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Antimetastatic effect of Avemar® in high-risk melanoma patients

L V Demidov[1], L V Manzjuk[2], G Y Kharkevitch[2], E V Artamonova[2], N A Pirogova[3]
[1]Department of General Surgery, N.N.Blokhin Cancer Research Center, Moscow, Russian Federation; [2]Department of New Anticancer Drug Investigation, N.N.Blokhin Cancer Research Center, Moscow, Russian Federation; [3]Department of Medical Statistics, N.N.Blokhin Cancer Research Center, Moscow, Russian Federation
Contact e-mail:eso.moscow@mtu-net.ru

Patients with stage III melanoma have a high risk of relapse and death from the disease, especially if they have clinically detectable lymph-node involvement. As immunotherapy with interferon α is very expensive and its results are controversial chemotherapy with DTIC still remains an alternative in this category of patients. The objectives of this randomised study was to compare the effect of post-surgery adjuvant DTIC chemotherapy with DTIC plus AVEMAR® in high-risk melanoma patients.

A total of 42 patients with resected regional melanoma metastases were entered into the study by the moment: 23 (Arm I) were allocated to receive 4 cycles of DTIC (2 g per cycle) and 19 (Arm II) - the same plus AVEMAR® - biotechnologically treated, microencapsulated wheat germ extract standardized to substituted benzoquinone derivatives - for 12 months. The arms of the study are well balanced for gender and age. Median follow-up is 10 months. Despite the fact that there was no significant difference in relapse rates we have observed a clear benefit for time to progression in Arm II: 8,9 months as compared with 4,2 months in Arm I. The estimated 1-year relapse free survival rate was 54,5% for patients treated with DTIC plus AVEMAR® versus 38,9% for those treated with DTIC alone. The study is still open.

These preliminary data show that combination of routine DTIC chemotherapy and AVEMAR® may decrease risk of relapse and postpone time of melanoma progression. The published preclinical results suggest that the antimetastatic effect of AVEMAR® is related to its cell adhesion inhibitory, cell proliferation inhibitory, apoptosis enhancing and antioxidant characteristics.

A medical nutriment supports dacarbazine treatment in stage III melanoma

Running title: Medical nutriment in melanoma

Lev V. Demidov, M.D.[1]
Ljudmila V. Manzjuk, M.D.[1]
Galina Y. Kharkevitch, M.D.[2]
Elena V. Artamonova, M.D.[2]
Nina A. Pirogova, Ph.D.[3]
Michele Nichelatti, Ph.D.[4]
Yehuda Shoenfeld, M.D., F.R.C.P.[5]

[1]Melanoma Unit, Department of General Surgery, [2]Department of New Anticancer Drug Investigation and [3]Department of Medical Statistics, N.N. Blokhin Cancer Research Center, Russian Academy of Medical Sciences, Moscow, Russia

[4]Biostatistics Unit, Associazione Malattie del Sangue, Niguarda Cà Granda Hospital, Milan, Italy

[5]Department of Medicine "B", Sheba Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Hashomer, Israel

Interim results of this study were presented at the 18th UICC International Cancer Congress. Oslo, Norway, 30 June – 5 July, 2002.

Correspondence: Yehuda Shoenfeld, Professor and Head, Department of Medicine "B", Sheba Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Hashomer 52621, Israel
Tel.: 972 3 5302652; Fax: 972 3 5352855
E-mail: Yehuda.Shoenfeld@sheba.health.gov.il

CONDENSED ABSTRACT

The supplementation of dacarbazine treatment with a continuous administration of a fermented wheat germ extract (MSC, Avemar) is beneficial for stage III melanoma patients in terms of progression-free survival.

ABSTRACT

BACKGROUND. A fermented wheat germ extract (MSC, Avemar) is a medical nutriment, which has been shown to support treatments in colorectal cancer.

METHODS. In an open-label randomised pilot study we compared, in postsurgical adjuvant setting, the effect of dacarbazine plus an up to 12 months long continuous MSC administration (MSC study group, 22 patients) against dacarbazine treatment on its own (control group, 24 pts) on the progression-free survival of stage III malignant skin melanoma patients.

RESULTS. At the end-point significantly more control patients had a progressive disease (MSC: 36% *vs* control: 75%; $P < 0.01$). Log-rank analysis (Kaplan-Meier estimate) showed a significant difference in the time-to-progression (median, days) in favour of the MSC group (MSC: 366±53 *vs* control: 231±77; P=0.004).

CONCLUSION. The supplementation of dacarbazine treatment with a continuous MSC administration is beneficial for stage III melanoma patients in terms of progression-free survival.

Keywords: fermented wheat germ extract, medical nutriment, stage III melanoma, dacarbazine, progression-free survival

Avemar (code name: MSC) is a standardized fermented wheat germ extract which has been approved as a medical nutriment for cancer patients in Hungary (lic. no. 503), in the Czech Republic (lic. no. HEM-3512-13.103-1178) and in Bulgaria (lic. no. 05180/2003). Previously, it had been reported that synchronous per oral (*po*) application of MSC and intraperitoneal (*ip*) 5-fluorouracyl (5FU) injection significantly reduced metastatic spread of C38 colorectal carcinoma in mice (1) and, later on, it was shown that MSC, applied as a supplementary nutriment, increased progression-free and overall survivals in colorectal cancer patients (2). Futhermore MSC (*po*), when used simultaneously with dacarbazine (DTIC) injection (*ip*) in B16 melanoma bearing mice, completely inhibited metastases spread (1). The aim of this study was to analyze whether this nutriment may supplement the treatment of skin melanoma patients receiving DTIC chemotherapy. 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, randomised pilot clinical study was carried out to test the added value of MSC in these patients.

PATIENTS AND METHODS

An open-label, randomised pilot clinical trial was conducted to assess the supportive value of MSC in postsurgical adjuvant setting, given simultaneously with adjuvant DTIC chemotherapy, and continued for up to 12 months on its own, in high risk stage III malignant skin melanoma patients. Postoperative patients with melanoma were randomised to either [DTIC plus MSC] (MSC) or to [DTIC alone] (control) groups. DTIC (400 mg per m^2 body surface) was given in short infusions. Each cycle lasted for five consecutive days, and was repeated monthly for up to 4 times or until the disease progressed. Beyond the adjuvant cytostatic DTIC monotherapy, patients of the MSC group took 9 grams of the MSC, dissolved in 150 ml of water, orally once daily

uninterruptedly and continuously from entry to the study up to 12 months, while the control patients had been followed up. To be eligible for this study, patients had to have histologically proved malignant skin melanoma with histologically proven lymphatic metastases (stage III disease); a World Health Organisation 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 complete removal of the primary tumor with further complete resection of the involved regional nodes (lymphatic metastases) resulting in macroscopically disease-free state. Accrual and randomization were done within one month following the establishment of the histological diagnosis. Exclusion criteria entailed: history of other type of cancer; pregnancy; 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 completion of chemotherapy. Clinical evaluation included physical examination, by imaging assessment of disease progression, laboratory tests (hematology, chemistry and urinalysis), and toxicity monitoring according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Primary and/or nodal disease recurrence and new lymphatic and/or distant metastatic spread were reckoned as progression-related events. The length of the study was planned to last for 12 months. Time-related events were measured from the date of entry to the trial. The end-point of this study was determined as progression-free survivals of the groups. For this purpose, 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.

RESULTS

Fifty six intent-to-treat patients were recruited to this study. In the MSC group 2 patients refused therapy due to nausea, and 3 patients had to receive other anticancer than the DTIC therapy due to the presence of a progressive disease at or close to study entry. In the control group two patients refused treatment (1 due to nausea, 1 due to hematological toxicity), 2 patients were lost to follow up (probably due to disease progression), and 1 patient just entered the study at the time of the present evaluation. These patients were not included in the data analysis. The baseline clinical characteristics of the treated patients are shown in Table 1. There were no statistical differences in the parameters between the two groups.

The administration of the medical nutriment was found to be safe. No adverse events were reported after completion of chemotherapy, i.e. during the MSC only treatment (MSC group) or follow up (control). In the course of DTIC plus MSC or DTIC only treatments, the following acute adverse events were registered. NCI-CTC *grade* (number of adverse episodes in MSC/control groups). Nausea/vomiting: *1* (29/29), *2* (6/9), *3* (0/2), *4* (0/1); diarrhoea: *1* (12/23), *2* (2/0); fatigue: *2* (0/7); fever/infection: *2* (2/8); leukopenia: *1* (0/2), *2* (0/1); thrombocytopenia: *1* (0/1), *2* (0/1), *3* (0/1). Notably there were less toxic side effects in patients receiving the combined therapy than in the DTIC only group.

At the end-point, the majority of progression-related events were significantly more frequent in the control group (Table 2). Log-rank analysis (Kaplan-Meier estimate) also showed significant difference in favour of the MSC patients in the cumulative probability of progression-free survival (Fig. 1), as well as in the time-to-progression values (Table 3).

DISCUSSION

Metastatic melanoma remains an uncurable condition. Thus, delay of disease progression in this condition is of a high clinical importance. Because the medical nutriment, MSC, had previously been shown to have synergism with DTIC in the prevention of metastatic spread of melanoma cells in mice (1), an open-label, randomised pilot clinical study was carried out. DTIC treatment in an adjuvant setting plus combined with an up to 12 months long continuous MSC administration was found to be superior to DTIC treatment alone in stage III melanoma patients when progression-free survival was compared. Therefore we think that to confirm these exciting preliminary clinical findings a long-term, multicentric, blinded, phase III clinical study of this nutriment with melanoma patients would be worth carrying out.

The explanation behind the benefits of MSC administration in melanoma may be explained by the poly(ADP-ribose) polymerase (PARP) mediated apoptosis induced by this nutriment. MSC has been shown to induce apoptosis in cancer cells by activating the caspase-3 catalysed cleavage of the PARP enzyme (3). It has been proposed that PARP inhibition may increase the cytotoxic potential of DTIC in melanoma cells (4). This might also be true in our study. As the activity of PARP is accelerated in cancer cells, these cells can be selectively sensitised by PARP inhibitors (like MSC) to agents (like 5-FU or DTIC) inducing base-excisions or lesions in DNA (5). Recently, it has been demonstrated that PARP-mediated trans-activation is essential for transcription of the melanoma growth stimulatory activity *CXCL1* gene, which is constitutively expressed during inflammation and progression of melanocytes into a malignant melanoma (6). MSC, through inducing PARP cleavage, may also inhibit the expression of the gene *CXCL1* thus, delaying further progression of the melanoma. In conclusion, the PARP mediated apoptosis inducing mechanism may explain the effect: counter to melanoma-progression, of this medical nutriment produced from a staple food of mankind: wheat.

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Table 1. Patient characteristics at baseline of the study.

		MSC (n = 22)		Control (n = 24)	
		#	%	#	%
Sex[1]	male	13	59.1	15	62.5
	female	9	40.9	9	37.5
Age[2] (years)	mean	49.9		49.4	
	range	25-73		17-72	
	< 40	5	22.7	4	16.7
	40-59	11	50.0	15	62.5
	> 60	6	27.3	5	20.8
WHO performance score[3]	0	1	4.5	5	20.8
	1	21	95.5	18	75.0
	2	0	0	1	4.2
Primary site	head/neck	2	9.1	0	0
	arm/shoulder/chest	6	27.3	5	20.8
	leg/hip	8	36.4	7	29.2
	abdomen/back/waist	5	22.7	12	50.0
	unknown	1	4.5	0	0
Clark level[4]	III	1	4.5	1	4.2
	IV	6	27.3	8	33.3
	V	10	45.4	12	50.0
	unknown	5	22.7	3	12.5
Positive nodes site	cervical	2	9.1	0	0
	axillary	11	50.0	15	62.5
	inguinal	9	40.9	9	37.5
Time from histological diagnosis to study entry[5] (days)	mean	21.1		27.6	
	s.d.[6]	12.7		16.5	
	range	0-49		0-57	

[1]Not significant difference (ND). [2]ND. [3]ND (P=0.148). [4]ND. [5]ND (t[44]=1.475; P=0.147). [6]Standard deviation.

Table 2. Progression-related events (end-point analysis) in stage III melanoma patients. Fisher's exact test.

	MSC (n = 22)		Control (n = 24)	
	#	%	#	%
Primary disease recurrence[1]	1	4.5	1	4.2
Nodal disease recurrence[2]	1	4.5	9	37.5
New nodal disease occurrence[3]	3	13.6	9	37.5
First distant metastasis occurrence[4]	5	22.7	14	58.3
Further distant metastasis occurrence[5]	0	0	5	20.8
Overall events	10	-	38	-
Patients with progressive disease[6]	8	36.3	18	75.0

[1]Not significant difference (ND) (P=0.733). [2]P<0.01. [3]ND (P=0.065). [4]P<0.05. [5]P<0.05. [6]P<0.01.

Table 3. Time-to-progression [days] in stage III melanoma patients (Kaplan-Meier analysis).

	MSC		Control	
	mean (SE[1])	median (SE)	mean (SE)	median (SE)
Progression-free survival[2]	306 (21)	366 (53)	213 (21)	231 (77)
Distant metastasis-free survival[3]	340 (12)	392 (28)	255 (23)	289 (40)

[1]Standard error. [2]Log-rank test: _ [2] = 8.21; P=0.0042. [3]Log-rank test: _ [2] = 7.23; P=0.0072.

Figure 1. Kaplan-Meier estimate of the cumulative probability (%) of remaining free from disease progression in stage III malignant skin melanoma patients. Log-rank test: $\chi^2 = 8.21$; P=0.0042.