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Fermented Wheat Germ Extract (FWGE) as a Treatment Additive for Castration-Resistant Prostate Cancer: A Pilot Clinical Trial

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ABSTRACT

Castration-resistant prostate cancer (CRPC) is a devastating and incurable disease. Combined therapy using conventional anticancer drugs and a proprietary medical nutriment, fermented wheat germ extract (FWGE), also known as Avemar, has been suggested as a treatment for progressing prostate cancer (PCa) patients, who have become resistant to first line hormonal therapy (gonadotropin releasing hormone, GnRH). The primary aim of this study was to test if this combined therapy would slow down disease progression in CRPC patients. We tested the nontoxic, readily available, inexpensive FWGE, together with the conventional treatment, GnRH analogue, in 36 CRPC patients. Although this is a pilot study, with the drawback of a statistically small sample size, some anticancer clinical activity of FWGE could be seen in the CRPC patients, as measured by prostate specific antigen doubling time (PSADT). We found that the intake of GnRH with FWGE for at least 4 months, improved the overall health as well as the quality of life (QOL) in 4 patients (11%) and was instrumental in extending the PSADT in about 17 (out of 26) patients (65.4%), six of whom were significant. Since no mentionable adverse events were noticed, this treatment may permit the postponement of chemotherapy for these patients.

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Introduction

Castration-resistant prostate cancer (CRPC) is an extremely aggressive progressive state of prostate cancer (PCa). It is the second highest cause of cancer-related deaths among men in Western countries (1). Treatment options for CRPC include, among others, the inhibition of steroid hormone synthesis, the blocking of androgen and endothelin receptors, and the inhibition of angiogenesis and growth factor function. They also include the use of new hormonal drugs (2), bone-directed therapy, novel radiotherapeutics, taxane-based chemotherapy (3), and the use of immunotherapeutic methods (4). Despite continuous research aimed at improving treatment outcomes, CRPC remains incurable (5, 6).

Novel substances and complex nutraceuticals, categorized as complementary and alternative medicines (CAM), may provide additional therapeutic benefits for CRPC patients (7). Although most CAM products have not been studied in clinical trials, they are commonly used by PCa patients (8, 9). One of the most thoroughly studied anticancer nutraceuticals is a proprietary fermented wheat germ extract (FWGE), also known as Avemar (10, 11). Its active ingredient, Avemar pulvis, has demonstrated a firmly established safety profile (12). Preclinical studies show a broad clinical oncology spectrum for the possible use of FWGE (13–15). The use of Avemar as a combination partner for anticancer drug regimens has been proposed (16). In cancer clinical studies, FWGE, administered in combination with chemotherapy, prolonged progression-free and overall survivals in colorectal cancer (17), oral cancer (18), and melanoma patients (19), improved quality of life in late stage head and neck cancer (20), and reduced chemotherapy-induced febrile neutropenia in pediatric cancer patients (21). FWGE has been approved as a dietary food for special medical purposes for cancer patients in Hungary and in other countries of the European

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Union, and has since been marketed, also as a dietary supplement, in other parts of the world (22).

Healthy cells break down glucose via glycolysis followed by transport of pyruvate into mitochondria for oxidative phosphorylation (OXPHOS). In contrast to healthy cells' glucose catabolism, even under sufficient oxygen supply, cells of most types of malignant tumors divert catabolic routes from mitochondria and convert pyruvate to lactate by lactate dehydrogenase (LDH) in the cytosol. This metabolic phenotype, called aerobic glycolysis or the Warburg effect, is the result of oncogene-directed metabolic reprogramming in cancer cells (23). In aerobic glycolysis, per mole of glucose consumed, 2 moles of adenosine 5′-triphosphate (ATP) is produced by substrate level phosphorylation while, in OXPHOS, this ratio is 36. The seemingly energy futile Warburg effect still provides an evolutionary advantage for cancer cells to survive and propagate in the competitive environment of the host. Most neoplastic cells consume a significantly larger amount of glucose than their differentiated counterparts. This results in enhanced aerobic glycolysis to provide sufficient free energy (ATP), to minimize the rates of entropy production (24) and to supply, via the up-regulated altered pentose phosphate pathway (PPP), reducing equivalents (NADPH), precursor molecules (e. g. ribose, fatty acids) and intermediates (e. g. nucleotides) to support anabolic growth (25).

In cancer cells, unlike in their healthy counterparts, FWGE has been seen to prevent glucose uptake, and inhibit key enzymes of glycolysis, such as hexokinase (HK) and LDH, and also dose-dependently inhibit the key enzymes, glucose-6-phosphate dehydrogenase (G6PD) and transketolase (TK), of the nonoxidative steps of the PPP, that are inevitable for nucleic acid precursor ribose synthesis and after all, for gene expression and replication. FWGE-treated cancer cells also became unable to regenerate reducing equivalents required for the reduction of ribonucleotides to deoxyribonucleotides and for other biochemical functions (e. g. to protect the cells against reactive oxygen species). Thus, Avemar, as a nutritional supplement with no known toxic effects, has been suggested for therapeutic use in human cancers where reversion of the transformed metabolic phenotype (aerobic glycolysis or the Warburg effect) is critically important (26, 27).

Manifestation of the Warburg effect in PCa is disease stage dependent. Early prostate cancers don't depend on aerobic glycolysis. Since glucose uptake is not increased in these cells, early PCa cannot be diagnosed by positron emission tomography using radio-labeled glucose analog (FDG PET). However, advanced stage prostate cancers reveal the Warburg effect and have a high glucose uptake (28). Thus, for the therapy of CRPC, targeting the glycolytic enzyme HK, has been suggested (29). As mentioned, Avemar has been seen to selectively and dose dependently inhibit HK enzyme activity in cancer cells with no such effect in healthy cells, and therefore this product seemed a suitable add-on therapeutic option in CRPC patients. It has been demonstrated that the core mechanism by which transformed androgen receptor signaling promoted PCa growth and disease progression to CRPC, embodied amplified carbon flux through the PPP, which was prompted by the mammalian target of rapamycin (mTOR)-mediated upregulation of G6PD, the rate-limiting enzyme of the pentose cycle (30). As previously mentioned, G6DP, the rate-limiting enzyme of the pentose phosphate shunt, was selectively and dose dependently inhibited by Avemar in tumor cells. It was also shown that Avemar in vitro and in vivo pharmacologically inhibited the mTOR-regulated synthesis of PPP-related enzymes (G6PD, TK) in tumor specimens obtained from patients (31). Recently, a preparative fraction of Avemar was demonstrated to reverse the Warburg effect and restore healthy mitochondrial functions in cancer cells. This Avemar fraction reduced lactic acid production, increased mitochondrial flux and OXPHOS, caused cytochrome c secretion from mitochondria into the cytosol thus, reversed the transformed metabolic phenotype, and initiated intrinsic mitochondrial dependent apoptotic signaling in tumor cells (32).

In a preclinical study, FWGE inhibited the growth of human PCa xenograft in laboratory mice, and it has been suggested that the inclusion of FWGE into the treatment protocol of PCa patients may be beneficial (33).

Materials and Methods

We initiated a pilot clinical study to test the clinical value of FWGE in progressing PCa patients who had become resistant to first-line hormone therapy, gonadotropin releasing hormone (GnRH).

Inclusion Criteria

1. Patients had to have cytologically or histologically confirmed PCa with disease progression while on GnRH treatment.
2. Patients' diseases had to be progressive, defined by prostate specific antigen (PSA) values greater

than 1.5 ng/ml and that rose within three consecutive measurements.
3. Patients had to have a World Health Organization (WHO) performance status score of 0, 1, or 2 (with adequate organ function).
4. Life expectancy had to be at least six months.

The study was approved by the Sheba Medical Center's Institutional Review Board (IRB) (Application Number: 4428/06).

GnRH was used either in the form of 10.8 mg of Zoladex or in the form of 12.5 mg of Goserlin acetate, injected every three months.

The FWGE was produced and supplied by Biropharma pharmaceutical company, a good manufacturing practice (GMP) certified manufacturer at Kunfeherto, Hungary. The FWGE was formulated as an instant granulate to be dissolved in water and consumed as a drink before meals. A single dose of FWGE contained 8.5 g of active ingredient (Avemar pulvis).

The FWGE was to be consumed daily. The dosage for patients 1–14 was as follows: patients with a body weight of 90 kg or less had one single dose per day, patients with a body weight greater than 90 kg had two single doses per day, one in the morning and one in the evening. Owing to the lack of toxicity of FWGE when consumed twice daily, patients 15–36 received two single doses of FWGE per day regardless of their body weight. The combined treatment of GnRH and FWGE was delivered for at least four months and continued until further progression of disease. Besides regular standard checkups, the patients' serum PSA levels were analyzed monthly throughout the study.

Statistical Analysis

PSADTs were analyzed for those patients who, after starting therapy, underwent enough PSA measurements, using the best-fitting spline method developed by Guess et al. (34) First, the PSA values were transformed into log (PSA) values. This conversion linearized the relationship between PSA and time and allowed the PSADT to be estimated from the slope of the line. Linear splines are lines that have different slopes but are joined continuously. In our case, there were two lines, before and after the start of FWGE therapy, with the joint at the start of the FWGE treatment. PSADTs before and after the start of FWGE therapy were estimated from the respective slopes of the two lines as follows: PSADT = log (2)/slope. Two graphs were drawn for each patient. The first showed the regression lines estimated separately before FWGE treatment, when we did not force them to meet at the time of FWGE treatment initiation. The second graph showed the linear spline, where the two lines were forced to meet at the time of FWGE treatment initiation. Our analysis was based on the second graph from each set, as it provided the more appropriate estimates of PSADT. Since it was agreed that any change in the PSADT between the first and second time points after FWGE administration could not be due to the biological activity of FWGE, we used the second PSA determination time point after the initiation of FWGE administration as our baseline (ie., zero-time point).

Evaluation of Quality of Life (QOL)

The health related QOL questionnaire used in this study, EORTC QLQ-C30 (version 3.0), was developed and copyrighted by The European Organization for Research and Treatment of Cancer (EORTC, Brussels, Belgium). The QOL assessments were planned to be completed monthly, before and during therapy. However, the timing and the number of the assessments varied for each patient. At the interim stage it was decided that only two general questions should be evaluated, the first relating to general health status in the previous week (Q29) and the second relating to general quality of life in the previous week (Q30). As the trial progressed, four additional points (Q9, Q14, Q16, and Q17) were examined as well. Q9 was related to the degree of pain, Q14 to nausea, Q16 to constipation, and Q17 to diarrhea. For each patient, the overall consistency and changes in general health (Q29) and general QOL (Q30) were examined. Consistency was defined as the occurrence of the same trend over the first five visits in both questions, Q29 and Q30. Change was defined as the average change from the baseline of more than one point compared to the baseline score over the following four visits. For the four additional questions (Q9, Q14, Q16, and Q17), a change was defined as a difference of one unit or more from the baseline to the average score over the four follow-up visits. Questions Q29 and Q30 had a discrete scale of 1–7, where one was considered "bad" and 7 "good." Questions Q9, Q14, Q16, and Q17 had a discrete scale of 1–4, where one was considered "good" and 4 "bad." For patients with less than four follow-up visits, the average follow-up score was calculated for the visits that were recorded.

Results

At the Chaim Sheba Medical Center (Tel Hashomer, Israel), between 2007 and 2010, 36 intent-to-treat CRPC patients were recruited, signed informed consent forms, and entered the study. At baseline, all the patients had already received prior hormonal therapy and, at the time of entry, out of the 36 patients, 28 had already suffered from stage IV (metastatic) disease with bone and/or soft tissue involvement. The baseline characteristics of the recruited patients are shown in Table 1.

After implementation of the zeroth-time point (baseline), out of the 36 intent-to-treat patients, three patients (#25, #28, and #34) had no PSA measurement on which the calculation of PSADT could be based; six patients (#6, #14, #21, #24, #27, and #30) had only one, and one patient (#19) was lost for follow-up. These ten patients were excluded from the PSADT analysis. For three patients (#5, #11, and #16), the earliest pre-FWGE observation was omitted because its determination was performed too long (several months) before the zeroth-time point (baseline) measurement. Although the ten excluded patients had in most cases received FWGE for less than two months and thus could be considered untreated or undertreated from this point of view, their QOL data will be presented here.

Table1. Baseline characteristics of all recruited CRPC patients ($N = 36$).

Characteristics	Values
Age, years	
Median	74.5
Range	58–86
Baseline PSA, ng/ml	
Median	28.385
Range	1.64–546
Hemoglobin, g/dl	
Median	13.04
Range	9.7–14.7
WHO Performance status	
0	23 (64%)
1	12 (33%)
2	1 (3%)
Extent of disease	
Rising PSA only	8 (22%)
Bone metastases	21 (58%)
Soft tissue metastases	3 (8%)
Bone and soft tissue metastases	4 (11%)
Prior local therapy	
Radical prostatectomy	1 (3%)
Radiation therapy	11 (31%)
Radical prostatectomy + Radiation therapy	8 (22%)
Cryotherapy or Cryotherapy + Radiation therapy A	2 (7%)
None	14 (39%)
Prior hormonal therapy	
Up to 2 lines	15 (42%)
More than 2 lines	21 (58%)

PSA Doubling Time

For each patient, two graphs were drawn, as is described in the statistical analysis section of this paper. As stated, our analysis is based on the second graph for each set, since this provides the most appropriate PSADT estimates. As an example, in Figure 1, the (log) PSA levels vs. time for Patient #36 are shown. Three time points were measured before and eight after the treatment commenced. The average slopes before and after FWGE treatment are shown on the graph. Figure 2 shows the PSA values vs. the time points for all 33 treated patients. There is no statistically significant difference between the average slope before and after FWGE treatment. Table 2 presents the PSADTs of the remaining 26 treated patients prior to and after FWGE initiation, as well as the percentage changes (% increase) in PSADT with the levels of statistical significance of the PSADT changes and the corresponding lengths of FWGE administration (from baseline), respectively. Seventeen (65.4%) of the treated patients experienced an apparent increase in their PSADT. Six of them (23.1%; #2, #8, #9, #11, #26, and #36) achieved a significant increase in their PSADT. Patient #26 experienced a major

Table 2. PSA doubling times, percent increase, level of statistical significance and duration of FWGE treatment in CRPC patients.

Patient#	PSADT1	PSADT2	% Increase	P	Duration in days
1	136.5	213.9	56.7	0.13	171
2	34.0	390.6	1050.5	0.005	145
3	88.3	82.6	−6.5	0.78	116
4	194.5	247.3	27.1	0.89	116
5	111.9	114.0	1.8	0.97	115
7	480.2	1095.9	128.2	0.63	225
8	100.4	903.6	800.0	0.00003	199
9	56.4	*	**	0.015	257
10	50.1	*	**	0.06	204
11	19.9	114.1	472.8	0.001	119
12	183.7	102.1	−44.4	0.39	166
13	167.5	201.2	20.1	0.89	145
15	132.4	114.2	−13.7	0.72	112
16	144.7	277.5	91.7	0.31	273
17	38.4	84.5	119.8	0.13	109
18	85.6	184.0	115.1	0.64	112
20	46.6	86.4	85.5	0.11	117
22	73.8	31.6	−57.2	0.13	78
23	221.6	*	**	0.09	279
26	107.1	*	**	0.00046	203
29	53.6	33.1	−38.2	0.16	93
31	202.3	183.6	−9.2	0.87	170
32	136.4	104.7	−23.2	0.48	109
33	77.4	67.8	−12.4	0.77	80
35	306.8	81.9	−73.3	0.07	84
36	56.5	1035.5	1733.7	0.00004	254

PSADT1 - PSA doubling time before treatment.
PSADT2 - PSA doubling time after treatment.
Negative value in % increase means % decrease.
Duration represents the length of FWGE administration in days.
*Negative slope after treatment (increase in PSADT).
**Cannot be determined.

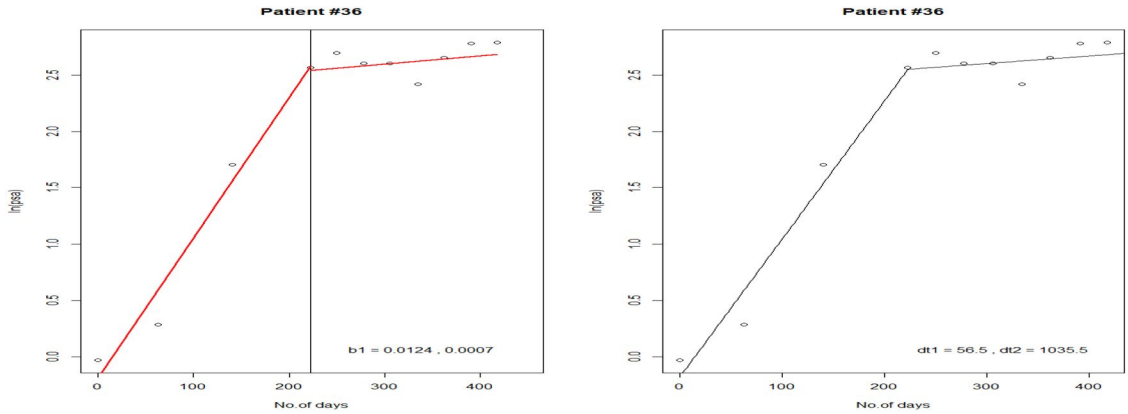

Figure 1. Diagram of (log) PSA levels vs time for CRPC Patient #36 before and after FWGE treatment. The second graph shows the best-fitting spline to estimate PSADTs before and after treatment initiation.

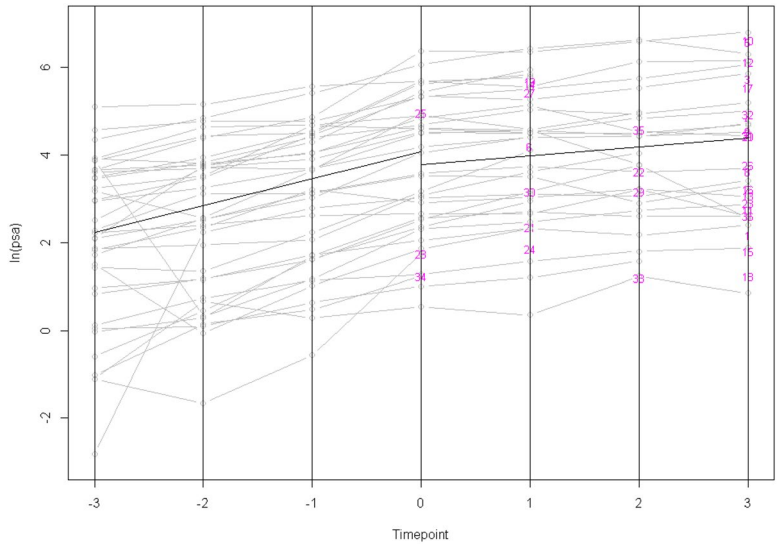

Figure 2: PSA measurements for all patients (with average slopes pre and post baseline). There is no statistically significant difference between the average slope before and after treatment.

improvement in his PSA levels, reaching a level that was less than the pre-baseline measurements. Nine patients (34.6%) experienced an apparent decrease in their PSADT; however, none of the changes were significant. If we use significant reduction in PSA levels or statistically significant increases in PSADT as the criteria of clinical response, 23.1% of the treated patients achieved these criteria.

Quality of Life (QOL)

The QOL scores for Q29 and Q30 for each patient are summarized in Table 3 (data is not shown for the other QOL questions). For the overall health question (Q29), there was an improvement for four patients (11%; #3, #8, #13, and #21) and a deterioration for three patients (8%; #2, #29, and #31), and for the overall QOL (Q30), there was an improvement in four patients (11%; #2, #17, #21, and #36) and a deterioration in three patients (8%; #27, #29, and #31) (see Table 3). For pain (Q9), five patients (14%; #1, #18, #21, #29, and #34) recorded a deterioration and five (14%; #13, #23, #24, #30, and #33) recorded an improvement. For nausea (Q14), six patients (17%; #18, #20, #29, #30, #31, and #24) experienced deterioration and two (6%; #24 and #25) experienced an improvement. For constipation (Q16), six patients (17%; #5, #6, #14, #17, #21, and #22) experienced deterioration and six (17%; #13, #20, #23, #24, #31, and #33) experienced an improvement, and for diarrhea (Q17), three patients (8%; #7, #18, and #33) experienced deterioration and two (6%; #17 and #24) experienced an improvement. Patient #19 generated no follow-up data. No serious or

Table 3. Overall health (Q29) and overall quality of life (Q30) scores in all the recruited CRPC patients.

Patient	Q29 Baseline	Q29 F/U Mean	Q30 Baseline	Q30 F/U Mean	Consistency	Change Q29/Q30
1	5	4.5	5	4.75	Yes	No change**/No change
2	7	5	1	5	No	Deterioration/Improvement
3	4	5.5	7	7	Yes	Improvement/No change
4	3	2.25	3	2.25	Yes	No change/No change
5	5	4.6	5	5.3	Yes	No change/No change
6	6	6	6	6	Yes	No change/No change
7*	5	4.25	5	4	Yes	No change/No change
8*	3	4.25	4	4.5	Yes	Improvement/No change
9*	7	6	7	6	Yes	No change/No change
10*	5	4.25	5	4.75	Yes	No change/No change
11	4	4	4	3.6	Yes	No change/No change
12	4	4	5	5	Yes	No change/No change
13*	4	5.25	5	6	Yes	Improvement/No change
14	5	5	6	6	Yes	No change/No change
15	6	6.25	7	7	Yes	No change/No change
16*	5	5.25	7	6.25	Yes	No change/No change
17	4	4.3	3	4.6	Yes	No change/Improvement
18	3	2.5	3	2.5	Yes	No change/No change
19	4	ND	5	ND	ND	ND
20	6	6	6	6	Yes	No change/No change
21	3	4.5	3	4.5	Yes	Improvement/Improvement
22	7	6	7	6	Yes	No change/No change
23*	4	3.5	4	3.25	Yes	No change/No change
24	6	6	6	6	Yes	No change/No change
25	4	4	4	4	Yes	No change/No change
26	3	3.5	3	4	Yes	No change/No change
27	6	5.5	7	5.5	Yes	No change/Deterioration
28	3	3	4	3	Yes	No change/No change
29	5	3.3	7	3.6	Yes	Deterioration/Deterioration
30	4	3.5	4	3	Yes	No change/No change
31*	5	3.75	5	3.75	Yes	Deterioration/Deterioration
32	4	3.75	4	3.75	Yes	No change/No change
33	3	3.3	3	3	Yes	No change/No change
34	5	5	4	4	Yes	No change/No change
35	4	4.3	5	5.3	Yes	No change/No change
36*	5	5.75	5	6.25	Yes	No change/Improvement

*Patients with more than four follow-up (F/U) visits.
**No change is defined as a difference of 1 unit or less between the baseline and the average post-baseline up to five visits.
ND: no data.

mentionable adverse events were registered during the study.

Discussion

CRPC is a devastating and incurable disease. A combined therapy using conventional anticancer drugs and a medical nutriment known as FWGE or Avemar has been suggested as a possible treatment. This therapy was based on the premise that FWGE hampered the manifestation of the Warburg effect characterized by the malignant metabolic phenotype in cancer cells which could thus indirectly attenuate disease progression in CRPC patients. The beneficial metabolic effects of FWGE, mentioned above, may explain why Avemar administration could contribute to the lengthening of CRPC patients' PSADTs, as presented in the current open-label, pilot clinical study.

The primary aim of this study was to test whether the combined treatment of FWGE and the GnRH analogue would slow or delay the disease progression in CRPC patients and thus enable the postponement of chemotherapy for these patients. In this study, FWGE, in combination with the conventional treatment GnRH analogue, was given to CRPC patients who had failed to improve with previous GnRH treatments. The efficacy of the combined therapy in this group of patients during the study was determined according to two parameters: PSADT and QOL. PSADT is a strong predictor of PCa progression, particularly in patients whose PSA is increasing despite surgery, radiation, or chemical treatment (35). Moreover, PSADT can also serve as a criterion for deciding whether chemotherapy treatment can be postponed. Here, we were able to show that FWGE was instrumental in extending the PSADT of about 17 (out of 26) patients (65.4%), six of whom were significant.

QOL is a subjective assessment and represents the patient's perspective. Some patients experienced improvements in their QOL parameters, while some

patients did not or experienced the opposite. However, no significant changes in QOL were detected, and no serious or mentionable adverse events were reported during the entirety of the study. The administration of the medical nutriment was safe; no toxicity was reported. Although this was a pilot study with the general drawback of a statistically small sample size, definite anticancer clinical activity of FWGE could be seen in the CRPC patients, as measured by PSADT. We found that the intake of GnRH with FWGE for at least four months may significantly prolong PSADT in about one out of four CRPC patients.

Thus, our results indicate the potential benefit of using the combined treatment for CRPC patients. This study, although conducted on a small population of CRPC patients, is encouraging. It demonstrated that the use of the nontoxic, readily available FWGE product improved the overall health as well as the QOL in 4 patients (11%) and was possibly instrumental in significantly prolonging the PSADT in about 23.1% of the CRPC patients. The combined treatment might, therefore, enable postponement of the time when it is crucial to initiate chemotherapy in these advanced PCa patients.

A limitation of the study is that, although the results were encouraging, the study was conducted with a small population of CRPC patients. Another limitation to be considered is an important caveat to the best fitting spline analysis used in this study. The comparison of slopes before and after treatment is subject to a statistical artifact known as regression to the mean. This would occur if patients were selected for the study according to the apparent pattern of their PSA levels. If those patients with the most obviously rising PSA levels are chosen, then, given the random variation involved in PSA level measurement, one would expect to see an increase in the doubling time following entry into the trial, even when no new treatment was given. It has also to be noted that in this study, patients were recruited between 2007 and 2010, before new treatments for CRPC emerged. The classification of CRPC has also been modified since: prostate cancers which progressed despite castrate levels of testosterone, have been considered castration resistant (36). Thus, determination of testosterone level in these patients is part of today's clinical practice. In the present study we did not measure the testosterone levels, because it was not our institute's routine at the time when the study was conducted. Instead, we monitored the regimen of the GnRH analogue injections. Advanced PCa patients, who have become resistant to the treatment of the antiandrogen drug, GnRH analogue, were routinely referred to chemotherapy, since no other hormonal treatment was available at that time. To postpone the chemotherapy, those who despite the antiandrogen treatment showed PSA progression, were defined as CRPC patients, and were recruited into the study.

At present, patients are routinely exposed to new biological therapies that were not available in 2010 (eg., Abiraterone, Enzalutamide), as well as chemotherapy agents (Cabazitaxel etc.) and isotopes like Radium 223 and Lutetium 177 PSMA. Avemar is a complex mixture of molecules with batch-to-batch uniformity, that is guaranteed by standardized GMP manufacturing protocols and robust quality control techniques (11). In preclinical and clinical studies, FWGE had single agent activity and did not compromise the pharmacokinetic and pharmacodynamic properties and the efficacy of anticancer drugs (37). Although we think that FWGE could also be beneficially combined with the new innovative drugs and therapies in PCa, further FWGE-drug interaction studies with the novel anticancer agents are warranted to prove this assumption.

In conclusion, our results indicate that there is potential benefit in the combined therapy using conventional anticancer drugs and Avemar, a proprietary medical nutriment in CRPC patients.

Author's Contribution

The study was initiated and designed by R.W, N.E, M.H, R.B. The data collection was performed by R.W, N.E, R.S, R.B. Analysis of data were made by R.W, N.E, B.O, R.B. The final statistical analysis was performed by B.O. The manuscript draft was made by R.W, N.E, B.O, M.H, R.B. Critical revision of the manuscript content was made by R.W, N.E, B.O, R.S, M.H, R.B. All authors reviewed and approved the final version of the article submitted for publication.

Disclosure statement

Dr. Mate Hidvegi received a consultation fee from Biropharma Company, the Avemar manufacturer. All the other five authors do not have any conflicts of interest.

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