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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

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ABSTRACT

Objective: *The fermented wheat germ extract (FWGE) nutraceutical (Avemar™), manufactured under "good manufacturing practice" conditions and, fulfilling the self-affirmed "generally recognized as safe" status in the United States, has been approved as a "dietary food for special medical purposes for cancer patients" in Europe. In this paper, we report the adjuvant use of this nutraceutical in the treatment of high-risk skin melanoma patients.* ***Methods:*** *In a randomized, pilot, phase II clinical trial, the efficacy of dacarbazine (DTIC)-based adjuvant chemotherapy on survival parameters of melanoma patients was compared to that of the same treatment supplemented with a 1-year long administration of FWGE.* ***Results:*** *At the end of an additional 7-year-long follow-up period, log-rank analyses (Kaplan-Meier estimates) showed significant differences in both progression-free (PFS) and overall survival (OS) in favor of the FWGE group. Mean PFS: 55.8 months (FWGE group) versus 29.9 months (control group), $p = 0.0137$. Mean OS: 66.2 months (FWGE group) versus 44.7 months (control group), $p = 0.0298$.* ***Conclusions:*** *The inclusion of Avemar into the adjuvant protocols of high-risk skin melanoma patients is highly recommended.*

Key words: fermented wheat germ extract, nutraceutical, Avemar, dacarbazine (DTIC), melanoma

INTRODUCTION

Although the molecular signaling pathways leading to the progression of normal melanocytes to melanoma have been explored to a great extent, clinical management of skin melanoma has remained a challenge, and the third and fourth stages of this neoplasia are still incurable.[1] Despite the fact that we have learned a lot about the independent prognostic factors influencing

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the clinical outcomes of this malignancy, and several treatment modalities (e.g., interleukin-2, interferon alpha, and vaccines, all also combined with cytotoxic drugs) have been tried in clinical studies, none of these resulted in satisfactory improvements in terms of survival parameters.[2,3] Among the cytotoxic drugs, dacarbazine (DTIC) on its own or in combination with other agents remains the standard of choice of adjuvant therapy. Nutritional interventions or regular or excessive intake of dietary supplements, herbal remedies, and/or different natural extracts or concentrates have also demonstrated no beneficial effect on the progression of this disease. Among the unorthodox anticancer methods, according to the National Cancer Institute's (NCI) "PDQ Cancer Information Summaries" on Complementary and Alternative Medicine; to date, only the Newcastle disease-virus-derived vaccine (also called Csatary vaccine) has shown signs of efficacy in slowing down the progression of stage III melanoma, but the level of evidence published so far has been considered by NCI as not solid.[4,5]

In the early 1990s, Mate Hidvegi, a Hungarian biochemist, developed a fermented wheat germ extract (FWGE) that showed anticancer efficacy in laboratory animals and, later on, it proved to be effective in cancer patients, too.[6,7] In Europe, this nutraceutical (Avemar™), produced under "good manufacturing practice" (GMP) conditions, has been approved as a "dietary food for special medical purposes for cancer patients." In the United States, this extract has fulfilled the self-affirmed "generally recognized as safe" (GRAS) status,[8] and it has been chosen the "best new product of the year" (NutrAward) at the annual Natural Products Expo West/Supply Expo 2006 in Anaheim, California. This dietary food has been extensively reviewed.[9–12]

Previously, it had been reported that synchronous per oral (p.o.) application of FWGE and intraperitoneal (i.p.) 5-fluorouracyl (5-FU) injection significantly reduced the metastatic spread of C38 colorectal carcinoma in mice, and later on, it was shown that the extract, applied as a supplementary nutriment, increased the progression-free (PFS) and overall survival (OS) in colorectal cancer patients.[13,14] Because FWGE (p.o.), when used simultaneously with a DTIC injection (i.p.) in B16-melanoma-bearing mice, completely inhibited the metastatic spread of cancer cells, a clinical study has been decided on to be carried out with FWGE in melanoma patients. Since the majority of the International Union Against Cancer (UICC) stage III malignant skin melanoma patients, treated with the standard anticancer therapies, will eventually develop a progressive disease, a comparative, randomized, pilot clinical study was initiated to test the efficacy and tolerability of postsurgery adjuvant FWGE in these patients.

PATIENTS AND METHODS

An open-label, randomized, pilot, phase II clinical trial was conducted to assess the supportive value of FWGE in the postsurgical adjuvant setting, given simultaneously with adjuvant DTIC chemotherapy-based treatment, and continued for up to 12 months on its own, in high-risk stage III skin melanoma patients. Postoperative patients were randomized to either the DTIC plus FWGE (FWGE) or to DTIC on its own (control) groups. DTIC (400 mg per m^2 body surface) was given in short infusions. Each cycle lasted for 5 consecutive days and was repeated monthly for up to four times or until the disease progressed. Beyond the adjuvant cytotoxic DTIC monotherapy, patients from the FWGE group took 8.5 g of FWGE (formulated as a water-soluble granulate with added sweetener and flavorings), dissolved in 150 mL of water, orally once-daily, uninterruptedly and continuously from entry to the study for up to 12 months. To be eligible for this study, patients had to have malignant skin melanoma with lymphatic metastases (stage III disease) proven by histology; a World Health Organization (WHO) performance status of 0, 1, or 2; adequate organ functions; and life expectation of at least 12 months. All of the patients had to undergo radical surgery, including the complete removal of the primary tumor with a further complete resection of the involved regional nodes (lymphatic metastases), resulting in a macroscopically disease-free state. Accrual and randomization were done within 1 month following the establishment of the histologic diagnosis. Exclusion criteria entailed: history of some other type of cancer; pregnancy; or lactation. The institutional review board approved the protocol, and all patients gave written, informed consent before entering into the study. All patients were evaluated at baseline, at the end of each DTIC cycle, and 1, 5, and 9 months after the completion of chemotherapy. Clinical evaluation included physical examination, imaging assessment of disease progression (chest X-ray, ultrasonic test of abdominal cavity, and peripheral

lymph nodes), laboratory tests (hematology, chemistry, and urinalysis), and toxicity monitoring according to the National Cancer Institute's Common Toxicity Criteria (NCI-CTC). Primary and/or nodal disease recurrence, new lymphatic and/or distant metastatic spread, and deaths were reckoned as progression-related events. The study was planned to last for 12 months (FWGE treatment), plus a long-term follow-up period was also set forth. Time-related events were measured from the date of entry into the trial, of which the calculation has now been generally accepted.[15] The main aim (i.e., primary endpoint) of this study was to compare PFS in the two groups. For this, a two-tailed, unstratified log-rank test (Kaplan-Meier method), where $p < 0.05$ indicated a statistical significance, was used. For other comparisons, the Fisher's exact test was applied. It was also aimed to collect data about the safety of FWGE in cancer patients.

Although the administration of FWGE lasted for 12 months to test if this dietary food had any effect on PFS, poststudy patients were followed up for about an additional 7-year period. Once progressed, patients received combination chemotherapy of cisplatin, vinblastine, and aranoza[16] and/or interferon (IFN)-alpha therapy, and were treated until the terminal state or death. Additionally, OS was also compared in the two groups.

RESULTS

At the N. N. Blokhin Cancer Research Center in Moscow, between 2000 and 2001, 58 intent-to-treat patients were recruited into this study. In the FWGE group (29 patients), 2 patients refused therapy due to nausea, and 1 patient had progressive disease just prior to study entry. These 3 patients were not included into the analysis. In the control group (29 patients), 2 patients refused treatments (1 due to nausea and 1 due to hematologic toxicity), and 1 patient, probably due to disease progression, was lost. These patients were not included in the data analysis.

Table 1. Patient Characteristics at Baseline of the Study

		FWGE (n = 26)		*Control (n = 26)*	
Patients' characteristics		*(#)*	*(%)*	*(#)*	*(%)*
Sex	Male	15	58	15	58
	Female	11	42	11	42
Age (years)	Mean	50.4 ± 12.6		47.7 ± 13.9	
	Range	25–73		17–72	
Primary site	Head, neck, trunk	18	69.3	22	84.6
	Limbs	5	19.2	4	15.4
	Other	3	11.5	—	—
Tumor thickness (Breslow)	T1: <1.0 mm	1	3.8	—	—
	T2: 1.1–2.0 mm	—	—	3	11.5
	T3: 2.1–4.0	6	23.1	7	26.9
	T4: >4.0 mm	11	42.3	12	46.2
	Unknown	8	30.8	4	15.4
Level of invasion (Clark)	2	1	3.8	2	7.7
	3	11	42.3	12	46.2
	4	4	15.4	3	11.5
	5	2	7.7	3	11.5
	Unknown	8	30.8	6	23.1
Ulceration	Yes	6	23.1	6	23.1
	No	13	50.0	20	76.9
	Unknown	7	26.9	—	—
Number of metastatic nodes	1	14	53.8	10	38.5
	2–3	7	27.0	7	27.0
	4 or more	1	3.8	2	7.7
	Unknown	4	15.4	7	26.8
Time from histologic diagnosis to study entry (days)	Mean	21.2 ± 12.3		25.5 ± 15.8	
	Range	0–49		0–57	

Table 2. Adverse Events (NCI-CTC Grades: G 1–4) by Treatment Arms

	Number of patients							
	FWGE				*Control*			
Event	G 1	G 2	G 3	G 4	G 1	G 2	G 3	G 4
Nausea/vomiting	26	6	0	0	26	9	2	1
Diarrhea	12	0	0	0	23	0	0	0
Fatigue	0	0	0	0	0	7	0	0
Fever/infection	0	2	0	0	0	8	0	0
Leukopenia	0	0	0	0	2	1	0	0
Thrombocytopenia	0	0	0	0	1	1	1	0

NCI-CTC, the National Cancer Institute's Common Toxicity Criteria.

The baseline clinical characteristics of the 52 treated patients are shown in Table 1. There were no statistical differences in the prognostic parameters (e.g., gender, age, primary site, Breslow's staging, Clark's invasiveness, ulceration, number of metastatic nodes, and time from diagnosis to study entry) between the two groups.

There were also no significant differences in the number of patients receiving combination chemotherapy (FWGE: 8; 30.8% versus control: 9; 37.5%) and IFN-alpha (FWGE: 4; 15.4% versus control: 8; 33.3%) treatments after DTIC therapies between the two groups.

The FWGE treatment lasted for 10.2 ± 3.4 months. The administration of the medical nutriment was found to be safe. The adverse events in the FWGE group were transient and mild (Table 2). Notably, there were fewer toxic side-effects in patients receiving the combined therapy than in those of the control group.

PFS

Log-rank analysis (Kaplan-Meier estimate) showed a significant difference, in favor of the FWGE patients, in the duration of PFS. Mean values were: 55.8 (FWGE) versus 29.9 months (control) ($p = 0.0137$) (Table 3, Fig. 1).

OS

Log-rank analysis (Kaplan-Meier estimate) also showed a significant difference in the OS values in favor of the FWGE group. Mean values were: 66.2 (FWGE) versus 44.7 months (control) ($p = 0.0298$) (Table 3, Fig. 2).

Endpoint Analysis

Percentage of patients with progressive disease was as follows: FWGE: 42.3 versus control: 73.1 (significant, $p < 0.05$); percentage of deaths:

Table 3. Survivals of Stage III Cutaneous Melanoma Patients

Survival type	*Groups*	*FWGE*	*Control*
Progression-free survival (PFS)[c]	Number of patients	26	26
	Patients without progression	15 (57.7%)	7 (26.9%)
	Median [CI[a]] (months)	See note[b]	8.5 [7.2–9.8]
	Mean [CI] (months)	55.8 [39.8–71.7]	29.9 [15.3–44.5]
	Patients alive	17 (65.4%)	10 (38.5%)
Overall survival (OS)[d]	Median [CI[a]] (months)	See note[b]	25.7 [11.3–40.1]
	Mean [CI] (months)	66.2 [53.1–79.4]	44.7 [30.2–59.2]
	5-year survival rate (%)	61.5	36.7

[a]95% confidential interval.
[b]Median cannot be defined if the cumulative survival ratio is less than 50%.
[c]Log-rank test: chi-square [1] = 6.08; $p = 0.0137$.
[d]Log-rank test: chi-square [1] = 4.72; $p = 0.0298$.

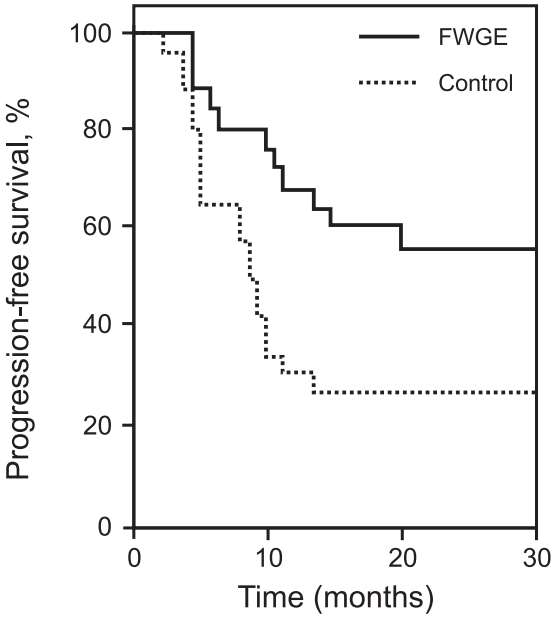

Figure 1. Kaplan-Meier estimate of the cumulative probability of remaining free from disease progression in stage III skin melanoma patients. Log-rank test: chi-square [1] = 6.08; $p = 0.0137$.

FWGE: 34.6 versus control: 61.5 (significant, $p < 0.05$).

DISCUSSION

A randomized, clinical study was carried out to test the supportive effect of FWGE administered orally in stage III skin melanoma patients receiving adjuvant chemotherapy. The wheat-germ-derived nutraceutical was given for about 1 year, while patients also received cycles of DTIC infusions. The latter regimen supplemented with FWGE was superior to chemotherapy on its own, in terms of PFS and the most important OS, determined after a long-term (7-year) follow-up period. We could also demonstrate a lesser amount of adverse events in the FWGE group than in the control group.

There are several anticancer mechanisms that have already been demonstrated in connection with the effects of FWGE.[17–21] The encouraging results of the above clinical study, showing even some long-lasting benefit of the adjuvant DTIC plus FWGE combination, might be explained by a preferable interaction between DTIC and FWGE, since these two agents were applied synchronously. As already mentioned, such interaction in the form of a synergism between the two agents had been found in a preclinical experiment, where DTIC plus FWGE completely inhibited the development of metastases in melanoma-bearing mice. The explanation of this synergism may come from a study where it was found that FWGE selectively and significantly inhibited the DNA repair enzyme, poly(ADP-ribose) polymerase, which is overactivated in cancer cells.[22] DTIC's mechanism of action has been well established, as this drug induced DNA lesions in cells synthesizing new DNA.[23] Thus, when poly(ADP-ribosylation) was inhibited by FWGE, repair of the dacarbazine-induced DNA lesions could be reduced. This inhibition could be paralleled by increased cytotoxicity of the drug, resulting in better efficacy of the adjuvant chemotherapy in the patients.

CONCLUSIONS

We, therefore, highly recommend the inclusion of this fermented wheat-germ-extract-based medical nutriment into the adjuvant protocols of high-risk skin melanoma patients. We also encourage colleagues worldwide to further test this nontoxic active preparation in melanoma and in other types of human cancers.

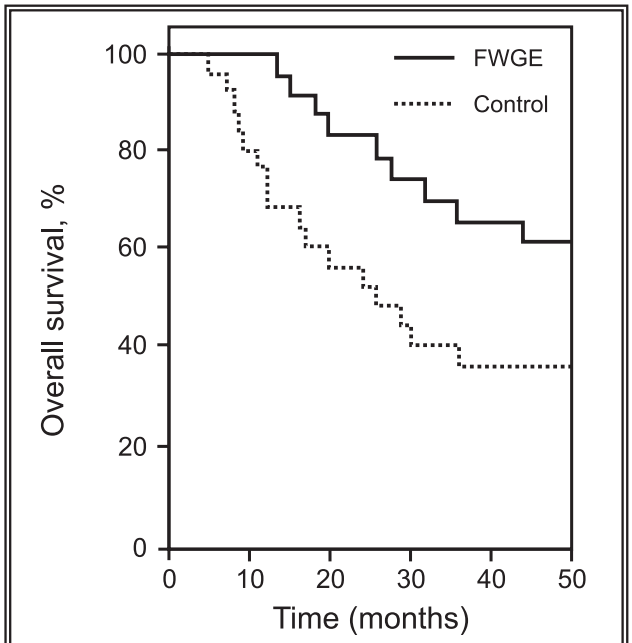

Figure 2. Kaplan-Meier estimate of the cumulative probability of overall survival in stage III skin melanoma patients. Log-rank test: chi-square [1] = 4.72; $p = 0.0298$.

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