiation-Therapy/Page-01), Cancer Surgery (/Protocols/Cancer/Cancer-Surgery/Page-01), Cancer Adjuvant Therapy (/Protocols/Cancer/Cancer-Adjuvant-Therapy/Page-01), Complementary Alternative Cancer Therapies (/Protocols/Cancer/Alternative-Cancer-Therapies/Page-01), and Cancer Vaccines and Immunotherapy (/Protocols/Cancer/Cancer-Vaccines-and-Immunotherapy/Page-01).

How Does Chemotherapy Work?

Traditional chemotherapy destroys rapidly dividing cells by disrupting processes vital for cell division and survival. The aim of chemotherapy drugs is to kill cancer cells, or at least stop their growth and multiplication (Mihlon 2010; Baszkowsky 2012). Chemotherapy is most successful at treating rapidly proliferating tumors, such as certain leukemias, lymphomas, and testicular tumors, as well as smaller tumors that are growing rapidly (Baszkowsky 2012; Mitchison 2012).

The field of cancer therapy has expanded considerably in recent decades, and specialized classes of medicines are now incorporated into treatment regimens alongside classical cell-killing (cytotoxic) chemotherapy. These include molecularly targeted therapies, immunotherapies, cancer vaccines, hormonal therapies, and others. Although these more specific types of cancer medicine have helped improve outcomes in some types of cancer, traditional systemic chemotherapy—along with its side effects—is still a mainstay of cancer treatment today, and will likely remain so for some time (Galmarini 2012; Slater 2001; Joo 2013; NCI 2014c).

This protocol will review cytotoxic drugs and their side effects. Specialized cancer therapies are discussed in other Life Extension *Disease Prevention and Treatment* protocols.

Types of Chemotherapy Drugs

There are many different types of chemotherapy drugs. They are grouped into classes based on their mechanism of action, chemical structure, and relationship to other drugs. Some chemotherapy drugs fit into more than one class. Generally, cancer patients receive chemotherapy drugs from more than one class at the same time (Mihlon 2010; Baszkowsky 2012; Doroshow 2017). This strategy, called *combination chemotherapy*, aims to maximize the number of cancer cells killed and minimize development of chemoresistance. Combination chemotherapy has historically increased treatment efficacy in many types of cancer (Galmarini 2012; Yardley 2013; Pritchard 2012).

Table 1: Examples of Chemotherapy Drug Classes and Their Mechanisms of Action

Chemotherapy Class	Mechanism of Action	Types of Cancer Treated
Alkylating Agents : eg, bendamustine, carboplatin, chlorambucil, cisplatin, cyclophosphamide, procarbazine, streptozotocin	Bind to DNA, causing cell death by inhibiting protein and DNA synthesis	Leukemias, lymphomas, myelomas, and sarcomas; lung, reproductive system (breast, prostate, cervical, testicular, endometrial, ovarian), gastric, and head and neck cancers; and many other types of cancer
Antimetabolites : eg, fludarabine phosphate, methotrexate, mercaptopurine, 5-fluorouracil (5-FU), hydroxyurea	Interfere with metabolic pathways, including DNA and RNA synthesis	Leukemias and lymphomas; reproductive system, gastrointestinal, lung, bladder, and head and neck cancers; and many other types of cancer
Antitumor Antibiotics : eg, daunorubicin, doxorubicin, epidoxorubicin, idarubicin, actinomycin-D, bleomycin, mitomycin-C, mitoxantrone	Interfere with DNA and RNA synthesis; inhibit topoisomerase enzymes, which are involved in DNA synthesis	Leukemias, lymphomas, multiple myeloma, sarcomas, and many solid cancers
Topoisomerase Inhibitors : eg, topotecan, irinotecan, etoposide, teniposide	Inhibit topoisomerase enzymes	Certain leukemias, as well as lung, ovarian, gastrointestinal, and other cancers
Mitotic Inhibitors : eg, paclitaxel, ixabepilone, vinblastine, vincristine, vinorelbine, estramustine	Interfere with cell division	Myelomas, lymphomas, leukemias, and breast, lung, and other cancers
Others (chemotherapy drugs that do not fit into typical classes) : eg, L-asparaginase, bortezomib	L-asparaginase breaks down the amino acid asparagine, which cannot be synthesized by some cancers	Acute lymphoblastic leukemia
	Bortezomib is a proteasome inhibitor that interferes with cells' ability to break down damaged proteins	Secondary treatment of multiple myeloma and certain lymphomas

(Doroshow 2017; ACS 2017a; Healthwise 2013; Millenium Pharmaceuticals 2014; Piatkowska-Jakubas 2008; ACS 2013a)

How Is Chemotherapy Administered?

Chemotherapy is usually given in cycles, with each cycle involving a treatment session followed by a rest period. Several cycles ordinarily make up a course of treatment (Chemocare 2017; ACS 2015; CRUK 2015).

Chemotherapy can be administered by various strategies with differing intent, depending on each patient's unique situation (Baszkowsky 2012; SHCI 2014; Attarian 2011):

- **Neoadjuvant chemotherapy**, sometimes called **induction chemotherapy**, is given prior to surgery or radiotherapy in order to shrink the original (primary) tumor.
- **Adjuvant chemotherapy** is given after surgery or radiation if there is high risk of recurrence or metastasis (the spread of cancer from the primary site to other parts of the body).
- **Palliative chemotherapy** is administered without curative intent, but rather to prolong life and/or relieve symptoms.
- **Consolidation chemotherapy**, or post-remission chemotherapy, is sometimes part of treatment for leukemias and a small number of other types of cancer. It involves multiple treatment cycles over several months in order to sustain remission.
- **Maintenance chemotherapy** generally refers to long-term low-dose treatment to maintain or prolong tumor control.
- **Combination chemotherapy** refers to the use of several drugs that have different mechanisms of action and different toxicities. It is typically used to prevent or overcome resistance during neoadjuvant or adjuvant chemotherapy; and
- **Combined modality therapy**, which refers to the use of classical cytotoxic chemotherapy drugs along with other cancer treatments, including surgery, radiation therapy, or newer classes of anticancer drugs such as molecularly targeted agents, monoclonal antibodies, hormonal treatments, or immunotherapy.

Chemotherapy can be administered by different routes, including (NCI 2014a; SHCI 2017):

- **Intravenous (IV)**: injection into a vein
  - Chemotherapy and other necessary medications (eg, fluids, antibiotics) can be administered intravenously. While in some cases these are injected into veins in an arm or hand, sometimes it is necessary to inject into a larger vein. This requires the use of a *central venous catheter*. Another method is an implantable venous access port, sometimes referred to by brand names including Port-a-Cath and Medi-port. The catheter is inserted into a vein, and the access port is surgically placed under the skin, typically resulting in a small lump where the port is located. Other types of catheters accessed without an implanted port may also be used. In these cases, the end of the catheter into which medicine is injected is visible outside the body. These types of catheters include the peripherally inserted central catheter, or PICC line, and the Hickman catheter. Catheters and ports allow administration of more than one IV chemotherapy drug; blood draws for tests, and/or blood transfusions, all on more than one occasion, without having to use multiple needle punctures or insert new IV lines (ACS 2017b; ASCO 2013).
- **Oral**: administration by mouth
- **Intrathecal**: infusion into the fluid surrounding the brain and spinal cord
- **Intra-arterial (IA)**: injection into an artery
- **Intraperitoneal (IP)**: injection into the abdominal cavity
- **Intravesical**: administration directly into the urinary bladder through a catheter
- **Intramuscular**: injection into a muscle
- **Topical**: application to the skin
- **Subcutaneous**: injection under the skin

Chemotherapy Dose Optimization

Conventional chemotherapy regimens are typically calibrated to deliver the maximum tolerable dose of cytotoxic drugs (Baszkowsky 2012; Galmarini 2012). Combination chemotherapy regimens are used more often than single agents, but the decision to use a combination or single agent depends on the cancer type (Cosman 2014; Peters 2000; Mihlon 2010; Galmarini 2012). In combination chemotherapy, drugs that are active against the tumor and have different toxicity profiles and mechanisms of action are used; the goal is to circumvent chemoresistance by using multiple drugs with different anticancer mechanisms (Doroshow 2017). The drugs are administered in repeated cycles at regular intervals (Chabner 2013a).

Most chemotherapy drugs show a steep dose-response curve, meaning even a small reduction in dose may lead to a significant reduction in tumor cell killing (Honkoop 1995; Lyman 2009; Lyman 2012). However, the side effects of chemotherapy are also dose-dependent, making it important to find the maximum tolerable dose (Remesh 2013; Galmarini 2012). A patient who does not suffer significant adverse reactions from chemotherapy may be better able to complete an entire course of treatment, and therefore have a better overall outcome (Remesh 2013; Baszkowsky 2012; Doroshow 2017).

Oral Chemotherapy

Oral chemotherapy creates mild drug concentrations in the blood for an extended time, which allows for prolonged exposure of cancer cells to the chemotherapy agent (Feng 2011; Molina-Garrido 2014). Oral chemotherapy provides the convenience of home use (rather than clinic visits for intravenous infusions), and can allow complex dosing schedules, which may vary day-to-day or even within a single day (Held 2013; Neuss 2013; Bedell 2003).

Oral chemotherapy is becoming a more common method of treating cancer, and it is often as effective as other forms of chemotherapy (Neuss 2013; ACS 2014). Some classic cytotoxic drugs, such as cyclophosphamide (Cytoxan) and methotrexate (Trexall), have been used in oral treatment for over 50 years. Since 1998, the Food and Drug Administration (FDA) has approved more than 30 cancer drugs for oral administration, including newer, targeted, small molecules such as imatinib (Gleevec). It is estimated that over 25% of all cancer drugs under development are planned as oral agents (Segal 2014; Weingart 2008). Unfortunately, many important chemotherapy drugs (eg, taxanes including paclitaxel [Taxol] and docetaxel [Taxotere, Docefrez]) exhibit poor oral bioavailability and are therefore not currently candidates for oral administration (DeMario 1998; Hendrikx 2013; Attili-Qadri 2013; Torne 2010).

Metronomic Chemotherapy: An Emerging Chemotherapy Dosing Paradigm

Conventional high-dose chemotherapy regimens often cause significant side effects and require cyclical dosing, with breaks in treatment to allow healthy cells to recover from toxicity. However, these breaks also permit the recovery of cancer cells and the expansion of drug-resistant cancer cell populations (Scharovsky 2009).

In an effort to overcome these problems, lower-dose chemotherapy with more frequent administration has been tested in several studies. This approach is called ***low-dose metronomic chemotherapy*** (Lien 2013). Metronomic chemotherapy uses doses of chemotherapy that range from about one-tenth to one-third of standard doses, but is given more often than traditional chemotherapy. Since lower doses cause less toxicity, fewer rest periods are required (Kerbel 2004; Maiti 2014). Early evidence suggests metronomic chemotherapy may be more effective in some cases and less likely to induce drug resistance than conventional dosing (Maiti 2014; Scharovsky 2009; Pasquier 2010). Metronomic chemotherapy is generally administered via the **oral** route (Maiti 2014). Some studies have investigated intravenous metronomic chemotherapy, though research in this area is sparse (Mross 2012).

Metronomic chemotherapy is effective because of an often-overlooked action of certain conventional chemotherapy drugs: they inhibit the production of new blood vessels (Maiti 2014; Scharovsky 2009; Kerbel 2004). Under normal circumstances, tumors promote the growth of new blood vessels to ensure they get the resources they need to grow and survive. This process is called **angiogenesis** (Maiti 2014; Scharovsky 2009; Kerbel 2004; Pasquier 2010).

Angiogenesis—the formation of new blood vessels—relies on activation of endothelial cells, which line the inside of blood vessels. Some chemotherapeutic drugs exert toxic effects against activated endothelial cells, thus inhibiting angiogenesis. The anti-angiogenic effect of chemotherapy agents are apparent at lower blood concentrations than those needed to kill proliferating tumor cells. Furthermore, unlike cyclical high-dose chemotherapy, metronomic chemotherapy induces a sustained concentration of chemotherapy in the blood over an extended period, which may be more effective at preventing angiogenesis and reducing the efficiency of the tumor's acquisition of new resources (Maiti 2014; Scharovsky 2009; Kerbel 2004).

Inhibiting angiogenesis may be a key mechanism by which metronomic chemotherapy undermines cancer, but other factors also appear to contribute. For example, metronomic chemotherapy may reduce populations of immune cells called regulatory T cells. Reducing regulatory T cells may promote a more robust anticancer immune response (Maiti 2014; Scharovsky 2009). Another potential effect of metronomic chemotherapy is induction of **senescence** in tumor cells. Cellular senescence is the gradual degradation of a cell's capacity for division (Rodier 2011; Maiti 2014). **Apoptosis**, in which cells undergo self-destruction, is also thought to occur with this type of chemotherapy regimen (Maiti 2014; Bahl 2012).

Several small trials have investigated low-dose metronomic chemotherapy in patients with breast, prostate, ovarian, neuroendocrine, and non-small cell lung cancers; as well as those with lymphoma, multiple myeloma, pediatric solid tumors, and melanoma. Overall, these studies have found this approach to be effective and well tolerated. Cyclophosphamide is the chemotherapy drug most frequently used in a metronomic dosing regimen. Larger randomized controlled trials and detailed mechanistic studies are needed to firmly establish the potential utility of metronomic chemotherapy before it is more widely accepted into practice (Maiti 2014; Lien 2013; Scharovsky 2009).

Chemoresistance

Cancer is often either intrinsically resistant to chemotherapy drugs or develops resistance to them during the course of treatment. This is called chemoresistance, and accounts for up to 90% of all drug failures in metastatic cancers (cancers that have spread) (Abdullah 2013; Boyland 1963; Martinez-Rivera 2012; CCS 2014; Shen 2012; Hendlisz 2013). Chemoresistance occurs when cancer cells have or develop the ability to tolerate exposure to one or more chemotherapy drugs. Several inherent factors within tumor cells and the surrounding tumor microenvironment in the body contribute to chemoresistance, as dose suboptimal chemotherapy dosing (Abdullah 2013; Martinez-Rivera 2012; Wang, Chen 2016; CCS 2014).

Natural Agents to Combat Chemoresistance

Natural compounds exhibit a number of interactions with cancer cells that may enhance the anticancer cytotoxicity of chemotherapeutic agents. Cancer cells have highly developed mechanisms to rid themselves of toxins and degrade cytotoxic agents, including chemotherapy drugs. One key mechanism by which cancer cells eliminate toxins depends upon a protein called P-glycoprotein. This cell-membrane protein, which occurs in high amounts on cancer cells, pumps chemotherapeutic agents out of cancer cells. It is one of the chief culprits in multi-drug resistant cancer. Several natural compounds, such as quercetin, epigallocatechin-3-gallate (EGCG) from green tea, genistein, and curcumin inhibit P-glycoprotein (Abdallah 2015; Bansal 2009; Boumendjel 2011).

Another way that natural compounds may improve the cytotoxicity of chemotherapeutic agents is by preventing the metabolism of an active drug into inactive compounds. This problem is a particular concern for paclitaxel, which is readily broken down into inactive metabolites in the liver. Certain natural compounds, including the polyphenols fisetin and quercetin, may prevent this degradation. In a preclinical model of human liver metabolism, fisetin and quercetin inhibited the metabolic inactivation of paclitaxel (Vaclavikova 2003; Gustafson 2005).

Some unexpected and compelling findings about chemotherapy effectiveness were published in the journal *Science* in 2013. In this study, researchers used an animal model of cancer to establish the potential role of the ecosystem of the digestive tract, called the gut microbiome, in determining whether chemotherapy will be effective. Antibiotic-treated "germ-free" mice with cancer exhibited a poor response to immunotherapy and chemotherapy. Interestingly, the mice lacking normal microbiota showed low cytotoxicity and deficient free radical production in response to platinum chemotherapy. The authors stated, "*optimal responses to cancer therapy require an intact commensal microbiota… These findings underscore the importance of the microbiota in the outcome of disease treatment*." (Iida 2013; Nelson 2015).

Numerous natural products have demonstrated potential as chemosensitizing agents, including (Shen 2012; Davenport 2010; Wesolowska 2011; Michalak 2012; Vinod 2013; Kim, Shin 2014; Sugiyama 2003):

Curcumin. Curcumin, a phytochemical derived from the spice turmeric (Somasundaram 2002; Saleh 2012), was shown to increase the effectiveness of various chemotherapeutic agents in laboratory and preclinical models of several types of cancer (Mitchell 2003). For instance, curcumin enhanced the effectiveness and decreased the toxicity of the antitumor antibiotics mitomycin-C and doxorubicin (Adriamycin) in cell and animal studies of breast and lung cancer (Wang, Shen 2013; Zhou 2009; Zhou, Wang, Liu, Zhang, Lu, Huang, 2011; Zhou, Wang, Liu, Zhang, Lu, Su 2011; Zhou 2014). A study in drug-resistant colon cancer cells found that curcumin enhanced chemosensitivity to 5-fluorouracil (5-FU) (Shakibaei 2014). Curcumin increased sensitivity to paclitaxel in cell culture and animals models of cervical cancer, and enhanced the antitumor effects of cisplatin (Platinol) in laryngeal carcinoma stem cells (Bava 2011; Sreekanth 2011; Zhang 2013). Furthermore, curcumin has demonstrated anticancer effects of its own, and may therefore be useful as an adjunct to conventional cancer treatment (Teiten 2010).

Poor oral bioavailability of many curcumin preparations might prevent adequate serum and cellular concentrations from being reached (Sunagawa 2015; Antony 2008; Chaurasia 2015; Sasaki 2011; Belcaro 2014; Catania 2013; Huang 2014).

Fortunately, BCM-95, a form of curcumin shown to have enhanced bioavailability (Antony 2008), may address this concern. One study showed that BCM-95 sensitized tumor cells to 5-FU and led to suppression of tumor growth. The authors first conducted a study using two 5-FU-resistant colorectal cancer cell lines. Treatment with BCM-95 curcumin and 5-FU showed synergism, with increased sensitivity and apoptosis compared with treatment with the drug alone. The second part of the study was conducted on mice that were transplanted with a 5-FU-resistant colorectal cancer cell line. These mice were injected intraperitoneally with 5-FU with or without 50 mg/kg of BCM-95 daily for 40 days. The 5-FU plus BCM-95 group showed greater inhibition of tumor growth compared with the 5-FU alone or control groups (Toden 2015).

Green tea. Multiple studies have shown the green tea constituents *EGCG* and *theanine* have antitumor activity and can enhance the anticancer effect of chemotherapeutic agents. In one study, the chemotherapy agent doxorubicin caused twice the tumor growth inhibition in mice given a green tea beverage compared with those that did not receive green tea. However, green tea did not increase doxorubicin uptake by normal tissue in the mice (Sadzuka 1998). Studies in mice with ovarian tumors showed that theanine plus doxorubicin was more effective in suppressing liver metastasis than doxorubicin alone. Theanine also enhances the antitumor effects of pirarubicin, irinotecan (Camptosar), and cisplatin (Sugiyama 2003; Sugiyama 1999).

Quercetin. In laboratory research, the flavonoid quercetin improved the sensitivity of several ovarian cancer cell lines to cisplatin and paclitaxel (Maciejczyk 2013). Quercetin plus cisplatin worked synergistically to suppress the growth of cultured hepatocellular carcinoma cells (Zhao 2014), and quercetin enhanced the ability of 5-FU to inhibit cell growth and stimulate apoptosis in esophageal cancer cells (Chuang-Xin 2012). In an oral cancer cell line, quercetin induced apoptosis and reversed drug resistance to vincristine (Oncovin) (Yuan 2015). An animal model of breast cancer found that a liposomal combination of vincristine and quercetin enhanced antitumor activity in tumors resistant to trastuzumab (Herceptin) (Wong 2011).

Omega-3 polyunsaturated fatty acids. The marine omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may have a role in cancer treatment alongside chemotherapy and radiation therapy (Calviello 2009; Shaikh 2010). In a clinical trial on 46 patients with non-small cell lung cancer, one group received chemotherapy alone (carboplatin [Paraplatin] plus vinorelbine [Navelbine] or gemcitabine [Gemzar]) and the other group received chemotherapy plus 2.5 grams of fish oil daily. The response rate in the chemotherapy and fish oil group was approximately two-fold greater compared with the chemotherapy-alone group. Patients in the fish oil group were able to undergo an average of one more cycle of treatment than those receiving chemotherapy alone. It is also important to note that the increase in efficacy of the drug regimen did not correlate with any increase in toxicity to healthy tissues (Murphy 2011).

In another clinical trial, patients with advanced breast cancer received cyclophosphamide, 5-FU, and epirubicin (Ellence) along with a DHA supplement. Twenty-five patients took 1.8 grams DHA daily for 7–10 days prior to chemotherapy and during five months of chemotherapy. At the end of the trial, the patients whose plasma DHA levels increased the most with supplementation had significantly better median survival and longer time to disease progression. For patients whose DHA levels increased the most, median overall survival was 34 months versus 18 months in participants whose DHA levels increased the least. Time to progession was also greater in those with more pronounced increases in DHA levels: 8.7 months versus 3.5 months. The researchers concluded that DHA can chemosensitize tumors (Bougnoux 2009). Support for this notion is provided by a laboratory study in which fish oil sensitized colon cancer cells to 5-FU, oxaliplatin (Eloxatin), and irinotecan (Granci 2013).

Melatonin. Comprehensive reviews of published scientific literature have found that melatonin, a hormone involved in the sleep-wake cycle, can increase tumor remission and one-year survival rates and alleviate chemotherapy and radiotherapy side effects in patients with a wide array of cancers (Wang 2012; Seely 2012). For instance, a meta-analysis of eight randomized controlled trials on individuals with solid tumor cancers found that melatonin supplementation increased the one-year survival rate from 28% to 52% when added as an adjuvant to chemotherapy or radiotherapy (Wang 2012). These studies typically used 20 mg of melatonin daily.

Protein-bound polysaccharide K (PSK). Protein-bound polysaccharide K (PSK) is a constituent of the mushroom ***Coriolus versicolor***. Its anticancer and chemotherapy-enhancing properties have been studied extensively in Japan. Clinical trials have shown that, when used with standard treatment, PSK can significantly prolong survival in patients with various cancers including gastric, esophageal, colorectal, breast, and lung cancers (Maehara 2012; Fisher 2002; Kidd 2000). The dose of PSK used in the majority of studies was three grams daily.

Vitamin C. A 2013 study on ovarian cancer cells found that high concentrations of vitamin C (ascorbic acid or ascorbate) activated several anticancer mechanisms (Ohno 2009; Park 2013). A clinical phase of this same study was carried out on 22 patients with newly diagnosed Stage III or IV ovarian cancer. Ten participants received high-dose intravenous ascorbate (75–100 grams per treatment) along with standard chemotherapy (paclitaxel and carboplatin) for six months. Then, they continued the vitamin C alone for another six months. A separate group of 12 participants received six months of standard chemotherapy alone. Those treated with the vitamin C had chemosensitivity and reduced chemotherapy-associated toxicity. In addition, the median time to disease progression or relapse was 8.75 months longer in the vitamin C plus chemotherapy group (Ma 2014).

A 2015 clinical study on 14 patients with advanced cancer found that combining high-dose intravenous vitamin C with chemotherapy was safe and well tolerated. In fact, three patients with different types of cancer had unexpected temporary disease stabilization, reported increased energy levels, and experienced functional improvement (Hoffer 2015).

Other agents. The well-known Asian herb ***Panax ginseng*** enhanced chemosensitivity to several chemotherapeutic drugs, including 5-FU, irinotecan, mitomycin-C, docetaxel, cisplatin, and doxorubicin in laboratory and animal studies (Chen 2014; Kim, Jung 2014). Several other natural agents may enhance chemosensitivity as well, including **gamma-tocotrienol**, a form of vitamin E (Rajendran 2011), and the amino acid **taurine**, which increased the antitumor activity of doxorubicin in mouse sarcoma cells (Sadzuka 2009). In addition, preclinical studies found that **vitamin D** works synergistically with multiple chemotherapy regimens (Ma 2010).

Metformin Enhances Chemosensitivity

Metformin (Glucophage), a first-line drug for treating type 2 diabetes, may reduce the risk of several types of cancer and cancer-related mortality, and improve the response to some types of chemotherapy (Chae 2016; Daugan 2016; Lee, Kim 2012; Jiralerspong 2009). In an observational study, more diabetic patients taking metformin during neoadjuvant chemotherapy for early-stage breast cancer experienced pathologic complete responses than those not taking metformin. “Pathologic complete response” was defined as no evidence of invasive cancer in the breast or axillary (armpit) lymph nodes at the time of surgery (Jiralerspong 2009). Another observational study found that metformin use in diabetic cancer patients was associated with less frequent tumor recurrence after surgery (Lee, Kim 2012).

A 2013 study of esophageal cancer patients receiving chemotherapy and radiation before surgery found that diabetics taking metformin had a significantly higher rate of complete response to treatment than those not taking emtformin. In addition, the response was dose-dependent, meaning a higher dose of metformin was more effective than a lower dose. In a follow-up laboratory study, researchers showed that metformin sensitized esophageal cancer cells to 5-FU (Skinner 2013; Honjo 2014). In a study of patients with diabetes and advanced non-small cell lung cancer receiving first-line chemotherapy, those taking metformin had significantly less cancer progression and significantly longer survival (20 months) compared with those taking insulin or other diabetes medications (13 months) (Tan 2011).

Numerous laboratory studies have shown that metformin enhances the sensitivity of many different types of cancer cells to chemotherapeutic agents. One laboratory study found that metformin increased the chemosensitivity of throat cancer cells to cisplatin and paclitaxel (Zhang 2014). Another laboratory study found metformin increased the anticancer effects of the chemotherapy drugs doxorubicin and cisplatin in thyroid cancer cells (Chen 2012). Metformin also enhanced the sensitivity of endometrial cells to cisplatin and paclitaxel (Dong 2012). When combined with doxorubicin, metformin killed both breast cancer cells and breast cancer stem cells in culture (Hirsch 2009). A laboratory study found metformin increased the response to temozolomide (Temodar) in six out of eight chemotherapy-resistant tumor cell cultures taken from patients with newly diagnosed high-grade glioma, a type of brain cancer (Soritau 2011).

In addition, metformin may have a specific effect on residual cells remaining after chemotherapy treatment. In a mouse study, metformin significantly suppressed the regrowth of lung tumor cells after effective treatment with gefitinib (Iressa) (Kitazono 2013).

Novel And Emerging Concepts In Chemotherapy

Chemosensitivity Testing

Not all patients with the same type of cancer will have the same response to treatment (Rice 2010; Huh 2009; Feddock 2010). Each person metabolizes drugs differently, and tumors and cancer cells—even among cancers of the same type—can differ markedly on a cellular, molecular, and genetic level (Sabaawy 2013; Rivenbark 2013; Ajani 2011; Duffy 2008; Hendlisz 2013; De Palma 2012; Doroshow 2017).

Treatment appraoches that some describe as “cookie-cutter” remain the standard of care in medical oncology, but their overall success rate is far from impressive (Gesme 2011; Kalia 2013; Ajani 2011; Mavroudi 2014; Bagnyukova 2010). A comprehensive review of medical literature on 22 types of adult cancers found that chemotherapy increased 5-year survival rates by just 2.1% in the United States (Morgan 2004). Other authors have questioned the value of non-curative chemotherapy, suggesting it only modestly prolongs life and has a limited impact on quality of life for most patients (Slater 2001; Boeck 2007; Kosuge 2006; Urschel 2002).

Chemosensitivity testing is a novel approach to identifying drugs most likely to be effective against an individual’s cancer (Grigsby 2013; Geng 2013; Herzog 2010; Smith 1990). This approach involves testing a patient’s tumor and cancer cells against a panel of chemotherapy drugs typically used to treat that type of cancer to determine which drugs elicit the most pronounced response (Yoon 2014; Ballard 2010; Smith 2010; Zhao 2011; Grendys 2014; Nakamura 2006; Wakatsuki 2010; Esserman 2012).

A 2012 study on patients with liver metastases from colorectal cancer compared a standard chemotherapy regimen (32 patients) to one selected based on chemosensitivity testing (31 patients). Before treatment, these patients were not eligible for surgery to remove their liver metastases. The response rate to chemosensitivity-based chemotherapy was significantly greater than to standard chemotherapy, resulting in a higher percentage of patients eligible for surgery after treatment (Hur 2012).

A 2013 study used a method called ATP-tumor chemosensitivity assay (ATP-TCA) to select chemotherapy regimens for patients with recurrent ovarian cancer. The ATP-TCA involves incubating tumor cells with chemotherapy drugs for several days, after which the amount of ATP (cellular energy) produced by the tumor cells is measured to determine their viability. Lower levels of ATP indicate reduced cell viability and greater sensitivity

to the drug(s) tested (Glaysher 2011; Yoon 2014). Patients chose either ATP-TCA-directed chemotherapy (56 patients) or physician's-choice chemotherapy (57 patients). Overall response rate and progression-free survival were significantly greater in the ATP-TCA group (66% and 7 months) compared with the physician's-choice group (46% and 4 months). The difference in favor of assay-selected therapy was even greater for patients with platinum-resistant cancer types (Gao, Wu 2013).

In a study of primary peritoneal carcinomatosis, a type of cancer that affects abdominal cavity tissue, and recurrent peritoneal carcinomatosis from ovarian cancer, chemosensitivity testing was a better predictor of clinical response than testing for levels of cancer gene expression biomarkers (Arienti 2011). A study on peritoneal carcinomatosis related to colorectal cancer found similar results (Arienti 2013).

Several private laboratories offer chemosensitivity testing, including:

1. **Rational Therapeutics** – Long Beach, California, USA
   - https://www.rational-t.com/ (https://www.rational-t.com/)
2. **Weisenthal Cancer Group** – Huntington Beach, California, USA
   - http://www.weisenthalcancer.com/ (http://www.weisenthalcancer.com/)
3. **Helomics** – Pittsburgh, Pennsylvania, USA
   - http://www.helomics.com/ (http://www.helomics.com/)
4. **BioFocus** – Recklinghausen, Germany
   - http://www.biofocus.de/de/onkologie/ueberblick/ueberblick/ (http://www.biofocus.de/de/onkologie/ueberblick/ueberblick/)
5. **Genostics** – New South Wales, Australia
   - http://www.genostics.com.au/#genostics (http://www.genostics.com.au/#genostics)
6. **Research Genetic Cancer Center Ltd**. – Clifton, Bristol, UK
   - http://www.rgcc-uk.com/chemosensitivity-testing/ (http://www.rgcc-uk.com/chemosensitivity-testing/)

These tests require a blood sample or a biopsy of the tumor (Andreotti 1995; Gazzaniga 2010; Gallant 2013). Chemosensitivity tests have limitations due to their inability to mimic the exact conditions inside the body of an individual patient. Chemosensitivity tests also have less predictive ability in metastatic cancer because cancer that has spread may have a different chemosensitivity profile than the primary tumor. Such differing characteristics result from the continuous mutations malignancies undergo, resulting in differing biochemical and genetic characteristics, even in the same tumor (Higashiyama 2012; Perry 2012; Meric-Bernstam 2012).

Genetic and Biomarker Profiling

Cancers are genetically variable. A breast tumor in one person, for instance, may have very different genetics than a breast tumor in another person.

Tumor gene expression analysis, also known as genetic profiling, is a method of characterizing the chemosensitivity of a patient's unique tumor to specific drugs (Taherian-Fard 2014; Dezso 2014; Michalski 2008; Cobo 2007). Some of the genetic characteristics of tumors can be targeted with specific chemotherapy drugs. This approach contrasts with the standard "one-size-fits-all" approach.

In the future, clinical oncology will likely focus on personalizing cancer treatment based on detailed molecular and genetic analysis of each individual's cancer (Perry 2012; Kalia 2013; McDermott 2009; Cronin 2011). This will help oncologists tailor treatments specifically for each patient (Garralda 2014; Guan 2012; Mavroudi 2014; Zarogoulidis 2013).

Research in this area is ongoing, and scientists have already made exciting discoveries. In patients with non-small cell lung cancer, for example, a tumor biomarker correlated with cisplatin resistance, excision repair cross-complementation group 1 (ERCC1), has been identified. The presence or absence of this tumor biomarker may also predict cisplatin resistance or response in patients with gastric, ovarian, and colorectal cancer (Cobo 2007). Early clinical studies on the use of new predictive biomarkers in chronic and acute leukemias, colon cancer, breast cancer, non-small cell lung cancer, and melanoma have shown promising results (Eustace 2014; Ugurel 2009; Yiu 2016; Selli 2016; Perez-Callejo 2016; Yeh 2016).

Some genetic tests are already commercially available. For example, organizations such as the International Strategic Cancer Alliance (http://www.isca.us/benefits-of-molecular-analysis/) offer molecular analysis of circulating tumor cells to help guide treatment. Their contact information is:

International Strategic Cancer Alliance

www.isca.us (http://www.isca.us/)
873 E. Baltimore Pike #333
Kennett Square, PA 19348
USA
By Phone at: 610-628-3419

Other commercially available prognostic gene expression signature tests include MammaPrint, Oncotype DX, and PAM50 (ProSigna). These tests are approved for use in certain populations to provide algorithmic scores that help inform clinical decisions (Wang 2014; Klein 2013; Slodkowska 2009; Colombo 2011). Patients determined through such testing to be high risk are offered adjuvant chemotherapy, whereas those that are low risk are not (Goncalves 2013; Rutgers 2011).

Monoclonal Antibody-Targeted Chemotherapy

Chemotherapeutic drugs' indiscriminate toxicity toward cancerous and non-cancerous cells is a major challenge for oncology medicine. Because most existing chemotherapeutic drugs enter cells indiscriminately, dosages necessary to kill cancer cells often exert considerable toxicity on rapidly dividing healthy cells (Hilchie 2011). Developing strategies for delivering chemotherapeutic drugs directly to cancer cells without affecting healthy cells is an active area of research.

One promising strategy is to attach chemotherapeutic drugs to molecular chaperones (antibodies) that specifically target cancer cells. These compounds, called antibody-drug conjugates, have shown promise in preclinical and clinical research (Sapra 2013; Beck 2012; Anderl 2013). Monoclonal antibodies, specialized antibodies that target certain cells or cell surface markers, are used in the preparation of antibody-drug conjugates (NCI 2014d).

One antibody-drug conjugate, trastuzumab emtansine (T-DM1, Kadcyla), targets breast cancer in patients whose tumors express a marker known as human epidermal growth factor receptor 2 (HER2). Trastuzumab emtansine is composed of the HER2-targeting monoclonal antibody trastuzumab

linked to the cytotoxic agent emtansine. A phase III trial compared trastuzumab emtansine to treatment chosen by physician in patients with advanced HER2-positive breast cancer. All of the participants had recurrent or metastatic breast cancer that was progressing despite two or more chemotherapy regimens directed specifically at HER2. The trial found that trastuzumab emtansine resulted in a higher rate of progression-free survival (median 6 months with trastuzumab versus 3 months in the physician's-choice group). The study also found that trastuzumab emtansine was associated with fewer severe adverse side effects than physician-choice treatment (Krop 2014). The FDA has approved trastuzumab emtansine for the treatment of patients with metastatic HER2-positive breast cancer previously treated with trastuzumab and a taxane (FDA 2013). Additional antibody-drug conjugates are currently in development for a variety of cancer types (Anderl 2013).

Hyperthermia as an Adjunct to Chemotherapy

Hyperthermia involves the use of heat to either directly treat a tumor or increase the vulnerability of cancer cells to other forms of treatment such as chemotherapy or radiation therapy. Types of hyperthermia include local, regional, and whole-body hyperthermia; heating methods include laser, ultrasound, radiofrequency, and microwave radiation (ACS 2013b; Brace 2010).

In local hyperthermia, heat is applied to a small area to heat the tumor and local blood vessels. In a type of local hyperthermia called thermal ablation, extremely high temperatures directly destroy cells. Regional hyperthermia involves heating a specific region of the body such as a limb, organ, or body cavity, generally to lower temperatures than local hyperthermia. In whole-body hyperthermia, the temperature of the entire body is increased to a temperature as high as 108°F; this method is being studied to improve the cytotoxic effect of chemotherapy in metastatic cancer (ACS 2013b; Skitzki 2009; Hildebrandt 2002).

Increasing tissue temperature exerts several anticancer actions, including direct cytotoxicity and activation of several aspects of the immune system. Hyperthermia may also sensitize tumors to chemotherapy and radiation, and appears to do so with minimal damage to normal, healthy cells. Hyperthermia is usually combined with chemotherapy or radiotherapy to treat advanced and recurrent cancers (Owusu 2013; NCI 2011; Hildebrandt 2002; Oei 2015; Skitzki 2009).

Hyperthermia is a promising treatment option for several types of cancer, including non-small cell lung cancer (Wang, Lin 2013), bladder cancer (Colombo 2013; Owusu 2013), advanced cervical cancer (Heijkoop 2012), rectal cancer (Shelygin 2014), and malignant pleural mesothelioma (Okonogi 2012).

The side effects of hyperthermia are usually temporary, but in rare cases can be serious. Local hyperthermia can lead to localized pain, burns, bleeding, infection, blood clots, and other problems. Regional and whole body hyperthermia can cause nausea, diarrhea, vomiting, and, less frequently, problems with blood vessels and the heart (ACS 2013b; NCI 2011).

Lessening Chemotherapy Side Effects

Prevention and mitigation of chemotherapy side effects can avert the need to interrupt or stop treatment and allow for more aggressive dosing schedules, thus increasing the chance of treatment success. Toxic effects of chemotherapy are generally managed with drug dose adjustment (Janus 2010; CCS 2017; Griggs 2002; Verstappen 2003; Jansman 2001). However, a broad range of natural compounds may mitigate chemotherapy side effects as well (Ohkawa 1988; Liu 2012).

Although some physicins cite concern about possible harmful interactions between natural products and chemotherapy, several thorough reviews of published research have concluded that such concerns are only theoretical (Cheng 2010; Hart 2012; Ma 2014; Simone 2007a; Simone 2007b; Block 2004). It is important to note that anyone who utilizes the information contained within this protocol should do so in collaboration with their oncology team.

Research Summary: Integrative Interventions to Lessen Chemotherapy Side Effects

The following table outlines some integrative therapies that may be helpful in mitigating side effects of chemotherapy. This table briefly summarizes the research detailed in the text of this protocol. Human evidence is identified below as either from randomized controlled trials (RCT) or preliminary studies, which may or may not include an untreated control group. Animal studies are also included in this table and clearly identified as such.

Table 2. Integrative Therapies to Lessen Chemotherapy Side Effects

Chemotherapy Side Effect	Integrative Therapy	Evidence
Fatigue	**Ashwagandha (*Withania somnifera*)**	Positive findings in a preliminary trial (Biswal 2013)
	Guarana (*Paullinia cupana*)	Positive findings in two preliminary trials (del Giglio 2013; de Oliveira Campos 2011); negative findings in one RCT (Martins 2016)
	American ginseng (*Panax quinquefolius*)	Positive findings from a large RCT (Barton 2013)
	Melatonin	Positive findings from multiple RCTs and confirmed in a meta-analysis (Wang 2012)
	L-Carnitine	Positive findings from two preliminary trials in patients with carnitine depletion (Graziano 2002; Cruciani 2006); negative findings from one large RCT (Cruciani 2012)
	IV Vitamin C	Positive findings from a preliminary trial (Hoffer 2015)
	Turkey tail mushroom (*Coriolus versicolor*) polysaccharide peptide (PSP)	Positive findings from multiple RCTs (Piotrowski 2015; Fritz 2015)
	Reishi (*Ganoderma lucidum*)	Positive findings from one small RCT (Zhao 2012)

	Fermented soybean extract	Positive findings from one preliminary trial (Chi 2014)
Immunosuppression/Neutropenia	**Eicosapentaenoic acid (EPA) from fish oil**	Positive findings from a preliminary trial (Takagi 2001)
	Fermented wheat germ extract (FWGE)	Positive findings from a preliminary trial in children (Garami 2004)
	Probiotic	Supportive animal research (Salva 2014; Von Bultzingslowen 2003)
	Zinc	Supportive animal research (Zhang 1992)
	Quercetin	Supportive animal research (Merzoug 2014)
	Ashwagandha (*Withania somnifera*)	Supportive animal research (Senthilnathan 2006; Gupta 2001)
Nausea/Vomiting	**Ginger**	Positive findings from one preliminary (Panahi 2012) and one RCT (Yekta 2012)
	Taurine	Positive findings from one RCT (Islambulchilar 2014)
Peripheral Neuropathy	**IV Calcium and Magnesium**	Positive findings from multiple RCTs and confirmed in a meta-analysis (Xu 2013)
	Vitamin E	Positive findings from multiple RCTs and confirmed in a meta-analysis (Eum 2013)
	Glutathione	Positive findings from a RCT (Cascinu 1995)
	N-Acetyl Cysteine	Positive findings from a preliminary trial (Lin 2006)
	Omega-3 Fatty Acids	Positive findings from one RCT (Ghoreishi 2012)
	Acetyl-L-Carnitine	Positive findings from two preliminary trials (Bianchi 2005; Maestri 2005) and one RCT (Campone 2013)
	Glutamine	Positive findings from several preliminary trials (Vahdat 2001; Wang 2007; Huang 2015)
	Alpha-Lipoic Acid	Positive findings from one preliminary trial (Gedlicka 2003)
Cardiotoxicity	**Coenzyme Q10**	Positive findings from several preliminary trials (Conklin 2005)
	Green Tea Extract/EGCG	Supportive animal research (Patil 2011; Khan 2014; Li, Nie 2010)
	Grape Seed Extract	Supportive animal research (Ray 2000; Boghdady 2013)
	Rhodiola	Positive findings from one preliminary trial (Shen 2010)
	Vitamin E	Supportive animal research (Sonneveld 1978)
	Cranberry, Bilberry, Hawthorne, Boswellia, Ginger, Onion, *Panax notoginseng*, Propolis, Glutamine	Supportive animal research; see text for references
	L-Carnitine	Positive findings in RCT and preliminary trials (De Leonardis 1987; Lissoni 1993)
Kidney Toxicity	**IV Magnesium**	Positive findings from preliminary trials (Hirai 2013; Yoshida 2014) and RCTs (Bodnar 2008; Muraki 2012)
	N-Acetyl Cysteine	Positive case reports (Sheikh-Hamad 1997; Nisar 2002) and supportive animal research (Chen 2008)
	IV Glutathione	Positive findings from one RCT (Smyth 1997)
	Milk Thistle	Supportive animal research (Shahbazi 2012)
	Ginkgo	Supportive animal research (Song 2013; Gulec 2006; Fukaya 1999)
	L-Carnitine (in various forms, see text)	Supportive animal research (Sayed-Ahmed 2004; Yurekli 2011; Sayed-Ahmed 2012)
	Selenium	Positive findings from preliminary trials (Ghorbani, Omidvar 2013; Naziroglu 2004) and two RCTs (Hu 1997; Hemati 2012)
	Lycopene, Melatonin, Carnosic Acid, Ellagic Acid, Fisetin, Alpha-Lipoic Acid, Taurine, Sulforaphane, EGCG, Capsaicin, Berberine	Supportive animal research; see text for references

Chemosensory Dysfunction	**Zinc**	A positive case report in a patient with low serum zinc (Nishijima 2011)
	***Synsepalum dulcificum* (Miracle Fruit)**	Positive findings in a preliminary trial (Wilken 2012)
Hand-Foot Syndrome	**Vitamin E**	Positive findings from preliminary trials (Bozkurt Duman 2011; Yamamoto 2010)
	Vitamin B_6	Positive preliminary findings (Chen, Zhang 2013)
Gastrointestinal Disturbances	**Probiotics for Diarrhea**	Positive findings from RCT and confirmed in a meta-analysis (Wang, Yao 2016)
	Glutamine for Diarrhea	RCT and a meta-analysis show reduced duration, but not severity, of diarrhea in patients taking glutamine (Sun 2012)
	Omega-3 Fatty Acids	Supportive animal research (Xue 2011)
	Senna Extract for Constipation	Preliminary support (Tao 2012)
Poor Nutritional Status/Cachexia	**Glutamine**	Positive findings from preliminary trials (Kuhn 2010)
	Omega-3 Fatty Acids	Positive findings from preliminary trials (Murphy 2012)
	L-Carnitine	Positive findings from preliminary trials (Isenring 2013) and one RCT (Kraft 2012)
Oral Mucositis	**Honey**	Positive findings from RCT and confirmed in a meta-analysis (Xu 2016)
	N-Acetyl Cysteine	Positive findings from one RCT (Moslehi 2014)
	Selenium	Positive findings from one RCT (Jahangard-Rafsanjani 2013)
	Glutamine	Positive findings from one RCT (Tsujimoto 2015)
	Topical Vitamin E	Preliminary evidence (El-Housseiny 2007)

Fatigue

Chemotherapy-related fatigue can include exhaustion, extreme weakness, depression, loss of motivation, difficulty concentrating, and a general sense of being unwell. Fatigue is the most common side effect of chemotherapy, with up to 96% of patients suffering from fatigue during treatment (Iop 2004; Tierney 1991; Visovsky 2003).

Conventional treatments for fatigue. Anemia is an important cause of chemotherapy-induced fatigue, and treating chemotherapy-induced anemia may prevent or improve fatigue (Mahoney 2014). Erythropoiesis-stimulating agents promote red blood cell formation. An analysis of four clinical trials that evaluated an erythropoiesis-stimulating agent known as darbepoetin alfa (Aranesp) found that it increased hemoglobin levels and improved chemotherapy-induced fatigue (Revicki 2012). A literature review found that erythropoiesis-stimulating agents made a clinically relevant difference in symptoms of chemotherapy-induced anemia (Bohlius 2014).

Integrative interventions for fatigue. Ashwagandha (*Withania somnifera*) is an herb with adaptogenic, anti-inflammatory, and anticancer properties. In an open-label trial in 100 breast cancer patients receiving two different chemotherapy regimens, ashwagandha plus chemotherapy was compared with chemotherapy alone. The dosage in this study was two grams of ashwagandha root extract every eight hours throughout the course of chemotherapy. Patients receiving chemotherapy alone had significantly higher fatigue scores than those who received ashwagandha. Ashwagandha treatment also improved quality of life (Biswal 2013).

Guarana (*Paullinia cupana*) is an Amazonian plant that contains catechins, epicatechins, and a small amount of caffeine (Subbiah 2008). In two small clinical studies, guarana improved chemotherapy-induced fatigue. In the first study, 40 cancer patients with solid tumors and increasing fatigue after one week of chemotherapy began receiving 37.5 mg guarana extract twice daily. After three weeks, 90% of participants showed improvement in fatigue scores (del Giglio 2013). The second study, which evaluated the effects of 50 mg guarana extract twice daily in 75 breast cancer patients experiencing chemotherapy-related fatigue, found guarana superior to placebo for relieving fatigue (de Oliveira Campos 2011).

American ginseng (*Panax quinquefolius*) is a close relative of the better-known Asian ginseng (*Panax ginseng*). It contains an array of biologically active compounds including ginsenosides and polysaccharides. American ginseng possesses adaptogenic and anti-inflammatory properties (Jia 2009; Wang 2009; Barton 2013). An 8-week randomized controlled trial found that 2000 mg of American ginseng improved cancer-related fatigue in 364 cancer patients. Participants in the trial had various types of cancer and were either receiving cancer treatment or had completed treatment. At the end of the trial, fatigue scores improved significantly more in the ginseng group compared with the placebo group. Participants in the ginseng group undergoing cancer treatment benefited more than those who had already completed cancer treatment (Barton 2013).

Melatonin is a hormone produced by the pineal gland; it helps regulate the sleep-wake cycle (Vural 2014; Brown 1994). Melatonin also has antioxidant properties and antitumor and immune-modulating effects. A review of eight randomized controlled trials, which included 761 patients with solid tumors, showed that 20 mg of melatonin per day significantly reduced chemotherapy-related side effects, including fatigue. Furthermore, melatonin use was associated with 40% reduced one-year mortality and did not cause any serious side effects (Seely 2012; Wang 2012).

L-carnitine is an amino acid that may benefit chemotherapy-related fatigue. Carnitine is involved in cellular energy metabolism and is often depleted in cancer patients, including as a result of chemotherapy (Fukawa 2016; Silverio 2011). A study evaluated the effects of L-carnitine in 50 fatigued patients with low plasma carnitine levels. These patients were undergoing treatment with either cisplatin or ifosfamide (Ifex) for stage IV cancer, but

they were not anemic. The participants received four grams of oral L-carnitine daily. Within seven days, plasma carnitine levels normalized in all patients, and 45 patients experienced significant relief from fatigue. This improvement in fatigue lasted until the next cycle of chemotherapy (Graziano 2002). In a smaller study in 21 patients with advanced cancer who had carnitine deficiency and moderate-to-severe fatigue, supplementation with up to three grams daily of oral L-carnitine led to improvements in fatigue scores that correlated with increases in blood carnitine levels. No toxicity or significant side effects were noted (Cruciani 2006).

Certain mushrooms and mushroom extracts have immune-modulating properties and are used along with chemotherapy in China and Japan. A review of studies found that supplementation with polysaccharide peptide (PSP), a compound derived from the mushroom ***Coriolus versicolor***, decreased side effects related to cancer treatment, including fatigue (Piotrowski 2015). In a randomized controlled trial in 48 breast cancer patients without anemia who were undergoing hormonal therapy, treatment with 3000 mg of ***Ganoderma lucidum*** (reishi) spore powder daily for four weeks resulted in significant improvements in fatigue and physical well-being, as well as in anxiety, depression, and overall quality of life (Zhao 2012).

Scores for fatigue and appetite significantly improved in a study of a **fermented soybean extract** in 143 patients undergoing chemotherapy (Chi 2014). Trials studying the effects of nutritional factors including **glutamine** and **fish oil** on cancer cachexia (weakness and weight loss) have also shown positive results with regards to improvement in fatigue (Schlemmer 2015; Cerchietti 2007). (These interventions are discussed further in the Nutritional Status and Cachexia section of this protocol.)

A rigorous study found that all tyoes of **exercise** (not just aerobic exercise) improved quality of life and fatigue in individuals undergoing cancer treatment, particularly when the exercise was moderate to vigorous in intensity (Mishra 2012). Other approaches that may be helpful include *Qigong, yoga*, *acupuncture*, *massage* and *healing touch*, *mindfulness-based stress reduction*, *cognitive behavioral therapy*, and other forms of stress-relieving or psychosocial support (Chien 2013; Mitchell 2014; Wang 2014; Taso 2014; Oh 2010).

Immunosuppression and Blood-Related Complications

Chemotherapy can damage the body's blood-forming system. In fact, suppression of blood cell formation in the bone marrow (myelosuppression) is one of the most serious and common side effects of chemotherapy (Carey 2003; Zangemeister-Wittke 2009; Repetto 2009). Myelosuppression can result in low red blood cells (anemia), low white blood cells (leukopenia), or low platelets (thrombocytopenia). Rarely, production of all three types of cells is reduced. This is called pancytopenia (Zangemeister-Wittke 2009; Gayathri 2011).

In neutropenia, the most serious type of leukopenia, levels of infection-fighting neutrophils (a type of white blood cell) fall far below normal, often accompanied by fever (Bhatt 2004; Crawford 2004; Levenga 2007). Neutropenia raises the risk of life-threatening infection and can interrupt treatment schedules (Crawford 2004; Levenga 2007; Carey 2003). Myelosuppression leading to low platelets increases the risk of excessive bleeding (Carey 2003; Vadhan-Raj 2009).

Conventional treatments for blood-related and immunosuppressive complications of chemotherapy. Granulocyte-colony stimulating factor (G-CSF), antibiotics, and dose reduction are primary management strategies for the immunosuppressive effects of chemotherapy (Dale 2003; Aapro 2011). A rigorous study found that G-CSF use is associated with lower all-cause mortality in patients receiving chemotherapy, especially in those on intensive dosing schedules (Lyman 2013). Depending on the proposed chemotherapy regimen and pretreatment blood cell counts, preventive G-CSF and/or antibiotics may be administered to patients at high risk of neutropenia. These treatments may also be used for neutropenia (Timmer-Bonte 2006; Krzemieniecki 2014; Timmer-Bonte 2005; Choi, Solid 2014; Aarts 2013; Pfeil 2014). The combination of G-CSF plus antibiotics is more effective than either alone (Timmer-Bonte 2006). Patients with chemotherapy-induced thrombocytopenia may be candidates for platelet transfusion (Apelseth 2011).

A comprehensive discussion of strategies for addressing low levels of blood cells and platelets is available in the Blood Disorders (/Protocols/Heart-Circulatory/Blood-Disorders/Page-01) protocol.

Integrative interventions for chemotherapy-associated immunosuppression. In 15 esophageal cancer patients scheduled to undergo surgery, perioperative supplementation with eicosapentaenoic acid (EPA), an omega-3 fatty acid found in **fish oil**, reduced immunosuppression caused by chemoradiation. Five subjects received 1.8 grams per day of EPA starting one week before their operation and continuing until hospital discharge; the other 10 did not take EPA. Subjects who had taken EPA exhibited more robust white blood cell proliferation in response to immune-stimulating chemicals and increased natural killer cell activity when compared with control subjects (Takagi 2001). Omega-3 fatty acid supplementation has been recommended for post-surgical and critically ill patients due to its anti-inflammatory and immune-enhancing effects (Calder 2004; Machon 2012; Goldfarb 2012; Moison 2001).

An **extract of fermented wheat germ (FWGE)** is approved in Europe, where it was developed, as a "dietary food for special medical purposes for cancer patients" (Demidov 2008). It is available in powdered form, has a favorable safety profile, and has been studied for a variety of conditions including cancer (Boros 2005). FWGE's potential to prevent neutropenia was demonstrated in an early-stage open-label trial in 11 pairs of children being treated with standard chemotherapy for various cancers. One child in each pair received six grams of FWGE per square meter of body surface area, dissolved in water twice daily throughout the study, and the other did not. Counterparts in each pair were matched for age, gender, diagnosis, stage of disease, and previous chemotherapy exposure; however, two patients in the FWGE group had metastatic disease at the beginning of the study, while their paired counterparts did not. At the end of the study, the FWGE and control groups had undergone essentially the same degree of treatment in terms of chemotherapy and other therapies; however, the FWGE group experienced on average 80% fewer monthly episodes of neutropenia with fever compared with the control group. Furthermore, during neutropenic episodes, the total white blood cell and lymphocyte counts were not as low in the FWGE group as the control group (Garami 2004).

Animal and human research suggests **probiotic** *lactobacilli* may decrease chemotherapy-induced immunosuppression. In mice treated with cyclophosphamide, a drug known to cause neutropenia, the probiotics *Lactobacillus casei* CRL431 and *Lactobacillus rhamnosus* CRL1506 increased the number of certain types of blood stem cells in the bone marrow and induced faster recovery of neutrophil levels (Gold Standard 2016b; Salva 2014). In addition, the mice that recieved the probiotics were less susceptible to infection with *Candida albicans*, a yeast that is part of the normal microbial community but can become pathogenic in immunocompromised individuals (Naglik 2003). The scientists who carried out these experiments remarked "…*probiotic lactobacilli have the potential to be used as alternatives for lessening chemotherapy-induced immunosuppression in cancer patients*" (Salva 2014). A rigorous literature review found that probiotics reduced the odds of moderate-to-severe antibiotic- and chemotherapy-associated diarrhea in cancer patients by 68% (Redman 2014).

In an animal model, **zinc** supplementation reduced several aspects of immune system suppression caused by cyclophosphamide. Mice that received zinc were resistant to cyclophosphamide-induced reductions in numbers of white blood cells and mature T lymphocytes, suppression of IgM antibody

production, and reduction of thymus weight (Zhang 1992). **Quercetin**, a flavonoid, was found in one study to modestly diminish doxorubicin-induced immunosuppression in rats. Quercetin treatment also resulted in lower levels of brain oxidative stress and fewer behaviors believed to indicate anxiety and depression (Merzoug 2014; Reagan-Shaw 2008).

Ashwagandha (*Withania somnifera*) helped control paclitaxel-induced immunosuppression in mice with lung cancer (Senthilnathan 2006). In another animal study, ashwagandha reversed paclitaxel-induced neutropenia in mice when administered for four days before paclitaxel treatment and continued for 12 days after treatment. The authors concluded that ashwagandha may be useful during cancer chemotherapy for the prevention of bone marrow suppression (Gupta 2001).

In a randomized controlled trial in 40 young adults with acute lymphoblastic leukemia, undergoing maintenance chemotherapy, supplementation with two grams of the amino acid **taurine** daily, compared with placebo, significantly reduced the number of episodes of fever and infection and increased white blood cell counts (Islambulchilar 2015).

Additional strategies for supporting healthy immune system function are reviewed in the Immune Senescence (http://www.lifeextension.com/Protocols/Immune-Connective-Joint/Immune-Senescence/Page-01) protocol.

Nausea and Vomiting

Chemotherapy-induced nausea and vomiting (CINV) is a burden for many cancer patients (Grunberg 2013). It can lead to malnutrition because patients with CINV may have diminished appetite (Marx 2016; Davidson 2012). CINV can also cause weight loss, fatigue, anxiety, treatment non-compliance, and poor treatment outcome (Janelsins 2013; Grunberg 2013). Cisplatin, doxorubicin, and cyclophosphamide are agents known to cause CINV (Janelsins 2013).

Conventional treatments for chemotherapy-induced nausea and vomiting. CINV can be prevented in almost 80% of patients with prescription antiemetics (ie, drugs to reduce nausea and vomiting) (Jordan 2014). Antiemetic drugs used to mitiagte CINV include (Viale 2005; Vrabel 2007; Gold Standard 2014; Gold Standard 2016a):

- palonosetron (Aloxi), a 5-HT_3 receptor blocker
- oral aprepitant or intravenous fosaprepitant (Emend), a neurokinin-1 receptor blocker
- ondansetron (Zofran)

Typically, a single intravenous dose of palonosetron is given 30 minutes prior to chemotherapy to prevent nausea and vomiting; this medication has a favorable safety profile (Gold Standard 2014; Popovic 2014; Schwartzberg 2014). Alternatively, a three-day regimen of oral aprepitant may be used, 125 mg one hour prior to chemotherapy on day one and 80 mg one hour prior to chemotherapy on days two and three (Gold Standard 2016a).

The steroid dexamethasone (Decadron) can also be combined with antiemetics to control CINV (Gralla 2016; Gao, Liang 2013). In addition, clinical studies show olanzapine (Zyprexa), an antipsychotic drug, may be helpful as a co-treatment for CINV prevention (Hocking 2014). Gabapentin (Neurontin), which is mainly used to treat neuropathic pain, has recently been found to have antiemetic effects and may be used for the treatment of CINV (Guttuso 2014). Another drug that may be used to treat CINV in some cases is megestrol acetate (Megace), a synthetic progesterone derivative. In one study, individuals undergoing chemotherapy were given megestrol acetate along with two other antiemetic medications, metoclopramide (Reglan) and granisetron (Kytril), or a combination of the two standard antiemetics without megestrol acetate. Complete protection against nausea and vomiting was observed in 45% of the megestrol acetate group versus only 17% of the group that did not receive megestrol acetate (Zang 2011).

Dronabinol (Marinol) is an oral form of delta-9-tetrahydrocannabinol, a cannabanoid from *Cannabis sativa* (marijuana), that has been FDA approved since 1985 to treat CINV that does not respond to usual treatment (May 2016). Among the more common possible side effects of dronabinol are drowsiness, dizziness, euphoria, paranoia, abnormal thoughts, and nausea and vomiting. One case study reported that a patient with end-stage ovarian cancer and peritoneal carcinomatosis whose nausea and vomiting did not respond to other treatments had a dramatic response to dronabinol (Hernandez 2013).

Integrative interventions for chemotherapy-induced nausea and vomiting. Several integrative strategies have been shown to mitigate chemotherapy-induced nausea and vomiting:

Ginger is a botanical antiemetic that has been used in traditional medicine for over 2000 years (Yekta 2012; Montazeri 2013; Palatty 2013; Lee 2013). The antiemetic effects of ginger are thought to involve the phytochemicals 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol. Interestingly, ginger may function via mechanisms similar to palonosetron (5-HT_3 receptor blocker) and aprepitant (neurokinin-1 receptor blocker) (Gold Standard 2016a; Gold Standard 2014; Haniadka 2012).

In a randomized controlled trial, 744 cancer patients were given either 0.5 grams, 1.0 gram, or 1.5 grams of ginger root extract, or placebo, twice daily for six days, starting three days before their first day of chemotherapy. All doses of ginger supplementation resulted in significantly reduced severity of acute chemotherapy-induced nausea (Ryan 2012). In another controlled clinical trial, 80 women with breast cancer undergoing chemotherapy and suffering from chemotherapy-induced vomiting were given one gram of ginger root extract per day or placebo for six days, starting three days prior to chemotherapy. Those taking ginger had significantly less vomiting (Yekta 2012). A randomized trial involving 100 women with advanced breast cancer found the combination of standard antiemetic treatment plus 500 mg of dry powdered ginger root three times daily reduced nausea after chemotherapy significantly better than standard treatment alone (Panahi 2012).

The amnio acid **taurine** helped reduce CINV in leukemia patients in a clinical trial. This study randomized 40 subjects aged 16 - 23 with acute lymphoblastic leukemia who were undergoing chemotherapy to receive either one gram of taurine twice daily or placebo six hours after each chemotherapy treatment for six months. Thirty-two subjects completed the study. Those who took taurine were less likely to experience CINV; they also had greater improvement in chemotherapy-related taste and smell disturbances, appetite, and fatigue (Islambulchilar 2014).

Concord **grape juice** was shown in early research to reduce the frequency and duration of nausea and vomiting when consumed before meals following chemotherapy cycles (Ingersoll 2010). In a randomized clinical trial, **acupressure** at the P6 point (located on the wrist) using an acupressure wrist device was found to reduce the amount and intensity of delayed CINV, which begins 24 hours or more after chemotherapy, in women undergoing chemotherapy for breast cancer (Rice 2011; Dibble 2007). Use of an acupressure wristband, called Sea Band, is one way of applying pressure to the P6 point (Dundee 1990).

Peripheral Neuropathy

The nervous system consists of two primary parts: the central nervous system includes the brain and spinal cord; the peripheral nervous system includes nerves that emanate from the brain and spinal cord, along with their sensory and motor endings (O'Rahilly 2008). Chemotherapy can damage peripheral nerves, leading to symptoms such as tingling, pain, and numbness, especially in the extremities. This is called chemotherapy-induced peripheral neuropathy (CIPN). Other organ systems, such as the digestive and cardiovascular systems, also contain peripheral nerves, so CIPN can lead to symptoms such as constipation and arrhythmias (Kolak 2013). CIPN occurs in as many as 70% of individuals who undergo chemotherapy. Some drugs associated with CIPN are platinum compounds, taxanes, vinca alkaloids, thalidomide (Thalomid), and bortezomib (Velcade) (Argyriou 2014; Gewandter 2014).

Conventional treatments for chemotherapy-induced peripheral neuropathy. Unfortunately, there is no effective treatment for CIPN. As of early 2017, no medications are approved for the treatment of CIPN. There are also no preventives, and a rigorous review of literature found insufficient evidence to conclude that antidepressants or anticonvulsants reduce CIPN (Chu 2015; Majithia 2016; Park 2014; Cavaletti 2015).

One randomized controlled trial of the antidepressant duloxetine (Cymbalta) in 231 patients taking oxaliplatin, paclitaxel or other taxanes, found those receiving duloxetine were significantly more likely to experience a 30% or 50% reduction in pain than those in the placebo group (Smith 2013). Other studies have also shown a modest benefit for venlafaxine (Effexor), topical amitriptyline, and oxcarbazepine (Trileptal) (Chu 2015).

In a pilot trial, intravenous mangafodipir (Teslascan), a drug composed of a vitamin B_6 derivative bonded to manganese, eased oxaliplatin-induced peripheral neuropathy (Coriat 2014). Vitamin B_6 helps maintain normal nerve function and has neuroprotective activity (Zysset-Burri 2013; Yu 2014).

Integrative interventions for chemotherapy-induced peripheral neuropathy. Several integrative interventions with neuroprotective and neuroregenerative effects hold promise in the prevention and treatment of CIPN (Argyriou 2014; Wolf 2008).

Calcium and **magnesium** infusions may prevent CIPN (Piccolo 2014). A rigorous analysis of 16 studies involving 1765 patients with gastrointestinal cancers found that calcium and magnesium infusions significantly reduced the incidence of low- or moderate-grade oxaliplatin-induced neuropathy without interfering with the anticancer effect of chemotherapy (Xu 2013).

Glutathione has been shown to reduce neuropathy associated with cisplatin-based chemotherapy in gastric cancer patients (Cascinu 1995). **N-acetyl cysteine (NAC)** was shown in one study on colon cancer patients to mitigate neuropathy caused by oxaliplatin (Lin 2006). A randomized controlled trial in breast cancer patients undergoing chemotherapy with paclitaxel found that supplementation with **omega-3 fatty acids** reduced the incidence and severity of peripheral neuropathy. The subjects took 640 mg of omega-3 fatty acids three times daily during chemotherapy and for one month after chemotherapy completion (Ghoreishi 2012).

A meta-analyis of five randomized controlled trials involving 319 patients found that 333–900 IU of supplemental **vitamin E** daily reduced the risk of CIPN by 57%; vitamin E was particularly effective for patients on cisplatin therapy, reducing CIPN risk by 74%. No adverse effects of vitamin E were reported in any of the trials included in this analysis (Eum 2013).

In a double-blind placebo-controlled clinical trial in patients with ovarian cancer or prostate cancer, administration of intravenous sagopilone (a chemotherapy drug in development) along with 1000 mg **acetyl-L-carnitine** (at a dosage of 1000 mg every three days) significantly reduced the incidence of severe neuropathy without diminishing response to treatment (Campone 2013). An 8-week trial assess the effects of three daily oral doses of 1000 mg of acetyl-L-carnitine in 25 patients with severe CIPN. The subjects were undergoing paclitaxel or cisplatin therapy during the trial, or had moderate CIPN persisting for at least three months after discontinuing chemotherapy. Sensory neuropathy severity improved in 60% of subjects, and motor neuropathy improved in 79%. The total neuropathy score improved in 92% of subjects. Symptomatic improvement was maintained in 12 of 13 patients who were followed for an average of 13 months (Bianchi 2005). In a trial on 26 individuals with CIPN due to paclitaxel or cisplatin treatment, a daily intravenous dose of 1000 mg acetyl-L-carnitine for a minimum of 10 days resulted in reduced severity of neuropathy in 73% of subjects (Maestri 2005).

Several studies have found that the amino acid **glutamine** reduced the severity of CIPN resulting from oxaliplatin or high-dose paclitaxel treatment (Amara 2008). In one trial, 12 patients were given 10 grams oral glutamine three times daily beginning 24 hours after completing treatment with high-dose paclitaxel. The severity of their neuropathy was significantly lower than in 33 patients undergoing the same treatment without glutamine (Vahdat 2001). In a trial in patients with metastatic colorectal cancer treated with oxaliplatin, those receiving 15 grams oral glutamine, twice daily for seven consecutive days every two weeks, beginning on the day of oxaliplatin treatment, had a lower incidence of moderate and severe neuropathy compared with those receiving oxaliplatin alone. The glutamine group experienced less interference with normal activities and was less likely to have to reduce their oxaliplatin dosage. Glutamine did not interfere with the response to chemotherapy (Wang 2007).

Alpha-lipoic acid may reduce the risk of peripheral neuropathy in patients undergoing chemotherapy (Melli 2008). An early-phase trial was conducted in 14 cancer patients with moderate or severe peripheral neuropathy, which developed during or after docetaxel plus cisplatin chemotherapy. Subjects received 600 mg alpha-lipoic acid intravenously once per week for three to five weeks, followed by 1800 mg oral alpha-lipoic acid three times daily, for a maximum of six months or until they completely recovered from neurological symptoms. Eight (57%) participants had improvement in their neuropathy within four months (Gedlicka 2003).

Balance retraining has been shown to improve measures of balance in patients with peripheral neuropathies (Stubblefield 2012). Patients with CIPN have reported that *exercise*, *mindfulness*, and *occupational therapy* were helpful self-management strategies in reducing the impact of CIPN symptoms (Speck 2012).

Cardiotoxicity

Cardiotoxicity (toxic damage to the heart and blood vessels) is a common complication of chemotherapy, particularly with anthracyclines such as doxorubicin, epirubicin, and daunorubicin (van Dalen, Caron 2011). Other chemotherapy agents, including 5-FU and its prodrug, capecitabine (Xeloda), cisplatin, paclitaxel, and docetaxel, can also cause cardiotoxicity (Molinaro 2015; Stewart 2010). Cardiotoxicity can appear soon after or long after chemotherapy, and may vary from subclinical heart muscle dysfunction to heart failure (Stewart 2010; Kalam 2013; Lenihan 2012). Oxidative stress is a central mechanism underlying the cardiotoxicity of many chemotherapy agents (Sterba 2013).

Conventional treatments for cardiotoxicity. Published reviews have concluded that dexrazoxane (Zinecard, an iron-chelating agent), carvedilol (Coreg, a beta-blocker), valsartan (Diovan, an angiotensin receptor blocker), statins (a class of cholesterol-lowering medications), and enalapril (Vasotec, an angiotensin-converting enzyme inhibitor [ACE]-inhibitor), are effective in preventing heart muscle dysfunction and reducing cardiac events in patients treated with anthracyclines (Kalam 2013; Lenihan 2012).

Dexrazoxane is highly effective in reducing anthracycline-induced cardiotoxicity (Wang, Zhang 2013). Anthracyclines such as doxorubicin produce

damaging reactive oxygen species via iron-dependent mechanisms, which are thought to be responsible for their cardiotoxicity (Xu 2005). Dexrazoxane is metabolized into a compound that binds free iron and protects the heart by preventing iron-related oxidative damage in cardiac tissue. This protection is particularly notable against anthracyclines (Sterba 2013; Hasinoff 2007). However, dexrazoxane can cause bone marrow suppression (Jordan 2009), and the manufacturer of this medication reported one clinical trial in which dexrazoxane may have interfered with the clinical response to doxorubicin (Gold Standard 2012).

Metformin, the most frequently prescribed antidiabetic drug, has been shown to mitigate doxorubicin-induced cardiotoxicity in several animal models (Ashour 2012; Argun 2016; Kelleni 2015). Two of these studies further examined the animals' cardiac cells and found metformin inhibited doxorubicin's oxidative and inflammatory effects (Ashour 2012; Kelleni 2015).

Enalapril is an ACE-inhibitor often used to treat heart failure (Sacks 2014; NLM 2017). In a trial in anthracycline-treated patients at high risk for cardiac side effects, early treatment with enalapril was found to prevent the development of late cardiotoxicity (Cardinale 2006).

Statin drugs may protect against late cardiotoxicity. In a study in 628 breast cancer patients who had been treated with anthracycline-based chemotherapy and were monitored for an average of just over 2.5 years, those taking a statin medication throughout the follow-up period had a 70% lower risk of developing heart failure (Seicean 2012).

Integrative interventions for cardiotoxicity. **Coenzyme Q10 (CoQ10)**, a natural substance present in every cell in the body, is essential for cellular energy metabolism (Zheng 2008; Singh 2007). Evidence from preclinical and clinical studies suggests that cardiotoxicity caused by anthracycline drugs, such as doxorubicin and daunorubicin, may be preventable with CoQ 10 supplementation. Indeed, a review of the literature found that CoQ10 protects against cardiotoxicity (Roffe 2004). Because cardiotoxicity is a dose-limiting side effect of anthracyclines, CoQ10's cardioprotective activity might enable higher dosages of anthracycline chemotherapy, and thus more effective cancer treatment, if administered along with treatment. Heart cell mitochondria contain a unique enzyme (an NADH dehydrogenase) on their inner mitochondrial membrane that is not present in other non-cardiac mitochondria. This enzyme converts anthracyclines to substances that cause severe oxidative stress, irreversible damage to mitochondrial DNA, and disruption of mitochondrial energy metabolism. This damage leads to death of heart cells, accounting for anthracyclines' cardiotoxicity. CoQ10 appears to prevent damage to cardiac mitochondria, protecting against anthracycline-induced cardiomyopathy. Doses of CoQ10 used in clinical studies in the context of doxorubicin toxicity have ranged from 30 mg to approximately 200 mg daily (Conklin 2005).

L-carnitine is involved in energy production from fatty acids in the mitochondria of cells. There is a high concentration of carnitine in muscle cells, and in particular, cardiac cells. Certain chemotherapy regimens can result in a carnitine deficiency that may be reversible with carnitine supplementation (Sayed-Ahmed, Al-Shabanah 2010).

Clinical studies support the efficacy of carnitine in reducing or preventing chemotherapy-induced cardiotoxicity. In a randomized trial in 30 cancer patients undergoing immunotherapy with interleukin-2 (IL-2), there were significantly fewer cardiac complications in those who received 1000 mg oral L-carnitine daily in addition to IL-2 compared with those who received IL-2 alone (Lissoni 1993). In a study of 15 patients with breast or lung cancer undergoing treatment with doxorubicin or the doxorubicin-related compound epirubicin, subjects were divided into three treatment groups: doxorubicin, doxorubicin plus L-carnitine, or epirubicin. Twenty-five healthy individuals served as controls. Left ventricular function of the heart was assessed by echocardiogram. After six chemotherapy treatment cycles, the group that received L-carnitine had preserved systolic left ventricular function (De Leonardis 1987).

Green tea extract and the green tea flavonoid **epigallocatechin-3-gallate (EGCG)** show promise in preclinical studies in reducing cardiac damage resulting from treatment with doxorubicin (Zheng 2011; Li, Nie 2010; Khan 2014; Patil 2011). Laboratory and animal studies have shown green tea extract and EGCG can decrease oxidative stress and prevent cardiac tissue damage (Khan 2014; Patil 2011; Li, Nie 2010). In one of these studies, the addition of 100 mg/kg/day of green tea extract to doxorubicin treatment normalized blood pressure and restored normal electrocardiogram results in the test animals, compared with those treated with doxorubicin alone (Patil 2011). In another study, animals that received doxorubicin alone showed signs of tissue damage and increased free radical activity, while those that also received green tea extract had increased free radical scavenging enzymes in their heart tissue (Khan 2014).

Proanthocyanidins are phytochemicals found in a wide range of foods and medicinal plants. In an animal model, pretreatment with a **grape seed extract** rich in proanthocyanidins significantly reduced doxorubicin-induced cardiotoxicity (Bagchi 2002). In a similar study, mice given proanthocyanidin-rich grape seed extract for 7–10 days before receiving doxorubicin injections were almost completely protected from the drug's toxic effects on blood chemistry and heart tissue; DNA damage was also reduced (Ray 2000). Findings from another study in which grape seed proanthocyanidins suppressed doxorubicin-related cardiotoxicity in rats indicated that the cardioprotective effects were mediated through antioxidant, anti-inflammatory, and antiapoptotic mechanisms (Boghdady 2013). A cell culture study found that proanthocyanidin-rich grape seed extract protected heart muscle cells from doxorubicin-induced toxicity without interfering with the antiproliferative effect of doxorubicin on breast cancer cells (Li, Liu 2010).

Rhodiola, an herbal adaptogen, was shown to improve cardiac function in cancer patients who received epidoxorubicin chemotherapy (Shen 2010). **Cranberry** (Elberry 2010), **hawthorn** (Shatoor 2014), and **bilberry** (Ashour 2011) extracts, which are known sources of free-radical-scavenging polyphenols (Dixon 2005; Kirakosyan 2003), have also prevented doxorubicin-induced cardiotoxicity in animal models. Animal research has found other compouds capable of combatting doxorubicin cardiotoxicity, including **boswellia** (Uma Mahesh 2013), **onion extract** (Alpsoy 2013), the Chinese herb ***Panax notoginseng*** (Liu 2008), the **ginger** phytochemical 6-gingerol (El-Bakly 2012), and a polyphenol-rich extract of the honeybee product **propolis** (Alyane 2008). In addition, the amino acid **glutamine** protected rats from cyclophosphamide-induced cardiotoxicity (Todorova 2009).

Vitamin E also has protective capacity aginst chemotherapy-induced cardiotoxicity. An animal model found that giving d-alpha-tocopherol, a form of vitamin E, to rats 24 hours before a high dose of doxorubicin reduced cardiotoxicity without interfering with the chemotherapeutic effects of doxorubicin on leukemia (Sonneveld 1978). In another study, rats that received seven weekly injections of doxorubicin in addition to a diet supplemented with alpha-tocopherol had 2- to 4-fold higher vitamin E concentrations in their cardiac mitochondrial membranes and reduced protein oxidation in their heart tissue (Berthiaume 2005).

Kidney Damage (Renal Toxicity/Nephrotoxicity)

Several chemotherapy drugs can cause kidney damage, notably cisplatin and methotrexate (Ries 1986; Widemann 2006; Miller 2010). Cisplatin causes acute kidney toxicity in about 25% of patients; kidney toxicity often necessitates treatment discontinuation (Solanki 2014). Two likely mechanisms for cisplatin-induced kidney damage are increased oxidative damage (dos Santos 2012) and altered metabolism of magnesium in the

kidneys (Solanki 2014). High-dose methotrexate has been shown to cause kidney impairment in 2–10% of patients (Widemann 2014).

Conventional treatments for chemotherapy-associated nephrotoxicity. Kidney damage caused by methotrexate therapy is typically treated with hydration, alkalinization, and leucovorin (calcium folinate) (Holmboe 2012; Takimoto 1996; Widemann 2006). Glucarpidase (Voraxaze), a bacterial enzyme that cleaves methotrexate to form inactive metabolites, was FDA approved in 2012 for the treatment of toxic methotrexate concentrations caused by impaired kidney clearance. Toxic levels of methotrexate can be rapidly and effectively decreased by intravenous administration of glucarpidase, which has been shown to induce a 99% or greater sustained reduction of serum methotrexate levels (Widemann 2014). Glucarpidase has rare and relatively mild adverse effects, including tingling, itchiness, flushing, nausea, vomiting, and headache (Green 2012).

Pentoxifylline (Trental, Pentoxil) is an anti-inflammatory and free radical scavenger that may provide kidney protection by improving cellular antioxidant activity, as well as by down-regulating tumor necrosis factor-alpha (TNF-α). An animal study demonstrated a protective effect of pentoxifylline on the kidney after methotrexate administration (Asvadi 2011).

The antioxidant drug amifostine (Ethyol) has been shown in preclinical and clinical studies to reduce the nephrotoxicity of cisplatin without interfering with antitumor activity (Akbulut 2014; Capizzi 1999). In a clinical trial involving 31 cancer patients who had solid tumors, amifostine plus chemotherapy (cisplatin and ifosfamide plus either etoposide or paclitaxel) was compared with chemotherapy alone. The subjects who received amifostine maintained a normal glomerular filtration rate (GFR), a measure of kidney function, after two chemotherapy cycles, whereas a 30% reduction in GFR occurred in subjects who did not receive amifostine (Hartmann 2000).

Avoid dehydration. Avoiding dehydration helps prevent kidney toxicity caused by chemotherapy (Sato 2011; Tiseo 2007). It is critical to maintain sufficient intake of fluid and electrolytes.

Integrative interventions for chemotherapy-associated nephrotoxicity. In a randomized controlled trial in ovarian cancer patients undergoing treatment with cisplatin plus paclitaxel, participants received either **magnesium** or placebo. Five grams of magnesium sulfate was administered intravenously every three weeks before each course of chemotherapy. Participants also took 500 mg of magnesium subcarbonate orally three times daily between treatments. Kidney function was better preserved in the magnesium-supplemented group (Bodnar 2008). Another trial compared traditional intravenous hydration therapy to hydration therapy with magnesium in patients with non-small cell lung cancer. The participants were treated with cisplatin and pemetrexed (Alimta), a folate antimetabolite with a mechanism of action similar to methotrexate. Thirty patients received traditional hydration therapy, consisting of saline, mannitol (Osmitrol), and the diuretic furosemide (Lasix), and 20 patients received modified hydration therapy, consisting of saline, mannitol, and magnesium, but not furosemide. The magnesium-treated group showed significantly greater creatinine clearance, a measure of kidney function (Muraki 2012).

A small two-week trial of intravenous magnesium sulfate administered before cisplatin and 5-FU chemotherapy was undertaken in patients with esophageal and hypopharyngeal cancer. Compared with those who did not receive magnesium (13 patients), subjects who received magnesium (10 patients) exhibited significantly less kidney toxicity (Hirai 2013). A 2014 study compared magnesium treatment prior to cisplatin chemotherapy for thoracic malignancies (161 patients) to cisplatin alone (335 patients). Kidney toxicity was considerably less common in the magnesium-treated group (Yoshida 2014).

A rodent and cell culture study showed that magnesium deficiency significantly increased markers of cisplatin-induced kidney damage. Magnesium treatment reversed these effects. Magnesium deficiency increased platinum accumulation in the kidney, which altered the expression of important kidney transport proteins, another effect reversed by magnesium replacement. Tests using ovarian, breast, and lung cancer cells found that magnesium treatment did not diminish cisplatin's effectiveness as a chemotherapeutic agent (Solanki 2014).

N-acetyl cysteine (NAC) can help replenish stores of the antioxidant **glutathione** (Matera 2016; Rushworth 2014). Both NAC and glutathione have been studied as preventives for kidney toxicity and neurotoxicity. In a phase III trial in 151 women with ovarian cancer being treated with cisplatin, 74 women were given intravenous glutathione before chemotherapy and 77 were given sterile saline as a placebo. The glutathione dose was three grams per square meter of body surface area. The women who received glutathione maintained better kidney function than those who did not, as evidenced by preservation of creatinine clearance rates. The glutathione group also had less depression, vomiting, peripheral neuropathy, hair loss, shortness of breath, and difficulty concentrating. Because of the reduction in side effects and improved quality of life, they were also more likely to tolerate all six cycles of cisplatin without a dose reduction (Smyth 1997).

Case reports demonstrate improvement in kidney function with NAC in individuals with cisplatin-induced kidney toxicity (Sheikh-Hamad 1997; Nisar 2002). NAC has also been found to protect against ifosfamide-induced kidney toxicity in experiments on cultured cells and in a study in rats (Chen 2007; Chen 2008). In addition, NAC does not appear to interfere with ifosfamide’s antitumor effect (Chen 2011).

Silybum marianum, or **milk thistle**, is well known for its liver-protective properties and has also been shown to protect the kidneys from chemotherapy-induced damage in rodent and cell studies. The active constituent **silymarin** has anti-inflammatory and antioxidant activity. Several studies indicate that silymarin rmitigates the nephrotoxic effects of cisplatin without compromising its antitumor effect (Shahbazi 2012). Milk thistle offers more pronounced kidney protection when used before rather than after chemotherapy (Karimi 2005; Shahbazi 2012).

Ginkgo biloba is a medicinal plant with a long history of use in traditional Chinese medicine. It is typically used to support cognitive function. Ginkgo’s antioxidant and anti-inflammatory properties may contribute to its ability to protect against cisplatin-induced kidney toxicity.

In a rodent model, a standardized ginkgo extract prevented cisplatin kidney toxicity. Serum levels of blood urea nitrogen (BUN) and creatinine, indicators of kidney function, improved in rodents given ginkgo compared with rats given cisplatin alone (Song 2013). Other studies in rats have demonstrated that ginkgo can provide kidney protection from cisplatin toxicity without interfering with the anticancer effect of the drug (Gulec 2006; Fukaya 1999).

L-carnitine has been shown in preclinical studies to protect against kidney toxicity from cisplatin and ifosfamide (Sayed-Ahmed 2010; Sayed-Ahmed 2012; Jafari 2013). Animal studies have shown that multiple forms of carnitine, including L-carnitine, acetyl-L-carnitine, and propionyl-L-carnitine, can protect against cisplatin-induced kidney toxicity (Yurekli 2011; Tufekci 2009; Aleisa 2007). A study in rodents identified carnitine deficiency as a risk factor for cisplatin-induced kidney damage. This study also found L-carnitine injections normalized markers of kidney function (Sayed-Ahmed 2004). Daily injections of L-carnitine in rats treated with ifosfamide resulted in less oxidative stress and kidney damage compared to treatment with ifosfamide alone (Sayed-Ahmed 2012).

In a trial involving 46 cancer patients, those who received **selenium** (200 mcg) and **vitamin E** (400 IU) had less cisplatin-induced kidney toxicity than those who received placebo (Hemati 2012). In a separate trial involving 122 cancer patients, a daily dose of 400 mcg oral selenium prevented

cisplatin-induced acute kidney injury when added to hydration therapy (Ghorbani, Omidvar 2013). Other studies have shown selenium supplementation may help reduce kidney toxicity and bone marrow suppression caused by cisplatin (Ghorbani 2013; Naziroglu 2004; Hu 1997).

Hair Loss (Alopecia)

Hair loss caused by chemotherapy is common and distressing (Randall 2005; Choi, Kim 2014). Chemotherapy drugs disrupt the rapidly proliferating cells responsible for hair growth, resulting in weakening of the hair shaft with subsequent breakage and hair loss (Yeager 2011).

Conventional treatments for chemotherapy-associated hair loss. Topical minoxidil (Rogaine) is an effective therapy to accelerate hair regrowth after chemotherapy (Yeager 2011). If a non-drug treatment is preferred, one such modality is scalp cooling. Cooling the scalp during chemotherapy can help prevent hair loss and has been shown to be safe and well tolerated. This approach uses a cooling cap placed snugly over the patient's scalp during chemotherapy infusion (Ekwall 2013). The cooling causes a reduction in blood flow to the scalp, so less of the chemotherapeutic drugs reach the hair follicles (van den Hurk 2013). Side effects, such as headache, dizziness, coldness, and claustrophobia, sometimes occur with scalp cooling (Komen 2011).

Chemosensory Dysfunction

Chemosensory functions, such as taste, smell, and hearing, are often distorted during chemotherapy. Platinum-based chemotherapies (eg, cisplatin, carboplatin) are notorious for causing chemosensory dysfunction. Fortunately, recovery typically occurs after treatment ends (Steinbach 2012; Bernhardson 2008). Currently, there is no approved treatment for chemotherapy-induced chemosensory dysfunction. However, strategies such as increasing the use of spices or flavoring agents during food preparation may be helpful (Steinbach 2012).

Integrative interventions for chemosensory dysfunction. Disorderd taste sensation, such as altered taste or metallic taste (termed *dysgeusia*), is associated with poor nutrition and can reduce quality of life (Sánchez-Lara 2010; Mattes-Kulig 1985).

Some early evidence suggests that **zinc** suopplementation may help alleviate taste distrubances in cancer patients receiving chemotherapy, though the evidence is not strong (Nishijima 2013; Asano 2012; Nishijima 2011).

Miracle fruit (*Synsepalum dulcificum*) contains a protein, miraculin, which produces a sweet taste in an acidic environment, thereby masking unpleasant tastes and increasing the palatability of foods for a short time. A preliminary clinical study on eight cancer patients undergoing chemotherapy found that consumption of miracle fruit improved chemotherapy-associated taste disturbances, which might then lead to better nutrition (Wilken 2012).

Hand-Foot Syndrome (HFS)

Hand-foot syndrome (HFS) is a reaction of the skin to certain chemotherapy agents, including 5-FU, capecitabine, cytarabine (Depocyt), and pegylated liposomal doxorubicin (Doxil, Caelyx). The symptoms of HFS include tingling, pain, redness, swelling, and blistering (Qiao 2012; Bartal 2011).

Conventional treatments for hand-foot syndrome. Supportive treatments include topical wound care, elevation of the affected body part, cold compresses, and avoiding clothing and activities that put pressure on hands and feet (Mayo Clinic 2013). The anti-inflammatory drug celecoxib (Celebrex) is a promising intervention to prevent HFS. However, celecoxib is not recommended for those with heart disease because it increases heart attack risk (De Vecchis 2014; Macedo 2014; Caldwell 2006; Zhang 2012; El-Rayes 2006).

Integrative interventions for hand-foot syndrome. In a randomized controlled trial, 106 patients with colorectal or breast cancer were given 50 mg **vitamin B6** (as pyridoxine) or placebo three times daily in addition to palliative treatment with capecitabine. In the pyridoxine group, there was a trend toward better capecitabine dosage maintenance and fewer high-grade HFS adverse effects (Corrie 2012). Pyridoxine has a history of successful use, at doses ranging from 50 to 800 mg per day, for the prevention and treatment of HFS caused by sorafenib (Nexavar), doxorubicin, 5-FU, docetaxel, or etoposide. Evidence suggests that 400 mg per day of pyridoxine may be more effective than lower dosages (Chen, Zhang 2013).

Vitamin E was used in a clinical study involving liver cancer patients treated with the chemotherapy agent sorafenib, which is known to cause HFS. Vitamin E at a dose of 333 to 450 IU per day controlled HFS after 10 to 12 days (Bozkurt Duman 2011). Another study described a positive effect of 100 to 600 IU of vitamin E daily in breast cancer patients experiencing HFS caused by capecitabine. Supplementation with vitamin E reduced skin complications within seven days, and the effects lasted throughout treatment. Neurological symptoms, skin peeling, and pain were reduced. Moreover, among those receiving vitamin E, the median time to cancer progression was 10.2 months, while those not taking vitamin E exhibited a median time to cancer progression of 6.1 months (Yamamoto 2010).

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a potentially life-threatening disorder that occurs when tumor cells undergo rapid lysis (breakdown), either spontaneously or in response to chemotherapy. TLS most often occurs after the start of cytotoxic therapy in patients with high-grade lymphomas (particularly the Burkitt lymphoma subtype) and acute leukemias, or after treatment of large or fast-growing tumors. These are highly metabolically active cancers that tend to have a strong response to cytotoxic chemotherapy—that is, large numbers of cancer cells die rapidly. The dying cancer cells release potassium, phosphorus, and nucleic acids into the bloodstream (Wilson 2012). Breakdown of nucleic acids to uric acid leads to a significant increase in uric acid excretion, which can result in acute kidney injury (Mughal 2010), while hyperkalemia (high levels of potassium), hyperphosphatemia (high levels of phosphorus), and secondary hypocalcemia (low levels of calcium) can quickly progress to medical emergencies (Wilson 2012).

Prevention of TLS is critical and requires identification of patients at risk of developing TLS during chemotherapy. Factors that affect TLS risk include tumor type (particularly hematologic malignancies), specific tumor characteristics (eg, bulky tumor, high cellular proliferation rate), and baseline creatinine (Wilson 2012). For intermediate-risk patients, hydration plus the uric acid-lowering drug allopurinol (Zyloprim) or rasburicase (Elitek), is recommended to prevent TLS. For those at high risk, hydration plus rasburicase is recommended for prevention (Coiffier 2008). When allopurinol is administered along with purine-based chemotherapy drugs such as mercaptopurine (Purinethol) or azathioprine (Imuran, Azasan), reduction of the chemotherapy dosage is required. Allopurinol is contraindicated for use with capecitabine (Mughal 2014; Held-Warmkessel 2010).

Conventional treatments for tumor lysis syndrome. Treatment of TLS requires vigorous intravenous hydration (Mughal 2014; Coiffier 2008). Monitoring of electrolyte abnormalities and therapy with uric acid-lowering drugs (allopurinol or rasburicase) are important in treating TLS (Coutsouvelis 2013; Lam 2013; Mughal 2014). Phosphate binders, such as aluminum hydroxide, or calcium acetate or carbonate may be used.

Hemodialysis may be required in some cases (Held-Warmkessel 2010).

"Chemo Brain" or "Chemo Fog"

"Chemo brain" and "chemo fog" refer to problems with cognitiino and memory following chemotherapy. The condition can last months to years (Raffa 2013). 5-FU is frequently associated with chemotherapy-associated cognitive impairment. What makes patients susceptible to chemo brain, and precisely what biologic mechanisms are involved, are not clearly established (Wigmore 2010; Taillibert 2010).

Cognitive problems associated with cancer chemotherapy may be related to elevation of inflammatory cytokines such as IL-6 and TNF-α, as well as to structural and functional brain changes (Kesler 2013). Systemic inflammation has been linked to impaired cognitive function and aberrations in brain structure in many settings (refer to the Age-Related Cognitive Decline (/Protocols/Neurological/Age-Related-Cognitive-Decline/Page-01) protocol for a more thorough discussion of the role of inflammation in cognitive dysfunction).

Another theory posits that the distress associated with a cancer diagnosis may contribute to altered cognitive function and eventually lead to depression and anxiety (Hess 2007). Thus, taking steps to manage stress may benefit individuals who experience cognitive deficits during cancer treatment. A comprehensive discussion about coping with stress is available in the Stress Management (/Protocols/Emotional-Health/Stress-Management/Page-01) protocol.

Gastrointestinal Disturbances

Chemotherapy can cause a range of adverse gastrointestinal effects ranging from nausea and vomiting to diarrhea, constipation, and loss of appetite (ACS 2015; NCI 2007; DeBoer 2008).

Conventional treatments for gastrointestinal disturbances. Conventional management of nausea and vomiting is covered in the section on chemotherapy-induced nausea and vomiting. It may be possible to manage some cases of chemotherapy-induced diarrhea with supportive measures (NCI 2012). Loperamide (Imodium) and diphenoxylate (Lomotil), an opioid agonist, are first-line medical treatments for chemotherapy-induced diarrhea. Octreotide (Sandostatin) may be used in persistent cases; hospitalization along with rehydration, antibiotics, and octreotide may be indicated in severe cases, and chemotherapy dose reduction is sometimes necessary (Kadowaki 2011; Maroun 2007).

Constipation is frequent in patients who undergo cancer treatment (Davila 2008). Often, constipation is not a result of the chemotherapy drug, but is secondary to drugs given to control chemotherapy side effects or relieve cancer symptoms, such as anti-nausea drugs and pain relievers (Gibson 2006). Other medications used in cancer care that are capable of causing constipation include vinca alkaloids, antidepressants and anti-anxiety medications, iron supplements, cardiovascular drugs, nonsteroidal anti-inflammatory drugs, antacids, anti-nausea drugs, and antispasmodics (Avila 2004). Stool softeners and laxatives, such as the osmotic agents lactulose (Generlac) and sorbitol, may be prescribed for constipation (Davila 2008; Avila 2004).

Integrative interventions for gastrointestinal disturbances. In a case study, a patient with stage IV breast cancer and severe chemotherapy-induced diarrhea with incontinence and abdominal cramping was successfully treated for diarrhea with a multispecies combination **probiotic** (Abd El-Atti 2009). The combination probiotic consisted of eight strains of live, freeze-dried lactic acid bacteria, but the specific strain swere not described in the paper that reported this case study. A review of studies in patients with abdominal and pelvic cancers concluded that probiotics may have a beneficial role in preventing moderate-to-severe chemotherapy-induced diarrhea (Wang, Yao 2016).

A meta-analysis found the amino acid **glutamine** significantly reduced duration of chemotherapy-induced diarrhea (Sun 2012). Other studies found glutamine helpful in ameliorating the gastrointestinal toxicity of chemotherapy (Kuhn 2010). In one study where glutamine was used along with chemoradiotherapy for non-small cell lung cancer, the nutrient did not interfere with treatment efficacy and helped prevent weight loss and unplanned treatment delays (Topkan 2012). **Omega-3 fatty acids** from fish oil may also prevent adverse gastrointestinal toxicity related to chemotherapy (Xue 2011).

Senna extract can be effective and is safe in treating chemotherapy-induced constipation (Tao 2012). Daily **exercise**, **adequate hydration**, and **dietary fiber** may also help prevent and alleviate chemotherapy-induced constipation (Lederle 1995). For more information on integrative management of constipation, please consult the Constipation (/protocols/gastrointestinal/constipation/page-01) protocol.

Nutritional Status and Cachexia

Cancer patients often become malnourished, either because of their disease or as a side effect of cancer treatment. Maintaining adequate nutritional status and body weight, as well as avoiding cachexia (wasting of muscle and fat tissue), is critically important for cancer patients, as these factors have been associated with reduced quality of life and greater chemotherapy toxicity (Fearon 2013). Maintaining adequate nutrition allows the patient to continue treatment and avoid further complications. Chemotherapeutic regimens that cause gastrointestinal disturbances such as nausea and vomiting, diarrhea, and constipation may impair nutritional status and worsen prognosis (Xue 2011; NCI 2014b).

Cachexia is more than just a nutritional problem. This condition is a complex side effect of cancer itself, in which tissues are broken down and protein synthesis decreases. Proinflammatory cytokines produced by the patient's tumor(s), such as TNF-α, IL-1, and IL-6, contribute to this process, and central nervous system and hormonal signaling may also be involved (Nicolini 2013; Fearon 2013; Chabner 2013b).

Medications and integrative interventions can aid in maintaining nutritional status. When food and caloric intake is reduced, nutritional support is important (Fearon 2013). A literature review found that megestrol acetate, a synthetic progesterone derivative, improved appetite and helped cancer patients gain weight (Ruiz Garcia 2013). However, megestrol acetate can cause significant side effects such as fluid retention, depression, and blood clots (Gold Standard 2016c). Dronabinol, a synthetic cannabinoid, may also be used in the treatment of chemotherapy-related weight loss; however, the evidence supporting the use of dronabinol for appetite remains preliminary, and one study found megestrol acetate was more effective (Jatoi 2002; Walsh 2005).

The conditionally essential amino acid **glutamine**, which is especially vital for the severely ill, has been shown to improve clinical status of cancer patients, aiding in the provision of adequate nutrition, without increasing tumor burden (Lacey 1990; Kuhn 2010). Omega-3 fatty acids in **fish oil** may help with cancer cachexia, preserving muscle mass and functional ability, and improve chemotherapy tolerance and response, leading to greater clinical benefit (Murphy 2012; Laviano 2013). **L-carnitine** is a promising integrative intervention for fatigue associated with cachexia. In one placebo-controlled study, L-carnitine helped maintain body weight, body fat, and nutritional status (Isenring 2013; Kraft 2012). A growing body of research points to multiple modality treatments that use nutrition, medication, and side-effect management to address cachexia in cancer (Solheim 2012).

Oral Mucositis

Oral mucositis is a very painful condition marked by ulcerative lesions on the oral surfaces. It is a common complication of cancer treatment, occurring in 40-80% of patients undergoing chemotherapy, and can predispose to infections of the oral mucosa (Campos 2014; Chaveli-Lopez 2016). Pain and risk of secondary infections from oral mucositis are generally managed with oral hygiene practices, local anesthetics, mouthwashes, and other agents with anti-inflammatory, analgesic, and antimicrobial properties (Campos 2014; Zhang 2011; Chaveli-Lopez 2016).

Conventional treatments for oral mucositis. Oral cryotherapy, which involves sucking on small ice cubes for about 30 minutes, provides relief of pain caused by mucositis. In addition, the application of ice for 5-10 minutes before, 15-35 minutes during, and 30 minutes after chemotherapy significantly reduces mucositis (Chaveli-Lopez 2016; Campos 2014). Low-intensity laser therapy is sometimes used as a pretreatment to reduce mucositis severity in patients undergoing chemotherapy; however, its use is limited due to the requirement for expensive equipment and specially trained operators. Oral mucosal protectant gels that form a barrier on the surface of the affected mucous membrane, protecting it against irritation from food and liquids, are also sometimes used (Campos 2014). Topical steroids, applied to surfaces of the oral cavity, may be used to treat mucositis (Raeessi 2014). Prescription mouthwashes, variably containing antibiotics, antihistamines, antifungals, corticosteroids, and antacids, are also frequently used to treat chemotherapy-induced oral mucositis. These formulations are colloquially referred to as “magic mouthwash” (Moynihan 2014).

Integrative interventions for oral mucositis. In an intriguing double-blind randomized clinical trial, researchers divided 75 adults with chemotherapy-induced oral mucositis into three groups. The first group received a syrup-like solution containing a steroid; the second group received a similar solution containing honey; and the third group received a solution with **honey plus coffee**. The study participants sipped 10 mL of the prescribed solution every three hours for one week. Although all three groups benefited from treatment, the group that received honey plus coffee showed the most improvement (Raeessi 2014). A meta-analysis of published studies concluded that honey could effectively prevent chemotherapy- and radiation therapy-induced oral mucositis (Xu 2016).

In a randomized controlled trial, leukemia patients undergoing bone marrow transplant, preceded by high-dose chemotherapy, were given 100 mg/kg **N-acetyl cysteine (NAC)** or placebo daily for 15 days after the procedure. The incidence of severe oral mucositis was significantly lower, and the duration shorter, in the NAC-treated group (Moslehi 2014).

Selenium protects cells through its participation in the glutathione peroxidase system, and prevents toxic effects caused by some chemotherapy drugs. A clinical study evaluated the efficacy of selenium for the prevention of oral mucositis in 77 leukemia patients undergoing bone marrow transplant. Thirty-seven patients received 200 mcg oral selenium twice daily while 40 matched patients received placebo from the first day of chemotherapy until 14 days after transplantation. The incidence of severe oral mucositis and the duration of moderate-to-severe symptoms were significantly lower in the selenium-treated group (Jahangard-Rafsanjani 2013).

Glutamine has been used topically, as an oral supplement, and intravenously to prevent and treat chemoradiotherapy-induced oral mucositis, with mixed results (Chaveli-Lopez 2016). In one randomized controlled trial, 40 previously untreated patients with head and neck cancer received either placebo or 10 grams of glutamine three times daily over the course of six weeks, during which time they were treated with radiation plus cisplatin and docetaxel. One-quarter of subjects in the placebo group, and none in the glutamine group, developed severe mucositis. From week four to six, mucositis severity was reduced and pain scores were lower in subjects taking glutamine (Tsujimoto 2015).

Topical **vitamin E** and **natural mouthwashes** containing herbs with antimicrobial activity such as *chamomile*, *sage*, and *myrrh* (a tree resin) have also been investigated as possible treatment aids for oral mucositis, but more research is needed (Campos 2014).

Vitamin D Insufficiency

Vitamin D has numerous beneficial effects throughout the body. It is especially pertinent in the context of immune system health, calcium metabolism, and cancer prevention (Dimitrov 2014; Feldman 2014). With regard to cancer, vitamin D helps regulate cell proliferation and slows growth of malignant cells in several tissue types (Moukayed 2013). Furthermore, laboratory studies suggest vitamin D can sensitize some types of cancer to the toxic effects of chemotherapy. For instance, pretreatment with vitamin D enhanced the cytotoxicity of doxorubicin on breast cancer cells in a laboratory study (Ravid 1999). In another study, vitamin D combined with all-trans retinoic acid lowered the threshold at which paclitaxel and doxorubicin were able to kill breast cancer cells (Wang 2000).

It appears that undergoing chemotherapy may decrease vitamin D levels. In a study on women with locally advanced breast cancer, over 79% of subjects had vitamin D insufficiency (25-hydroxyvitamin D levels below 30 ng/mL) before chemotherapy, and that number increased to over 97% after chemotherapy (Jacot 2012). A study of 50 colorectal cancer patients found that people undergoing chemotherapy had a markedly attenuated rise in vitamin D blood levels in response to vitamin D supplementation compared with people not undergoing chemotherapy (Fakih 2012).

Mitigating Chemotherapy Side Effects with Intermittent Fasting

Fasting induces an array of biochemical and physiological changes that may delay aging and the onset of chronic degenerative diseases, including cancer (Lee 2011; Brandhorst 2015; Stipp 2015; Safdie 2012). Some forms of fasting or caloric restriction may also protect animals and cancer patients from some chemotherapy side effects and sensitize cancer cells to the effects of chemotherapy (Lee 2011; Brandhorst 2013; Horne 2014; Stipp 2015; Safdie 2012). Interestingly, preliminary reports suggest that fasting for several days followed by normal food consumption may protect patients against chemotherapy toxicity without causing long-term weight loss (Lee 2011).

In a randomized early-stage trial, a 48-hour fast reduced chemotherapy immunotoxicity in women with breast cancer. Thirteen women with HER2-negative stage II or III breast cancer participated in the study. Seven women fasted for 24 hours before and after receiving neo-adjuvant chemotherapy, while the remaining women ate normally. The women received a chemotherapy regimen that included docetaxel, doxorubicin, and cyclophosphamide. Laboratory studies of subjects’ blood 30 minutes after chemotherapy revealed significantly less DNA damage in lymphocytes and monocytes in blood samples from the fasting women compared with those from the women who ate normally. This protective effect was still detectable seven days after chemotherapy treatment (de Groot 2015).

There are several potential mechanisms by which fasting may interfere with tumor progression and protect healthy cells against chemotherapy toxicity, but reductions in levels of glucose and insulin-like growth factor-1 (IGF-1) are often cited as important mediators of these benefits (Lee 2010; Hine 2014; Safdie 2009; Cheng 2014; Brandhorst 2013). In a chemotherapy toxicity study, one group of mice underwent a 48-hour fast, while another group underwent a 48-hour fast but also received injections of IGF-1. Both groups received injections of the cytotoxic agent

doxorubicin. In the fasting-only group, the survival rate after injection of doxorubicin was 100%; in the group who fasted and received IGF-1 injections, the survival rate was only 38% (Lee 2010).

Fasting triggers healthy cells to switch into a "protected mode" that confers resistance to toxins, including chemotherapy. In cancer cells, pro-cancer genes called oncogenes prevent this switch. In other words, under fasting conditions, healthy cells are protected against toxicity from chemotherapy but cancer cells are not. This phenomenon has been called ***differential stress resistance*** (Raffaghello 2010).

In a report on 10 cases, subjects with various types of cancer voluntarily fasted for 48–140 hours before receiving chemotherapy and/or 5–56 hours after chemotherapy. Six of the patients underwent chemotherapy in both a fed and a fasted state at different times; they reported reduced fatigue, weakness, and gastrointestinal side effects while fasting. The other four subjects underwent all of their chemotherapy treatments while fasting; the severity of most side effects was reported to be low relative to typical experience. In cases in which cancer progression could be assessed, fasting did not reduce the efficacy of chemotherapy (Safdie 2009).

Abundant preclinical evidence indicates fasting itself may retard cancer growth. A series of studies in cancer cell lines showed cycles of fasting were as effective as chemotherapy in delaying the progression of various tumors. Moreover, fasting increased the ability of chemotherapy to kill several types of cancer cells. The researchers who conducted this investigation concluded "*These studies suggest that multiple cycles of fasting promote differential stress sensitization in a wide range of tumors and could potentially replace or augment the efficacy of certain chemotherapy drugs in the treatment of various cancers*" (Lee, Raffaghello 2012).

To learn more about the health benefits of caloric restriction, refer to the Caloric Restriction (/Protocols/Lifestyle-Longevity/Caloric-Restriction /Page-01) protocol.

The Controversy: Antioxidant Supplementation And Chemotherapy

Taking antioxidant supplements during chemotherapy is controversial. Some cancer patients may wish to take antioxidants during chemotherapy in the hope of reducing side effects or improving their prognosis. However, many physicians are hesitant to recommend antioxidants to their cancer patients during treatment. Their concern is that antioxidant supplements might interfere with chemotherapy because some chemotherapy drugs kill cancer cells by generating oxidative stress. However, this concern is largely theoretical and is not supported by the weight of evidence from human clinical trials.

The reality is that many human studies show antioxidant supplements do not reduce the efficacy of chemotherapy. On the contrary, some studies have found that antioxidants may reduce negative side effects and even improve outcomes from cancer therapies (Zhu 2004; Erhola 1996; Conklin 2004a; Conklin 2004b; Alam 2011; Victorino 2014; Nakayama 2011; Block 2004; Drisko 2003; Sak 2012; Block 2007; Seifried 2003; Lawenda 2008).

A recent large systematic review addressed the concern vigorously (Yasueda 2015). Researchers from The Osaka University School of Medicine in Japan scoured the scientific literature and identified 399 reports of antioxidant supplementation in the context of cancer therapy. After excluding all but the best-designed studies, they were left with 49 reports to include in their analysis. They evaluated the outcomes of studies that used vitamin-, mineral-, phytochemical-, or amino acid-based antioxidants alongside cancer therapy. These scientists concluded as follows:

"Although there are many opinions about the risks or benefits of antioxidant supplementation, the only supportable conclusions based on the present research are… that there is no evidence of antioxidant supplementation causing harm alongside cancer therapy, except for smokers undergoing radiotherapy."

The caveat for smokers is based on a trial in head and neck cancer patients in which supplementing with alpha-tocopherol and beta-carotene during radiotherapy had a negative impact on rates of cancer recurrence and death in participants who smoked during the trial (Meyer 2008). Although the mechanism behind this finding is not fully understood, several theories exist, all of which involve beta-carotene. One of these theories is based on evidence that, when oxidized, high levels of beta-carotene are transformed into strong free radicals that could enhance smoke-induced oxidative stress, damaging DNA and leading to carcinogenesis (Black 2010; Palozza 2006). Also, an analysis of blood chemistries of smokers supplementing with beta-carotene revealed that the combination of beta-carotene and cigarette smoke may increase cancer cell growth by promoting certain detoxification pathways and raising the levels of specific metabolites (Mondul 2013). Overall, more research in this area is needed, and smokers interested in supplementing with beta-carotene are encouraged to consult with their healthcare provider. In non-smokers, the use of antioxidant supplements during cancer therapy appears to have neutral or beneficial effects.

The authors of a 2007 systematic review (Block 2007), which included 19 randomized controlled trials, reached a similar conclusion. They noted that, despite the consistent lack of statistical power in the body of literature on this topic, "*None of the trials reported evidence of significant decreases in efficacy from antioxidant supplementation during chemotherapy. Many of the studies indicated that antioxidant supplementation resulted in increased survival times, increased tumor responses, or both, as well as fewer toxicities than controls.*"

Even at high doses, antioxidant supplements were shown not to interfere with cancer treatment. In one trial, 136 patients with non-small cell lung cancer were randomized to receive chemotherapy alone (paclitaxel and carboplatin) or in combination with *high-dose antioxidant supplements*. The daily antioxidants included 6100 mg ascorbic acid, 1050 mg dl-alpha-tocopherol (a form of vitamin E), and 60 mg beta-carotene. There were no statistically significant differences in one- and two-year overall survival between groups, suggesting the high-dose antioxidants did not reduce the efficacy of chemotherapy (Pathak 2005).

Table 3 summarizes selected studies that have evaluated antioxidant supplements in the context of chemotherapy. Many more examples of the beneficial effects of antioxidant use before, during, or after chemotherapy are described throughout this protocol.

Table 3: Clinical Trials and Meta-Analyses of Antioxidants and Chemotherapy

Population	Intervention	Type of Trial	Outcomes	Citation
136 patients with stage III and IV non-small cell lung cancer	Chemotherapy with paclitaxel and carboplatin alone or with a daily combination antioxidant supplement (6100 mg **vitamin C**; 1,050 mg **vitamin E;** and 60 mg **beta-carotene**)	Randomized controlled trial	No significant differences in treatment response rates or overall survival between groups	(Pathak 2005)

103 cervical cancer patients	Oral antioxidant supplement (10 mg **vitamin C**, 200 IU **vitamin E**, 15 mcg **selenium**, and 8000 IU **beta-carotene**) or placebo once daily during six weeks of treatment with cisplatin and radiation therapy	Randomized placebo-controlled trial	Significantly higher hemoglobin concentrations—a potential proxy for improved general status—and lower levels of oxidative stress markers in the antioxidant group Significantly improved quality of life in those receiving antioxidants	(Fuchs-Tarlovsky 2013)
48 patients with various cancers (testicular-16; osteosarcoma-13; gastrointestinal-6; urogenital-5; head and neck-5; and melanoma-3)	Oral antioxidant supplement (1000 mg **vitamin C**, 600 IU **vitamin E**, and 100 mcg **selenium**) or placebo daily during multiple courses of cisplatin-based chemotherapy	Randomized placebo-controlled trial	Significantly reduced rates of ototoxicity in those who achieved the highest blood levels of vitamins C and E and selenium More patients receiving antioxidants were able to receive optimal doses of cisplatin Treatment response rates were similar between groups	(Weijl 2004)
52 individuals with advanced colorectal cancer	Intravenous **glutathione**, 1500 mg per square meter of body surface area, before oxaliplatin administration	Randomized, double-blind, placebo-controlled trial	Significantly lower rates of moderate-to-severe neurotoxicity in the glutathione group after 12 months No reduction in oxaliplatin activity	(Cascinu 2002)
50 patients with advanced gastric cancer	Intravenous **glutathione**, 1500 mg per square meter of body surface area, immediately before cisplatin administration plus 600 mg glutathione by intramuscular injection on days 2 to 5	Randomized, double-blind, placebo-controlled trial	Significantly reduced neurotoxicity in the glutathione group No reduction in clinical activity of the chemotherapeutic drugs	(Cascinu 1995)
151 women with stage I–IV ovarian cancer	Six courses of intravenous cisplatin, and intravenous **glutathione**, 3 grams per square meter of body surface area, or placebo, every three weeks	Randomized, double-blind, placebo-controlled trial	Significant improvement in depression, emesis, peripheral neurotoxicity, hair loss, shortness of breath, and difficulty concentrating in the glutathione group Trends toward better clinical outcomes and receiving (tolerating) higher doses of cisplatin in the glutathione group More patients in the glutathione group were able to complete a higher number of cycles of chemotherapy Rates of complete remission were 46% in cisplatin plus glutathione group and 9% in the cisplatin alone group	(Smyth 1997)
54 women with advanced ovarian cancer	Cisplatin alone or with 2.5 grams of intravenous **glutathione** immediately before chemotherapy	Randomized controlled trial	Significantly lower rates of neurotoxicity in the glutathione group Glutathione did not impair cisplatin effectiveness	(Bogliun 1996)
33 women with relapsed ovarian carcinoma, after being disease free for at least one year	Cisplatin alone or with 2.5 grams of intravenous **glutathione**, every week for nine weeks	Randomized controlled trial	More than twice the percentage of women in the glutathione group were able to receive the full cisplatin dosage (56% vs. 27%), and the response rate was higher in the glutathione group; no reduction in antitumor response rate was noted	(Colombo 1995)
6 patients with advanced non-small cell lung cancer and 14 patients with head and neck cancer	Cisplatin along with etoposide and 5-FU every four weeks; 11 patients received 5 grams of intravenous **glutathione** and 9 patients received 2000 mL electrolyte infusion (placebo) immediately before cisplatin; and all patients were treated with 2000 mL normal saline and forced diuresis following cisplatin	Randomized placebo-controlled trial	Significantly less pronounced blood cell toxicity, as indicated by hemoglobin, white blood cell count, and platelet count, in those receiving glutathione Although not statistically significant, survival time in the glutathione group was 3 months (29%) longer	(Schmidinger 2000)
100 patients with metastatic non-small cell lung cancer	Cisplatin and etoposide, with or without 20 mg oral **melatonin** each evening	Randomized controlled trial	Significantly higher overall tumor regression rate and 5-year survival, as well as better tolerance of chemotherapy, in those receiving melatonin No patient treated with cisplatin/etoposide alone was alive after two years, but nearly 30% of patients who received melatonin along with treatment were alive after two years	(Lissoni 2003)

250 patients with metastatic solid tumors (lung cancer-104; breast cancer-77; gastrointestinal tract-42; head and neck cancers-27)	Chemotherapy alone or with 20 mg per day of oral **melatonin** Chemotherapy consisted of cisplatin (CDDP) plus etoposide or gemcitabine alone for lung cancer; doxorubicin alone, mitoxantrone alone, or paclitaxel alone for breast cancer; 5-FU plus folinic acid for gastrointestinal tumours; and 5-FU plus CDDP for head and neck cancers	Randomized controlled trial	Significantly higher one-year survival rate and objective tumor regression rate in those who received melatonin Significantly reduced frequency of low platelets, nerve and cardiac toxicity, oral ulcers, and fatigue in the melatonin group	(Lissoni 1999)
108 patients with various cancers	Chemotherapy using cisplatin plus 600 IU of oral **vitamin E** per day or placebo beginning prior to chemotherapy and continuing for three months after the end of treatment	Randomized placebo-controlled trial	Significantly lower neurotoxicity incidence and severity in the vitamin E group Treatment response was similar in the two groups	(Pace 2010)
27 patients with solid tumors	Six cycles of cisplatin alone or with **vitamin E** (alpha-tocopherol, 448 IU) daily during and for three months following treatment	Randomized controlled trial	Significant reductions in incidence and severity of neurotoxicity in those receiving vitamin E Vitamin E did not interfere with response to cisplatin treatment	(Pace 2003)
22 women with newly diagnosed stage III or IV ovarian cancer	High-dose intravenous **vitamin C** at up to 100 grams per infusion (12 months) added to paclitaxel /carboplatin therapy (6 months)	Randomized controlled trial	Significantly decreased rates of mild-to-moderate toxicities, with reduced toxicity to nervous system, pancreas/gallbladder/liver, gastrointestinal tract, bone marrow, kidney and urinary tract, lungs, and skin in the vitamin C group A trend toward improved overall survival in the vitamin C group	(Ma 2014)
48 men with hormone-refractory prostate cancer who had not yet undergone chemotherapy	Weekly chemotherapy with vinorelbine and estramustine for six weeks, with or without 180 mg per day of **ellagic acid** (in the form of ellagic tannins) from pomegranate seeds	Randomized controlled trial	Reduced systemic toxicity, with statistical significance in reduction of neutropenia, in the ellagic acid group Higher average number of rounds of chemotherapy in the ellagic acid group (6.5 vs. 4.0) Better objective and biochemical response to treatment with ellagic acid Complete response in 25% of those receiving chemotherapy plus ellagic acid and none of those receiving chemotherapy alone; partial response in 33% and 25%, respectively A trend toward improved overall survival in the ellagic acid group	(Falsaperla 2005)
32 stage I and II melanoma patients who had surgical removal of primary lesions	Low-dose recombinant interferon (IFN) alpha-2b administered twice daily plus 400 mg per day of **coenzyme Q10 (CoQ10)**, or interferon only, for three years	Controlled trial	Approximately 10-fold lower risk of metastases in those receiving IFN plus CoQ10 Lower rate of recurrence in patients with stage II disease receiving CoQ10	(Rusciani 2007)
153 chronic myelogenous leukemia patients	Oral busulfan for four days every four weeks, with or without high-dose **vitamin A** (50 000 IU/day)	Randomized controlled trial	Trend toward increased progression-free and overall survival times in those receiving vitamin A	(Meyskens 1995)
100 patients with metastatic breast cancer	Various doses and schedules of chemotherapy, alone or with oral **vitamin A**, 350,000–500,000 IU per day based on body weight	Randomized controlled trial	Significantly increased treatment response rate, duration of response, and projected survival in those receiving vitamin A who were also post-menopausal	(Israel 1985)
353 participants from six randomized controlled trials	**Vitamin E** in combination with chemotherapy	Meta-analysis	Significantly reduced neurotoxicity from cisplatin when combined with vitamin E Four of six studies included safety assessment, and no adverse events were reported	(Huang 2016)
768 participants from eight randomized controlled trials	**Melatonin** in combination with chemotherapy or radiation therapy	Meta-analysis	Significantly increased complete or partial tumor remission and one-year survival in patients receiving concurrent melatonin Significantly lower occurrences of thrombocytopenia, neurotoxicity, and fatigue in those receiving melatonin	(Wang 2012)

Participants in 21 trials, all of whom had solid tumors	**Melatonin** in cancer therapy, including in combination with chemotherapy	Meta-analysis	Significant 40% decreased 1-year mortality in those receiving melatonin along with chemotherapy 2.5-fold increased rate of complete response with the addition of melatonin to chemotherapy Significant reductions in chemotherapy-related weakness, neutropenia, nausea and vomiting, low blood pressure, and thrombocytopenia in those receiving concurrent melatonin	(Seely 2012)

Antioxidant Drugs Used With Chemotherapy

Aside from the controversy surrounding antioxidant supplements in chemotherapy, readers may be unaware that several FDA-approved antioxidant drugs are regularly used to reduce chemotherapy-associated side effects (Moss 2006). These prescription antioxidant drugs have been investigated in many clinical cancer studies (Antman 1993; Komaki 2002).

Dexrazoxane

Dexrazoxane, a powerful antioxidant drug (Junjing 2010), was approved by the FDA in 2002 and is recommended by the American Society of Clinical Oncology for preventing doxorubicin-associated cardiotoxicity (Steiner 2013; Ichikawa 2014; Hensley 2009). Dexrazoxane is used in people with metastatic breast cancer, as well as other malignancies, who have received more than 300 mg of doxorubicin per square meter of body surface area and for whom continued doxorubicin therapy may be indicated (Hensley 2009). In early trials of dexrazoxane, myelosuppression was a dose-limiting toxicity (Wang, Zhang 2013; Jones 2008). Dexrazoxane may be used when the risk of chemotherapy-associated cardiac damage is expected to be high, but its benefits need to be weighed against the possible risk of bone marrow suppression (Jones 2008; van Dalen, van den Berg 2011).

Intravenous dexrazoxane (Totect) is approved for treatment of accidental anthracycline extravasations (Muthuramalingam 2013; Kissei Pharmaceuticals 2014). Extravasation, which is the leaking of chemotherapy drugs from blood vessels into surrounding tissues, is a medical emergency; patients undergoing intravenous chemotherapy must be closely monitored to prevent extravasation, and immediate attention is required if it occurs (Vidall 2013; Perez Fidalgo 2012).

Mesna

The antioxidant agent mesna (Mesnex) was developed to mitigate the urinary tract toxicity of some chemotherapy drugs, such as cyclophosphamide and ifosfamide, without reducing their antitumor effects (Brock 1980). Mesna tablets were approved by the FDA in 2002 as a preventive agent to reduce the occurrence of a complication called ifosfamide-induced hemorrhagic cystitis, in which the bladder becomes inflamed and bleeds (Cohen 2002; Mashiach 2001; Yeh 2008; Manikandan 2010). Intravenous mesna has been approved for this indication since 1988. The FDA also acknowledged that mesna does not appear to protect tumor cells against chemotherapy-induced cytotoxicity (Cohen 2002).

Based on findings from animal research, the bladder-protective effect of mesna may be enhanced by the addition of antioxidants such as **alpha-tocopherol**, **melatonin**, **quercetin**, and **EGCG** (Yildirim 2004; Ozcan 2005).

Several studies have reported on the use of mesna concurrently with chemotherapy. In two case reports in women with recurrent uterine leiomyosarcoma being treated with mesna along with the chemotherapy agents doxorubicin, ifosfamide, and dacarbazine (a regimen known as “MAID”), one achieved partial remission and the other complete remission (Minobe 2011). A trial in 38 patients treated for aggressive non-Hodgkin lymphoma evaluated the long-term efficacy and toxicity of a regimen that includes mesna, ifosfamide, mitoxantrone (Novantrone), and etoposide (known as “MINE”) as a post-remission treatment. These patients already achieved complete remission, or presumed complete remission, after six cycles of first-line standard therapy. After a median follow-up time of approximately 118 months, side effects of the “MINE” protocol were found to be mild and infrequent, and 5- and 10-year disease-free survival rates were both 65%. The authors concluded this regimen may be an effective consolidation strategy in such patients (Dincol 2010).

Amifostine

Amifostine is another antioxidant drug shown in laboratory studies to neutralize several types of free radicals (Taylor 1997; Mehta 1998; Spencer 2005; Marzatico 2000; Beijers 2012). Amifostine is FDA approved for the reduction of cumulative kidney toxicity from repeated cisplatin administration in patients with advanced ovarian cancer and non-small cell lung cancer (Ethyol 1999). However, the major side effects of amifostine, which include nausea, vomiting, and transient low blood pressure, often result in treatment discontinuation, limiting its wide acceptance (Schuchter 1996; Soref 2012).

In patients with advanced non-small cell lung cancer, subcutaneous amifostine (1000 mg), together with hematopoietic growth factors, may have contributed to a decrease in observed toxicity of combination therapy with docetaxel, gemcitabine, and liposomal doxorubicin (Patlakas 2005). In a study on 25 patients with metastatic non-small cell lung cancer, the addition of amifostine to a chemotherapy regimen of cisplatin and vinblastine (Velban) resulted in high response rates and a 64% one-year survival rate. In this trial, amifostine may have protected against long-term kidney insufficiency from cumulative doses of cisplatin, and the combination treatment appeared highly active against the cancer (Schiller 1996). A 2013 trial in which amifostine was added to carboplatin- and paclitaxel-based chemoradiation therapy in patients with locally advanced non-small cell lung cancer produced results comparable to other treatment regimens without compromising survival (Lawrence 2013).

A review concluded that patients with cervical cancer may benefit from receiving subcutaneous amifostine before chemotherapy (De Los Santos 2004). In a randomized controlled trial, 71 patients were pretreated with intravenous amifostine before platinum/taxane-based chemotherapy for ovarian cancer in order to determine whether such premedication changed the incidence of neurotoxic side effects. While nausea and vomiting were significantly more common in the amifostine group, sensory neuropathy was significantly less common (Hilpert 2005). A randomized trial in 242 patients with advanced ovarian cancer used six cycles of cyclophosphamide and cisplatin, with or without amifostine pretreatment before each cycle. Amifostine significantly reduced multiple types of chemotherapy toxicity without reducing the anticancer effects of cyclophosphamide and cisplatin (Kemp 1996).

A meta-analysis found a trend toward decreased ototoxicity (ear toxicity or hearing impairment) in patients receiving amifostine infusion prior to

cisplatin chemotherapy (Duval 2012). A non-randomized trial found that amifostine protected against cisplatin-induced serious hearing loss in average-risk but not high-risk patients with medulloblastoma (a type of brain tumor) (Gurney 2014).

Integrative Strategies To Complement Chemotherapy

Astragalus

Astragalus membranaceus has been reported to increase efficacy and reduce toxicity of several chemotherapy agents (Li 2008; Duan 2002; Zou 2003; McCulloch 2006). In a meta-analysis of studies on non-small cell lung cancer patients, astragalus-based traditional Chinese herbal formulas increased the effectiveness of platinum-based chemotherapy, reducing one-year mortality by 33% and improving tumor response, and reduced side effects (McCulloch 2006). Another meta-analysis found that Chinese herbal preparations that contained astragalus increased levels of white blood cells and reduce the the prevalence of nausea and vomiting in people undergoing chemotherapy for colorectal cancer (Taixiang 2005).

European Mistletoe Extract

European mistletoe extract (eg, Iscador) is a botanical medicine derived from the plant *Viscum album* and is commonly used in integrative oncology in Europe (Steele, Axtner, Happe 2014). Mistletoe extract is generally well tolerated with few serious side effects. Intravenous administration of mistletoe extract appears better tolerated than subcutaneous administration, while intratumoral injection is associated with frequent but usually mild-to-moderate side effects (Steele, Axter 2014; Mansky 2013; Steele, Axter, Happe 2014; Steele 2015).

Mistletoe extracts, including lectin-rich mistletoe extract, have been reported to induce tumor remission in single-case studies. A mouse study, using human pancreatic tumor tissue, found that lectin-rich mistletoe extract had potent antitumor activity (Rostock 2005). An uncontrolled study involving 39 patients with advanced, inoperable pancreatic cancer showed that intratumoral mistletoe injections in combination with first- and second-line chemotherapy and palliative surgery is safe (Schad 2013). Other studies have shown an improvement in quality of life in breast cancer patients treated with mistletoe while undergoing chemotherapy (Troger 2014; Eisenbraun 2011). A study in gastric cancer patients taking oral chemotherapy with a 5-FU prodrug found that those who received subcutaneous injections of mistletoe extract experienced improved quality of life compared with those who did not (Kim 2012). A randomized trial of Iscador in advanced non-small cell lung cancer patients receiving carboplatin-based chemotherapy found that those receiving Iscador were less likely to need a chemotherapy dose reduction and experienced less frequent side effects and hospitalizations (Bar-Sela 2013).

Enzymatically Modified Rice Bran

Another natural agent that has shown promise as a chemosensitizer is enzymatically modified rice bran. Preclinical studies show this compound can increase the ability of paclitaxel to kill both metastatic and non-metastatic breast cancer cells. One such study found that enzymatically modified rice bran increased the susceptibility of breast cancer cells to paclitaxel by more than 100-fold. The extract worked in synergy with paclitaxel, causing DNA damage, enhancing apoptosis, and inhibiting proliferation of metastatic breast cancer cells (Ghoneum 2014). In other laboratory studies, specially modified rice bran increased the ability of the chemotherapeutic agent daunorubicin to kill breast cancer cells (Gollapudi 2008) and promoted apoptosis in leukemia cells (Ghoneum 2003).

Enzymatically modified rice bran was also shown to complement conventional treatment of liver cancer. In a randomized controlled trial on 68 liver cancer patients, enzymatically modified rice bran was shown to improve the efficacy of common treatment approaches including chemoembolization, ethanol injection, cryoablation, and radiofrequency ablation. Thirty-eight subjects underwent interventional therapy and received one gram of rice bran extract daily for three years, while 30 underwent interventional therapy alone. Compared with interventional therapy alone, enzymatically modified rice bran in combination with interventional therapy led to reduced rates of disease recurrence (31% vs. 46%), an improved survival rate after two years (35% vs. 6.7%), and significantly reduced tumor volume (Bang 2010). Moreover, adverse side effects were less common in the group that received the rice bran extract.

Enzymatically modified rice bran has been termed a “biological response modifier” because it can modulate several aspects of immune function (Ghoneum 2011). Studies show that enzymatically modified rice bran activates natural killer cells, T cells, macrophages, and monocytes (Ghoneum 2011; Ghoneum 2004). These effects, along with an ability to stimulate endogenous free radical scavenging enzymes (Noaman 2008), may account for the potent anticancer and chemosensitizing actions of enzymatically modified rice bran extract (Ghoneum 2011; Ghoneum 2003).

Fermented Wheat Germ Extract

Fermented wheat germ extract (FWGE) is a natural product developed in Europe, where it is approved as a “dietary food for special medical purposes in cancer patients.” It is available in powder form, and has been the subject of numerous preclinical and clinical studies investigating its potential as both a direct chemotherapeutic agent as well as a complement to standard cancer radiotherapy and chemotherapy. In these capacities, this novel natural compound shows considerable promise without apparent toxicities or interference with chemotherapy efficacy. FWGE, as an addition to standard cancer treatment, has been the subject of a number of open-label trials (Boros 2005).

In one open-label trial, 21 patients with oral cancer received standard treatment, which included surgery and post-operative radiation and/or chemotherapy, while 22 patients received FWGE in addition to standard treatment. The FWGE group had significantly better outcomes compared with the control group. Local tumor recurrence and cancer progression occurred at a rate of 57.1% and 61.9%, respectively, in the control group, with corresponding rates of 4.5% and 9.1% in the FWGE group. The addition of FWGE to the standard treatment reduced the risk of cancer progression by 85% (Boros 2005).

In another open-label trial in 170 colorectal cancer patients who had previously received surgical treatment, FWGE supplementation resulted in significantly fewer progression-related events. In 66 patients who took the supplement for at least six months in addition to standard radiation and/or chemotherapy, only 3% had cancer recurrences compared with a 17.3% recurrence rate in the 104 patients who received standard treatment alone. Compared with those receiving standard treatment alone, subjects who received FWGE along with treatment also had a lower rate of new cancer metastases (7.6% vs. 23.1%), lower risk of death (12.1% vs. 31.7%), and greater chance of progression-free survival (83.3% vs. 57.7%). In this study, FWGE treatment was a stronger predictor of survival than either radiation or chemotherapy treatment (Jakab 2003).

A randomized open-label clinical trial in melanoma patients compared FWGE supplementation with dacarbazine chemotherapy. After surgery, the participants took dacarbazine alone or with FWGE (8.5 grams daily). After seven years, those receiving FWGE had longer average progression-free survival (55.8 months vs. 29.9 months) and average overall survival (66.2 months vs. 44.7 months) (Demidov 2008).

Genistein

Genistein is an isoflavone, the best-known source of which is soybeans, and widely available as a nutritional supplement (Liggins 2000; Spagnuolo 2015). A preclinical study found genistein sensitized cancer cells to the chemotherapy agent cytarabine (Shen 2007). In a cell culture study and an animal model, genistein plus cabazitaxel (Jevtana) significantly slowed the growth of metastatic castration-resistant prostate cancer more than a control solution or either alone (Zhang 2013). In a similar set of preclinical studies, genistein sensitized the diffuse large cell lymphoma subtype of non-Hodgkin lymphoma to the standard chemotherapeutic combination for this disease (cyclophosphamide, doxorubicin, vincristine, and prednisone), increasing the antitumor effect of the chemotherapy (Mohammad 2003). Genistein enhanced the cytotoxic effect of doxorubicin in HER2-positive breast cancer cells in a laboratory study, and the combination appeared to inactivate the HER2 receptor (Satoh 2003). Studies performed in prostate, breast, lung, and pancreatic cancer cells indicate genistein pretreatment may enhance cell growth inhibition and cancer cell death from cisplatin, docetaxel, and doxorubicin (Li 2005; Li 2004).

Green Tea

In an animal model of non-small cell lung cancer, treatment with cisplatin and the green tea polyphenol EGCG inhibited tumor growth more effectively than either agent alone. The authors hypothesized that EGCG might favorably modify blood supply and tumor microenvironment in non-small cell lung cancer (Deng 2013).

Cholangiocarcinoma is a type of cancer of the bile ducts that ordinarily responds poorly to chemotherapy (Lang 2009). In a mouse tumor model, oral green tea increased doxorubicin concentration in the tumor and enhanced doxorubicin's inhibition of tumor growth 2.5-fold (Sadzuka 1998). Another study using the same mouse tumor model found that, in mice given a high dose of EGCG, there was a greater degree of tumor reduction than in mice given cisplatin. In addition, when used with cisplatin, EGCG enhanced cytotoxicity and reduced kidney toxicity (El-Mowafy 2010). Green tea polyphenols in drinking water, supplied before and after exposure to the chemotherapy drug irinotecan, protected against oxidative stress in mouse gastrointestinal tracts (Wessner 2007).

Sulforaphanes and Related Compounds

Sulfur-containing phytochemicals from broccoli and other cruciferous vegetables have shown promising complementary effects in the context of cancer chemotherapy (Jadhav 2007; Li, Zhang 2010; Conaway 2000). These compounds include glucosinolates and isothiocyanates, such as sulforaphane (Higdon 2008; Shapiro 2006).

Preclinical research has demonstrated the potential for sulfur compounds to enhance chemotherapy effectiveness. In an esophageal cancer cell line, sulforaphane decreased the expression of multidrug resistance proteins (which pump cancer drugs out of cancer cells) and increased the anticancer effects of chemotherapy drugs (Qazi 2010). In ovarian cancer, resistance to the effects of cisplatin is a major barrier to successful treatment (Hunakova 2014). In a laboratory study, cisplatin-sensitive and cisplatin-resistant ovarian cancer cells were exposed to cisplatin, cisplatin plus EGCG from green tea, or cisplatin plus sulforaphane; both sulforaphane and EGCG increased cisplatin-induced cell death and interruption of cell division (Chen, Landen 2013). A watercress-derived isothiocyanate successfully sensitized cervical cancer cells to cisplatin, enhancing cancer cell death (Wang 2011). In a rodent model of breast cancer, daily injections of sulforaphane reduced cancer stem cells and down-regulated cancer cell self-renewal signaling pathways (Li, Zhang 2010).

Sulforaphane may also have a role in protecting healthy cells from toxic damage due to cancer treatment. Sulforaphane reduced signs of DNA damage in cultured white blood cells exposed to radiation, as well as doxorubicin and bleomycin (Blenoxane) (Katoch 2013), suggesting it may protect healthy cells against chemotherapy-induced toxicity. A rodent study showed that pretreatment with sulforaphane diminished cisplatin-induced oxidative damage to the liver and preserved mitochondrial function (Gaona-Gaona 2011).

Ashwagandha (Withania somnifera)

Ashwagandha may reduce the side effects of cyclophosphamide, paclitaxel, and doxorubicin without diminishing the anticancer actions of these drugs. In animal models, ashwagandha improved white blood cell and bone marrow response, reduced toxic damage to healthy tissues, and preserved organ function in animals treated with these chemotherapy agents. Ashwagandha also reduced proliferation of tumor cells while increasing survival time of the animals (Winters 2006). In one study, tumor-bearing mice that received ashwagandha root exhibited reductions in tumor cell counts and tumor weight, as well as a 27.5% increase in lifespan, compared with tumor-bearing mice that did not receive ashwagandha (Winters 2006).

Table 4: Selected Integrative Interventions and Their Influence on Chemotherapy Outcomes in Human Studies

Drug Class	Drug	Natural Agents Shown to Improve Outcomes in Combination with Chemotherapy	Human Data
Alkylating agents	**Cyclophosphamide**	**European Mistletoe Extract (*Viscum album*)**	**Tröger 2014** – Treatment with mistletoe extract in addition to cyclophosphamide, doxorubicin, and 5-FU led to better quality of life in patients with breast cancer than cyclophosphamide, doxorubicin, and 5-FU without mistletoe extract.
	Carbazilquinone	**Polysaccharide K (PSK)**	**Kondo 1991** – Treatment with PSK plus carbazilquinone following curative surgery increased survival compared with carbazilquinone alone in patients with moderately advanced (stage 1 or 2) gastric carcinoma.
	Carboplatin	**Eicosapentaenoic acid (EPA)/Docosahexaenoic acid (DHA)**	**Murphy 2011** – Treatment with fish oil (EPA + DHA) along with carboplatin and vinorelbine or gemcitabine increased response rate (defined as complete plus partial response to chemotherapy) compared with chemotherapy alone in patients with non-small cell lung cancer. However, there was no significant between-group difference in 1-year survival.

		European Mistletoe Extract	**Bar-Sela 2013** – A randomized trial of mistletoe extract in advanced non-small cell lung cancer patients receiving carboplatin-based treatment found those receiving mistletoe extract were able to reduce their chemotherapy dose and experienced less frequent severe non-hematological side effects and hospitalizations.
	Cisplatin	**Astragalus**	**Guo 2012** – No improvement in overall survival or tumor regression was observed for patients with non-small cell lung cancer treated with injections of astragalus polysaccharide along with cisplatin and vinorelbine. However, patients showed improvement in quality of life compared with those receiving cisplatin and vinorelbine without astragalus. **Zou 2003** – Prolonged average length of remission, increased median survival period, and improved quality of life were observed for patients with non-small cell lung cancer treated with astragalus injection along with mitomycin-C, vinblastine, and cisplatin compared with chemotherapy alone. **McCulloch 2006** – Meta-analysis investigating astragalus-based Chinese herbal medicine preparations in combination with platinum-based chemotherapy compared with platinum-based chemotherapy alone in patients with advanced non-small cell lung cancer. Findings in favor of astragalus included 33% reduced risk of death at 12 months (12 studies) and 34% improved tumor-response rate (30 studies).
		Ginseng	**Chen 2009** – Treatment with intravenous Shengmai injection (consisting of red ginseng, lilyturf root, and magnolia vine fruit) and oral Gujin granule (consisting of milkvetch root, asiabell root, mulberry bark, lilyturf root, balloon flower root, magnolia vine fruit, and licorice root) along with vinorelbine and cisplatin chemotherapy increased response rate and median survival time compared with chemotherapy alone in patients with non-small cell lung cancer. However, there was no between-group difference in 1-year survival or median time to progression. **Huang 2009** – Treatment with Shenyi Capsule (which contained ginsenoside Rg3) along with chemotherapy consisting of gemcitabine plus cisplatin improved quality of life and 1-year survival rate, but did not significantly improve total response rate compared with chemotherapy alone in patients with advanced esophageal cancer.
		Melatonin	**Lissoni 2007** – Treatment with melatonin plus cisplatin and etoposide increased the percentage of patients with non-small cell lung cancer who achieved complete response or partial response compared with chemotherapy alone. **Lissoni 2003** – Treatment with melatonin plus cisplatin and etoposide increased 5-year survival rate in patients with metastatic non-small cell lung cancer compared with chemotherapy alone. **Lissoni 1999** – Treatment with melatonin plus cisplatin plus etoposide or gemcitabine alone increased the percentage of patients with lung cancer who achieved complete response or partial response, as well as the percentage of patients who survived for one year, compared with chemotherapy alone. Also, melatonin plus 5-FU and cisplatin increased 1-year survival rate compared with 5-FU plus cisplatin without melatonin in patients with head and neck cancers. **Lissoni 1997** – Treatment with melatonin plus cisplatin and etoposide increased tumor response rate (defined as partial response plus complete response) compared with chemotherapy alone in patients with non-small cell lung cancer.
		PSK	**Nishiwaki 1990** – Treatment with PSK plus cisplatin and vindesine increased response rate compared with cisplatin and vindesine alone in patients with stage III but not stage IV lung cancer.
	Dacarbazine	**Fermented Wheat Germ Extract (FWGE)**	**Demidov 2008** – A randomized, early-stage, open-label clinical trial in melanoma patients examined the effect of up to one year of FWGE supplementation added to dacarbazine adjuvant chemotherapy compared with dacarbazine alone. After seven years, mean progression-free survival was 55.8 months in the treatment group and 29.9 months in the control group. Mean overall survival in the treatment group was 66.2 months and 44.7 months in the control group. The dosage of FWGE in this study was 8.5 grams, once daily, taken continuously for up to 12 months.
	Oxaliplatin	**Melatonin**	**Lissoni 2007** – Treatment with melatonin plus oxaliplatin and 5-FU/folinic acid increased the percentage of patients with colorectal cancer who achieved complete response or partial response compared with chemotherapy alone.
Antimetabolites	**Doxifluridine (5-FU prodrug)**	**European Mistletoe Extract**	**Kim 2012** – In gastric cancer patients who had undergone surgery, treatment with mistletoe extract plus doxifluridine led to better global health status and quality of life than doxifluridine alone.

	5-Fluorouracil (5-FU)	**Melatonin**	**Lissoni 2007** – Treatment with melatonin plus oxaliplatin and 5-FU/folinic acid increased the percentage of patients with colorectal cancer who achieved complete response or partial response compared with chemotherapy alone. **Yan 2002** – Treatment with melatonin plus transcatheter arterial chemoembolization (TACE) using mitomycin-C, doxorubicin, and 5-FU increased effective rates as well as 6-month, 1-year, and 2-year survival in patients with advanced primary hepatocellular carcinoma compared with TACE alone. **Lissoni 1999** – Treatment with melatonin plus 5-FU and folinic acid increased the percentage of patients with gastrointestinal tumors who achieved complete response or partial response compared with chemotherapy alone. Also, melatonin plus 5-FU and cisplatin increased 1-year survival rate compared with 5-FU plus cisplatin alone in patients with head and neck cancers.
		PSK	**Takahashi 2005** – Treatment with PSK plus 5-FU increased 7-year overall survival and 7-year disease-free survival compared with 5-FU alone in patients with colorectal cancer. **Ito 2004** – Treatment with PSK plus 5-FU improved rate of cancer-related mortality but not 7-year disease-free survival or overall survival compared with 5-FU alone in patients with colon cancer. **Nakazato 1994** – Administering PSK plus mitomycin and 5-FU following curative gastrectomy improved 5-year survival and 5-year disease-free survival rates compared with mitomycin and 5-FU alone in patients with gastric cancer. **Mitomi 1992** – Administering PSK plus mitomycin-C and 5-FU following curative resection improved disease-free survival and overall survival compared with mitomycin-C and 5-FU alone in patients with colorectal cancer. **Nakazato 1989** – Treatment with PSK plus 5-FU following radical gastrectomy increased disease-free survival and overall survival compared with 5-FU alone in patients with gastric cancer. **Mitomi 1989** – Administering PSK plus mitomycin-C and 5-FU following curative resection improved disease-free survival and overall survival compared with mitomycin-C and 5-FU alone in patients with colorectal cancer.
	Futraful	**PSK**	**Toge 2000** – Treatment with PSK plus mitomycin-C and futraful following macroscopically curative resection improved 5-year survival rate compared with mitomycin-C and futraful alone in patients with gastric cancer who had a preoperative granulocyte and lymphocyte count ratio of at least 2.0. **Niimoto 1988** – Treatment with PSK plus mitomycin-C and futraful following curative surgery increased 5-year survival rate compared with mitomycin-C and futraful alone in patients with gastric cancer.
	Gemcitabine	**EPA/DHA**	**Murphy 2011** – Treatment with fish oil (EPA + DHA) along with carboplatin and vinorelbine or gemcitabine increased response rate (defined as complete plus partial response to chemotherapy) compared with chemotherapy alone in patients with non-small cell lung cancer, but there was no significant between-group difference in 1-year survival.
		Ginseng	**Huang 2009** – Treatment with Shenyi Capsule (which contained ginsenoside Rg3) along with chemotherapy consisting of gemcitabine plus cisplatin improved quality of life and 1-year survival rate but did not improve total response rate compared with chemotherapy alone in patients with advanced esophageal cancer.
		Melatonin	**Lissoni 1999** – Treatment with melatonin plus gemcitabine increased 1-year survival compared with gemcitabine alone in patients with lung cancer.
	Tegafur-Uracil (UFT)	**PSK**	**Totsuka 2013** – Treatment with PSK plus UFT improved 5-year survival compared with UFT alone in patients with colorectal cancer who had a low preoperative lymphocyte ratio. **Akagi 2010** – Treatment with PSK plus UFT improved overall survival compared with UFT alone in patients with gastric cancer. **Ohwada 2004** – Treatment with PSK plus UFT and mitomycin-C improved 5-year disease-free survival compared with UFT and mitomycin-C in patients with stage II or III colorectal cancer and increased overall survival in patients with stage III colorectal cancer. **Ohwada 2003** – Treatment with PSK plus UFT and mitomycin improved 3-year disease-free survival compared with UFT and mitomycin alone in patients with stage II or III colorectal cancer. Also, PSK plus UFT and mitomycin improved 3-year overall survival and prevented distant metastases compared with UFT and mitomycin alone in patients with stage III colorectal cancer
Antitumor antibiotics	**Doxorubicin**	**Melatonin**	**Yan 2002** – Treatment with melatonin plus TACE using mitomycin-C, doxorubicin, and 5-FU increased effective rates as well as 6-month, 1-year, and 2-year survival in patients with advanced primary hepatocellular carcinoma compared with TACE alone.

		Melatonin	**Lissoni 1999** – Treatment with melatonin and doxorubicin increased the percentage of breast cancer patients who achieved complete or partial response and the percentage of patients who survived for one year compared with chemotherapy alone.
	Mitomycin-C	**Astragalus**	**Zou 2003** – Increased effective rate, prolonged remission rate, increased overall survival, and improved quality of life were observed for patients with non-small cell lung cancer treated with astragalus injection along with mitomycin-C, vinblastine, and cisplatin compared with chemotherapy alone.
		Melatonin	**Yan 2002** – Treatment with melatonin plus TACE using mitomycin-C, doxorubicin, and 5-FU increased effective rates as well as 6-month, 1-year, and 2-year survival in patients with advanced primary hepatocellular carcinoma compared with TACE alone.
		PSK	**Ohwada 2004** – Treatment with PSK plus UFT and mitomycin-C improved 5-year disease-free survival compared with UFT and mitomycin-C in patients with stage II or III colorectal cancer and increased overall survival in patients with stage III colorectal cancer. **Ohwada 2003** – Treatment with PSK plus UFT and mitomycin improved 3-year disease-free survival compared with UFT and mitomycin alone in patients with stage II or III colorectal cancer. Also, PSK plus UFT and mitomycin improved 3-year overall survival and prevented distant metastases compared with UFT and mitomycin alone in patients with stage III colorectal cancer. **Toge 2000** – Treatment with PSK plus mitomycin-C and futraful following macroscopically curative resection improved 5-year survival rate compared with mitomycin-C and futraful alone in patients with gastric cancer who had a preoperative granulocyte and lymphocyte count ratio of at least 2.0. **Nakazato 1994** – Administering PSK plus mitomycin and 5-FU following curative gastrectomy improved 5-year survival and 5-year disease-free rates compared with mitomycin and 5-FU alone in patients with gastric cancer. **Mitomi 1992** – Administering PSK plus mitomycin-C and 5-FU following curative resection improved disease-free survival and overall survival compared with mitomycin-C and 5-FU alone in patients with colorectal cancer. **Niimoto 1988** – Treatment with PSK plus mitomycin-C and futraful following curative surgery increased 5-year survival and overall survival rate compared with mitomycin-C and futraful alone in patients with gastric cancer.
Camptothecin analogues	**Irinotecan**	**Melatonin**	**Cerea 2003** – Treatment with melatonin plus irinotecan increased disease control (defined as partial response plus stable disease) in patients with metastatic colorectal cancer compared with irinotecan alone.
Cytokines	**Interleukin-2 (IL-2)**	**Melatonin**	**Barni 1995** – Treatment with low-dose IL-2 plus melatonin increased 1-year survival rate compared with supportive care in patients with metastatic colorectal cancer. **Lissoni 1995** – Treatment with melatonin plus low-dose IL-2 increased 1-year survival and improved performance status compared with supportive care in patients with metastatic solid tumors. **Lissoni, Meregalli 1994** – Treatment with melatonin plus low-dose IL-2 increased 1-year survival rate compared with cisplatin plus etoposide in patients with advanced non-small cell lung cancer. **Lissoni, Barni 1994** – Treatment with melatonin plus low-dose IL-2 increased response rate and 1-year survival rate compared with IL-2 alone in patients with locally advanced or metastatic solid tumors.
Protein kinase inhibitors	**Imatinib**	**Curcumin**	**Ghalaut 2012** – Treatment with curcumin-containing turmeric powder plus imatinib decreased nitric oxide levels compared with imatinib alone in patients with leukemia. Increased nitric oxide levels have been associated with different leukemias.
Taxanes	**Docetaxel**	**Vitamin D_3**	**Beer 2007** – Treatment with docetaxel plus high-dose calcitriol improved survival compared with docetaxel alone in patients with metastatic androgen-independent prostate cancer.
	Paclitaxel	**Melatonin**	**Lissoni 1999** – Treatment with melatonin plus paclitaxel increased 1-year survival compared with paclitaxel alone in patients with breast cancer.

Topoisomerase inhibitors	**Etoposide**	**Melatonin**	**Lissoni 2007** – Treatment with melatonin plus cisplatin and etoposide increased the percentage of patients with non-small cell lung cancer who achieved complete response or partial response compared with chemotherapy alone. **Lissoni 2003** – Treatment with melatonin plus cisplatin and etoposide increased 5-year survival rate in patients with metastatic non-small cell lung cancer compared with chemotherapy alone. **Lissoni 1999** – Treatment with melatonin plus cisplatin and etoposide increased the percentage of patients with lung cancer who achieved complete response or partial response, as well as the percentage of patients who survived for one year, compared with chemotherapy alone. **Lissoni 1997** – Treatment with melatonin plus cisplatin and etoposide increased the tumor response rate (partial response plus complete response) compared with chemotherapy alone in patients with non-small cell lung cancer.
Vinca Alkaloids	**Vinblastine**	**Astragalus**	**Zou 2003** – Prolonged median remission time, increased median survival period, and improved quality of life were observed for patients with non-small cell lung cancer treated with astragalus injection along with mitomycin-C, vinblastine, and cisplatin compared with those treated with chemotherapy alone.
	Vindesine	**PSK**	**Nishiwaki 1990** – PSK plus cisplatin and vindesine increased response rate compared with cisplatin and videsine alone in patients with stage III but not stage IV lung cancer.
	Vinorelbine	**Astragalus**	**Guo 2012** – No improvement in overall survival was observed for patients with non-small cell lung cancer treated with injections of astragalus polysaccharide along with cisplatin and vinorelbine. However, patients showed improvement in quality of life compared with those receiving cisplatin and vinorelbine alone.
		EPA/DHA	**Murphy 2011** – Treatment with fish oil (EPA + DHA) along with carboplatin and vinorelbine or gemcitabine increased response rate (defined as complete plus partial response to chemotherapy) compared with chemotherapy alone in patients with non-small cell lung cancer, but there was no significant between-group difference in 1-year survival.
		Ginseng	**Chen 2009 –** Treatment with intravenous Shengmai injection (consisting of red ginseng, lilyturf root, and magnolia vine fruit) and oral Gujin granule (consisting of milkvetch root, asiabell root, mulberry bark, lilyturf root, balloon flower root, magnolia vine fruit, and licorice root) along with navelbine and cisplatin chemotherapy increased response rate and median survival time compared with chemotherapy alone in patients with non-small cell lung cancer. However, there was no significant between-group difference in 1-year survival or median time to progression.

Clinical Trials

Cancer patients undergoing chemotherapy may wish to consider participating in a clinical trial, particularly if their type of cancer is known to be resistant or refractory to chemotherapy. ClinicalTrials.gov (https://clinicaltrials.gov/) is an excellent and easy-to-use resource for ongoing and planned chemotherapy clinical trials. For example, if one is interested in a particular therapy, such as “hyperthermia,” a search of the clinicaltrials.gov database (“hyperthermia” AND “cancer”) will show all clinical trials studying hyperthermia in the context of cancer. Alternatively, simply entering the name or type of cancer (eg, “glioblastoma”) will show all of the clinical trials evaluating various treatments for that particular type of cancer.

Note: this protocol should be consulted in conjunction with Cancer Treatment: The Critical Factors (/Protocols/Cancer/Cancer-Critical-Factors/Page-01). Other protocols potentially of interest include Cancer Radiation Therapy (/Protocols/Cancer/Radiation-Therapy/Page-01), Cancer Surgery (/Protocols/Cancer/Cancer-Surgery/Page-01), Cancer Adjuvant Therapy (/Protocols/Cancer/Cancer-Adjuvant-Therapy/Page-01), Complementary Alternative Cancer Therapies (/Protocols/Cancer/Alternative-Cancer-Therapies/Page-01), and Cancer Vaccines and Immunotherapy (/Protocols/Cancer/Cancer-Vaccines-and-Immunotherapy/Page-01).

Chemotherapy

References

Aapro MS, Bohlius J, Cameron DA., et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011;47(1):8-32.

Aarts MJ, Peters FP, Mandigers CM, et al. Primary granulocyte colony-stimulating factor prophylaxis during the first two cycles only or throughout all chemotherapy cycles in patients with breast cancer at risk for febrile neutropenia. J. Clin Oncol. 2013;31(34):4290-6.

Abd El-Atti S, Wasicek K, Mark S, Hegazi R. Use of probiotics in the management of chemotherapy-induced diarrhea: a case study. JPEN J Parenter Enteral Nutr. 2009 Sep-Oct;33(5):569-70.

Abdallah HM, Al-Abd AM, El-Dine RS, El-Halawany AM. P-glycoprotein inhibitors of natural origin as potential tumor chemo-sensitizers: A review. J Adv Res. Jan 2015;6(1):45-62.

Abdullah LN, Chow EK. Mechanisms of chemoresistance in cancer stem cells. Clin Transl Med. 2013;2(1):3.

ACS. American Cancer Society. A Guide to Chemotherapy. Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003025-pdf.pdf. Last updated 6/9/2015. Accessed 2/16/2017.

ACS. American Cancer Society. Different types of chemotherapy drugs. Available at: http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/chemotherapy/chemotherapyprinciplesanin-depthdiscussionofthetechniquesanditsroleintreatment/chemotherapy-principles-types-

of-chemo-drugs. Last updated 2/7/2013a. Accessed 2/16/2017.

ACS. American Cancer Society. Find Support & Treatment page. Hyperthermia to Treat Cancer. Available at: http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/hyperthermia. Last updated 6/24/2013b. Accessed 2/16/2017.

ACS. American Cancer Society. How Chemotherapy Drugs Work. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/chemotherapy/how-chemotherapy-drugs-work.html. Copyright 2017a. Accessed 2/21/2017.

ACS. American Cancer Society. Treatments & Side Effects: Central Venous Catheters. https://www.cancer.org/treatment/treatments-and-side-effects/central-venous-catheters.html. Copyright 2017b. Accessed 2/20/2017.

ACS. American Cancer Socity. Find Support & Treatment page. Oral Chemotherapy: What You Need to Know. Available at: http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/chemotherapy/oral-chemotherapy. Last updated 7/17/2014. Accessed 2/16/2017.

Ajani JA, Mangu PB, Burstein HJ. Peek before you treat? Is it a fantasy or reality? J Oncol Pract. 2011;7(5):338-9.

Akagi J, Baba H. PSK may suppress CD57(+) T cells to improve survival of advanced gastric cancer patients. Int J Clin Oncol. 2010;15(2):145-52.

Akbulut S, Elbe H, Eris C, Dogan Z, Toprak G, Otan E, . . . Turkoz Y. Cytoprotective effects of amifostine, ascorbic acid and N-acetylcysteine against methotrexate-induced hepatotoxicity in rats. World journal of gastroenterology: WJG. Aug 7 2014;20(29):10158-10165.

Alam SS, Hafiz NA, Abd El-Rahim AH. Protective role of taurine against genotoxic damage in mice treated with methotrexate and tamoxfine. Environmental toxicology and pharmacology. Jan 2011;31(1):143-152.

Aleisa AM, Al-Majed AA, Al-Yahya AA, Al-Rejaie SS, Bakheet SA, Al-Shabanah OA, Sayed-Ahmed MM. Reversal of cisplatin-induced carnitine deficiency and energy starvation by propionyl-L-carnitine in rat kidney tissues. Clinical and experimental pharmacology & physiology. Dec 2007;34(12):1252-1259.

Alpsoy S, Aktas C, Uygur R, et al. Antioxidant and anti-apoptotic effects of onion (Allium cepa) extract on doxorubicin-induced cardiotoxicity in rats. J Appl Toxicol. 2013;33(3):202-8.

Alyane M, Kebsa LB, Boussenane H, Rouibah H, Lahouel M. Cardioprotective effects and mechanism of action of polyphenols extracted from propolis against doxorubicin toxicity. Pak J Pharm Sci. 2008;21(3):201-9.

Amara S. Oral glutamine for the prevention of chemotherapy-induced peripheral neuropathy. Ann Pharmacother. 2008 Oct;42(10):1481-5.

Anderl J, Faulstich H, Hechler T, Kulke M. Antibody-drug conjugate payloads. Methods Mol Biol. 2013;1045:51-70.

Andreotti PE, Cree IA, Kurbacher CM, Hartmann DM, Linder D, Harel G, . . . et al. Chemosensitivity testing of human tumors using a microplate adenosine triphosphate luminescence assay: clinical correlation for cisplatin resistance of ovarian carcinoma. Cancer research. Nov 15 1995;55(22):5276-5282.

Antman K, Crowley J, Balcerzak SP, Rivkin SE, Weiss GR, Elias A, Natale RB, Cooper RM, Barlogie B, Trump DL, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. J Clin Oncol. 1993 Jul;11(7):1276-85.

Antony B, Merina B, Iyer VS, Judy N, Lennertz K, Joyal S. A Pilot Cross-Over Study to Evaluate Human Oral Bioavailability of BCM-95CG (Biocurcumax), A Novel Bioenhanced Preparation of Curcumin. Indian J Pharm Sci. 2008;70(4):445-449.

Apelseth TO, Hervig T, Bruserud O. Current practice and future directions for optimization of platelet transfusions in patients with severe therapy-induced cytopenia. Blood Rev. 2011 May;25(3):113-22.

Argun M, Uzum K, Sonmez MF, Ozyurt A, Derya K, Cilenk KT, . . . Narin N. Cardioprotective effect of metformin against doxorubicin cardiotoxicity in rats. Anatolian journal of cardiology. Apr 2016;16(4):234-241.

Argyriou AA, Kyritsis AP, Makatsoris T, Kalofonos HP. Chemotherapy-induced peripheral neuropathy in adults: a comprehensive update of the literature. Cancer Manag Res. 2014;6:135-47.

Arienti C, Tesei A, Verdecchia GM, Framarini M, Virzi S, Grassi A, . . . Zoli W. Role of conventional chemosensitivity test and tissue biomarker expression in predicting response to treatment of peritoneal carcinomatosis from colon cancer. Clinical colorectal cancer. Jun 2013;12(2):122-127.

Arienti C, Tesei A, Verdecchia GM, Framarini M, Virzì S, Grassi A, Scarpi E, Turci L, Silvestrini R, Amadori D, Zoli W. Peritoneal carcinomatosis from ovarian cancer: chemosensitivity test and tissue markers as predictors of response to chemotherapy. J Transl Med. 2011 Jun 20;9:94.

Asano S, Ueno K, Niitani M, Uemura K, Murakami Y, Sudo T, Hirata E, Suzuki T, Tsutani Y, Narahara H, Kataoka T. [Examination of taste threshold and serum zinc level change after chemotherapy]. Gan To Kagaku Ryoho. 2012 Sep;39(9):1389-93.

ASCO. American Society of Clinical Oncology. Navigating Cancer Care. Catheters and Ports in Cancer Treatment. Available at: http://www.cancer.net/navigating-cancer-care/how-cancer-treated/chemotherapy/catheters-and-ports-cancer-treatment. 2/2013. Accessed 1/20/2015.

ASCO. American Society of Clinical Oncology. Navigating Cancer Care. What is Chemotherapy? Available at: http://www.cancer.net/navigating-cancer-care/how-cancer-treated/chemotherapy/what-chemotherapy. Copyright 2014. Accessed 1/7/2015.

Ashour AE, Sayed-Ahmed MM, Abd-Allah AR, Korashy HM, Maayah ZH, Alkhalidi H, . . . Alhaider A. Metformin rescues the myocardium from doxorubicin-induced energy starvation and mitochondrial damage in rats. Oxid Med Cell Longev. 2012;2012:434195.

Ashour OM, Elberry AA, Alahdal A, et al. Protective effect of bilberry (Vaccinium myrtillus) against doxorubicin-induced oxidative cardiotoxicity in rats. Med Sci Monit. 2011;17(4):BR110-5.

Asvadi I, Hajipour B, Asvadi A, Asl NA, Roshangar L, Khodadadi A. Protective effect of pentoxyfilline in renal toxicity after methotrexate administration. Eur Rev Med Pharmacol Sci. 2011 Sep;15(9):1003-9.

Attarian H, Rezvani H, Ghadyani M, Eshaghi F. Consolidation Chemotherapy with Docetaxel after Platinum-Based Chemotherapy in Patients with Non-Small Cell Lung Cancer: A Preliminary Report. Tanaffos. 2011;10(3):20-23.

Attili-Qadri S, Karra N, Nemirovski A, Schwob O, Talmon Y, Nassar T, Benita S. Oral delivery system prolongs blood circulation of docetaxel

nanocapsules via lymphatic absorption. Proceedings of the National Academy of Sciences of the United States of America. 2013;110(43):17498-17503.

Avila JG. Pharmacologic treatment of constipation in cancer patients. Cancer Control. 2004 May-Jun;11(3 Suppl):10-8.

Bagchi D, Ray SD, Bagchi M, Preuss HG, Stohs SJ. Mechanistic pathways of antioxidant cytoprotection by a novel IH636 grape seed proanthocyanidin extract. Indian J Exp Biol. 2002;40(6):717-726.

Bagnyukova TV, Serebriiskii IG, Zhou Y, Hopper-Borge EA, Golemis EA, Astsaturov I. Chemotherapy and signaling: How can targeted therapies supercharge cytotoxic agents? Cancer Biol Ther. 2010 Nov 1;10(9):839-53.

Bahl A, Bakhshi S. Metronomic chemotherapy in progressive pediatric malignancies: old drugs in new package. Indian journal of pediatrics. Dec 2012;79(12):1617-1622.

Ballard KS, Homesley HD, Hodson C, Presant CA, Rutledge J, Hallquist A, Perree M. Endometrial carcinoma in vitro chemosensitivity testing of single and combination chemotherapy regimens using the novel microculture kinetic apoptosis assay: implications for endometrial cancer treatment. Journal of gynecologic oncology. Mar 2010;21(1):45-49.

Bang MH, Van Riep T, Thinh NT, Song le H, Dung TT, Van Truong L, . . . Ghoneum M. Arabinoxylan rice bran (MGN-3) enhances the effects of interventional therapies for the treatment of hepatocellular carcinoma: a three-year randomized clinical trial. Anticancer research. Dec 2010;30(12):5145-5151.

Bansal T, Jaggi M, Khar RK, Talegaonkar S. Emerging significance of flavonoids as P-glycoprotein inhibitors in cancer chemotherapy. Journal of pharmacy & pharmaceutical sciences: a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques. 2009;12(1):46-78.

Barni S, Lissoni P, Cazzaniga M, et al. A randomized study of low-dose subcutaneous interleukin-2 plus melatonin versus supportive care alone in metastatic colorectal cancer patients progressing under 5-fluorouracil and folates. Oncology. 1995;52(3):243-5.

Bar-Sela G, Wollner M, Hammer L, Agbarya A, Dudnik E, Haim N. Mistletoe as complementary treatment in patients with advanced non-small-cell lung cancer treated with carboplatin-based combinations: a randomised phase II study. Eur J Cancer. 2013 Mar;49(5):1058-64.

Bartal A, Matrai Z, Szucs A, Liszkay G. [Main treatment and preventive measures for hand-foot syndrome, a dermatologic side effect of cancer therapy]. Magyar onkologia. Jun 2011;55(2):91-98.

Barton DL, Liu H, Dakhil SR, Linquist B, Sloan JA, Nichols CR, . . . Loprinzi CL. Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. Journal of the National Cancer Institute. Aug 21 2013;105(16):1230-1238.

Baszkowsky LS, Supko JG, Chabner BA. Principles of Chemotherapy. In: Gunderson LL, Tepper JE, eds. Clinical Radiation Oncology, 3rd Edition: Saunders, An Imprint of Elsevier Inc.; 2012:165-179.

Bava SV, Sreekanth CN, Thulasidasan AK, Anto NP, Cheriyan VT, Puliyappadamba VT, . . . Anto RJ. Akt is upstream and MAPKs are downstream of NF-kappaB in paclitaxel-induced survival signaling events, which are down-regulated by curcumin contributing to their synergism. The international journal of biochemistry & cell biology. Mar 2011;43(3):331-341.

Beck A, Lambert J, Sun M, Lin K. Fourth World Antibody-Drug Conjugate Summit: February 29-March 1, 2012, Frankfurt, Germany. mAbs. Nov-Dec 2012;4(6):637-647.

Beck PL, Wong JF, Li Y, Swaminathan S, Xavier RJ, Devaney KL, Podolsky DK. Chemotherapy- and radiotherapy-induced intestinal damage is regulated by intestinal trefoil factor. Gastroenterology. Mar 2004;126(3):796-808.

Bedell CH. A changing paradigm for cancer treatment: the advent of new oral chemotherapy agents. Clin J Oncol Nurs. 2003;7(6 Suppl):5-9.

Beer TM, Bubalo JS. Complications of chemotherapy for prostate cancer. Seminars in urologic oncology. Aug 2001;19(3):222-230.

Beer TM, Ryan CW, Venner PM, et al.; ASCENT Investigators. Double-blinded randomized study of high-dose calcitriol plus docetaxel compared with placebo plus docetaxel in androgen-independent prostate cancer: a report from the ASCENT Investigators. J Clin Oncol. 2007;25(6):669-74.

Beijers AJ, Jongen JL, Vreugdenhil G. Chemotherapy-induced neurotoxicity: the value of neuroprotective strategies. Neth J Med. 2012 Jan;70(1):18-25.

Belcaro G, Hosoi M, Pellegrini L, Appendino G, Ippolito E, Ricci A, . . . Togni S. A controlled study of a lecithinized delivery system of curcumin (Meriva(R)) to alleviate the adverse effects of cancer treatment. Phytotherapy research : PTR. Mar 2014;28(3):444-450.

Bernhardson BM, Tishelman C, Rutqvist LE. Self-reported taste and smell changes during cancer chemotherapy. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. Mar 2008;16(3):275-283.

Berthiaume JM, Oliveira PJ, Fariss MW, Wallace KB. Dietary vitamin E decreases doxorubicin-induced oxidative stress without preventing mitochondrial dysfunction. Cardiovascular toxicology. 2005;5(3):257-267.

Bhatt V, Saleem A. Drug-Induced Neutropenia – Pathophysiology, Clinical Features, and Management. Annals of Clinical & Laboratory Science. 2004;34(2):131-137.

Bianchi G, Vitali G, Caraceni A, Ravaglia S, Capri G, Cundari S, . . . Gianni L. Symptomatic and neurophysiological responses of paclitaxel- or cisplatin-induced neuropathy to oral acetyl-L-carnitine. European journal of cancer (Oxford, England: 1990). Aug 2005;41(12):1746-1750.

Biswal BM, Sulaiman SA, Ismail HC, Zakaria H, Musa KI. Effect of Withania somnifera (Ashwagandha) on the development of chemotherapy-induced fatigue and quality of life in breast cancer patients. Integr Cancer Ther. 2013 Jul;12(4):312-22.

Black HS. Interaction of ascorbic acid and tocopherol on beta-carotene modulated carcinogenesis. *Hemoglobin*. Jun 2010;34(3):284-290.

Block KI, Koch AC, Mead MN, Tothy PK, Newman RA, Gyllenhaal C. Impact of antioxidant supplementation on chemotherapeutic efficacy: a systematic review of the evidence from randomized controlled trials. Cancer treatment reviews. Aug 2007;33(5):407-418.

Block KI. Antioxidants and cancer therapy: furthering the debate. Integrative cancer therapies. Dec 2004;3(4):342-348.

Bodnar L, Wcislo G, Gasowska-Bodnar A, Synowiec A, Szarlej-Wcislo K, Szczylik C. Renal protection with magnesium subcarbonate and magnesium sulphate in patients with epithelial ovarian cancer after cisplatin and paclitaxel chemotherapy: a randomised phase II study. European journal of cancer (Oxford, England: 1990). Nov 2008;44(17):2608-2614.

Boeck S, Ankerst DP, Heinemann V. The role of adjuvant chemotherapy for patients with resected pancreatic cancer: systematic review of randomized controlled trials and meta-analysis. Oncology. 2007;72(5-6):314-321.

Boghdady NA. Antioxidant and antiapoptotic effects of proanthocyanidin and ginkgo biloba extract against doxorubicin-induced cardiac injury in rats. Cell biochemistry and function. Jun 2013;31(4):344-351.

Bogliun G, Marzorati, L., Marzola, M., Miceli, M.D., Cantù, M.G. and Cavaletti, G. Neurotoxicity of cisplatin +/– reduced glutathione in the first-line treatment of advanced ovarian cancer. International Journal of Gynecological Cancer, 6: 415–419. 1996.

Bohlius J, Tonia T, Nuesch E, Juni P, Fey MF, Egger M, Bernhard J. Effects of erythropoiesis-stimulating agents on fatigue- and anaemia-related symptoms in cancer patients: systematic review and meta-analyses of published and unpublished data. British journal of cancer. Jul 8 2014;111(1):33-45.

Boros LG, Nichelatti M, Shoenfeld Y. Fermented wheat germ extract (Avemar) in the treatment of cancer and autoimmune diseases. Annals of the New York Academy of Sciences. 2005;1051(1):529-542.

Bougnoux P, Hajjaji N, Ferrasson MN, Giraudeau B, Couet C, Le Floch O. Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial. British journal of cancer. Dec 15 2009;101(12):1978-1985.

Boumendjel A, Macalou S, Valdameri G, Pozza A, Gauthier C, Arnaud O, Nicolle E, Magnard S, Falson P, Terreux R, Carrupt PA, Payen L, Di Pietro A. Targeting the multidrug ABCG2 transporter with flavonoidic inhibitors: in vitro optimization and in vivo validation. Curr Med Chem. 2011;18(22):3387-3401.

Bove L, Picardo M, Maresca V, Jandolo B, Pace A. A pilot study on the relation between cisplatin neuropathy and vitamin E. Journal of experimental & clinical cancer research: CR. Jun 2001;20(2):277-280.

Boyland E. Critical review of problems of chemotherapy. Proc R Soc Med. 1963;56:640-2.

Bozkurt Duman B, Kara B, Oguz Kara I, Demiryurek H, Aksungur E. Hand-foot syndrome due to sorafenib in hepatocellular carcinoma treated with vitamin E without dose modification; a preliminary clinical study. J BUON. 2011 Oct-Dec;16(4):759-64.

Brace CL. Microwave tissue ablation: biophysics, technology, and applications. Critical reviews in biomedical engineering. 2010;38(1):65-78.

Brandhorst S, Wei M, Hwang S, Morgan TE, Longo VD. Short-term calorie and protein restriction provide partial protection from chemotoxicity but do not delay glioma progression. Experimental gerontology. Oct 2013;48(10):1120-1128.

Brandhorst S, Choi IY, Wei M, et al. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. Cell Metab. 2015;22(1):86-99.

Brock N. The development of mesna for the inhibition of urotoxic side effects of cyclophosphamide, ifosfamide, and other oxazaphosphorine cytostatics. Recent Results Cancer Res. 1980;74:270-8.

Brown GM. Light, melatonin and the sleep-wake cycle. Journal of psychiatry & neuroscience : JPN. Nov 1994;19(5):345-353.

Calder PC. n-3 fatty acids, inflammation, and immunity--relevance to postsurgical and critically ill patients. Lipids. Dec 2004;39(12):1147-1161.

Caldwell B, Aldington S, Weatherall M, Shirtcliffe P, Beasley R. Risk of cardiovascular events and celecoxib: a systematic review and meta-analysis. Journal of the Royal Society of Medicine. Mar 2006;99(3):132-140.

Calviello G, Serini S, Piccioni E, Pessina G. Antineoplastic effects of n-3 polyunsaturated fatty acids in combination with drugs and radiotherapy: preventive and therapeutic strategies. Nutrition and cancer. 2009;61(3):287-301.

Campone M, Berton-Rigaud D, Joly-Lobbedez F, Baurain JF, Rolland F, Stenzl A, Fabbro M, van Dijk M, Pinkert J, Schmelter T, de Bont N, Pautier P. A double-blind, randomized phase II study to evaluate the safety and efficacy of acetyl-L-carnitine in the prevention of sagopilone-induced peripheral neuropathy. Oncologist. 2013;18(11):1190-1.

Campos MI, Campos CN, Aarestrup FM, Aarestrup BJ. Oral mucositis in cancer treatment: Natural history, prevention and treatment. Mol Clin Oncol. 2014 May;2(3):337-340.

Capizzi RL. Amifostine reduces the incidence of cumulative nephrotoxicity from cisplatin: laboratory and clinical aspects. Seminars in oncology. Apr 1999;26(2 Suppl 7):72-81.

Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, Martinelli G, Veglia F, Fiorentini C, Cipolla CM. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation. 2006 Dec 5;114(23):2474-81.

Carey PJ. Drug-induced myelosuppression: diagnosis and management. Drug safety: an international journal of medical toxicology and drug experience. 2003;26(10):691-706.

Cascinu S, Catalano V, Cordella L, Labianca R, Giordani P, Baldelli AM, . . . Catalano G. Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Aug 15 2002;20(16):3478-3483.

Cascinu S, Cordella L, Del Ferro E, Fronzoni M, Catalano G. Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomized double-blind placebo-controlled trial. J Clin Oncol. 1995 Jan;13(1):26-32.

Catania A, Barrajon-Catalan E, Nicolosi S, Cicirata F, Micol V. Immunoliposome encapsulation increases cytotoxic activity and selectivity of curcumin and resveratrol against HER2 overexpressing human breast cancer cells. Breast Cancer Res Treat. Aug 2013;141(1):55-65.

Cavaletti G, Marmiroli P. Chemotherapy-induced peripheral neurotoxicity. Current opinion in neurology. Oct 2015;28(5):500-507.

CCS. Canadian Cancer Society. Cancer information page. Side effects of chemotherapy. http://www.cancer.ca/en/cancer-information/diagnosis-

and-treatment/chemotherapy-and-other-drug-therapies/chemotherapy/side-effects-of-chemotherapy/?region=on. Copyright 2017. Accessed 1/13/2017.

CCS. Canadian Cancer Society. How Chemotherapy Works. Drug Resistance. Available at: http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/chemotherapy-and-other-drug-therapies/chemotherapy/how-chemotherapy-works/?region=on#Drug_resistance. Accessed 08/25/2014.

Cerchietti LC, Navigante AH, Castro MA. Effects of eicosapentaenoic and docosahexaenoic n-3 fatty acids from fish oil and preferential Cox-2 inhibition on systemic syndromes in patients with advanced lung cancer. Nutrition and cancer. 2007;59(1):14-20.

Cerea G, Vaghi M, Ardizzoia A, et al. Biomodulation of cancer chemotherapy for metastatic colorectal cancer: a randomized study of weekly low-dose irinotecan alone versus irinotecan plus the oncostatic pineal hormone melatonin in metastatic colorectal cancer patients progressing on 5-fluorouracil-containing combinations. Anticancer Res. 2003;23(2C):1951-4.

Chabner BA, Thompson EC. Merck Manuals. The Merck Manual Professional Edition. Modalities of Cancer Therapy. Chemotherapy. Available at http://www.merckmanuals.com/professional/hematology_and_oncology/principles_of_cancer_therapy/ modalities_of_cancer_therapy.html. Last updated 9/2013a. Accessed 08/27/2014.

Chabner BA, Thompson EC. Merck Manuals. The Merck Manual Professional Edition. Principles of Cancer Therapy. Cachexia and Cancer. Available at: http://www.merckmanuals.com/professional/hematology_and_oncology/principles_of_cancer_therapy/ cachexia_in_cancer.html. Last updated 9/2013b. Accessed 10/27/2014.

Chae YK, Arya A, Malecek MK, Shin DS, Carneiro B, Chandra S, . . . Giles F. Repurposing metformin for cancer treatment: current clinical studies. Oncotarget. Jun 28 2016;7(26):40767-40780.

Chaurasia S, Patel RR, Chaubey P, Kumar N, Khan G, Mishra B. Lipopolysaccharide based oral nanocarriers for the improvement of bioavailability and anticancer efficacy of curcumin. Carbohydrate polymers. Oct 5 2015;130:9-17.

Chaveli-Lopez B, Bagan-Sebastian JV. Treatment of oral mucositis due to chemotherapy. Journal of clinical and experimental dentistry. Apr 2016;8(2):e201-209.

Chemocare. How Long is Chemotherapy Given? http://chemocare.com/chemotherapy/what-is-chemotherapy/how-long-is-chemotherapy-given.aspx. Copyright 2017. Accessed 3/17/2017.

Chen G, Xu S, Renko K, Derwahl M. Metformin inhibits growth of thyroid carcinoma cells, suppresses self-renewal of derived cancer stem cells, and potentiates the effect of chemotherapeutic agents. J Clin Endocrinol Metab. 2012;97(4):E510-20.

Chen H, Landen CN, Li Y, Alvarez RD, Tollefsbol TO. Enhancement of Cisplatin-Mediated Apoptosis in Ovarian Cancer Cells through Potentiating G2/M Arrest and p21 Upregulation by Combinatorial Epigallocatechin Gallate and Sulforaphane. Journal of oncology. 2013;2013:872957.

Chen M, Zhang L, Wang Q, Shen J. Pyridoxine for prevention of hand-foot syndrome caused by chemotherapy: a systematic review. PLoS One. 2013;8(8):e72245.

Chen N, Aleksa K, Woodland C, Rieder M, Koren G. N-Acetylcysteine prevents ifosfamide-induced nephrotoxicity in rats. British journal of pharmacology. Apr 2008;153(7):1364-1372.

Chen N, Aleksa K, Woodland C, Rieder M, Koren G. The effect of N-acetylcysteine on ifosfamide-induced nephrotoxicity: in vitro studies in renal tubular cells. Translational research : the journal of laboratory and clinical medicine. Jul 2007;150(1):51-57.

Chen N, Hanly L, Rieder M, Yeger H, Koren G. The effect of N-acetylcysteine on the antitumor activity of ifosfamide. Canadian journal of physiology and pharmacology. May 2011;89(5):335-343.

Chen S, Wang Z, Huang Y, O'Barr SA, Wong RA, Yeung S, Chow MS. Ginseng and anticancer drug combination to improve cancer chemotherapy: a critical review. Evid Based Complement Alternat Med. 2014;2014:168940.

Chen YZ, Li ZD, Gao F, et al. Effects of combined Chinese drugs and chemotherapy in treating advanced non-small cell lung cancer. Chin J Integr Med. 2009;15(6):415-9.

Cheng CW, Adams GB, Perin L, Wei M, Zhou X, Lam BS, . . . Longo VD. Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regeneration and reverse immunosuppression. Cell stem cell. Jun 5 2014;14(6):810-823.

Cheng CW, Fan W, Ko SG, Song L, Bian ZX. Evidence-based management of herb-drug interaction in cancer chemotherapy. Explore (New York, N.Y.). Sep-Oct 2010;6(5):324-329.

Chi KH, Chiou TJ, Li CP, Chen SY, Chao Y. MS-20, a chemotherapeutical adjuvant, reduces chemo-associated fatigue and appetite loss in cancer patients. Nutrition and cancer. 2014;66(7):1211-1219.

Chien TJ, Liu CY, Hsu CH. Integrating acupuncture into cancer care. Journal of traditional and complementary medicine. Oct 2013;3(4):234-239.

Choi EK, Kim IR, Chang O, Kang D, Nam SJ, Lee JE, Lee SK, Im YH, Park YH, Yang JH, Cho J. Impact of chemotherapy-induced alopecia distress on body image, psychosocial well-being, and depression in breast cancer patients. Psychooncology. 2014 Mar 24. doi: 10.1002/pon.3531

Choi MR, Solid CA, Chia VM, Blaes AH, Page JH, Barron R, Arneson TJ. Granulocyte colony-stimulating factor (G-CSF) patterns of use in cancer patients receiving myelosuppressive chemotherapy. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. Jun 2014;22(6):1619-1628.

Chu SH, Lee YJ, Lee ES, Geng Y, Wang XS, Cleeland CS. Current use of drugs affecting the central nervous system for chemotherapy-induced peripheral neuropathy in cancer patients: a systematic review. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. Feb 2015;23(2):513-524.

Chuang-Xin L, Wen-Yu W, Yao C, Xiao-Yan L, Yun Z. Quercetin enhances the effects of 5-fluorouracil-mediated growth inhibition and apoptosis of esophageal cancer cells by inhibiting NF-kappaB. Oncology letters. Oct 2012;4(4):775-778.

Cobo M, Isla D, Massuti B, Montes A, Sanchez JM, Provencio M, Viñolas N, Paz-Ares L, Lopez-Vivanco G, Muñoz MA, Felip E, Alberola V, Camps C, Domine M, Sanchez JJ, Sanchez-Ronco M, Danenberg K, Taron M, Gandara D, Rosell R. Customizing cisplatin based on quantitative excision repair

cross-complementing 1 mRNA expression: a phase III trial in non-small-cell lung cancer. J Clin Oncol. 2007 Jul 1;25(19):2747-54.

Cohen MH, Dagher R, Griebel DJ, Ibrahim A, Martin A, Scher NS, Sokol GH, Williams GA, Pazdur R. U.S. Food and Drug Administration drug approval summaries: imatinib mesylate, mesna tablets, and zoledronic acid. Oncologist. 2002;7(5):393-400.

Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Jun 1 2008;26(16):2767-2778.

Colombo N, Bini S, Miceli D, Bogliun G, Marzorati L, Cavaletti G, . . . Mangioni C. Weekly cisplatin +/- glutathione in relapsed ovarian carcinoma. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society. Mar 1995;5(2):81-86.

Colombo PE, Milanezi F, Weigelt B, Reis-Filho JS. Microarrays in the 2010s: the contribution of microarray-based gene expression profiling to breast cancer classification, prognostication and prediction. Breast cancer research: BCR. 2011;13(3):212.

Colombo R, Moschini M. [Role of the combined regimen with local chemotherapy and Mw-induced hyperthermia for non-muscle invasive bladder cancer management. A systematic review]. Urologia. Apr-Jun 2013;80(2):112-119.

Conaway CC, Getahun SM, Liebes LL, Pusateri DJ, Topham DK, Botero-Omary M, Chung FL. Disposition of glucosinolates and sulforaphane in humans after ingestion of steamed and fresh broccoli. Nutrition and cancer. 2000;38(2):168-178.

Conklin KA. Cancer Chemotherapy and Antioxidants. The Journal of nutrition. November 1, 2004 2004a;134(11):3201S-3204S.

Conklin KA. Chemotherapy-associated oxidative stress: impact on chemotherapeutic effectiveness. Integr Cancer Ther. 2004b;3(4):294-300.

Conklin KA. Coenzyme q10 for prevention of anthracycline-induced cardiotoxicity. Integrative cancer therapies. Jun 2005;4(2):110-130.

Coriat R, Alexandre J, Nicco C, Quinquis L, Benoit E, Chéreau C, Lemaréchal H, Mir O, Borderie D, Tréluyer JM, Weill B, Coste J, Goldwasser F, Batteux F. Treatment of oxaliplatin-induced peripheral neuropathy by intravenous mangafodipir. J Clin Invest. 2014 Jan 2;124(1):262-72.

Corrie PG, Bulusu R, Wilson CB, Armstrong G, Bond S, Hardy R, Lao-Sirieix S, Parashar D, Ahmad A, Daniel F, Hill M, Wilson G, Blesing C, Moody AM, McAdam K, Osborne M. A randomised study evaluating the use of pyridoxine to avoid capecitabine dose modifications.Br J Cancer. 2012 Aug 7;107(4):585-7.

Cosman R, Brown CS, DeBraganca KC, Khasraw M. Patterns of care in adult medulloblastoma: results of an international online survey. J Neurooncol. 2014;120(1):125-9.

Coutsouvelis J, Wiseman M, Hui L, Poole S, Dooley M, Patil S, Avery S, Wei A, Spencer A. Effectiveness of a single fixed dose of rasburicase 3 mg in the management of tumour lysis syndrome. Br J Clin Pharmacol. 2013 Feb;75(2):550-3.

Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer. Jan 15 2004;100(2):228-237.

Cronin M, Ross JS. Comprehensive next-generation cancer genome sequencing in the era of targeted therapy and personalized oncology. Biomarkers in Medicine. 2011;5(3):293-305.

Cruciani RA, Dvorkin E, Homel P, Malamud S, Culliney B, Lapin J, . . . Esteban-Cruciani N. Safety, tolerability and symptom outcomes associated with L-carnitine supplementation in patients with cancer, fatigue, and carnitine deficiency: a phase I/II study. Journal of pain and symptom management. Dec 2006;32(6):551-559.

Cruciani RA, Zhang JJ, Manola J, Cella D, Ansari B, Fisch MJ. L-carnitine supplementation for the management of fatigue in patients with cancer: an eastern cooperative oncology group phase III, randomized, double-blind, placebo-controlled trial. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Nov 01 2012;30(31):3864-3869.

CRUK. Cancer Research UK. Why plan chemotherapy. http://www.cancerresearchuk.org/about-cancer/cancers-in-general/treatment/chemotherapy/plan/why-plan-chemotherapy#cycle. Last updated 1/6/2015. Accessed 3/17/2017.

Dale DC. Optimizing the management of chemotherapy-induced neutropenia. Clinical advances in hematology & oncology: H&O. Nov 2003;1(11):679-684.

Daugan M, Dufay Wojcicki A, d'Hayer B, Boudy V. Metformin: An anti-diabetic drug to fight cancer. Pharmacological research: the official journal of the Italian Pharmacological Society. Nov 2016;113(Pt A):675-685.

Davenport A, Frezza M, Shen M, Ge Y, Huo C, Chan TH, Dou QP. Celastrol and an EGCG pro-drug exhibit potent chemosensitizing activity in human leukemia cells. International journal of molecular medicine. 2010;25(3):465-470.

Davidson W, Teleni L, Muller J, Ferguson M, McCarthy AL, Vick J, Isenring E. Malnutrition and chemotherapy-induced nausea and vomiting: implications for practice. Oncol Nurs Forum. 2012;39(4):E340-5.

Davila M, Bresalier RS. Gastrointestinal complications of oncologic therapy. Nat Clin Pract Gastroenterol Hepatol. 2008 Dec;5(12):682-96.

de Groot S, Vreeswijk MP, Welters MJ, Gravesteijn G, Boei JJ, Jochems A, . . . Kroep JR. The effects of short-term fasting on tolerance to (neo) adjuvant chemotherapy in HER2-negative breast cancer patients: a randomized pilot study. BMC cancer. 2015;15:652.

De Leonardis V, De Scalzi M, Neri B, Bartalucci S, Cinelli P. Echocardiographic assessment of anthracycline cardiotoxicity during different therapeutic regimens. International journal of clinical pharmacology research. 1987;7(4):307-311.

De Los Santos JF, Small W. The role of amifostine in the treatment of carcinoma of the uterine cervix: an update of RTOG-0116 and review of future directions. Semin Oncol. 2004 Dec;31(6 Suppl 18):37-41.

de Oliveira Campos MP, Riechelmann R, Martins LC, Hassan BJ, Casa FB, Del Giglio A. Guarana (Paullinia cupana) improves fatigue in breast cancer patients undergoing systemic chemotherapy. J Altern Complement Med. 2011 Jun;17(6):505-12

De Palma M, Hanahan D. The biology of personalized cancer medicine: facing individual complexities underlying hallmark capabilities. Molecular oncology. Apr 2012;6(2):111-127.

De Vecchis R, Baldi C, Di Biase G, Ariano C, Cioppa C, Giasi A, . . . Cantatrione S. Cardiovascular risk associated with celecoxib or etoricoxib: a

meta-analysis of randomized controlled trials which adopted comparison with placebo or naproxen. Minerva cardioangiologica. Dec 2014;62(6):437-448.

DeBoer MD. Emergence of ghrelin as a treatment for cachexia syndromes. Nutrition (Burbank, Los Angeles County, Calif.). Sep 2008;24(9):806-814.

del Giglio AB, Cubero Dde I, Lerner TG, Guariento RT, de Azevedo RG, Paiva H, Goldman C, Carelli B, Cruz FM, Schindler F, Pianowski L, de Matos LL, del Giglio A. Purified dry extract of Paullinia cupana (guaraná) (PC-18) for chemotherapy-related fatigue in patients with solid tumors: an early discontinuation study. J Diet Suppl. 2013 Dec;10(4):325-34.

DeMario MD, Ratain MJ. Oral chemotherapy: rationale and future directions. J Clin Oncol. 1998;16(7):2557-67.

Demidov LV, Manziuk LV, Kharkevitch GY, Pirogova NA, Artamonova EV. Adjuvant fermented wheat germ extract (Avemar™) nutraceutical improves survival of high-risk skin melanoma patients: a randomized, pilot, phase II clinical study with a 7-year follow-up. Cancer biotherapy & radiopharmaceuticals. 2008;23(4):477-482.

Deng PB, Hu CP, Xiong Z, Yang HP, Li YY. Treatment with EGCG in NSCLC leads to decreasing interstitial fluid pressure and hypoxia to improve chemotherapy efficacy through rebalance of Ang-1 and Ang-2. Chin J Nat Med. 2013 May;11(3):245-53.

Dezso Z, Oestreicher J, Weaver A, Santiago S, Agoulnik S, Chow J, . . . Funahashi Y. Gene Expression Profiling Reveals Epithelial Mesenchymal Transition (EMT) Genes Can Selectively Differentiate Eribulin Sensitive Breast Cancer Cells. PloS one. 2014;9(8):e106131.

Dhandapani KM, Mahesh VB, Brann DW. Curcumin suppresses growth and chemoresistance of human glioblastoma cells via AP-1 and NFkappaB transcription factors. Journal of neurochemistry. Jul 2007;102(2):522-538.

Dibble SL, Luce J, Cooper BA, Israel J, Cohen M, Nussey B, Rugo H. Acupressure for chemotherapy-induced nausea and vomiting: a randomized clinical trial. Oncol Nurs Forum. 2007 Jul;34(4):813-20.

Dimitrov V, Salehi-Tabar R, An BS, White JH. Non-classical mechanisms of transcriptional regulation by the vitamin D receptor: Insights into calcium homeostasis, immune system regulation and cancer chemoprevention. The Journal of steroid biochemistry and molecular biology. Oct 2014;144pa:74-80.

Dincol D, Buyukcelik A, Dogan M, Akbulut H, Samur M, Demirkazik A, Senler FC, Onur H, Icli F. Long-term outcome of mesna, ifosfamide, mitoxantrone, etoposide (MINE) regimen as a consolidation in patients with aggressive non-Hodgkin lymphoma responding to CHOP. Med Oncol. 2010 Sep;27(3):942-5.

Dixon RA, Xie DY, Sharma SB. Proanthocyanidins--a final frontier in flavonoid research? The New phytologist. Jan 2005;165(1):9-28.

Dong L, Zhou Q, Zhang Z, Zhu Y, Duan T, Feng Y. Metformin sensitizes endometrial cancer cells to chemotherapy by repressing glyoxalase I expression. J Obstet Gynaecol Res. 2012;38(8):1077-85.

Doroshow JH, Goldman L (ed.), Schafer Ae. Goldman's Cecil Medicine, Twenty-Fifth Edition. Chapter 179: Approach To The Patient With Cancer; 1206-1222e2. Copyright 2017 Saunders, an imprint of Elsevier, Inc. Available at: www.clinicalkey.com Accessed 1/11/2017.

Dorr RT. Chemoprotectants for cancer chemotherapy. Seminars in oncology. Feb 1991;18(1 Suppl 2):48-58.

dos Santos NA, Carvalho Rodrigues MA, Martins NM, dos Santos AC. Cisplatin-induced nephrotoxicity and targets of nephroprotection: an update. Archives of toxicology. Aug 2012;86(8):1233-1250.

Drisko JA, Chapman J, Hunter VJ. The use of antioxidant therapies during chemotherapy. Gynecologic oncology. 2003;88(3):434-439.

Duan P, Wang ZM. [Clinical study on effect of Astragalus in efficacy enhancing and toxicity reducing of chemotherapy in patients of malignant tumor]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2002 Jul;22(7):515-7.

Duffy MJ, Crown J. A personalized approach to cancer treatment: how biomarkers can help. Clin Chem. 2008 Nov;54(11):1770-9.

Dundee JW, Yang J. Prolongation of the antiemetic action of P6 acupuncture by acupressure in patients having cancer chemotherapy. J R Soc Med. Jun 1990;83(6):360-362.

Duval M, Daniel SJ. Meta-analysis of the efficacy of amifostine in the prevention of cisplatin ototoxicity. J Otolaryngol Head Neck Surg. 2012 Oct;41(5):309-15.

Eisenbraun J, Scheer R, Kröz M, Schad F, Huber R. Quality of life in breast cancer patients during chemotherapy and concurrent therapy with a mistletoe extract. Phytomedicine. 2011 Jan 15;18(2-3):151-7.

Ekwall EM, Nygren LM, Gustafsson AO, Sorbe BG. Determination of the most effective cooling temperature for the prevention of chemotherapy-induced alopecia. Molecular and clinical oncology. Nov 2013;1(6):1065-1071.

El-Bakly WM, Louka ML, El-Halawany AM, Schaalan MF. 6-gingerol ameliorated doxorubicin-induced cardiotoxicity: role of nuclear factor kappa B and protein glycation. Cancer chemotherapy and pharmacology. Dec 2012;70(6):833-841.

Elberry AA, Abdel-Naim AB, Abdel-Sattar EA, Nagy AA, Mosli HA, Mohamadin AM, Ashour OM. Cranberry (Vaccinium macrocarpon) protects against doxorubicin-induced cardiotoxicity in rats. Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association. May 2010;48(5):1178-1184.

El-Housseiny AA, Saleh SM, El-Masry AA, Allam AA. The effectiveness of vitamin "E" in the treatment of oral mucositis in children receiving chemotherapy. The Journal of clinical pediatric dentistry. Spring 2007;31(3):167-170.

El-Mowafy AM, Al-Gayyar MM, Salem HA, El-Mesery ME, Darweish MM. Novel chemotherapeutic and renal protective effects for the green tea (EGCG): role of oxidative stress and inflammatory-cytokine signaling. Phytomedicine. 2010 Dec 1;17(14):1067-75.

El-Rayes BF, Shields AF, Vaishampayan U, Heilbrun LK, Zalupski MM, Philip PA. A dose attenuated schedule of irinotecan and capecitabine in combination with celecoxib in advanced colorectal cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Jun 20 2006;24(18_suppl):3584.

Erhola M, Kellokumpu-Lehtinen P, Metsä-Ketelä T, Alanko K, Nieminen MM. Effects of anthracyclin-based chemotherapy on total plasma antioxidant

capacity in small cell lung cancer patients. Free Radical Biology and Medicine. 1996;21(3):383-390.

Esserman L, Berry D, Cheang MU, Yau C, Perou C, Carey L, . . . Hylton N. Chemotherapy response and recurrence-free survival in neoadjuvant breast cancer depends on biomarker profiles: results from the I-SPY 1 TRIAL (CALGB 150007/150012; ACRIN 6657). Breast cancer research and treatment. 2012;132(3):1049-1062.

Ethyol. [Package Insert]. Ben Venue, Inc., Bedford, OH. http://www.accessdata.fda.gov/drugsatfda_docs/label/1999/20221s12lbl.pdf. Last updated 6/1999. Accessed 2/22/2017.

Eum S, Choi HD, Chang MJ, Choi HC, Ko YJ, Ahn JS, Shin WG, Lee JY. Protective effects of vitamin E on chemotherapy-induced peripheral neuropathy: a meta-analysis of randomized controlled trials. Int J Vitam Nutr Res. 2013;83(2):101-11.

Eustace AJ, Kennedy S, Larkin AM, Mahgoub T, Tryfonopoulos D, O'Driscoll L, . . . O'Donovan N. Predictive biomarkers for dasatinib treatment in melanoma. Oncoscience. 2014;1(2):158-166.

Fakih MG, Andrews C, McMahon J, Muindi JR. A prospective clinical trial of cholecalciferol 2000 IU/day in colorectal cancer patients: evidence of a chemotherapy-response interaction. Anticancer Res. 2012 Apr;32(4):1333-8.

Falsaperla M, Morgia G, Tartarone A, Ardito R, Romano G. Support ellagic acid therapy in patients with hormone refractory prostate cancer (HRPC) on standard chemotherapy using vinorelbine and estramustine phosphate. *Eur Urol.* Apr 2005;47(4):449-454; discussion 454-445.

FDA. U.S. Food and Drug Administration website. Drugs page. Ado-Trastuzumab Emtansine. Available at: http://www.fda.gov/drugs /informationondrugs/approveddrugs/ucm340913.htm. Last updated 2/25/2013. Accessed 8/7/2014.

Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. Nature reviews. Clinical oncology. Feb 2013;10(2):90-99.

Feddock J, Kudrimoti M, Randall M. No cookie-cutter oncology: individualized treatment approaches for women with corpus endometrial cancer. Expert review of anticancer therapy. Jul 2010;10(7):1087-1100.

Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer. May 2014;14(5):342-357.

Feng SS, Zhao L, Tang J. Nanomedicine for oral chemotherapy. Nanomedicine (Lond). 2011;6(3):407-10.

Fisher M, Yang LX. Anticancer effects and mechanisms of polysaccharide-K (PSK): implications of cancer immunotherapy. Anticancer research. May-Jun 2002;22(3):1737-1754.

Fritz H, Kennedy DA, Ishii M, Fergusson D, Fernandes R, Cooley K, Seely D. Polysaccharide K and Coriolus versicolor extracts for lung cancer: a systematic review. Integrative cancer therapies. May 2015;14(3):201-211.

Fuchs-Tarlovsky V, Rivera MA, Altamirano KA, Lopez-Alvarenga JC, Ceballos-Reyes GM. Antioxidant supplementation has a positive effect on oxidative stress and hematological toxicity during oncology treatment in cervical cancer patients. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* May 2013;21(5):1359-1363.

Fukawa T, Yan-Jiang BC, Min-Wen JC, Jun-Hao ET, Huang D, Qian CN, . . . Shyh-Chang N. Excessive fatty acid oxidation induces muscle atrophy in cancer cachexia. Nat Med. Jun 2016;22(6):666-671.

Fukaya H, Kanno H. [Experimental studies of the protective effect of ginkgo biloba extract (GBE) on cisplatin-induced toxicity in rats]. Nihon Jibiinkoka Gakkai kaiho. Jul 1999;102(7):907-917.

Gallant JN, Matthew EM, Cheng H, Harouaka R, Lamparella NE, Kunkel M, . . . El-Deiry WS. Predicting therapy response in live tumor cells isolated with the flexible micro spring array device. Cell cycle (Georgetown, Tex.). Jul 1 2013;12(13):2132-2143.

Galmarini D, Galmarini CM, Galmarini FC. Cancer chemotherapy: a critical analysis of its 60 years of history. Crit Rev Oncol Hematol. 2012 Nov;84(2):181-99

Gao HF, Liang Y, Zhou NN, Zhang DS, Wu HY. Aprepitant plus palonosetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy. Internal medicine journal. Jan 2013;43(1):73-76.

Gao YT, Wu LY, Zhang W, Zhao D, Li N, Tian HM, . . . Li XG. [A prospective study of adenosine triphosphate-tumor chemosensitivity assay directed chemotherapy in patients with recurrent ovarian cancer]. Zhonghua fu chan ke za zhi. May 2013;48(5):358-363.

Gaona-Gaona L, Molina-Jijon E, Tapia E, Zazueta C, Hernandez-Pando R, Calderon-Oliver M, . . . Pedraza-Chaverri J. Protective effect of sulforaphane pretreatment against cisplatin-induced liver and mitochondrial oxidant damage in rats. Toxicology. Aug 15 2011;286(1-3):20-27.

Garami M, Schuler D, Babosa M, Borgulya G, Hauser P, Müller J, . . . Fekete G. Fermented wheat germ extract reduces chemotherapy-induced febrile neutropenia in pediatric cancer patients. Journal of pediatric hematology/oncology. 2004;26(10):631-635.

Garralda E, Paz K, Lopez-Casas PP, Jones S, Katz A, Kann LM, . . . Hidalgo M. Integrated next-generation sequencing and avatar mouse models for personalized cancer treatment. Clinical cancer research: an official journal of the American Association for Cancer Research. May 1 2014;20(9):2476-2484.

Gayathri BN, Rao KS. Pancytopenia: a clinico hematological study. J Lab Physicians. 2011 Jan;3(1):15-20.

Gazzaniga P, Naso G, Gradilone A, Cortesi E, Gandini O, Gianni W, . . . Cristofanilli M. Chemosensitivity profile assay of circulating cancer cells: prognostic and predictive value in epithelial tumors. International journal of cancer. Journal international du cancer. May 15 2010;126(10):2437-2447.

Gedlicka C, Kornek GV, Schmid K, Scheithauer W. Amelioration of docetaxel/cisplatin induced polyneuropathy by α-lipoic acid. Annals of Oncology. 2003;14(2):339-340.

Geng M, Wang L, Li P. Correlation between chemosensitivity to anticancer drugs and Bcl-2 expression in gastric cancer. International journal of clinical and experimental pathology. 2013;6(11):2554-2559.

Gesme DH, Wiseman M. Strategic Use of Clinical Pathways. Journal of oncology practice / American Society of Clinical Oncology. Jan

2011;7(1):54-56.

Gewandter JS, Mohile SG, Heckler CE, Ryan JL, Kirshner JJ, Flynn PJ, Hopkins JO, Morrow GR. A phase III randomized, placebo-controlled study of topical amitriptyline and ketamine for chemotherapy-induced peripheral neuropathy (CIPN): a University of Rochester CCOP study of 462 cancer survivors. Support Care Cancer. 2014 Jul;22(7):1807-14.

Ghalaut VS, Sangwan L, Dahiya K, et al. Effect of imatinib therapy with and without turmeric powder on nitric oxide levels in chronic myeloid leukemia. J Oncol Pharm Pract. 2012;18(2):186-90.

Ghoneum M, Agrawal S. Activation of human monocyte-derived dendritic cells in vitro by the biological response modifier arabinoxylan rice bran (MGN-3/Biobran). International journal of immunopathology and pharmacology. Oct-Dec 2011;24(4):941-948.

Ghoneum M, Badr El-Din NK, Ali DA, El-Dein MA. Modified arabinoxylan from rice bran, MGN-3/biobran, sensitizes metastatic breast cancer cells to paclitaxel in vitro. Anticancer research. Jan 2014;34(1):81-87.

Ghoneum M, Gollapudi S. Modified arabinoxylan rice bran (MGN-3/Biobran) sensitizes human T cell leukemia cells to death receptor (CD95)-induced apoptosis. Cancer letters. Nov 10 2003;201(1):41-49.

Ghoneum M, Matsuura M. Augmentation of macrophage phagocytosis by modified arabinoxylan rice bran (MGN-3/biobran). International journal of immunopathology and pharmacology. Sep-Dec 2004;17(3):283-292.

Ghorbani A, Omidvar B, Parsi A. Protective effect of selenium on cisplatin induced nephrotoxicity: A double-blind controlled randomized clinical trial. J Nephropathol. 2013 Apr;2(2):129-34

Ghorbani A. Renal protective effect of selenium on cisplatin-induced nephrotoxicity. J Ren Inj Prev. 2013;1(1):31-32.

Ghoreishi Z, Esfahani A, Djazayeri A, Djalali M, Golestan B, Ayromlou H, Hashemzade S, Asghari Jafarabadi M, Montazeri V, Keshavarz SA, Darabi M. Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: a randomized double-blind placebo controlled trial. BMC Cancer. 2012 Aug 15;12:355.

Gibson RJ, Keefe DM. Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies. Support Care Cancer. 2006 Sep;14(9):890-900.

Glaysher S, Cree IA. Cell sensitivity assays: the ATP-based tumor chemosensitivity assay. Methods in molecular biology (Clifton, N.J.). 2011;731:247-257.

Gold Standard. Drug Monograph. Aprepitant, Fosaprepitant. www.clinicalkey.com. Last updated 2/24/2016a. Accessed 1/13/2017.

Gold Standard. Drug Monograph. Cyclophosphamide. www.clinicalkey.com. Last updated 2/19/2016b. Accessed 1/13/2017.

Gold Standard. Drug Monograph. Dexrazoxane. www.clinicalkey.com. Last updated 7/16/2012. Accessed 7/21/2015.

Gold Standard. Drug Monograph. Megestrol. www.clincalkey.com. Last updated 3/25/2016c. Accessed 2/20/2017.

Gold Standard. Drug Monograph. Palonosetron. www.clinicalkey.com. Last updated 9/23/2014. Accessed 1/13/2017.

Goldfarb Y, Shapiro H, Singer P, Kalderon Y, Levi B, Glasner A, . . . Ben-Eliyahu S. Fish oil attenuates surgery-induced immunosuppression, limits post-operative metastatic dissemination and increases long-term recurrence-free survival in rodents inoculated with cancer cells. Clinical nutrition (Edinburgh, Scotland). Jun 2012;31(3):396-404.

Gollapudi S, Ghoneum M. MGN-3/Biobran, modified arabinoxylan from rice bran, sensitizes human breast cancer cells to chemotherapeutic agent, daunorubicin. Cancer detection and prevention. 2008;32(1):1-6.

Goncalves R, Bose R. Using multigene tests to select treatment for early-stage breast cancer. J Natl Compr Canc Netw. 2013 Feb 1;11(2):174-82; quiz 182.

Gralla RJ. Updated CINV Guidelines: New Evidence for Change and Practical Issues. http://www.medscape.org/viewarticle/851712_2. Copyright 2016. Accessed 1/13/2017.

Granci V, Cai F, Lecumberri E, Clerc A, Dupertuis YM, Pichard C. Colon cancer cell chemosensitisation by fish oil emulsion involves apoptotic mitochondria pathway. The British journal of nutrition. Apr 14 2013;109(7):1188-1195.

Graziano F, Bisonni R, Catalano V, Silva R, Rovidati S, Mencarini E, . . . Lai V. Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anaemic cancer patients. British journal of cancer. Jun 17 2002;86(12):1854-1857.

Green JM. Glucarpidase to combat toxic levels of methotrexate in patients. Ther Clin Risk Manag. 2012;8:403-13.

Grendys EC, Jr., Fiorica JV, Orr JW, Jr., Holloway R, Wang D, Tian C, . . . Herzog TJ. Overview of a chemoresponse assay in ovarian cancer. Clinical & translational oncology: official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico. Sep 2014;16(9):761-769.

Griggs J, Weiss M. Ask-the-Expert Online Conference: Chemotherapy Updates. http://www.breastcancer.org/treatment/chemotherapy /ask_expert#qcriteria-for-reducing-chemo-doses. 2/2002. Accessed 1/13/2017.

Grigsby PW, Zighelboim I, Powell MA, Mutch DG, Schwarz JK. In vitro chemoresponse to cisplatin and outcomes in cervical cancer. Gynecologic oncology. Jul 2013;130(1):188-191.

Grunberg SM, Slusher B, Rugo HS. Emerging treatments in chemotherapy-induced nausea and vomiting. Clinical advances in hematology & oncology: H&O. Feb 2013;11(2 Suppl 1):1-18; quiz 12 p following 18.

Guan YF, Li GR, Wang RJ, Yi YT, Yang L, Jiang D, . . . Peng Y. Application of next-generation sequencing in clinical oncology to advance personalized treatment of cancer. Chinese journal of cancer. Oct 2012;31(10):463-470.

Gulec M, Iraz M, Yilmaz HR, Ozyurt H, Temel I. The effects of ginkgo biloba extract on tissue adenosine deaminase, xanthine oxidase, myeloperoxidase, malondialdehyde, and nitric oxide in cisplatin-induced nephrotoxicity. Toxicology and industrial health. Apr 2006;22(3):125-130.

Guo L, Bai SP, Zhao L, Wang XH. Astragalus polysaccharide injection integrated with vinorelbine and cisplatin for patients with advanced non-small cell lung cancer: effects on quality of life and survival. Med Oncol. 2012;29(3):1656-62.

Gupta YK, Sharma SS, Rai K, Katiyar CK. Reversal of paclitaxel induced neutropenia by Withania somnifera in mice. Indian J Physiol Pharmacol. 2001 Apr;45(2):253-7.

Gurney JG, Bass JK, Onar-Thomas A, Huang J, Chintagumpala M, Bouffet E, Hassall T, Gururangan S, Heath JA, Kellie S, Cohn R, Fisher MJ, Panandiker AP, Merchant TE, Srinivasan A, Wetmore C, Qaddoumi I, Stewart CF, Armstrong GT, Broniscer A, Gajjar A. Evaluation of amifostine for protection against cisplatin-induced serious hearing loss in children treated for average-risk or high-risk medulloblastoma. Neuro Oncol. 2014 Jun;16(6):848-55.

Gustafson DL, Long ME, Bradshaw EL, Merz AL, Kerzic PJ. P450 induction alters paclitaxel pharmacokinetics and tissue distribution with multiple dosing. Cancer chemotherapy and pharmacology. 2005;56(3):248-254.

Guttuso T Jr. Gabapentin's anti-nausea and anti-emetic effects: a review. Exp Brain Res. 2014;232(8):2535-9.

Haniadka R, Rajeev AG, Palatty PL, Arora R, Baliga MS. Zingiber officinale (ginger) as an anti-emetic in cancer chemotherapy: a review. J Altern Complement Med. 2012 May;18(5):440-4.

Hart J. Data Support Antioxidant Use During Chemotherapy: An Interview with Keith I. Block, MD. Alternative and Complementary Therapies. 2012;18(2):91-97.

Hartmann JT, Knop S, Fels LM, van Vangerow A, Stolte H, Kanz L, Bokemeyer C. The use of reduced doses of amifostine to ameliorate nephrotoxicity of cisplatin/ifosfamide-based chemotherapy in patients with solid tumors. Anti-cancer drugs. Jan 2000;11(1):1-6.

Hasinoff BB, Herman EH. Dexrazoxane: how it works in cardiac and tumor cells. Is it a prodrug or is it a drug? Cardiovasc Toxicol. 2007;7(2):140-4.

Healthwise. Cigna website. Health & Wellness page. Antitumor Antibiotics for Chemotherapy. Available at: http://www.cigna.com/healthwellness/hw/medications/antitumor-antibiotics-for-chemotherapy-tv7464. Last updated 8/14/2013. Accessed 9/4/2014.

Heijkoop ST, Franckena M, Thomeer MG, Boere IA, Van Montfort C, Van Doorn HC. Neoadjuvant chemotherapy followed by radiotherapy and concurrent hyperthermia in patients with advanced-stage cervical cancer: a retrospective study. International journal of hyperthermia: the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2012;28(6):554-561.

Held K, Ryan R, Champion JM, August K, Radhi MA. Caregiver survey results related to handling of oral chemotherapy for pediatric patients with acute lymphoblastic leukemia. Journal of pediatric hematology/oncology. 2013;35(6):e249-253.

Held-Warmkessel J. How to prevent and manage tumor lysis syndrome. Nursing. 2010 Feb;40(2):26-31; quiz 31-2.

Hemati S, Arbab JN, Rafienia M, Ghavamnasiri M. The effects of vitamin E and selenium on cisplatin-induced nephrotoxicity in cancer patients treated with cisplatin-based chemotherapy: A randomized, placebo-controlled study. J Res Med Sci. 2012;17:S49–58.

Hendlisz A, Golfinopoulos V, Deleporte A, Paesmans M, Mansy H, Garcia C, Peeters M, Annemans L, Vandeputte C, Maetens M, Borbath I, Dresse D, Houbier G, Fried M, Awada A, Piccart M, Laethem JL, Flamen P. Preoperative chemosensitivity testing as Predictor of Treatment benefit in Adjuvant stage III colon cancer (PePiTA): Protocol of a prospective BGDO (Belgian Group for Digestive Oncology) multicentric study. BMC Cancer. 2013;13(1):190.

Hendrikx JJ, Lagas JS, Rosing H, Schellens JH, Beijnen JH, Schinkel AH. P-glycoprotein and cytochrome P450 3A act together in restricting the oral bioavailability of paclitaxel.Int J Cancer. 2013;132(10):2439-47.

Hensley ML, Hagerty KL, Kewalramani T, Green DM, Meropol NJ, Wasserman TH, Cohen GI, Emami B, Gradishar WJ, Mitchell RB, Thigpen JT, Trotti A 3rd, von Hoff D, Schuchter LM. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. J Clin Oncol. 2009 Jan 1;27(1):127-45.

Hernandez SL, Sheyner I, Stover KT, Stewart JT. Dronabinol Treatment of Refractory Nausea and Vomiting Related to Peritoneal Carcinomatosis. Am J Hosp Palliat Care. 2013 Sep 19. [Epub ahead of print].

Herzog TJ, Krivak TC, Fader AN, Coleman RL. Chemosensitivity testing with ChemoFx and overall survival in primary ovarian cancer. American journal of obstetrics and gynecology. Jul 2010;203(1):68.e61-66.

Hess LM, Insel KC. Chemotherapy-related change in cognitive function: a conceptual model. Oncology nursing forum. Sep 2007;34(5):981-994.

Higashiyama M, Okami J, Maeda J, Tokunaga T, Fujiwara A, Kodama K, Imamura F, Kobayashi H. Differences in chemosensitivity between primary and paired metastatic lung cancer tissues: In vitro analysis based on the collagen gel droplet embedded culture drug test (CD-DST). J Thorac Dis. 2012 Feb;4(1):40-7.

Higdon J. OSU: Linus Pauling Institute web page. Isothiocyanates. Available at: http://lpi.oregonstate.edu/infocenter/phytochemicals/isothio/. Last updated 11/2008. Accessed 9/9/2014.

Hilchie AL, Doucette CD, Pinto DM, Patrzykat A, Douglas S, Hoskin DW. Pleurocidin-family cationic antimicrobial peptides are cytolytic for breast carcinoma cells and prevent growth of tumor xenografts. Breast cancer research: BCR. 2011;13(5):R102.

Hildebrandt B, Wust P, Ahlers O, Dieing A, Sreenivasa G, Kerner T, . . . Riess H. The cellular and molecular basis of hyperthermia. Critical reviews in oncology/hematology. Jul 2002;43(1):33-56.

Hilpert F, Stähle A, Tomé O, Burges A, Rossner D, Späthe K, Heilmann V, Richter B, du Bois A; Arbeitsgemeinschaft Gynäkologische Onkologoie (AGO) Ovarian Cancer Study Group. Neuroprotection with amifostine in the first-line treatment of advanced ovarian cancer with carboplatin/paclitaxel-based chemotherapy—a double-blind, placebo-controlled, randomized phase II study from the Arbeitsgemeinschaft Gynäkologische Onkologoie (AGO) Ovarian Cancer Study Group. Support Care Cancer. 2005 Oct;13(10):797-805.

Hine C, Mitchell JR. Saying no to drugs: fasting protects hematopoietic stem cells from chemotherapy and aging. Cell stem cell. Jun 5 2014;14(6):704-705.

Hirai S, Kaida S, Ito T, Hasebe S, Ueno M, Udagawa H, Hayashi M. [Magnesium premedication prevents Cisplatin-induced nephrotoxicity in patients

with esophageal and hypopharyngeal cancer]. Gan to kagaku ryoho. Cancer & chemotherapy. Jun 2013;40(6):743-747.

Hirsch HA, Iliopoulos D, Tsichlis PN, Struhl K. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. Cancer research. 2009;69(19):7507-7511.

Hocking CM, Kichenadasse G. Olanzapine for chemotherapy-induced nausea and vomiting: a systematic review. Support Care Cancer. 2014 Apr;22(4):1143-51.

Hoffer LJ, Robitaille L, Zakarian R, Melnychuk D, Kavan P, Agulnik J, . . . Miller WH, Jr. High-Dose Intravenous Vitamin C Combined with Cytotoxic Chemotherapy in Patients with Advanced Cancer: A Phase I-II Clinical Trial. PloS one. 2015;10(4):e0120228.

Holmboe L, Andersen AM, Mørkrid L, Slørdal L, Hall KS. High dose methotrexate chemotherapy: pharmacokinetics, folate and toxicity in osteosarcoma patients.Br J Clin Pharmacol. 2012 Jan;73(1):106-14.

Honjo S, Ajani JA, Scott AW, Chen Q, Skinner HD, Stroehlein J, Johnson RL, Song S. Metformin sensitizes chemotherapy by targeting cancer stem cells and the mTOR pathway in esophageal cancer. Int J Oncol. 2014;45(2):567-74.

Honkoop A, Pinedo H. High-dose chemotherapy in the treatment of breast-cancer. International journal of oncology. 1995;6(4):911-918.

Horne BD, Cox JE, Muhlestein JB, Le VT, Butler AR, May HT, . . . Anderson JL. Abstract 13412: 24-Hour Water-Only Fasting Acutely Reduces Trimethylamine N-Oxide: the FEELGOOD Trial. Circulation. November 25, 2014 2014;130(Suppl 2):A13412.

Howells LM, Sale S, Sriramareddy SN, Irving GR, Jones DJ, Ottley CJ, . . . Brown K. Curcumin ameliorates oxaliplatin-induced chemoresistance in HCT116 colorectal cancer cells in vitro and in vivo. International journal of cancer. J international du cancer. Jul 15 2011;129(2):476-486.

Hu YJ, Chen Y, Zhang YQ, Zhou MZ, Song XM, Zhang BZ, Luo L, Xu PM, Zhao YN, Zhao YB, Cheng G. The protective role of selenium on the toxicity of cisplatin-contained chemotherapy regimen in cancer patients. Biol Trace Elem Res. 1997 Mar;56(3):331-41.

Huang JS, Wu CL, Fan CW, Chen WH, Yeh KY, Chang PH. Intravenous glutamine appears to reduce the severity of symptomatic platinum-induced neuropathy: a prospective randomized study. Journal of chemotherapy (Florence, Italy). Aug 2015;27(4):235-240.

Huang JY, Sun Y, Fan QX, Zhang YQ. [Efficacy of Shenyi Capsule combined with gemcitabine plus cisplatin in treatment of advanced esophageal cancer: a randomized controlled trial]. Zhong Xi Yi Jie He Xue Bao. 2009;7(11):1047-51.

Huang L, Cai M, Xie X, Chen Y, Luo X. Uptake enhancement of curcumin encapsulated into phosphatidylcholine-shielding micelles by cancer cells. Journal of biomaterials science. Polymer edition. 2014;25(13):1407-1424.

Huang H, He M, Liu L, Huang L. Vitamin E does not decrease the incidence of chemotherapy-induced peripheral neuropathy: a meta-analysis. *Contemp Oncol (Pozn).* 2016;20(3):237-241.

Huh JW, Park YA, Lee KY, Sohn SK. Heterogeneity of adenosine triphosphate-based chemotherapy response assay in colorectal cancer--secondary publication. Yonsei medical journal. Oct 31 2009;50(5):697-703.

Hunakova L, Gronesova P, Horvathova E, Chalupa I, Cholujova D, Duraj J, Sedlak J. Modulation of cisplatin sensitivity in human ovarian carcinoma A2780 and SKOV3 cell lines by sulforaphane. Toxicol Lett. 2014 Nov 4;230(3):479-86.

Hur H, Kim NK, Kim HG, Min BS, Lee KY, Shin SJ, . . . Choi SH. Adenosine triphosphate-based chemotherapy response assay-guided chemotherapy in unresectable colorectal liver metastasis. British journal of cancer. Jan 3 2012;106(1):53-60.

Ichikawa Y, Ghanefar M, Bayeva M, Wu R, Khechaduri A, Naga Prasad SV, . . . Ardehali H. Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. The Journal of clinical investigation. Feb 3 2014;124(2):617-630.

Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, . . . Goldszmid RS. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science (New York, N.Y.). Nov 22 2013;342(6161):967-970.

Ingersoll GL, Wasilewski A, Haller M, Pandya K, Bennett J, He H, Hoffmire C, Berry C. Effect of concord grape juice on chemotherapy-induced nausea and vomiting: results of a pilot study. Oncol Nurs Forum. 2010 Mar;37(2):213-21.

Iop A, Manfredi AM, Bonura S. Fatigue in cancer patients receiving chemotherapy: an analysis of published studies. Ann Oncol. 2004 May;15(5):712-20.

Isenring EA, Teleni L. Nutritional counseling and nutritional supplements: a cornerstone of multidisciplinary cancer care for cachectic patients. Current opinion in supportive and palliative care. Dec 2013;7(4):390-395.

Islambulchilar M, Asvadi I, Sanaat Z, Esfahani A, Sattari M. Effect of taurine on febrile episodes in acute lymphoblastic leukemia. Adv Pharm Bull. Mar 2015;5(1):103-108.

Islambulchilar M, Asvadi I, Sanaat Z, Esfahani A, Sattari M. Taurine attenuates chemotherapy-induced nausea and vomiting in acute lymphoblastic leukemia. Amino acids. Oct 17 2014.

Israel L, Hajji O, Grefft-Alami A, Desmoulins D, Succari M, Cals MJ, . . . Morere JF. [Vitamin A augmentation of the effects of chemotherapy in metastatic breast cancers after menopause. Randomized trial in 100 patients]. *Annales de medecine interne.* 1985;136(7):551-554.

Ito K, Nakazato H, Koike A, et al.; Study Group of Immunochemotherapy with PSK for Colon Cancer. Long-term effect of 5-fluorouracil enhanced by intermittent administration of polysaccharide K after curative resection of colon cancer. A randomized controlled trial for 7-year follow-up. Int J Colorectal Dis. 2004;19(2):157-64.

Jacot W, Pouderoux S, Thezenas S, Chapelle A, Bleuse JP, Romieu G, Lamy PJ. Increased prevalence of vitamin D insufficiency in patients with breast cancer after neoadjuvant chemotherapy. Breast Cancer Res Treat. 2012 Jul;134(2):709-17.

Jadhav U, Ezhilarasan R, Vaughn SF, Berhow MA, Mohanam S. Iberin induces cell cycle arrest and apoptosis in human neuroblastoma cells. International journal of molecular medicine. Mar 2007;19(3):353-361.

Jafari A, Dashti-Khavidaki S, Khalili H, Lessan-Pezeshki M. Potential nephroprotective effects of l-carnitine against drug-induced nephropathy: a review of literature. Expert opinion on drug safety. Jul 2013;12(4):523-543.

Jahangard-Rafsanjani Z, Gholami K, Hadjibabaie M, Shamshiri AR, Alimoghadam K, Sarayani A, Mojtahedzadeh M, Ostadali-Dehaghi M, Ghavamzadeh A. The efficacy of selenium in prevention of oral mucositis in patients undergoing hematopoietic SCT: a randomized clinical trial. Bone Marrow Transplant. 2013 Jun;48(6):832-6.

Jakab F, Shoenfeld Y, Balogh A, Nichelatti M, Hoffmann A, Kahan Z, . . . Hidvegi M. A medical nutriment has supportive value in the treatment of colorectal cancer. British journal of cancer. Aug 4 2003;89(3):465-469.

Janelsins MC, Tejani MA, Kamen C, Peoples AR, Mustian KM, Morrow GR. Current pharmacotherapy for chemotherapy-induced nausea and vomiting in cancer patients. Expert Opin Pharmacother. 2013 Apr;14(6):757-66.

Jansman FG, Sleijfer DT, de Graaf JC, Coenen JL, Brouwers JR. Management of chemotherapy-induced adverse effects in the treatment of colorectal cancer. Drug safety: an international journal of medical toxicology and drug experience. 2001;24(5):353-367.

Janus N, Thariat J, Boulanger H, Deray G, Launay-Vacher V. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO. Jul 2010;21(7):1395-1403.

Jatoi A, Windschitl HE, Loprinzi CL, Sloan JA, Dakhil SR, Mailliard JA, . . . Christensen B. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Jan 15 2002;20(2):567-573.

Jia L, Zhao Y, Liang XJ. Current evaluation of the millennium phytomedicine- ginseng (II): Collected chemical entities, modern pharmacology, and clinical applications emanated from traditional Chinese medicine. Current medicinal chemistry. 2009;16(22):2924-2942.

Jiralerspong S, Palla SL, Giordano SH, Meric-Bernstam F, Liedtke C, Barnett CM, Hsu L, Hung MC, Hortobagyi GN, Gonzalez-Angulo AM. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol. 2009 Jul 10;27(20):3297-302.

Jones RL. Utility of dexrazoxane for the reduction of anthracycline-induced cardiotoxicity. Expert review of cardiovascular therapy. Nov 2008;6(10):1311-1317.

Joo WD, Visintin I, Mor G. Targeted cancer therapy--are the days of systemic chemotherapy numbered? Maturitas. Dec 2013;76(4):308-314.

Jordan K, Behlendorf T, Mueller F, Schmoll HJ. Anthracycline extravasation injuries: management with dexrazoxane. Therapeutics and clinical risk management. Apr 2009;5(2):361-366.

Jordan K, Gralla R, Jahn F, Molassiotis A. International antiemetic guidelines on chemotherapy induced nausea and vomiting (CINV): content and implementation in daily routine practice. European journal of pharmacology. Jan 5 2014;722:197-202.

Junjing Z, Yan Z, Baolu Z. Scavenging effects of dexrazoxane on free radicals. Journal of clinical biochemistry and nutrition. Nov 2010;47(3):238-245.

Kadowaki S, Yamaguchi K. [Chemotherapy-induced stomatitis and diarrhea]. Gan To Kagaku Ryoho. 2011 Nov;38(11):1761-6.

Kalam K, Marwick TH. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. Eur J Cancer. 2013 Sep;49(13):2900-9.

Kalia M. Personalized oncology: Recent advances and future challenges. Metabolism. 2013;62(Suppl 1):S11-4.

Kamil N, Kamil S, Ahmed SP, Ashraf R, Khurram M, Ali MO. Toxic effects of multiple anticancer drugs on skin. Pakistan journal of pharmaceutical sciences. Jan 2010;23(1):7-14.

Karimi G, Ramezani M, Tahoonian Z. Cisplatin Nephrotoxicity and Protection by Milk Thistle Extract in Rats. Evid Based Complement Alternat Med. 2005;2(3):383-386.

Katoch O, Kumar A, Adhikari JS, Dwarakanath BS, Agrawala PK. Sulforaphane mitigates genotoxicity induced by radiation and anticancer drugs in human lymphocytes. Mutation research. Dec 12 2013;758(1-2):29-34.

Kelleni MT, Amin EF, Abdelrahman AM. Effect of Metformin and Sitagliptin on Doxorubicin-Induced Cardiotoxicity in Rats: Impact of Oxidative Stress, Inflammation, and Apoptosis. Journal of toxicology. 2015;2015:424813.

Kemp G, Rose P, Lurain J, Berman M, Manetta A, Roullet B, Homesley H, Belpomme D, Glick J. Amifostine pretreatment for protection against cyclophosphamide-induced and cisplatin-induced toxicities: results of a randomized control trial in patients with advanced ovarian cancer. J Clin Oncol. 1996 Jul;14(7):2101-12.

Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy. Nature reviews. Cancer. Jun 2004;4(6):423-436.

Kesler S, Janelsins M, Koovakkattu D, Palesh O, Mustian K, Morrow G, Dhabhar FS. Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors. Brain, behavior, and immunity. Mar 2013;30 Suppl:S109-116.

Keyomarsi K, Pardee AB. Selective protection of normal proliferating cells against the toxic effects of chemotherapeutic agents. Progress in cell cycle research. 2003;5:527-532.

Khan G, Haque SE, Anwer T, Ahsan MN, Safhi MM, Alam MF. Cardioprotective effect of green tea extract on doxorubicin-induced cardiotoxicity in rats. Acta poloniae pharmaceutica. Sep-Oct 2014;71(5):861-868.

Kidd PM. The use of mushroom glucans and proteoglycans in cancer treatment. Alternative medicine review : a journal of clinical therapeutic. Feb 2000;5(1):4-27.

Kim DG, Jung KH, Lee DG, Yoon JH, Choi KS, Kwon SW, Shen HM, Morgan MJ, Hong SS, Kim YS. 20(S)-Ginsenoside Rg3 is a novel inhibitor of autophagy and sensitizes hepatocellular carcinoma to doxorubicin. Oncotarget. 2014;5(12):4438-51.

Kim KC, Yook JH, Eisenbraun J, Kim BS, Huber R. Quality of life, immunomodulation and safety of adjuvant mistletoe treatment in patients with gastric carcinoma – a randomized, controlled pilot study. BMC Complement Altern Med. 2012;12:172.

Kim TH, Shin YJ, Won AJ, Lee BM, Choi WS, Jung JH, Chung HY, Kim HS. Resveratrol enhances chemosensitivity of doxorubicin in multidrug-resistant human breast cancer cells via increased cellular influx of doxorubicin. Biochim Biophys Acta. 2014;1840(1):615-25.

Kirakosyan A, Seymour E, Kaufman PB, Warber S, Bolling S, Chang SC. Antioxidant capacity of polyphenolic extracts from leaves of Crataegus laevigata and Crataegus monogyna (Hawthorn) subjected to drought and cold stress. Journal of agricultural and food chemistry. Jul 02 2003;51(14):3973-3976.

Kissei Pharmaceuticals. Press Release. Announcment of the launch of "SAVENE® Injectable 500 mg" for the Treatment of Anthracycline Extravasation in Japan." Available at: http://www.evaluategroup.com/Universal/View.aspx?type=Story&id=501114. 4/17/2014. Accessed 10/27/2014.

Kitazono S, Takiguchi Y, Ashinuma H, Saito-Kitazono M, Kitamura A, Chiba T, Sakaida E, Sekine I, Tada Y, Kurosu K, Sakao S, Tanabe N, Iwama A, Yokosuka O, Tatsumi K. Effect of metformin on residual cells after chemotherapy in a human lung adenocarcinoma cell line. Int J Oncol. 2013;43(6):1846-54.

Klein ME, Dabbs DJ, Shuai Y, Brufsky AM, Jankowitz R, Puhalla SL, Bhargava R. Prediction of the Oncotype DX recurrence score: use of pathology-generated equations derived by linear regression analysis. Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc. May 2013;26(5):658-664.

Kolak A, Staroslawska E, Kubiatowski T, Kieszko D, Cisek P, Patyra KI, . . . Burdan F. [Chemotherapy induced peripheral neuropathy]. Polski merkuriusz lekarski: organ Polskiego Towarzystwa Lekarskiego. Nov 2013;35(209):292-296.

Komaki R, Lee JS, Kaplan B, Allen P, Kelly JF, Liao Z, Stevens CW, Fossella FV, Zinner R, Papadimitrakopoulou V, Khuri F, Glisson B, Pisters K, Kurie J, Herbst R, Milas L, Ro J, Thames HD, Hong WK, Cox JD. Randomized phase III study of chemoradiation with or without amifostine for patients with favorable performance status inoperable stage II-III non-small cell lung cancer: preliminary results. Semin Radiat Oncol. 2002 Jan;12(1 Suppl 1):46-9.

Komen MM, Smorenburg CH, van den Hurk CJ, Nortier JW. [Scalp cooling for chemotherapy-induced alopecia]. Ned Tijdschr Geneeskd. 2011;155(45):A3768.

Kondo T, Sakamoto J, Nakazato H. Alternating immunochemotherapy of advanced gastric carcinoma: a randomized comparison of carbazilquinone and PSK to carbazilquinone in patients with curative gastric resection. Biotherapy. 1991;3(4):287-95.

Kosuge T, Kiuchi T, Mukai K, Kakizoe T. A multicenter randomized controlled trial to evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. Japanese journal of clinical oncology. Mar 2006;36(3):159-165.

Kraft M, Kraft K, Gartner S, Mayerle J, Simon P, Weber E, . . . Lerch MM. L-Carnitine-supplementation in advanced pancreatic cancer (CARPAN)--a randomized multicentre trial. Nutrition journal. 2012;11:52.

Krop IE, Kim SB, González-Martín A, LoRusso PM, Ferrero JM, Smitt M, Yu R, Leung AC, Wildiers H; TH3RESA study collaborators. Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014 Jun;15(7):689-99.

Krzemieniecki K, Sevelda P, Erdkamp F, Smakal M, Schwenkglenks M, Puertas J, . . . Maenpaa J. Neutropenia management and granulocyte colony-stimulating factor use in patients with solid tumours receiving myelotoxic chemotherapy--findings from clinical practice. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. Mar 2014;22(3):667-677.

Kuhn KS, Muscaritoli M, Wischmeyer P, Stehle P. Glutamine as indispensable nutrient in oncology: experimental and clinical evidence. European journal of nutrition. Jun 2010;49(4):197-210.

Lacey JM, Wilmore DW. Is glutamine a conditionally essential amino acid? Nutrition reviews. Aug 1990;48(8):297-309.

Lam MP, Yeung CK, Cheung BM. Pharmacogenetics of allopurinol--making an old drug safer. J Clin Pharmacol. 2013 Jul;53(7):675-9.

Lang M, Henson R, Braconi C, Patel T. Epigallocatechin-gallate modulates chemotherapy-induced apoptosis in human cholangiocarcinoma cells. Liver Int. 2009 May;29(5):670-7.

Laviano A, Rianda S, Molfino A, Rossi Fanelli F. Omega-3 fatty acids in cancer. Current opinion in clinical nutrition and metabolic care. Mar 2013;16(2):156-161.

Lawenda BD, Kelly KM, Ladas EJ, Sagar SM, Vickers A, Blumberg JB. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? Journal of the National Cancer Institute. Jun 4 2008;100(11):773-783.

Lawrence YR, Paulus R, Langer C, Werner-Wasik M, Buyyounouski MK, Komaki R, Machtay M, Smith C, Axelrod RS, Wasserman T, Bradley JD, Movsas B. The addition of amifostine to carboplatin and paclitaxel based chemoradiation in locally advanced non-small cell lung cancer: long-term follow-up of Radiation Therapy Oncology Group (RTOG) randomized trial 9801. Lung Cancer. 2013 Jun;80(3):298-305.

Lederle FA. Epidemiology of constipation in elderly patients. Drug utilisation and cost-containment strategies. Drugs Aging. 1995 Jun;6(6):465-9.

Lee C, Longo VD. Fasting vs dietary restriction in cellular protection and cancer treatment: from model organisms to patients. Oncogene. 2011;30(30):3305-3316.

Lee C, Raffaghello L, Brandhorst S, Safdie FM, Bianchi G, Martin-Montalvo A, . . . Longo VD. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. Sci Transl Med. 2012;4(124):124ra127.

Lee C, Safdie FM, Raffaghello L, Wei M, Madia F, Parrella E, . . . Longo VD. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. Cancer research. 2010;70(4):1564-1572.

Lee DJ, Kim B, Lee JH, Park SJ, Hong SP, Cheon JH, Kim TI, Kim WH. [The effect of metformin on responses to chemotherapy and survival in stage IV colorectal cancer with diabetes]. Korean J Gastroenterol. 2012;60(6):355-61.

Lee J, Oh H. Ginger as an antiemetic modality for chemotherapy-induced nausea and vomiting: a systematic review and meta-analysis. Oncol Nurs Forum. 2013;40(2):163-70.

Lenihan DJ, Cardinale DM. Late cardiac effects of cancer treatment. J Clin Oncol. 2012 Oct 20;30(30):3657-64.

Levenga TH, Timmer-Bonte JN. Review of the value of colony stimulating factors for prophylaxis of febrile neutropenic episodes in adult patients treated for haematological malignancies. British journal of haematology. Jul 2007;138(2):146-152.

Li J, Liu H, Ramachandran S, Waypa GB, Yin JJ, Li CQ, . . . Shao ZH. Grape seed proanthocyanidins ameliorate Doxorubicin-induced cardiotoxicity. The American journal of Chinese medicine. 2010;38(3):569-584.

Li RJ, Qiu SD, Chen HX, Wang LR. [Immunomodulatory effects of Astragalus polysaccharide in diabetic mice]. Zhong xi yi jie he xue bao = Journal of Chinese integrative medicine. Feb 2008;6(2):166-170.

Li W, Nie S, Xie M, Chen Y, Li C, Zhang H. A major green tea component, (-)-epigallocatechin-3-gallate, ameliorates doxorubicin-mediated cardiotoxicity in cardiomyocytes of neonatal rats. Journal of agricultural and food chemistry. Aug 25 2010;58(16):8977-8982.

Li Y, Ahmed F, Ali S, Philip PA, Kucuk O, Sarkar FH. Inactivation of nuclear factor kappaB by soy isoflavone genistein contributes to increased apoptosis induced by chemotherapeutic agents in human cancer cells. Cancer Res. 2005 Aug 1;65(15):6934-42.

Li Y, Ellis KL, Ali S, El-Rayes BF, Nedeljkovic-Kurepa A, Kucuk O, Philip PA, Sarkar FH. Apoptosis-inducing effect of chemotherapeutic agents is potentiated by soy isoflavone genistein, a natural inhibitor of NF-kappaB in BxPC-3 pancreatic cancer cell line. Pancreas. 2004 May;28(4):e90-5.

Li Y, Zhang T, Korkaya H, Liu S, Lee HF, Newman B, . . . Sun D. Sulforaphane, a dietary component of broccoli/broccoli sprouts, inhibits breast cancer stem cells. Clinical cancer research: an official journal of the American Association for Cancer Research. May 1 2010;16(9):2580-2590.

Lien K, Georgsdottir S, Sivanathan L, Chan K, Emmenegger U. Low-dose metronomic chemotherapy: a systematic literature analysis. European journal of cancer (Oxford, England: 1990). 2013;49(16):3387-3395.

Liggins J, Bluck LJ, Runswick S, Atkinson C, Coward WA, Bingham SA. Daidzein and genistein content of fruits and nuts. The Journal of nutritional biochemistry. Jun 2000;11(6):326-331.

Lin CM, Abcouwer SF, Souba WW. Effect of dietary glutamate on chemotherapy-induced immunosuppression. Nutrition (Burbank, Los Angeles County, Calif.). Sep 1999;15(9):687-696.

Lin PC, Lee MY, Wang WS, Yen CC, Chao TC, Hsiao LT, Yang MH, Chen PM, Lin KP, Chiou TJ. N-acetylcysteine has neuroprotective effects against oxaliplatin-based adjuvant chemotherapy in colon cancer patients: preliminary data. Support Care Cancer. 2006 May;14(5):484-7.

Lissoni P, Barni S, Fossati V, et al. A randomized study of neuroimmunotherapy with low-dose subcutaneous interleukin-2 plus melatonin compared to supportive care alone in patients with untreatable metastatic solid tumour. Support Care Cancer. 1995;3(3):194-7.

Lissoni P, Barni S, Mandalà M, et al. Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status. Eur J Cancer. 1999;35(12):1688-92.

Lissoni P, Barni S, Tancini G, et al. A randomised study with subcutaneous low-dose interleukin 2 alone vs interleukin 2 plus the pineal neurohormone melatonin in advanced solid neoplasms other than renal cancer and melanoma. Br J Cancer. 1994;69(1):196-9.

Lissoni P, Chilelli M, Villa S, Cerizza L, Tancini G. Five years survival in metastatic non-small cell lung cancer patients treated with chemotherapy alone or chemotherapy and melatonin: a randomized trial. J Pineal Res. 2003;35(1):12-5.

Lissoni P, Galli MA, Tancini G, Barni S. Prevention by L-carnitine of interleukin-2 related cardiac toxicity during cancer immunotherapy. Tumori. Jun 30 1993;79(3):202-204.

Lissoni P, Meregalli S, Fossati V, et al. A randomized study of immunotherapy with low-dose subcutaneous interleukin-2 plus melatonin vs chemotherapy with cisplatin and etoposide as first-line therapy for advanced non-small cell lung cancer. Tumori. 1994;80(6):464-7.

Lissoni P, Palorossi F, Ardizzoia A, et al. A randomized study of chemotherapy with cisplatin plus etoposide versus chemoendocrine therapy with cisplatin, etoposide and the pineal hormone melatonin as a first-line treatment of advanced non-small cell lung cancer patients in a poor clinical state. J Pineal Res. 1997;23(1):15-19.

Lissoni P. Biochemotherapy with standard chemotherapies plus the pineal hormone melatonin in the treatment of advanced solid neoplasms. Pathol Biol (Paris). 2007;55(3-4):201-4.

Liu L, Shi R, Shi Q, Cheng Y, Huo Y. Protective effect of saponins from Panax notoginseng against doxorubicin-induced cardiotoxicity in mice. Planta medica. Feb 2008;74(3):203-209.

Liu Y, Li BH, Sun XM, Lin AH, Wang DB. Effect of selenium on the interaction between daunorubicin and cardiac myosin. Biological trace element research. Jun 2012;147(1-3):240-245.

Lyman GH, Dale DC, Culakova E, Poniewierski MS, Wolff DA, Kuderer NM, . . . Crawford J. The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO. Oct 2013;24(10):2475-2484.

Lyman GH. Impact of chemotherapy dose intensity on cancer patient outcomes. J Natl Compr Canc Netw. 2009 Jan;7(1):99-108.

Lyman GH. Weight-based chemotherapy dosing in obese patients with cancer: back to the future. J Oncol Pract. 2012 Jul;8(4):e62-4.

Ma Y, Chapman J, Levine M, Polireddy K, Drisko J, Chen Q. High-dose parenteral ascorbate enhanced chemosensitivity of ovarian cancer and reduced toxicity of chemotherapy. Sci Transl Med. 2014;6(222):222ra18.

Ma Y, Trump DL, Johnson CS. Vitamin D in combination cancer treatment. Journal of Cancer. 2010;1:101-107.

Macedo LT, Lima JP, dos Santos LV, Sasse AD. Prevention strategies for chemotherapy-induced hand-foot syndrome: a systematic review and meta-analysis of prospective randomised trials. Support Care Cancer. 2014 Jun;22(6):1585-93.

Machon C, Thezenas S, Dupuy AM, Assenat E, Michel F, Mas E, . . . Cristol JP. Immunonutrition before and during radiochemotherapy: improvement of inflammatory parameters in head and neck cancer patients. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. Dec 2012;20(12):3129-3135.

Maciejczyk A, Surowiak P. Quercetin inhibits proliferation and increases sensitivity of ovarian cancer cells to cisplatin and paclitaxel. Ginekologia polska. Jul 2013;84(7):590-595.

Maehara Y, Tsujitani S, Saeki H, Oki E, Yoshinaga K, Emi Y, . . . Baba H. Biological mechanism and clinical effect of protein-bound polysaccharide K

(KRESTIN((R))): review of development and future perspectives. Surgery today. Jan 2012;42(1):8-28.

Maestri A, De Pasquale Ceratti A, Cundari S, Zanna C, Cortesi E, Crino L. A pilot study on the effect of acetyl-L-carnitine in paclitaxel- and cisplatin-induced peripheral neuropathy. Tumori. Mar-Apr 2005;91(2):135-138.

Mahoney SE, Davis JM, Murphy EA, McClellan JL, Pena MM. Dietary Quercetin Reduces Chemotherapy-Induced Fatigue in Mice. Integr Cancer Ther. 2014 Sep;13(5):417-24.

Maiti R. Metronomic chemotherapy. Journal of pharmacology & pharmacotherapeutics. 2014;5(3):186-192.

Majithia N, Loprinzi CL, Smith TJ. New Practical Approaches to Chemotherapy-Induced Neuropathic Pain: Prevention, Assessment, and Treatment. Oncology (Williston Park, N.Y.). Nov 15 2016;30(11).

Manikandan R, Kumar S, Dorairajan LN. Hemorrhagic cystitis: A challenge to the urologist. Indian journal of urology: IJU: journal of the Urological Society of India. Apr 2010;26(2):159-166.

Mansky PJ, Wallerstedt DB, Sannes TS, Stagl J, Johnson LL, Blackman MR, . . . Monahan BP. NCCAM/NCI Phase 1 Study of Mistletoe Extract and Gemcitabine in Patients with Advanced Solid Tumors. Evidence-based complementary and alternative medicine: eCAM. 2013;2013:964592.

Marin JJ, Sanchez de Medina F, Castano B, Bujanda L, Romero MR, Martinez-Augustin O, . . . Briz O. Chemoprevention, chemotherapy, and chemoresistance in colorectal cancer. Drug metabolism reviews. May 2012;44(2):148-172.

Maroun JA, Anthony LB, Wong R. Prevention and management of chemotherapy-induced diarrhea in patients with colorectal cancer: a consensus statement by the Canadian Working Group on Chemotherapy-Induced Diarhea. Curr Oncol. 2007;14(1):13-20.

Martinez-Rivera M, Siddik ZH. Resistance and gain-of-resistance phenotypes in cancers harboring wild-type p53. Biochem Pharmacol. 2012;83(8):1049-62.

Martins SP, Ferreira CL, Del Giglio A. Placebo-Controlled, Double-Blind, Randomized Study of a Dry Guarana Extract in Patients with Head and Neck Tumors Undergoing Chemoradiotherapy: Effects on Fatigue and Quality of Life. Journal of dietary supplements. Jun 20 2016:1-10.

Marx W, Kiss N, McCarthy AL, McKavanagh D, Isenring L. Chemotherapy-Induced Nausea and Vomiting: A Narrative Review to Inform Dietetics Practice. Journal of the Academy of Nutrition and Dietetics. May 2016;116(5):819-827.

Marzatico F, Porta C, Moroni M, Bertorelli L, Borasio E, Finotti N, Pansarasa O, Castagna L. In vitro antioxidant properties of amifostine (WR-2721, Ethyol). Cancer Chemother Pharmacol. 2000;45(2):172-6.

Mashiach E, Sela S, Weinstein T, Cohen HI, Shasha SM, Kristal B. Mesna: a novel renoprotective antioxidant in ischaemic acute renal failure. Nephrol Dial Transplant. 2001 Mar;16(3):542-51.

Matera MG, Calzetta L, Cazzola M. Oxidation pathway and exacerbations in COPD: the role of NAC. Expert review of respiratory medicine. 2016;10(1):89-97.

Mattes-Kulig DA, Henkin RI. Energy and nutrient consumption of patients with dysgeusia. Journal of the American Dietetic Association. Jul 1985;85(7):822-826.

Mavroudi M, Zarogoulidis P, Porpodis K, Kioumis I, Lampaki S, Yarmus L, . . . Malecki M. Stem cells' guided gene therapy of cancer: New frontier in personalized and targeted therapy. Journal of cancer research & therapy. 2014;2(1):22-33.

May MB, Glode AE. Dronabinol for chemotherapy-induced nausea and vomiting unresponsive to antiemetics. Cancer management and research. 2016;8:49-55.

Mayo Clinic. Diseases and conditions: Cancer: How to manage hand-foot syndrome. Available at http://www.mayoclinic.org/diseases-conditions/cancer/expert-blog/hand-foot-syndrome/bgp-20056309. Last updated 04/20/2013. Accessed 12/17/2016. http://www.mayoclinic.org/diseases-conditions/cancer/expert-blog/hand-foot-syndrome/bgp-20056309.

Mayo Clinic. Tests and Procedures. Chemotherapy. Definition. Available at: http://www.mayoclinic.org/tests-procedures/chemotherapy/basics/definition/prc-20023578. Copyright 2015. Accessed 1/7/2015.

McCulloch M, See C, Shu XJ, Broffman M, Kramer A, Fan WY, Gao J, Lieb W, Shieh K, Colford JM Jr. Astragalus-based Chinese herbs and platinum-based chemotherapy for advanced non-small-cell lung cancer: meta-analysis of randomized trials. J Clin Oncol. 2006 Jan 20;24(3):419-430.

McDermott U, Settleman J. Personalized cancer therapy with selective kinase inhibitors: an emerging paradigm in medical oncology. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Nov 20 2009;27(33):5650-5659.

Mehta MP. Protection of normal tissues from the cytotoxic effects of radiation therapy: focus on amifostine. Semin Radiat Oncol. 1998 Oct;8(4 Suppl 1):14-6.

Melli G, Taiana M, Camozzi F, Triolo D, Podini P, Quattrini A, Taroni F, Lauria G. Alpha-lipoic acid prevents mitochondrial damage and neurotoxicity in experimental chemotherapy neuropathy. Exp Neurol. 2008 Dec;214(2):276-84.

Meric-Bernstam F, Mills GB. Overcoming implementation challenges of personalized cancer therapy. Nature Reviews Clinical Oncology. 2012;9(9):542-548.

Merzoug S, Toumi ML, Tahraoui A. Quercetin mitigates Adriamycin-induced anxiety- and depression-like behaviors, immune dysfunction, and brain oxidative stress in rats. Naunyn Schmiedebergs Arch Pharmacol. 2014 Oct;387(10):921-33.

Meyer F, Bairati I, Fortin A, Gelinas M, Nabid A, Brochet F, Tetu B. Interaction between antioxidant vitamin supplementation and cigarette smoking during radiation therapy in relation to long-term effects on recurrence and mortality: a randomized trial among head and neck cancer patients. *International journal of cancer.* Apr 01 2008;122(7):1679-1683.

Meyskens FL, Jr., Kopecky KJ, Appelbaum FR, Balcerzak SP, Samlowski W, Hynes H. Effects of vitamin A on survival in patients with chronic myelogenous leukemia: a SWOG randomized trial. *Leukemia research.* Sep 1995;19(9):605-612.

Michalak K, Wesolowska O. Polyphenols counteract tumor cell chemoresistance conferred by multidrug resistance proteins. Anti-cancer agents in

medicinal chemistry. 2012;12(8):880-890.

Michalski CW, Erkan M, Sauliunaite D, Giese T, Stratmann R, Sartori C, . . . Kleeff J. Ex vivo chemosensitivity testing and gene expression profiling predict response towards adjuvant gemcitabine treatment in pancreatic cancer. British journal of cancer. Sep 2 2008;99(5):760-767.

Mihlon F 4th, Ray CE Jr, Messersmith W. Chemotherapy agents: a primer for the interventional radiologist. Semin Intervent Radiol. 2010 Dec;27(4):384-90.

Millenium Pharmaceuticals, Inc. Velcade (bortezomib) [package insert]. Cambridge, MA; 2014. http://www.velcade-hcp.com/contact-us.aspx

Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of Cisplatin Nephrotoxicity. Toxins. 2010;2(11):2490-2518.

Minobe S, Todo Y, Suzuki Y, Aoyagi Y, Umazume T, Okamoto K, Kato H. Mesna, doxorubicin, ifosfamide and dacarbazine chemotherapy for uterine leiomyosarcoma: a report of 2 cases. J Obstet Gynaecol Res. 2011 Jun;37(6):645-9.

Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. The Cochrane database of systematic reviews. 2012;8:Cd008465.

Mitchell SA, Hoffman AJ, Clark JC, DeGennaro RM, Poirier P, Robinson CB, Weisbrod BL. Putting evidence into practice: an update of evidence-based interventions for cancer-related fatigue during and following treatment. Clinical journal of oncology nursing. Dec 2014;18 Suppl:38-58.

Mitchell TM. Correspondence re: Somasundaram et al., Dietary Curcumin Inhibits Chemotherapy-induced Apoptosis in Models of Human Breast Cancer. Cancer Res., 62: 3868–3875, 2002. Cancer research. 2003;63(16):5165-5167.

Mitchison TJ. The proliferation rate paradox in antimitotic chemotherapy. Molecular Biology of the Cell. 2012;23(1):1-6.

Mitomi T, Tsuchiya S, Iijima N, et al. Randomized, controlled study on adjuvant immunochemotherapy with PSK in curatively resected colorectal cancer. The Cooperative Study Group of SurgicalAdjuvant Immunochemotherapy for Cancer of Colon and Rectum (Kanagawa). Dis Colon Rectum. 1992;35(2):123-30.

Mitomi T, Tsuchiya S, Iijima N, et al. [Randomized controlled study on adjuvant immunochemotherapy with PSK in curatively resected colorectal cancer. The Cooperative Study Group of Surgical Adjuvant Immunochemotherapy for Cancer of Colon and Rectum]. Gan To Kagaku Ryoho. 1989;16(6):2241-9.

Mohammad RM, Al-Katib A, Aboukameel A, Doerge DR, Sarkar F, Kucuk O. Genistein sensitizes diffuse large cell lymphoma to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy. Mol Cancer Ther. 2003 Dec;2(12):1361-8.

Moison RM, Beijersbergen Van Henegouwen GM. Dietary eicosapentaenoic acid prevents systemic immunosuppression in mice induced by UVB radiation. Radiation research. Jul 2001;156(1):36-44.

Molina-Garrido MJ, Mora-Rufete A, Guillen-Ponce C. Oral chemotherapy in elderly women with metastatic breast cancer. Anticancer Agents Med Chem. 2014;14(5):665-72.

Molinaro M, Ameri P, Marone G, Petretta M, Abete P, Di Lisa F, . . . Tocchetti CG. Recent Advances on Pathophysiology, Diagnostic and Therapeutic Insights in Cardiac Dysfunction Induced by Antineoplastic Drugs. BioMed research international. 2015;2015:138148.

Mondul AM, Sampson JN, Moore SC, Weinstein SJ, Evans AM, Karoly ED, . . . Albanes D. Metabolomic profile of response to supplementation with beta-carotene in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *The American journal of clinical nutrition.* Aug 2013;98(2):488-493.

Montazeri AS, Raei M, Ghanbari A, Dadgari A, Montazeri AS, Hamidzadeh A. Effect of herbal therapy to intensity chemotherapy-induced nausea and vomiting in cancer patients. Iranian Red Crescent medical journal. Feb 2013;15(2):101-106.

Morgan G, Ward R, Barton M. The contribution of cytotoxic chemotherapy to 5-year survival in adult malignancies. Clin Oncol (R Coll Radiol). 2004 Dec;16(8):549-60.

Moslehi A, Taghizadeh-Ghehi M, Gholami K, Hadjibabaie M, Jahangard-Rafsanjani Z, Sarayani A, Javadi M, Esfandbod M, Ghavamzadeh A. N-acetyl cysteine for prevention of oral mucositis in hematopoietic SCT: a double-blind, randomized, placebo-controlled trial. Bone Marrow Transplant. 2014 Jun;49(6):818-23.

Moss RW. Should patients undergoing chemotherapy and radiotherapy be prescribed antioxidants? Integrative cancer therapies. Mar 2006;5(1):63-82.

Moukayed M, Grant WB. Molecular link between vitamin D and cancer prevention. Nutrients. Oct 2013;5(10):3993-4021.

Mouser CL, Antoniou ES, Tadros J, Vassiliou EK. A model of hematopoietic stem cell proliferation under the influence of a chemotherapeutic agent in combination with a hematopoietic inducing agent. Theoretical biology & medical modelling. 2014;11:4.

Moynihan TJ. Mayo Clinic. Tests and Procedures. Chemotherapy. Expert Answers page. Available at: http://www.mayoclinic.org/tests-procedures /chemotherapy/expert-answers/magic-mouthwash/faq-20058071. 12/10/2014. Accessed 1/16/2015.

Mross K, Steinbild S. Metronomic anti-cancer therapy – an ongoing treatment option for advanced cancer patients. journal of Cancer Therapeutics and Research. 2012 2012;1(1).

Mughal T. ePocrates online. Tumor Lysis Syndrome. Last updated 5/8/2014. Accessed 1/13/2015. Available at: https://online.epocrates.com/noFrame /showPage?method=diseases&MonographId=936&ActiveSectionId=11.

Mughal TI, Ejaz AA, Foringer JR, Coiffier B. An integrated clinical approach for the identification, prevention, and treatment of tumor lysis syndrome. Cancer Treat Rev. 2010 Apr;36(2):164-76.

Muraki K, Koyama R, Honma Y, Yagishita S, Shukuya T, Ohashi R, . . . Takahashi K. Hydration with magnesium and mannitol without furosemide prevents the nephrotoxicity induced by cisplatin and pemetrexed in patients with advanced non-small cell lung cancer. Journal of thoracic disease. Dec 2012;4(6):562-568.

Murphy RA, Mourtzakis M, Chu QS, Baracos VE, Reiman T, Mazurak VC. Supplementation with fish oil increases first-line chemotherapy efficacy in

patients with advanced nonsmall cell lung cancer. Cancer. 2011;117(16):3774-3780.

Murphy RA, Mourtzakis M, Mazurak VC. n-3 polyunsaturated fatty acids: the potential role for supplementation in cancer. Current opinion in clinical nutrition and metabolic care. May 2012;15(3):246-251.

Muthuramalingam S, Gale J, Bradbury J. Dexrazoxane efficacy for anthracycline extravasation: use in UK clinical practice. International journal of clinical practice. Mar 2013;67(3):244-249.

Naglik JR, Challacombe SJ, Hube B. Candida albicans secreted aspartyl proteinases in virulence and pathogenesis. Microbiology and molecular biology reviews: MMBR. Sep 2003;67(3):400-428, table of contents.

Nakamura R, Saikawa Y, Kubota T, Kumagai A, Kiyota T, Ohashi M, Yoshida M, Otani Y, Kumai K, Kitajima M. Role of the MTT chemosensitivity test in the prognosis of gastric cancer patients after postoperative adjuvant chemotherapy. Anticancer Res. 2006 Mar-Apr;26(2B):1433-7.

Nakayama A, Alladin KP, Igbokwe O, White JD. Systematic review: generating evidence-based guidelines on the concurrent use of dietary antioxidants and chemotherapy or radiotherapy. Cancer Invest. 2011 Dec;29(10):655-67.

Nakazato H, Koike A, Ichihashi H, et al. [An effect of adjuvant immunochemotherapy using krestin and 5-FU on gastric cancer patients with radical surgery (first report)--a randomized controlled trial by the cooperative study group. Study Group of Immuno-chemotherapy with PSK for Gastric Cancer]. Gan To Kagaku Ryoho. 1989;16(8 Pt 1):2563-76.

Nakazato H, Koike A, Saji S, Ogawa N, Sakamoto J. Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. Study Group of Immunochemotherapy with PSK for Gastric Cancer. Lancet. 1994;343(8906):1122-6.

Naveed S, Aslam M, Ahmad A. Starvation based differential chemotherapy: a novel approach for cancer treatment. Oman medical journal. Nov 2014;29(6):391-398.

Naziroglu M, Karaoglu A, Aksoy AO. Selenium and high dose vitamin E administration protects cisplatin-induced oxidative damage to renal, liver and lens tissues in rats. Toxicology. Feb 15 2004;195(2-3):221-230.

NCI. National Cancer Institute at National Institute of Health. Chemotherapy and You. Questions and Answers About Chemotherapy. How is chemotherapy given? Available at: http://www.cancer.gov/cancertopics/coping/chemotherapy-and-you/page2. 10/17/2014a. Accessed 08/22/2014.

NCI. National Cancer Institute at National Institute of Health. Hyperthermia in Cancer Treatment. Available at: http://www.cancer.gov/cancertopics /factsheet/Therapy/hyperthermia. Last updated 8/31/2011. Accessed 10/12/2014.

NCI. National Cancer Institute. Cancer Topics page. Nutrition Therapy. Available at: http://www.cancer.gov/cancertopics/pdq/supportivecare/nutrition /HealthProfessional/page4. Last updated 6/25/2014b. Accessed 9/3/2014.

NCI. National Cancer Institute. Cancer Topics page. Targeted Cancer Therapies. Available at: http://www.cancer.gov/cancertopics/factsheet/Therapy /targeted. 4/25/2014d. Accessed 1/21/2015.

NCI. National Cancer Institute. Chemotherapy and You: Support for People With Cancer. Side Effects and Ways To Manage Them: Constipation. Available at: http://www.cancer.gov/cancertopics/coping/chemotherapy-and-you/page7#SE4. 6/29/2007. Accessed 8/9/2014.

NCI. National Cancer Institute. Managing Chemotheapy Side Effects: Diarrhea. Available at: http://www.cancer.gov/cancertopics/coping/chemo-side-effects/diarrhea.pdf. 2/2012. Accessed 10/24/2014.

NCI. National Cancer Institute. National Cancer Institute FactSheet. Targeted Cancer Therapies. Available at: http://www.cancer.gov/cancertopics /factsheet/Therapy/targeted. Last updated 4/25/2014c. Accessed 8/27/2014.

Nelson MH, Diven MA, Huff LW, Paulos CM. Harnessing the Microbiome to Enhance Cancer Immunotherapy. J Immunol Res. 2015;2015:368736.

Neuss MN, Polovich M, McNiff K, Esper P, Gilmore TR, LeFebvre KB, . . . Jacobson JO. 2013 updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards including standards for the safe administration and management of oral chemotherapy. Journal of oncology practice / American Society of Clinical Oncology. 2013;9(2 Suppl):5s-13s.

Neuwelt EA, Pagel MA, Kraemer DF, Peterson DR, Muldoon LL. Bone marrow chemoprotection without compromise of chemotherapy efficacy in a rat brain tumor model. The Journal of pharmacology and experimental therapeutics. May 2004;309(2):594-599.

Nicolini A, Ferrari P, Masoni MC, Fini M, Pagani S, Giampietro O, Carpi A. Malnutrition, anorexia and cachexia in cancer patients: A mini-review on pathogenesis and treatment. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. Oct 2013;67(8):807-817.

Niimoto M, Hattori T, Tamada R, et al. Postoperative adjuvant immunochemotherapy with mitomycin C, futraful and PSK for gastric cancer. An analysis of data on 579 patients followed for five years. Jpn J Surg. 1988;18(6):681-6.

Nisar S, Feinfeld DA. N-acetylcysteine as salvage therapy in cisplatin nephrotoxicity. Renal failure. Jul 2002;24(4):529-533.

Nishijima S, Yanase T, Hata Y, Tamura R, Tsuneki I, Tamura M, Kurabayashi T. [Orally administered polaprezinc significantly improves taste disorders in ovarian cancer patient undergoing chemotherapy]. Gan To Kagaku Ryoho. 2011 Apr;38(4):689-92.

Nishijima S, Yanase T, Tsuneki I, Tamura M, Kurabayashi T. Examination of the taste disorder associated with gynecological cancer chemotherapy. Gynecol Oncol. 2013 Dec;131(3):674-8.

Nishiwaki Y, Furuse K, Fukuoka M, et al. [A randomized controlled study of PSK combined immuno-chemotherapy for adenocarcinoma of the lung. The Advanced Lung Cancer Immuno-chemotherapy Study Group]. Gan To Kagaku Ryoho. 1990;17(1):131-6.

NLM. U.S. National Library of Medicine. Enalapril. Section 7.8: Therapeutic Uses. https://pubchem.ncbi.nlm.nih.gov/compound /5388962#section=Therapeutic-Uses. Last updated 2/18/2017. Accessed 2/21/2017.

Noaman E, Badr El-Din NK, Bibars MA, Abou Mossallam AA, Ghoneum M. Antioxidant potential by arabinoxylan rice bran, MGN-3/biobran, represents a mechanism for its oncostatic effect against murine solid Ehrlich carcinoma. Cancer letters. Sep 18 2008;268(2):348-359.

Oei AL, Vriend LE, Crezee J, Franken NA, Krawczyk PM. Effects of hyperthermia on DNA repair pathways: one treatment to inhibit them all. Radiation oncology (London, England). Aug 07 2015;10:165.

Oh B, Butow P, Mullan B, Clarke S, Beale P, Pavlakis N, . . . Rosenthal D. Impact of medical Qigong on quality of life, fatigue, mood and inflammation in cancer patients: a randomized controlled trial. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. Mar 2010;21(3):608-614.

Ohkawa K, Tsukada Y, Dohzono H, Koike K, Terashima Y. The effects of co-administration of selenium and cis-platin (CDDP) on CDDP-induced toxicity and antitumour activity. British journal of cancer. Jul 1988;58(1):38-41.

Ohno S, Ohno Y, Suzuki N, Soma G, Inoue M. High-dose vitamin C (ascorbic acid) therapy in the treatment of patients with advanced cancer. Anticancer research. Mar 2009;29(3):809-815.

Ohwada S, Ikeya T, Yokomori T, et al. Adjuvant immunochemotherapy with oral Tegafur/Uracil plus PSK in patients with stage II or III colorectal cancer: a randomised controlled study. Br J Cancer. 2004;90(5):1003-10.

Ohwada S, Kawate S, Ikeya T,; Gunma Oncology Study Group (GOSG). Adjuvant therapy with protein-bound polysaccharide K and tegafur uracil in patients with stage II or III colorectal cancer: randomized, controlled trial. Dis Colon Rectum. 2003;46(8):1060-8.

Okonogi N, Ebara T, Ishikawa H, Yoshida D, Ueno M, Maeno T, Suga T, Nakano T. A 7-year disease-free survivor of malignant pleural mesothelioma treated with hyperthermia and chemotherapy: a case report. J Med Case Rep. 2012 Dec 28;6(1):427.

O'Rahilly R, Müller F, Carpenter S, Swenson R. Basic Human Anatomy. Chapter 3: The nerveous system. Available at: http://www.dartmouth.edu /~humananatomy/part_1/chapter_3.html. Copyright 2008. Accessed 1/16/2015.

Owusu RA, Abern MR, Inman BA. Hyperthermia as adjunct to intravesical chemotherapy for bladder cancer. Biomed Res Int. 2013;2013:262313

Ozcan A, Korkmaz A, Oter S, Coskun O. Contribution of flavonoid antioxidants to the preventive effect of mesna in cyclophosphamide-induced cystitis in rats. Arch Toxicol. 2005 Aug;79(8):461-5.

Pace A, Giannarelli D, Galie E, Savarese A, Carpano S, Della Giulia M, . . . Cognetti F. Vitamin E neuroprotection for cisplatin neuropathy: a randomized, placebo-controlled trial. Neurology. Mar 2 2010;74(9):762-766.

Pace A, Savarese A, Picardo M, Maresca V, Pacetti U, Del Monte G, . . . Bove L. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Mar 1 2003;21(5):927-931.

Palatty PL, Haniadka R, Valder B, Arora R, Baliga MS. Ginger in the prevention of nausea and vomiting: a review. Crit Rev Food Sci Nutr. 2013;53(7):659-69

Palozza P, Serini S, Trombino S, Lauriola L, Ranelletti FO, Calviello G. Dual role of beta-carotene in combination with cigarette smoke aqueous extract on the formation of mutagenic lipid peroxidation products in lung membranes: dependence on pO2. *Carcinogenesis.* Dec 2006;27(12):2383-2391.

Panahi Y, Saadat A, Sahebkar A, Hashemian F, Taghikhani M, Abolhasani E. Effect of ginger on acute and delayed chemotherapy-induced nausea and vomiting: a pilot, randomized, open-label clinical trial. Integr Cancer Ther. 2012 Sep;11(3):204-11.

Park HJ. Chemotherapy induced peripheral neuropathic pain. Korean journal of anesthesiology. Jul 2014;67(1):4-7.

Park S. The effects of high concentrations of vitamin C on cancer cells. Nutrients. Sep 2013;5(9):3496-3505.

Pasquier E, Kavallaris M, Andre N. Metronomic chemotherapy: new rationale for new directions. Nature reviews. Clinical oncology. 2010;7(8):455-465.

Pathak AK, Bhutani M, Guleria R, Bal S, Mohan A, Mohanti BK, . . . Kochupillai V. Chemotherapy alone vs. chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer. *Journal of the American College of Nutrition.* Feb 2005;24(1):16-21.

Patil L, Balaraman R. Effect of green tea extract on Doxorubicin induced cardiovascular abnormalities: antioxidant action. Iranian journal of pharmaceutical research: IJPR. Winter 2011;10(1):89-96.

Patlakas G, Bouros D, Tsantekidou-Pozova S, Koukourakis MI. Triplet chemotherapy with docetaxel, gemcitabine and liposomal doxorubicin, supported with subcutaneous amifostine and hemopoietic growth factors, in advanced non-small cell lung cancer. Anticancer Res. 2005 Mar-Apr;25(2B):1427-31.

Perez Fidalgo JA, Garcia Fabregat L, Cervantes A, Margulies A, Vidall C, Roila F. Management of chemotherapy extravasation: ESMO-EONS Clinical Practice Guidelines. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO. Oct 2012;23 Suppl 7:vii167-173.

Perez-Callejo D, Romero A, Provencio M, Torrente M. Liquid biopsy based biomarkers in non-small cell lung cancer for diagnosis and treatment monitoring. Transl Lung Cancer Res. Oct 2016;5(5):455-465.

Perry MC, Goldman L, Schafer AI. Goldman's Cecil Medicine, Twenty-Fourth Edition. Copyright 2012. Saunders, and imprint of Elsevier Inc. Chapter 182: Approach to the Patient with Cancer; 1164-1177.

Peters GJ, van der Wilt CL, van Moorsel CJ, Kroep JR, Bergman AM, Ackland SP. Basis for effective combination cancer chemotherapy with antimetabolites. Pharmacology & therapeutics. 2000;87(2-3):227-253.

Pfeil AM, Allcott K, Pettengell R, von Minckwitz G, Schwenkglenks M, Szabo Z. Efficacy, effectiveness and safety of long-acting granulocyte colony-stimulating factors for prophylaxis of chemotherapy-induced neutropenia in patients with cancer: a systematic review. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. Oct 7 2014.

Piatkowska-Jakubas B, Krawczyk-Kuliś M, Giebel S, et al. Use of L-asparaginase in acute lymphoblastic leukemia: recommendations of the Polish Adult Leukemia Group. Pol Arch Med Wewn. 2008;118(11):664-9.

Piccolo J, Kolesar JM. Prevention and treatment of chemotherapy-induced peripheral neuropathy. Am J Health Syst Pharm. 2014 Jan 1;71(1):19-25.

Piotrowski J, Jedrzejewski T, Kozak W. Immunomodulatory and antitumor properties of polysaccharide peptide (PSP). Postepy higieny i medycyny

doswiadczalnej (Online). 2015;69(0):91-97.

Popovic M, Warr DG, Deangelis C, Tsao M, Chan KK, Poon M, Yip C, Pulenzas N, Lam H, Zhang L, Chow E. Efficacy and safety of palonosetron for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV): a systematic review and meta-analysis of randomized controlled trials. Support Care Cancer. 2014 Jun;22(6):1685-97.

Pritchard JR, Lauffenburger DA, Hemann MT. Understanding Resistance to Combination Chemotherapy. Drug resistance updates : reviews and commentaries in antimicrobial and anticancer chemotherapy. Oct 2012;15(0):249-257.

Qazi A, Pal J, Maitah M, Fulciniti M, Pelluru D, Nanjappa P, . . . Shammas MA. Anticancer activity of a broccoli derivative, sulforaphane, in barrett adenocarcinoma: potential use in chemoprevention and as adjuvant in chemotherapy. Translational oncology. 2010;3(6):389-399.

Qiao J, Fang H. Hand-foot syndrome related to chemotherapy. CMAJ. 2012 Oct 16;184(15):E818.

Raeessi MA, Raeessi N, Panahi Y, Gharaie H, Davoudi SM, Saadat A, . . . Jalalian H. "Coffee plus honey" versus "topical steroid" in the treatment of chemotherapy-induced oral mucositis: a randomised controlled trial. BMC complementary and alternative medicine. 2014;14:293.

Raffa RB. Cancer 'survivor-care': II. Disruption of prefrontal brain activation top-down control of working memory capacity as possible mechanism for chemo-fog/brain (chemotherapy-associated cognitive impairment). J Clin Pharm Ther. 2013 Aug;38(4):265-8.

Raffaghello L, Safdie F, Bianchi G, Dorff T, Fontana L, Longo VD. Fasting and differential chemotherapy protection in patients. Cell Cycle. 2010 Nov 15;9(22):4474-6.

Rajendran P, Li F, Manu KA, Shanmugam MK, Loo SY, Kumar AP, Sethi G. gamma-Tocotrienol is a novel inhibitor of constitutive and inducible STAT3 signalling pathway in human hepatocellular carcinoma: potential role as an antiproliferative, pro-apoptotic and chemosensitizing agent. British journal of pharmacology. 2011;163(2):283-298.

Randall J, Ream E. Hair loss with chemotherapy: at a loss over its management? European journal of cancer care. Jul 2005;14(3):223-231.

Ravid A, Rocker D, Machlenkin A, Rotem C, Hochman A, Kessler-Icekson G, Liberman UA, Koren R. 1,25-Dihydroxyvitamin D3 enhances the susceptibility of breast cancer cells to doxorubicin-induced oxidative damage. Cancer Res. 1999 Feb 15;59(4):862-7.

Ray SD, Patel D, Wong V, Bagchi D. In vivo protection of dna damage associated apoptotic and necrotic cell deaths during acetaminophen-induced nephrotoxicity, amiodarone-induced lung toxicity and doxorubicin-induced cardiotoxicity by a novel IH636 grape seed proanthocyanidin extract. Research communications in molecular pathology and pharmacology. 2000;107(1-2):137-166.

Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. FASEB journal: official publication of the Federation of American Societies for Experimental Biology. Mar 2008;22(3):659-661.

Redman MG, Ward EJ, Phillips RS. The efficacy and safety of probiotics in people with cancer: a systematic review. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO. Oct 2014;25(10):1919-1929.

Remesh A. Tackling the problems of tumour chemotherapy by optimal drug scheduling. J Clin Diagn Res. 2013;7(7):1404-7.

Repetto L. Incidence and clinical impact of chemotherapy induced myelotoxicity in cancer patients: An observational retrospective survey. Critical reviews in oncology/hematology. 2009;72(2):170-179.

Revicki DA, Stull D, Vernon M, Rader M, Tomita D, Viswanathan HN. Assessing the effect of darbepoetin alfa on patient-reported fatigue in chemotherapy-induced anemia in 4 randomized, placebo-controlled clinical trials. Qual Life Res. 2012 Mar;21(2):311-21.

Rice M. Management of Chemotherapy-Induced Nausea and Vomiting. https://www.oncolink.org/healthcare-professionals/o-pro-portal/articles-about-cancer-treatment-and-medications/management-of-chemotherapy-induced-nausea-and-vomiting. Last updated 7/16/2011. Accessed 2/21/2017.

Rice SD, Heinzman JM, Brower SL, Ervin PR, Song N, Shen K, Wang D. Analysis of chemotherapeutic response heterogeneity and drug clustering based on mechanism of action using an in vitro assay. Anticancer research. Jul 2010;30(7):2805-2811.

Ries F, Klastersky J. Nephrotoxicity induced by cancer chemotherapy with special emphasis on cisplatin toxicity. American journal of kidney diseases: the official journal of the National Kidney Foundation. Nov 1986;8(5):368-379.

Rivenbark AG, O'Connor SM, Coleman WB. Molecular and cellular heterogeneity in breast cancer: challenges for personalized medicine. The American journal of pathology. Oct 2013;183(4):1113-1124.

Rodier F, Campisi J. Four faces of cellular senescence. The Journal of Cell Biology. February 21, 2011 2011;192(4):547-556.

Roffe L, Schmidt K, Ernst E. Efficacy of coenzyme Q10 for improved tolerability of cancer treatments: a systematic review. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Nov 1 2004;22(21):4418-4424.

Rostock M, Huber R, Greiner T, Fritz P, Scheer R, Schueler J, Fiebig HH. Anticancer activity of a lectin-rich mistletoe extract injected intratumorally into human pancreatic cancer xenografts. Anticancer research. May-Jun 2005;25(3b):1969-1975.

Ruiz Garcia V, López-Briz E, Carbonell Sanchis R, Gonzalvez Perales JL, Bort-Marti S. Megestrol acetate for treatment of anorexia-cachexia syndrome. Cochrane Database Syst Rev. 2013 Mar 28;3:CD004310.

Rusciani L, Proietti I, Paradisi A, Rusciani A, Guerriero G, Mammone A, . . . Lippa S. Recombinant interferon alpha-2b and coenzyme Q10 as a postsurgical adjuvant therapy for melanoma: a 3-year trial with recombinant interferon-alpha and 5-year follow-up. *Melanoma research.* Jun 2007;17(3):177-183.

Rushworth GF, Megson IL. Existing and potential therapeutic uses for N-acetylcysteine: the need for conversion to intracellular glutathione for antioxidant benefits. Pharmacology & therapeutics. Feb 2014;141(2):150-159.

Rutgers E, Piccart-Gebhart MJ, Bogaerts J, Delaloge S, Veer LV, Rubio IT, Viale G, Thompson AM, Passalacqua R, Nitz U, Vindevoghel A, Pierga JY, Ravdin PM, Werutsky G, Cardoso F. The EORTC 10041/BIG 03-04 MINDACT trial is feasible: results of the pilot phase. Eur J Cancer. 2011 Dec;47(18):2742-9.

Ryan JL, Heckler CE, Roscoe JA, Dakhil SR, Kirshner J, Flynn PJ, Hickok JT, Morrow GR. Ginger (Zingiber officinale) reduces acute chemotherapy-

induced nausea: a URCC CCOP study of 576 patients. Support Care Cancer. 2012 Jul;20(7):1479-89.

Sabaawy HE. Genetic Heterogeneity and Clonal Evolution of Tumor Cells and their Impact on Precision Cancer Medicine. Journal of leukemia (Los Angeles, Calif.). Nov 18 2013;1(4):1000124.

Sacks CA, Jarcho JA, Curfman GD. Paradigm Shifts in Heart-Failure Therapy — A Timeline. New England Journal of Medicine. 2014;371(11):989-991.

Sadzuka Y, Matsuura M, Sonobe T. The effect of taurine, a novel biochemical modulator, on the antitumor activity of doxorubicin. Biol Pharm Bull. 2009;32(9):1584-7.

Sadzuka Y, Sugiyama T, Hirota S. Modulation of cancer chemotherapy by green tea. Clin Cancer Res. 1998;4(1):153-6.

Safdie F, Brandhorst S, Wei M, Wang W, Lee C, Hwang S, . . . Longo VD. Fasting enhances the response of glioma to chemo- and radiotherapy. PloS one. 2012;7(9):e44603.

Safdie FM, Dorff T, Quinn D, Fontana L, Wei M, Lee C, . . . Longo VD. Fasting and cancer treatment in humans: A case series report. Aging. Dec 2009;1(12):988-1007.

Sak K. Chemotherapy and dietary phytochemical agents. Chemotherapy research and practice. 2012;2012:282570.

Saleh EM, El-awady RA, Eissa NA, Abdel-Rahman WM. Antagonism between curcumin and the topoisomerase II inhibitor etoposide: a study of DNA damage, cell cycle regulation and death pathways. Cancer biology & therapy. Sep 2012;13(11):1058-1071.

Salva S, Marranzino G, Villena J, Aguero G, Alvarez S. Probiotic Lactobacillus strains protect against myelosuppression and immunosuppression in cyclophosphamide-treated mice. International immunopharmacology. Sep 2014;22(1):209-221.

Samuni Y, Goldstein S, Dean OM, Berk M. The chemistry and biological activities of N-acetylcysteine. Biochimica et biophysica acta. Aug 2013;1830(8):4117-4129.

Sánchez-Lara K, Sosa-Sánchez R, Green-Renner D, Rodríguez C, Laviano A, Motola-Kuba D, Arrieta O. Influence of taste disorders on dietary behaviors in cancer patients under chemotherapy.Nutr J. 2010 Mar 24;9:15.

Sapra P, Betts A, Boni J. Preclinical and clinical pharmacokinetic/pharmacodynamic considerations for antibody-drug conjugates. Expert review of clinical pharmacology. Sep 2013;6(5):541-555.

Sasaki H, Sunagawa Y, Takahashi K, Imaizumi A, Fukuda H, Hashimoto T, . . . Morimoto T. Innovative preparation of curcumin for improved oral bioavailability. Biological & pharmaceutical bulletin. 2011;34(5):660-665.

Sato J, Kudo K, Hino K, Takahashi K. [Usefulness of oral rehydration solution for hydration in cancer chemotherapy: toward the application of outpatient chemotherapy with high-dose Cisplatin therapy-]. Gan to kagaku ryoho. Cancer & chemotherapy. Sep 2011;38(9):1471-1476.

Satoh H, Nishikawa K, Suzuki K, Asano R, Virgona N, Ichikawa T, Hagiwara K, Yano T. Genistein, a soy isoflavone, enhances necrotic-like cell death in a breast cancer cell treated with a chemotherapeutic agent. Res Commun Mol Pathol Pharmacol. 2003;113-114:149-58.

Sayed-Ahmed MM, Al-Shabanah OA, Hafez MM, Aleisa AM, Al-Rejaie SS. Inhibition of gene expression of heart fatty acid binding protein and organic cation/carnitine transporter in doxorubicin cardiomyopathic rat model. European journal of pharmacology. Aug 25 2010;640(1-3):143-149.

Sayed-Ahmed MM, Eissa MA, Kenawy SA, Mostafa N, Calvani M, Osman AM. Progression of cisplatin-induced nephrotoxicity in a carnitine-depleted rat model. Chemotherapy. Oct 2004;50(4):162-170.

Sayed-Ahmed MM, Hafez MM, Aldelemy ML, Aleisa AM, Al-Rejaie SS, Al-Hosaini KA, . . . Al-Shabanah OA. Downregulation of oxidative and nitrosative apoptotic signaling by L-carnitine in Ifosfamide-induced Fanconi syndrome rat model. Oxidative medicine and cellular longevity. 2012;2012:696704.

Sayed-Ahmed MM. Role of carnitine in cancer chemotherapy-induced multiple organ toxicity. Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society. Oct 2010;18(4):195-206.

Schad F, Atxner J, Buchwald D, Happe A, Popp S, Kroz M, Matthes H. Intratumoral Mistletoe (Viscum album L) Therapy in Patients With Unresectable Pancreas Carcinoma: A Retrospective Analysis. Integrative cancer therapies. Dec 19 2013;13(4):332-340.

Scharovsky OG, Mainetti LE, Rozados VR. Metronomic chemotherapy: changing the paradigm that more is better. Current oncology (Toronto, Ont.). 2009;16(2):7-15.

Schiller JH, Storer B, Berlin J, Wittenkeller J, Larson M, Pharo L, Larson M, Berry W. Amifostine, cisplatin, and vinblastine in metastatic non-small-cell lung cancer: a report of high response rates and prolonged survival. J Clin Oncol. 1996 Jun;14(6):1913-21.

Schlemmer M, Suchner U, Schapers B, Duerr EM, Alteheld B, Zwingers T, . . . Zimmer HG. Is glutamine deficiency the link between inflammation, malnutrition, and fatigue in cancer patients? Clinical nutrition (Edinburgh, Scotland). Jan 10 2015.

Schmidinger M, Budinsky AC, Wenzel C, Piribauer M, Brix R, Kautzky M, . . . Steger GG. Glutathione in the prevention of cisplatin induced toxicities. A prospectively randomized pilot trial in patients with head and neck cancer and non small cell lung cancer. Wiener klinische Wochenschrift. Jul 28 2000;112(14):617-623.

Schuchter LM. Guidelines for the administration of amifostine. Seminars in oncology. Aug 1996;23(4 Suppl 8):40-43.

Schwartzberg L, Barbour SY, Morrow GR, Ballinari G, Thorn MD, Cox D. Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. Feb 2014;22(2):469-477.

Seely D, Wu P, Fritz H, Kennedy DA, Tsui T, Seely AJ, Mills E. Melatonin as adjuvant cancer care with and without chemotherapy: a systematic review and meta-analysis of randomized trials. Integrative cancer therapies. Dec 2012;11(4):293-303.

Segal EM, Flood MR, Mancini RS, Whiteman RT, Friedt GA, Kramer AR, Hofstetter MA. Oral chemotherapy food and drug interactions: a comprehensive review of the literature. Journal of oncology practice / American Society of Clinical Oncology. Jul 2014;10(4):e255-268.

Seicean S, Seicean A, Plana JC, Budd GT, Marwick TH. Effect of statin therapy on the risk for incident heart failure in patients with breast cancer receiving anthracycline chemotherapy: an observational clinical cohort study. J Am Coll Cardiol. 2012 Dec 11;60(23):2384-90.

Seifried HE, McDonald SS, Anderson DE, Greenwald P, Milner JA. The Antioxidant Conundrum in Cancer. Cancer research. August 1, 2003 2003;63(15):4295-4298.

Selli C, Dixon JM, Sims AH. Accurate prediction of response to endocrine therapy in breast cancer patients: current and future biomarkers. Breast cancer research: BCR. Dec 01 2016;18(1):118.

Senthilnathan P, Padmavathi R, Banu SM, Sakthisekaran D. Enhancement of antitumor effect of paclitaxel in combination with immunomodulatory Withania somnifera on benzo(a)pyrene induced experimental lung cancer. Chem Biol Interact. 2006 Feb 25;159(3):180-5.

Shahbazi F, Dashti-Khavidaki S, Khalili H, et al. Potential Renoprotective Effects of Silymarin Against Nephrotoxic Drugs: A Review of Literature. J Pharm Pharmaceut Sci. 2012;15(1):112-123.

Shaikh IA, Brown I, Wahle KW, Heys SD. Enhancing cytotoxic therapies for breast and prostate cancers with polyunsaturated fatty acids. Nutrition and cancer. 2010;62(3):284-296.

Shakibaei M, Buhrmann C, Kraehe P, Shayan P, Lueders C, Goel A. Curcumin chemosensitizes 5-fluorouracil resistant MMR-deficient human colon cancer cells in high density cultures. PLoS One. 2014;9(1):e85397.

Shapiro TA, Fahey JW, Dinkova-Kostova AT, Holtzclaw WD, Stephenson KK, Wade KL, . . . Talalay P. Safety, tolerance, and metabolism of broccoli sprout glucosinolates and isothiocyanates: a clinical phase I study. Nutrition and cancer. 2006;55(1):53-62.

Shatoor AS, Ahmed MAAS. syn. Azarolus (L) Aqueous Extract Against Doxorubicin-Induced Cardiotoxicity and Heart Failure in Wistar Rats. 2014.

SHCI. The Scott Hamilton CARES Initiative. Chemotherapy Terms. Available at: http://chemocare.com/chemotherapy/what-is-chemotherapy /chemotherapy-terms.aspx#.U-NwsXnQdZR. Accessed 8/7/2014.

SHCI. The Scott Hamilton CARES Initiative. How Is Chemotherapy Given? Available at: http://chemocare.com/chemotherapy/what-is-chemotherapy /how-chemotherapy-is-given.aspx#.U-Nx3HnQdZR. Accessed 2/16/2017.

Sheikh-Hamad D, Timmins K, Jalali Z. Cisplatin-induced renal toxicity: possible reversal by N-acetylcysteine treatment. Journal of the American Society of Nephrology: JASN. Oct 1997;8(10):1640-1644.

Shelygin Iu A, Alekseev MV, Rybakov EG, Eropkin PV. [Effect of intraoperative intrapelvic chemotherapy with hyperthermia on the incidence of rectal cancer recurrences]. Voprosy onkologii. 2014;60(1):64-70.

Shen J, Tai YC, Zhou J, Stephen Wong CH, Cheang PT, Fred Wong WS, Xie Z, Khan M, Han JH, Chen CS. Synergistic antileukemia effect of genistein and chemotherapy in mouse xenograft model and potential mechanism through MAPK signaling. Exp Hematol. 2007 Jan;35(1):75-83.

Shen M, Chan TH, Dou QP. Targeting tumor ubiquitin-proteasome pathway with polyphenols for chemosensitization. Anti-cancer agents in medicinal chemistry. 2012;12(8):891-901.

Shen WS, Gao CH, Zhang H. [Effect of rhodiola on serum troponin 1, cardiac integral backscatter and left ventricle ejective fraction of patients who received epirubicin-contained chemotherapy]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2010;30(12):1250-2.

Silverio R, Laviano A, Rossi Fanelli F, Seelaender M. l-carnitine and cancer cachexia: Clinical and experimental aspects. Journal of cachexia, sarcopenia and muscle. Mar 2011;2(1):37-44.

Simone CB 2nd, Simone NL, Simone V, Simone CB. Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, Part 2. Altern Ther Health Med. 2007b;13(2):40-7

Simone CB, 2nd, Simone NL, Simone V, Simone CB. Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival, Part 1. Altern Ther Health Med. 2007a;13(1):22-28.

Singh U, Devaraj S, Jialal I. Coenzyme Q10 supplementation and heart failure. Nutrition reviews. Jun 2007;65(6 Pt 1):286-293.

Skinner HD, McCurdy MR, Echeverria AE, Lin SH, Welsh JW, O'Reilly MS, . . . Guerrero TM. Metformin use and improved response to therapy in esophageal adenocarcinoma. Acta oncologica (Stockholm, Sweden). 2013;52(5):1002-1009.

Skitzki JJ, Repasky EA, Evans SS. Hyperthermia as an immunotherapy strategy for cancer. Current opinion in investigational drugs (London, England: 2000). Jun 2009;10(6):550-558.

Slater S. Non-curative chemotherapy for cancer--is it worth it? Clinical medicine (London, England). May-Jun 2001;1(3):220-222.

Slodkowska EA, Ross JS. MammaPrint 70-gene signature: another milestone in personalized medical care for breast cancer patients. Expert review of molecular diagnostics. Jul 2009;9(5):417-422.

Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, . . . Shapiro CL. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. Jama. Apr 03 2013;309(13):1359-1367.

Smith HS, Zoli W, Volpi A, Hiller A, Lippman M, Swain S, Mayall B, Dollbaum C, Hackett AJ, Amadori D. Preliminary correlations of clinical outcome with in vitro chemosensitivity of second passage human breast cancer cells. Cancer Res. 1990 May 15;50(10):2943-8.

Smith SC, Baras AS, Lee JK, Theodorescu D. The COXEN principle: translating signatures of in vitro chemosensitivity into tools for clinical outcome prediction and drug discovery in cancer. Cancer Res. 2010 Mar 1;70(5):1753-8.

Smyth JF, Bowman A, Perren T, Wilkinson P, Prescott RJ, Quinn KJ, Tedeschi M. Glutathione reduces the toxicity and improves quality of life of women diagnosed with ovarian cancer treated with cisplatin: results of a double-blind, randomised trial. Annals of oncology: official journal of the European Society for Medical Oncology / ESMO. Jun 1997;8(6):569-573.

Solanki MH, Chatterjee PK, Gupta M, Xue X, Plagov A, Metz MH, . . . Metz CN. Magnesium protects against cisplatin-induced acute kidney injury by regulating platinum accumulation. American journal of physiology. Renal physiology. Aug 15 2014;307(4):F369-384.

Solheim TS, Laird BJ. Evidence base for multimodal therapy in cachexia. Current opinion in supportive and palliative care. Dec 2012;6(4):424-431.

Somasundaram S, Edmund NA, Moore DT, et al. Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer. Cancer Res. 2002 Jul 1;62(13):3868-3875.

Song J, Liu D, Feng L, Zhang Z, Jia X, Xiao W. Protective Effect of Standardized Extract of Ginkgo biloba against Cisplatin-Induced Nephrotoxicity. Evidence-based complementary and alternative medicine : eCAM. 2013;2013:846126.

Sonneveld P. Effect of alpha-tocopherol on the cardiotoxicity of adriamycin in the rat. Cancer treatment reports. Jul 1978;62(7):1033-1036.

Soref CM, Hacker TA, Fahl WE. A new orally active, aminothiol radioprotector-free of nausea and hypotension side effects at its highest radioprotective doses. International journal of radiation oncology, biology, physics. Apr 1 2012;82(5):e701-707.

Soritau O, Tomuleasa C, Aldea M, Petrushev B, Susman S, Gheban D, Ioani H, Cosis A, Brie I, Irimie A, Kacso G, Florian IS. Metformin plus temozolomide-based chemotherapy as adjuvant treatment for WHO grade III and IV malignant gliomas. J BUON. 2011;16(2):282-9.

Spagnuolo C, Russo GL, Orhan IE, Habtemariam S, Daglia M, Sureda A, . . . Nabavi SM. Genistein and cancer: current status, challenges, and future directions. Adv Nutr. Jul 2015;6(4):408-419.

Speck RM, DeMichele A, Farrar JT, Hennessy S, Mao JJ, Stineman MG, Barg FK. Scope of symptoms and self-management strategies for chemotherapy-induced peripheral neuropathy in breast cancer patients. Support Care Cancer. 2012 Oct;20(10):2433-9.

Spencer A, Horvath N, Gibson J, Prince HM, Herrmann R, Bashford J, Joske D, Grigg A, McKendrick J, Prosser I, Lowenthal R, Deveridge S, Taylor K; Australasian Leukemia and Lymphoma Group. Prospective randomised trial of amifostine cytoprotection in myeloma patients undergoing high-dose melphalan conditioned autologous stem cell transplantation. Bone Marrow Transplant. 2005 May;35(10):971-7.

Sreekanth CN, Bava SV, Sreekumar E, Anto RJ. Molecular evidences for the chemosensitizing efficacy of liposomal curcumin in paclitaxel chemotherapy in mouse models of cervical cancer. Oncogene. Jul 14 2011;30(28):3139-3152.

Steele ML, Axtner J, Happe A, Kroz M, Matthes H, Schad F. Safety of Intravenous Application of Mistletoe (Viscum album L.) Preparations in Oncology: An Observational Study. Evidence-based complementary and alternative medicine: eCAM. 2014;2014:236310.

Steele ML, Axtner J, Happe A, Kroz M, Matthes H, Schad F. Use and safety of intratumoral application of European mistletoe (Viscum album L) preparations in Oncology. Integrative cancer therapies. Mar 2015;14(2):140-148.

Steele ML, Axtner J. Adverse Drug Reactions and Expected Effects to Therapy with Subcutaneous Mistletoe Extracts (Viscum album L.) in Cancer Patients. 2014;2014:724258.

Steinbach S, Hundt W, Schmalfeldt B, Böhner C, Berktold S, Wolf P, Harbeck N. Effect of platinum-containing chemotherapy on olfactory, gustatory, and hearing function in ovarian cancer patients. Arch Gynecol Obstet. 2012 Aug;286(2):473-80.

Steiner R, Hellmann K. Dexrazoxane prevention of anthracycline cardiomyopathy. J Clin Oncol. 2013 Apr 1;31(10):1379.

Sterba M, Popelova O, Vavrova A, Jirkovsky E, Kovarikova P, Gersl V, Simunek T. Oxidative stress, redox signaling, and metal chelation in anthracycline cardiotoxicity and pharmacological cardioprotection. Antioxidants & redox signaling. Mar 10 2013;18(8):899-929.

Stewart T, Pavlakis N, Ward M. Cardiotoxicity with 5-fluorouracil and capecitabine: more than just vasospastic angina. Internal medicine journal. Apr 2010;40(4):303-307.

Stipp D. How Intermittent Fasting Might Help You Live a Longer and Healthier Life - Scientific American. http://www.scientificamerican.com/article/how-intermittent-fasting-might-help-you-live-longer-healthier-life/. Accessed 7/24/2015.

Stubblefield MD, McNeely ML, Alfano CM, Mayer DK. A prospective surveillance model for physical rehabilitation of women with breast cancer: chemotherapy-induced peripheral neuropathy. Cancer. 2012 Apr 15;118(8 Suppl):2250-60.

Subbiah MT, Yunker R. Studies on the nature of anti-platelet aggregatory factors in the seeds of the Amazonian Herb Guarana (Paullinia cupana). International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal international de vitaminologie et de nutrition. Mar 2008;78(2):96-101.

Sugiyama T, Sadzuka Y, Nagasawa K, Ohnishi N, Yokoyama T, Sonobe T. Membrane transport and antitumor activity of pirarubicin, and comparison with those of doxorubicin. Japanese journal of cancer research: Gann. Jul 1999;90(7):775-780.

Sugiyama T, Sadzuka Y. Theanine and glutamate transporter inhibitors enhance the antitumor efficacy of chemotherapeutic agents. Biochimica et biophysica acta. Dec 5 2003;1653(2):47-59.

Sun J, Wang H, Hu H. Glutamine for chemotherapy induced diarrhea: a meta-analysis. Asia Pac J Clin Nutr. 2012;21(3):380-5

Sunagawa Y, Hirano S, Katanasaka Y, Miyazaki Y, Funamoto M, Okamura N, . . . Morimoto T. Colloidal submicron-particle curcumin exhibits high absorption efficiency-a double-blind, 3-way crossover study. J Nutr Sci Vitaminol (Tokyo). 2015;61(1):37-44.

Sung B, Kunnumakkara AB, Sethi G, Anand P, Guha S, Aggarwal BB. Curcumin circumvents chemoresistance in vitro and potentiates the effect of thalidomide and bortezomib against human multiple myeloma in nude mice model. Molecular cancer therapeutics. Apr 2009;8(4):959-970.

Taherian-Fard A, Srihari S, Ragan MA. Breast cancer classification: linking molecular mechanisms to disease prognosis. Briefings in bioinformatics. Jun 20 2014.

Taillibert S. Is systemic anti-cancer therapy neurotoxic? Does chemo brain exist? And should we rename it? Adv Exp Med Biol. 2010;678:86-95.

Taixiang W, Munro AJ, Guanjian L. Chinese medical herbs for chemotherapy side effects in colorectal cancer patients. Cochrane Database Syst Rev. 2005 Jan 25;(1):CD004540.

Takagi K, Yamamori H, Furukawa K, Miyazaki M, Tashiro T. Perioperative supplementation of EPA reduces immunosuppression induced by postoperative chemoradiation therapy in patients with esophageal cancer. Nutrition (Burbank, Los Angeles County, Calif.). Jun 2001;17(6):478-479.

Takahashi Y, Mai M, Nakazato H. Preoperative CEA and PPD values as prognostic factors for immunochemotherapy using PSK and 5-FU. Anticancer Res. 2005;25(2B):1377-84.

Takimoto CH. New Antifolates: Pharmacology and Clinical Applications. The oncologist. 1996;1(1 & 2):68-81.

Tan BX, Yao WX, Ge J, Peng XC, Du XB, Zhang R, Yao B, Xie K, Li LH, Dong H, Gao F, Zhao F, Hou JM, Su JM, Liu JY. Prognostic influence of metformin as first-line chemotherapy for advanced nonsmall cell lung cancer in patients with type 2 diabetes. Cancer. 2011;117(22):5103-11.

Tao LM, Xiong JP, Liu TX. [A crossover control study of prophylactic treatment of chemotherapy-induced constipation by senna extract]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2012 Jan;32(1):47-9.

Taso CJ, Lin HS, Lin WL, Chen SM, Huang WT, Chen SW. The effect of yoga exercise on improving depression, anxiety, and fatigue in women with breast cancer: a randomized controlled trial. The journal of nursing research: JNR. Sep 2014;22(3):155-164.

Taylor CW, Wang LM, List AF, Fernandes D, Paine-Murrieta GD, Johnson CS, Capizzi RL. Amifostine protects normal tissues from paclitaxel toxicity while cytotoxicity against tumour cells is maintained. European journal of cancer (Oxford, England: 1990). Sep 1997;33(10):1693-1698.

Teiten MH, Eifes S, Dicato M, Diederich M. Curcumin-the paradigm of a multi-target natural compound with applications in cancer prevention and treatment. Toxins. Jan 2010;2(1):128-162.

Thomas Dickey D, Muldoon LL, Kraemer DF, Neuwelt EA. Protection against cisplatin-induced ototoxicity by N-acetylcysteine in a rat model. Hearing research. Jul 2004;193(1-2):25-30.

Tierney AJ, Leonard RC, Taylor J, Closs SJ, Chetty U, Rodger A. Side effects expected and experienced by women receiving chemotherapy for breast cancer. BMJ. 1991 Feb 2;302(6771):272.

Timmer-Bonte JN, de Boo TM, Smit HJ, Biesma B, Wilschut FA, Cheragwandi SA, . . . Tjan-Heijnen VC. Prevention of chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte colony-stimulating factor in small-cell lung cancer: a Dutch Randomized Phase III Study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. Nov 1 2005;23(31):7974-7984.

Timmer-Bonte JN, Tjan-Heijnen VC. Febrile neutropenia: highlighting the role of prophylactic antibiotics and granulocyte colony-stimulating factor during standard dose chemotherapy for solid tumors. Anti-cancer drugs. Sep 2006;17(8):881-889.

Tiseo M, Martelli O, Mancuso A, Sormani MP, Bruzzi P, Di Salvia R, . . . Ardizzoni A. Short hydration regimen and nephrotoxicity of intermediate to high-dose cisplatin-based chemotherapy for outpatient treatment in lung cancer and mesothelioma. Tumori. Mar-Apr 2007;93(2):138-144.

Toden S, Okugawa Y, Jascur T, Wodarz D, Komarova NL, Buhrmann C, . . . Goel A. Curcumin mediates chemosensitization to 5-fluorouracil through miRNA-induced suppression of epithelial-to-mesenchymal transition in chemoresistant colorectal cancer. Carcinogenesis. Feb 4 2015.

Todorova V, Vanderpool D, Blossom S, Nwokedi E, Hennings L, Mrak R, Klimberg VS. Oral glutamine protects against cyclophosphamide-induced cardiotoxicity in experimental rats through increase of cardiac glutathione. Nutrition (Burbank, Los Angeles County, Calif.). 2009;25(7–8):812-817.

Toge T, Yamaguchi Y. Protein-bound polysaccharide increases survival in resected gastric cancer cases stratified with a preoperative granulocyte and lymphocyte count. Oncol Rep. 2000;7(5):1157-1161.

Topkan E, Parlak C, Topuk S, Pehlivan B. Influence of oral glutamine supplementation on survival outcomes of patients treated with concurrent chemoradiotherapy for locally advanced non-small cell lung cancer. BMC cancer. 2012;12:502.

Torne SJ, Ansari KA, Vavia PR, Trotta F, Cavalli R. Enhanced oral paclitaxel bioavailability after administration of paclitaxel-loaded nanosponges. Drug delivery. 2010;17(6):419-425.

Totsuka O, Kawate S, Hirai K, et al. [Subset analysis of preoperative lymphocyte ratio in stage II or III colorectal cancer patients treated with oral tegafur-uracil and protein-bound polysaccharide K]. Gan To Kagaku Ryoho. 2013;40(13):2525-8.

Troger W, Zdrale Z, Tisma N, Matijasevic M. Additional Therapy with a Mistletoe Product during Adjuvant Chemotherapy of Breast Cancer Patients Improves Quality of Life: An Open Randomized Clinical Pilot Trial. Evidence-based complementary and alternative medicine: eCAM. 2014;2014:430518.

Tröger W, Zdrale Z, Tisma N, Matijasevic M. Additional Therapy with a Mistletoe Product during Adjuvant Chemotherapy of Breast Cancer Patients Improves Quality of Life: An Open Randomized Clinical Pilot Trial. Evidence-based complementary and alternative medicine: eCAM. 2014;2014:430518.

Tsujimoto T, Yamamoto Y, Wasa M, Takenaka Y, Nakahara S, Takagi T, . . . Ito T. L-glutamine decreases the severity of mucositis induced by chemoradiotherapy in patients with locally advanced head and neck cancer: a double-blind, randomized, placebo-controlled trial. Oncol Rep. Jan 2015;33(1):33-39.

Tufekci O, Gunes D, Ozogul C, Kolatan E, Altun Z, Yilmaz O, . . . Olgun N. Evaluation of the effect of acetyl L-carnitine on experimental cisplatin nephrotoxicity. Chemotherapy. 2009;55(6):451-459.

Ugurel S, Utikal J, Becker JC. Tumor biomarkers in melanoma. Cancer control : journal of the Moffitt Cancer Center. Jul 2009;16(3):219-224.

Uma Mahesh B, Shrivastava S, Kuncha M, Sahu BD, Swamy CV, Pragada RR, . . . Sistla R. Ethanolic extract of Boswellia ovalifoliolata bark and leaf attenuates doxorubicin-induced cardiotoxicity in mice. Environmental toxicology and pharmacology. Nov 2013;36(3):840-849.

Urschel JD, Vasan H, Blewett CJ. A meta-analysis of randomized controlled trials that compared neoadjuvant chemotherapy and surgery to surgery alone for resectable esophageal cancer. American journal of surgery. Mar 2002;183(3):274-279.

Vaclavikova R, Horsky S, Simek P, Gut I. Paclitaxel metabolism in rat and human liver microsomes is inhibited by phenolic antioxidants. Naunyn-Schmiedeberg's archives of pharmacology. Sep 2003;368(3):200-209.

Vadhan-Raj S. Management of chemotherapy-induced thrombocytopenia: current status of thrombopoietic agents. Seminars in hematology. Jan 2009;46(1 Suppl 2):S26-32.

Vahdat L, Papadopoulos K, Lange D, Leuin S, Kaufman E, Donovan D, . . . Balmaceda C. Reduction of paclitaxel-induced peripheral neuropathy with glutamine. Clinical cancer research: an official journal of the American Association for Cancer Research. May 2001;7(5):1192-1197.

van Dalen EC, Caron HN, Dickinson HO, Kremer LC. Cardioprotective interventions for cancer patients receiving anthracyclines. The Cochrane database of systematic reviews. 2011(6):Cd003917.

van Dalen EC, van den Berg H, Raphaël MF, Caron HN, Kremer LC. Should anthracyclines and dexrazoxane be used for children with cancer? Lancet Oncol. 2011 Jan;12(1):12-3.

van den Hurk CJ, van de Poll-Franse LV, Breed WP, Coebergh JW, Nortier JW. Scalp cooling to prevent alopecia after chemotherapy can be considered safe in patients with breast cancer. Breast. 2013 Oct;22(5):1001-4

Verstappen CC, Heimans JJ, Hoekman K, Postma TJ. Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. Drugs. 2003;63(15):1549-1563.

Viale PH. Integrating aprepitant and palonosetron into clinical practice: a role for the new antiemetics. Clinical journal of oncology nursing. Feb 2005;9(1):77-84.

Victorino VJ, Pizzatti L, Michelletti P, Panis C. Oxidative stress, redox signaling and cancer chemoresistance: putting together the pieces of the puzzle. Current medicinal chemistry. 2014;21(28):3211-3226.

Vidall C, Roe H, Dougherty L, Harrold K. Dexrazoxane: a management option for anthracycline extravasations. Br J Nurs. 2013 Sep 12-25;22(17):S6 -12.

Vinod BS, Maliekal TT, Anto RJ. Phytochemicals as chemosensitizers: from molecular mechanism to clinical significance. Antioxid Redox Signal. 2013;18(11):1307-48.

Visovsky C, Schneider S. Cancer-Related Fatigue. Online Journal of Issues in Nursing. 2003;8(3).

Von Bultzingslowen I, Adlerberth I, Wold AE, Dahlen G, Jontell M. Oral and intestinal microflora in 5-fluorouracil treated rats, translocation to cervical and mesenteric lymph nodes and effects of probiotic bacteria. Oral Microbiol Immunol. Oct 2003;18(5):278-284.

Vrabel M. Is ondansetron more effective than granisetron for chemotherapy-induced nausea and vomiting? A review of comparative trials. Clinical journal of oncology nursing. Dec 2007;11(6):809-813.

Vural EM, van Munster BC, de Rooij SE. Optimal dosages for melatonin supplementation therapy in older adults: a systematic review of current literature. Drugs & aging. Jun 2014;31(6):441-451.

Wakatsuki T, Irisawa A, Imamura H, Terashima M, Shibukawa G, Takagi T, . . . Ohira H. Complete response of anaplastic pancreatic carcinoma to paclitaxel treatment selected by chemosensitivity testing. International journal of clinical oncology. 2010;15(3):310-313.

Walsh D, Kirkova J, Davis MP. The efficacy and tolerability of long-term use of dronabinol in cancer-related anorexia: a case series. Journal of pain and symptom management. Dec 2005;30(6):493-495.

Wang BL, Shen YM, Zhang QW, Li YL, Luo M, Liu Z, . . . Shi HS. Codelivery of curcumin and doxorubicin by MPEG-PCL results in improved efficacy of systemically administered chemotherapy in mice with lung cancer. International journal of nanomedicine. 2013;8:3521-3531.

Wang DY, Done SJ, Mc Cready DR, Leong WL. Validation of the prognostic gene portfolio, ClinicoMolecular Triad Classification using an independent prospective breast cancer cohort and external patient populations. Breast cancer research: BCR. Jul 4 2014;16(4):R71.

Wang H, Peng D, Xie J. Ginseng leaf-stem: bioactive constituents and pharmacological functions. Chinese medicine. 2009;4:20.

Wang P, Zhang S, Zhang XB, Li WJ, Hao XM, Zhang J. [Protective effect of dexrazoxane on cardiotoxicity in breast cancer patients who received anthracycline-containing chemotherapy]. Zhonghua Zhong Liu Za Zhi. 2013 Feb;35(2):135-9.

Wang Q, Yang W, Uytingco MS, Christakos S, Wieder R. 1,25-Dihydroxyvitamin D3 and all-trans-retinoic acid sensitize breast cancer cells to chemotherapy-induced cell death. Cancer Res. 2000 Apr 1;60(7):2040-8.

Wang WS, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, . . . Chen PM. Oral glutamine is effective for preventing oxaliplatin-induced neuropathy in colorectal cancer patients. The oncologist. Mar 2007;12(3):312-319.

Wang X, Govind S, Sajankila SP, Mi L, Roy R, Chung FL. Phenethyl isothiocyanate sensitizes human cervical cancer cells to apoptosis induced by cisplatin. Molecular nutrition & food research. Oct 2011;55(10):1572-1581.

Wang YH, Yao N, Wei KK, Jiang L, Hanif S, Wang ZX, Pei CX. The efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer: a systematic review and meta-analysis. European journal of clinical nutrition. Nov 2016;70(11):1246-1253.

Wang YM, Jin BZ, Ai F, Duan CH, Lu YZ, Dong TF, Fu QL. The efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumors: a meta-analysis of randomized controlled trials. Cancer Chemother Pharmacol. May 2012;69(5):1213-1220.

Wang YY, Lin SX, Yang GQ, Liu HC, Sun DN, Wang YS. Clinical efficacy of CyberKnife combined with chemotherapy and hyperthermia for advanced non-small cell lung cancer. Molecular and clinical oncology. May 2013;1(3):527-530.

Wang Z, Chen JQ, Liu JL, Tian L. Exosomes in tumor microenvironment: novel transporters and biomarkers. J Transl Med. Oct 19 2016;14(1):297.

Weijl NI, Elsendoorn TJ, Lentjes EG, Hopman GD, Wipkink-Bakker A, Zwinderman AH, . . . Osanto S. Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study. *European journal of cancer (Oxford, England: 1990).* Jul 2004;40(11):1713-1723.

Weingart SN, Brown E, Bach PB, Eng K, Johnson SA, Kuzel TM, . . . Walters RS. NCCN Task Force Report. Journal of the National Comprehensive Cancer Network. Volume 6, Supplement 3. March 2008. <http://www.nccn.org/JNCCN/PDF/JNSU3_combined_Oral_Chemo_2008.pdf>.

Wesolowska O. Interaction of phenothiazines, stilbenes and flavonoids with multidrug resistance-associated transporters, P-glycoprotein and MRP1. Acta biochimica Polonica. 2011;58(4):433-448.

Wessner B, Strasser EM, Koitz N, Schmuckenschlager C, Unger-Manhart N, Roth E. Green tea polyphenol administration partly ameliorates chemotherapy-induced side effects in the small intestine of mice. J Nutr. 2007 Mar;137(3):634-40.

Widemann BC, Adamson PC. Understanding and Managing Methotrexate Nephrotoxicity. The Oncologist. June 1, 2006 2006;11(6):694-703.

Widemann BC, Schwartz S, Jayaprakash N, Christensen R, Pui CH, Chauhan N, Daugherty C, King TR, Rush JE, Howard SC. Efficacy of

glucarpidase (carboxypeptidase g2) in patients with acute kidney injury after high-dose methotrexate therapy. Pharmacotherapy. 2014 May;34(5):427-39.

Wigmore PM, Mustafa S, El-Beltagy M, Lyons L, Umka J, Bennett G. Effects of 5-FU. Adv Exp Med Biol. 2010;678:157-64.

Wilken MK, Satiroff BA. Pilot study of "miracle fruit" to improve food palatability for patients receiving chemotherapy. Clin J Oncol Nurs. 2012 Oct;16(5):E173-7.

Wilson FP, Berns JS. Onco-nephrology: tumor lysis syndrome. Clin J Am Soc Nephrol. 2012 Oct;7(10):1730-9.

Winters M. Ancient medicine, modern use: Withania somnifera and its potential role in integrative oncology. Altern Med Rev. 2006 Dec;11(4):269-77.

Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. European journal of cancer (Oxford, England: 1990). Jul 2008;44(11):1507-1515.

Wong MY, Chiu GN. Liposome formulation of co-encapsulated vincristine and quercetin enhanced antitumor activity in a trastuzumab-insensitive breast tumor xenograft model. Nanomedicine: nanotechnology, biology, and medicine. Dec 2011;7(6):834-840.

Xian CJ. Roles of growth factors in chemotherapy-induced intestinal mucosal damage repair. Current pharmaceutical biotechnology. Aug 2003;4(4):260-269.

Xu JL, Xia R, Sun ZH, Sun L, Min X, Liu C, . . . Zhu YM. Effects of honey use on the management of radio/chemotherapy-induced mucositis: a meta-analysis of randomized controlled trials. International journal of oral and maxillofacial surgery. Dec 2016;45(12):1618-1625.

Xu X, Persson HL, Richardson DR. Molecular pharmacology of the interaction of anthracyclines with iron. Molecular pharmacology. Aug 2005;68(2):261-271.

Xu XT, Dai ZH, Xu Q, Qiao YQ, Gu Y, Nie F, Zhu MM, Tong JL, Ran ZH. Safety and efficacy of calcium and magnesium infusions in the chemoprevention of oxaliplatin-induced sensory neuropathy in gastrointestinal cancers. J Dig Dis. 2013 Jun;14(6):288-98.

Xue H, Sawyer MB, Wischmeyer PE, Baracos VE. Nutrition modulation of gastrointestinal toxicity related to cancer chemotherapy: from preclinical findings to clinical strategy. JPEN J Parenter Enteral Nutr. 2011 Jan;35(1):74-90.

Yamamoto D, Yamamoto C, Iwase S, Kuroda Y, Odagiri H, Nagumo Y. Efficacy of Vitamin E Treatment for Hand-Foot Syndrome in Patients Receiving Capecitabine. Breast Care (Basel). 2010;5(6):415-416.

Yan JJ, Shen F, Wang K, Wu MC. Patients with advanced primary hepatocellular carcinoma treated by melatonin and transcatheter arterial chemoembolization: a prospective study. Hepatobiliary Pancreat Dis Int. 2002;1(2):183-6.

Yardley DA. Drug Resistance and the Role of Combination Chemotherapy in Improving Patient Outcomes. International Journal of Breast Cancer. 2013;2013:15.

Yasueda A, Urushima H, Ito T. Efficacy and Interaction of Antioxidant Supplements as Adjuvant Therapy in Cancer Treatment: A Systematic Review. *Integrative cancer therapies*. Oct 26 2015.

Yeager CE, Olsen EA. Treatment of chemotherapy-induced alopecia. Dermatol Ther. 2011 Jul-Aug;24(4):432-42

Yeh CH, Moles R, Nicot C. Clinical significance of microRNAs in chronic and acute human leukemia. Molecular cancer. May 14 2016;15(1):37.

Yeh J, Kim BS, Peresie J. Protection against cisplatin-induced ovarian damage by the antioxidant sodium 2-mercaptoethanesulfonate (mesna) in female rats. Am J Obstet Gynecol. 2008 Apr;198(4):463.e1-6; discussion 463.e6-7.

Yekta ZP, Ebrahimi SM, Hosseini M, Nasrabadi AN, Sedighi S, Surmaghi MH, Madani H. Ginger as a miracle against chemotherapy-induced vomiting. Iran J Nurs Midwifery Res. 2012 Jul;17(5):325-9.

Yildirim I, Korkmaz A, Oter S, Ozcan A, Oztas E. Contribution of antioxidants to preventive effect of mesna in cyclophosphamide-induced hemorrhagic cystitis in rats. Cancer Chemother Pharmacol. 2004 Nov;54(5):469-73.

Yiu AJ, Yiu CY. Biomarkers in Colorectal Cancer. Anticancer research. Mar 2016;36(3):1093-1102.

Yoon YS, Kim JC. Recent applications of chemosensitivity tests for colorectal cancer treatment. World journal of gastroenterology: WJG. Nov 28 2014;20(44):16398-16408.

Yoshida T, Niho S, Toda M, Goto K, Yoh K, Umemura S, . . . Ohe Y. Protective effect of magnesium preloading on cisplatin-induced nephrotoxicity: a retrospective study. Japanese journal of clinical oncology. Apr 2014;44(4):346-354.

Yu CZ, Liu YP, Liu S, Yan M, Hu SJ, Song XJ. Systematic administration of B vitamins attenuates neuropathic hyperalgesia and reduces spinal neuron injury following temporary spinal cord ischaemia in rats. Eur J Pain. 2014 Jan;18(1):76-85.

Yu LL, Wu JG, Dai N, Yu HG, Si JM. Curcumin reverses chemoresistance of human gastric cancer cells by downregulating the NF-kappaB transcription factor. Oncology reports. 2011;26(5):1197-1203.

Yu M, Xue J, Li Y, Zhang W, Ma D, Liu L, Zhang Z. Resveratrol protects against arsenic trioxide-induced nephrotoxicity by facilitating arsenic metabolism and decreasing oxidative stress. Archives of toxicology. Jun 2013;87(6):1025-1035.

Yu Y, Ramena G, Elble RC. The role of cancer stem cells in relapse of solid tumors. Frontiers in bioscience (Elite edition). 2012;4:1528-1541.

Yuan Z, Wang H, Hu Z, Huang Y, Yao F, Sun S, Wu B. Quercetin Inhibits Proliferation and Drug Resistance in KB/VCR Oral Cancer Cells and Enhances Its Sensitivity to Vincristine. Nutrition and cancer. Jan 2015;67(1):126-136.

Yurekli Y, Unak P, Yenisey C, Ertay T, Biber Muftuler FZ, Medine EI. L-Carnitine Protection Against Cisplatin Nephrotoxicity In Rats: Comparison with Amifostin Using Quantitative Renal Tc 99m DMSA Uptake. Molecular imaging and radionuclide therapy. Apr 2011;20(1):1-6.

Zang J, Hou M, Gou HF, Qiu M, Wang J, Zhou XJ, . . . Yi C. Antiemetic activity of megestrol acetate in patients receiving chemotherapy. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. May 2011;19(5):667-673.

Zangemeister-Wittke U, Simon H-U. Myelosuppression. In: Schwab M, ed. Encyclopedia of Cancer. Berlin, Heidelberg: Springer Berlin Heidelberg;

2009:2008-2010.

Zarogoulidis P, Darwiche K, Sakkas A, Yarmus L, Huang H, Li Q, . . . Malecki M. Suicide Gene Therapy for Cancer - Current Strategies. Journal of genetic syndrome & gene therapy. 2013;4.

Zhang H, Yu T, Wen L, Wang H, Fei D, Jin C. Curcumin enhances the effectiveness of cisplatin by suppressing CD133 cancer stem cells in laryngeal carcinoma treatment. Experimental and therapeutic medicine. Nov 2013;6(5):1317-1321.

Zhang M, Li X, Lu X. [Metformin inhibits the proliferation of hypopharyngeal carcinoma Fadu cells and enhances the chemotherapeutic sensitivity of cells]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2014;49(4):317-22.

Zhang RX, Wu XJ, Wan DS, Lu ZH, Kong LH, Pan ZZ, Chen G. Celecoxib can prevent capecitabine-related hand-foot syndrome in stage II and III colorectal cancer patients: result of a single-center, prospective randomized phase III trial. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. May 2012;23(5):1348-1353.

Zhang S, Wang Y, Chen Z, Kim S, Iqbal S, Chi A, Ritenour C, Wang YA, Kucuk O, Wu D. Genistein enhances the efficacy of cabazitaxel chemotherapy in metastatic castration-resistant prostate cancer cells. Prostate. 2013;73(15):1681-9

Zhang XH, Wang L, Dong ZZ. [Study on zinc resistance to the immunosuppression caused by cyclophosphamidum in the mouse]. Sheng li xue bao : [Acta physiologica Sinica]. Oct 1992;44(5):528-532.

Zhang XX, Ma L, Wang JL, Wu WM, Feng LC, Huang DL. [Management of oral mucositis in patients with head and neck cancer receiving chemoradiotherapy and/or molecular targeted therapy]. Zhonghua er bi yan hou tou jing wai ke za zhi = Chinese journal of otorhinolaryngology head and neck surgery. Jun 2011;46(6):505-508.

Zhao D, Zhang W, Li XG, Wang XB, Zhang LF, Li M, . . . Wu LY. [Predicting clinical chemo-sensitivity of primary ovarian cancer using adenosine triphosphate-tumor chemosensitivity assay combined with detection of drug resistance genes]. Zhonghua fu chan ke za zhi. Mar 2011;46(3):193-198.

Zhao H, Zhang Q, Zhao L, Huang X, Wang J, Kang X. Spore Powder of Ganoderma lucidum Improves Cancer-Related Fatigue in Breast Cancer Patients Undergoing Endocrine Therapy: A Pilot Clinical Trial. Evidence-based complementary and alternative medicine: eCAM. 2012;2012:809614.

Zhao JL, Zhao J, Jiao HJ. Synergistic growth-suppressive effects of quercetin and cisplatin on HepG2 human hepatocellular carcinoma cells. Applied biochemistry and biotechnology. Jan 2014;172(2):784-791.

Zheng A, Moritani T. Influence of CoQ10 on autonomic nervous activity and energy metabolism during exercise in healthy subjects. J Nutr Sci Vitaminol (Tokyo). 2008 Aug;54(4):286-90.

Zheng J, Lee HC, Bin Sattar MM, Huang Y, Bian JS. Cardioprotective effects of epigallocatechin-3-gallate against doxorubicin-induced cardiomyocyte injury. European journal of pharmacology. Feb 10 2011;652(1-3):82-88.

Zhou QM, Chen QL, Du J, Wang XF, Lu YY, Zhang H, Su SB. Synergistic effect of combinatorial treatment with curcumin and mitomycin C on the induction of apoptosis of breast cancer cells: a cDNA microarray analysis. International journal of molecular sciences. 2014;15(9):16284-16301.

Zhou QM, Wang XF, Liu XJ, Zhang H, Lu YY, Huang S, Su SB. Curcumin improves MMC-based chemotherapy by simultaneously sensitising cancer cells to MMC and reducing MMC-associated side-effects. European journal of cancer (Oxford, England: 1990). Sep 2011;47(14):2240-2247.

Zhou QM, Wang XF, Liu XJ, Zhang H, Lu YY, Su SB. Curcumin enhanced antiproliferative effect of mitomycin C in human breast cancer MCF-7 cells in vitro and in vivo. Acta pharmacologica Sinica. Nov 2011;32(11):1402-1410.

Zhou QM, Zhang H, Lu YY, Wang XF, Su SB. Curcumin reduced the side effects of mitomycin C by inhibiting GRP58-mediated DNA cross-linking in MCF-7 breast cancer xenografts. Cancer science. Nov 2009;100(11):2040-2045.

Zhu BD, Li X, Zhao QC, Huang XL. [Enhancement of antioxidant capability of cancer patients during chemotherapy by reduced glutathione]. Ai zheng = Aizheng = Chinese journal of cancer. Apr 2004;23(4):452-455.

Zou YH, Liu XM. [Effect of astragalus injection combined with chemotherapy on quality of life in patients with advanced non-small cell lung cancer]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2003 Oct;23(10):733-735.

Zysset-Burri DC, Bellac CL, Leib SL, Wittwer M. Vitamin B6 reduces hippocampal apoptosis in experimental pneumococcal meningitis. BMC infectious diseases. 2013;13:393.