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Cytotoxic Chemotherapy of Disseminated Cutaneous Malignant Melanoma—A Prospective and Randomized Clinical Trial of Procarbazine, Vindesine and Lomustine versus Procarbazine, DTIC and Lomustine

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Abstract—*Forty-three patients with measurable disseminated cutaneous malignant melanoma, stages III–IV, and without previous cytotoxic chemotherapy or immunotherapy, were randomly allocated from* 30 *June* 1980 *to* 30 *November* 1984, *to receive either a schedule of procarbazine* (100 mg/m^2 p.o., *max* 150 mg) *days* 1–10, *vindesine* (3 mg/m^2 i.v., *max* 5 mg) *days* 1 *and* 8, *and CCNU* (150 mg/m^2 p.o., *max* 200 mg) *day* 1, (*regimen A*), *with* 4–6 weeks *interval between the courses, or a combination of procarbazine* (100 mg/m^2 p.o., *max* 150 mg) *days* 1–10, *DTIC* (250 mg/m^2 i.v. *max* 400 mg) *days* 1–5, *and CCNU* (150 mg/m^2 p.o. *max* 200 mg) *day* 1 (*regimen B*), *also repeated every* 4–6 weeks. *Twenty-one patients were treated according to regimen A and* 22, *by regimen B. Objective responses* (*three PR, two CR*) *were seen in* 5 *out of* 21 *patients* (23.8%) *in group A and* 8 *out of* 22 (*four PR, four CR*), (36%) *in the group B, this difference not being statistically significant. The median duration of response was* 8 *and* 10 months, *respectively, and the estimated median survival* 10 months *for regimen A and* 14 months *for regimen B. Regimens A and B must be regarded as of no value in view of poor response rate and the unacceptable toxicity, respectively. Therefore, we are now conducting a further phase* II *study, to determine, prospectively, whether the previously noted high response rate obtained with our previous POC protocol can be reaffirmed.*

INTRODUCTION

DESPITE much effort in the medical treatment of disseminated cutaneous malignant melanoma using different regimens of single or combination cytotoxic chemotherapy, the results have remained extremely disappointing and unsatisfactory [1–6]. Since 1973, we have studied different schedules of combination chemotherapy, including mainly nitrosureas, procarbazine and DTIC [7,8].

The introduction of a promising new agent, vindesine [6], created some optimism for the management of the disease. Therefore, in 1980, we initiated a study of two different schedules of combination chemotherapy, modifications of our previous POC regimen [9], one including procarbazine, vindesine and CCNU, compared to our previous POC combination, in which DTIC replaced vincristine, to try to increase the percentage of objective remissions, duration of response and survival. The results of this prospective and randomized study, with 43 evaluable patients with disseminated cutaneous malignant melanoma without previous chemotherapy, are reported here.

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PATIENTS AND METHODS

From 30 June 1980 to 30 November 1984, 43 ambulatory patients with histologically proven cutaneous malignant melanoma (stages III/IV), were selected for this trial (last follow-up 30.11.1985). Eligibility criteria included: measurable disease; no previous chemotherapy or immunotherapy; age < 80 yr; a performance status $\geq 50\%$ (Karnofsky scale), or ≤ 2 (ECOG scale); no evidence of brain metastases. Only patients with cutaneous melanoma were included in this trial;

melanomas of ocular or unknown origin were excluded.

The patients were randomly allocated to receive either a schedule of procarbazine 100 mg/m^2 p.o. (max. 150 mg), days 1–10, vindesine 3 mg/m^2 i.v. (max. 5 mg), days 1 and 8, and CCNU 150 mg/m^2 p.o. (max. 200 mg), day 1 (Regimen A), with 4–6 weeks interval between the courses, or a combination of procarbazine 100 mg/m^2 p.o. (max. 150 mg) days 1–10, DTIC 250 mg/m^2 i.v. (max. 400 mg), days 1–5, and CCNU 150 mg/m^2 p.o. (max. 200 mg) day 1 (Regimen B), also repeated every 4–6 weeks. The interval between the cycles was delayed in presence of persistent myelosuppression. The following dose modifications were adopted according to the grade of toxicity.

Grade of toxicity	White blood count (per μl)	Platelet count (per μl)	Drug dosage (%)
0	≥ 4000	≥ 100000	100
1	3000–3999	80000–99999	75
2	≤ 2999	≤ 79999	0

With grade 2 toxicity, the therapy was stopped until at least grade 1 recovery when therapy was resumed with 75% doses. Only with a leukocyte count 4000 cells/mm^3 and a platelet count 100000 elements/mm^3 were the planned doses given. An adequate therapeutic trial was defined only when two cycles of therapy were administered, to have a firm evidence that the schedule is not effective.

Before randomization baseline investigations were performed, including a full blood count, biochemical screen, chest X-ray, skeletal survey and scans, if clinically indicated. Patients with brain metastases were excluded. A full physical examination was carried out and repeated at 2-month intervals and ultrasound scans at 4 months. Admission criteria of patients included age < 80 yr, normal hepatic and renal functions, no brain metastases, a minimum white blood count of 4000 elements/mm^3 and a platelet count ≧ 100 000 cells/mm^3.

The two treatment schedules were evaluated regarding the overall response rate, the median duration of response, the median survival and drug toxicity. Objective regressions were assessed according to the following criteria:

Complete remission (CR)—total disappearance of all evidence of tumor.

Partial response (PR)—decrease of at least 50% in the sum of the product of the two longest perpendicular diameters of all evaluable lesions, without appearance of new lesions. The response to therapy was calculated by at least two observations not less than 1 month apart. All patients not reaching CR or PR as defined above were classed as nonresponders.

The duration of response was counted from the beginning of cytotoxic chemotherapy until disease progression. Survival was dated from the first course of therapy to death or date of the last follow-up for patients still alive (30 November 1985), and was analysed according to the life-table method. The significance of differences between responses was determined by the chi-square test and the log rank method was used to study the differences for duration of response to treatment and survival.

Table 1. *Clinical characteristics*

	Regimen A	Regimen B
Number of patients	21	22
Male/female	9/12	12/10
Median age in yr (range)	51 (32–77)	49 (30–79)
Median performance status (range) ECOG scale	2 (0–4)	2 (0–4)
Primary Site (no. patients)		
Trunk	8	7
Extremities	13	15
Disease-free interval (yr)		
< 1	8	10
1–5	8	9
> 5	5	3
Metastatic site		
Skin and/or nodes	13	14
Visceral		
Lung	4	3
Lung + Cutaneous	2	3
Lung + Liver + Cutaneous	1	0
Liver	1	2

Table 2. Results

	Number of patients			
	Regimen A		Regimen B	
Number of patients	21		22	
Objective regression				
Complete response	2	5 (23.8%)*	4	8 (36%)*
Partial response	3		4	
Duration (months)				
Median	8+		10	
Range	4–33+		4–28	
Median survival (months)	10		14	

* $\chi^2 = 0.802$: $P > 0.05$.

RESULTS

Twenty-one (21) patients were randomized to receive the regimen A, and 22, the regimen B. The clinical characteristics of each group are summarized in Table 1. Essentially, both groups were comparable with regard to ratio male/female, median age at diagnosis, median performance status, primary site of origin, disease-free interval, and predominant location of metastatic lesions.

Antitumor effects

The results of treatment are shown in Table 2. With the regimen A (including vindesine), five patients (24%) achieved an objective remission, being two, complete (9.5%), as against eight patients (36%) who achieve objective regression with the regimen B, four of them attaining complete remission (18%). Responses were observed in patients with cutaneous and/or nodal, and pulmonary metastases. Objective remissions were not obtained in patients with liver involvement. Three of the patients included in regimen A died with brain metastases. None of them received previous regimens of cytotoxic chemotherapy or immunotherapy. The median duration of remission with the regimen A was 8 months (range 4–33+), and of 10 months (range 4–28), in the group B, these differences not being statistically significant. The survival life-table curve is shown in Fig. 1. The estimated median survival was 10 months for the schedule including vindesine, and for 14 months for the protocol including DTIC; this difference is not statistically significant ($P > 0.05$).

Toxicity

The toxicity of both regimens is shown in Table 3. As previously reported in other studies, the haematological toxicity was, in some cases, severe and the recovery slower. In four cases with the regimen B, and in four, with regimen A, blood transfusions were needed for anaemia. Platelets and white cell transfusions were not required in these patients for either regimen. Despite the severity of the haematological toxicity observed, no drug-related deaths occurred. In three cases, with regimen A, the procarbazine had to be stopped because a "flushing reaction" was observed and the patients refused to go on with this drug; in one of them this was probably because the patient was being treated, concomitantly, with methyldopa.

The leukocyte nadir was 700 cells/mm^3 and the lowest platelet count 30 000 elements/mm^3, in a patient on regimen B. On regimen A, the lowest leukocyte count was 1.400 cells/mm^3 and the platelets were always greater than 100.000/mm^3. One case of sepsis was detected in regimen A, but treated successfully with antibiotics. Nausea and/or vomiting were observed in all the cases treated with either regimen A or B, but moderately well-controlled with antiemetics. Alopecia was detected only in regimen A in 11 cases. No signs of neurotoxicity were observed in group A.

DISCUSSION

The role of either vindesine or DTIC in combination with CCNU and procarbazine has been evaluated in the management of disseminated cutaneous malignant melanoma. The percentage of objective responses to the schedule including vindesine was inferior to the regimen incorporating DTIC, but the difference was not statistically significant. These results typify of the difficulties that have been found in making advances in the treatment of this tumor. Although, in this disease, due to low numbers of patients, the objective remission rates obtained can be over-optimistic and misleading because of the selection of cases with different metastatic patterns (nodal disease, widespread soft tissue dissemination or visceral life-threatening metastases) this did not occur in this

Table 3. Toxicity

Toxic effects	Number of patients Regimen A	Regimen B
Haematologic		
Leukocytes (cells/μl)		
⩾ 4000	5 (24%)	6 (27%)
3000–3999	4 (19%)	4 (18%)
2000–2999	9 (43%)	5 (23%)
< 2000	3 (14%)	7 (32%)
Lowest wbc count:	1400	700
Platelets (cells/μl)	21 (100%)	12 (55%)
⩾ 100.000	0	6 (27%)
80.000–99.999	0	4 (18%)
⩽ 79.999		
Lowest platelet count	120.000	30.000
Gastrointestinal		
Nausea and/or vomiting	21 (100%)	22 (100%)
Diarrhoea	1	0
Alopecia	11 (52%)	0
"Flushing"	3 (14%)	0
Sepsis	1	0
Neurotoxicity	0	0

study. The percentage of regressions with the protocol including vindesine was only 23.8%, similar to that published when the drug is used as single-agent. On the other hand, the inclusion of DTIC in regimen B increased significantly the haematological toxicity of the schedule which was sometimes severe and life-threatening. The administration of that drug, for 5 consecutive days, is difficult for patients to accept.

Objective regressions were not seen in patients with liver metastases with either protocols. With regimen B, three patients died with brain metastases and so, the use of CCNU did not have any prophylactic effect on the subsequent appearance of those lesions.

In conclusion, regimen A, with the promising

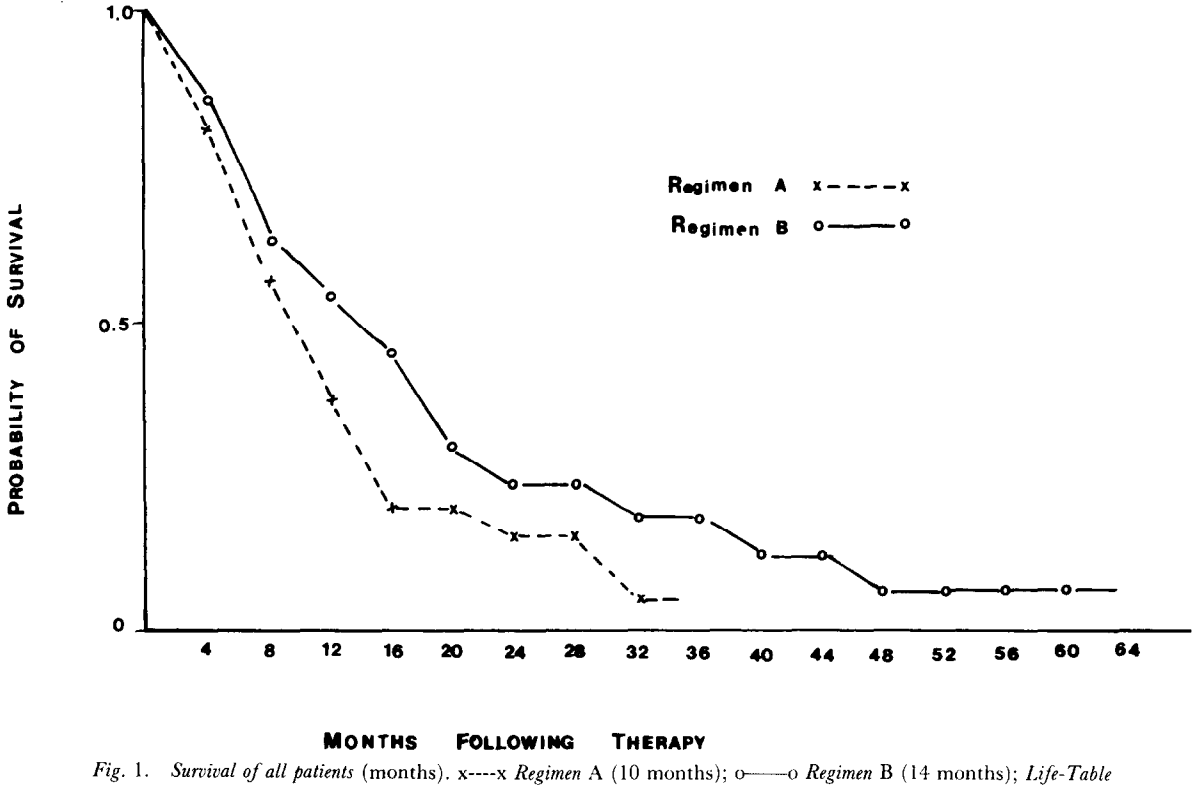

Fig. 1. Survival of all patients (months). x----x *Regimen* A (10 months); o——o *Regimen* B (14 months); *Life-Table method.*

new agent vindesine, must be regarded as of no value, in view of the poor response rate obtained. The discouraging results of regimen A and the unacceptable toxicity of regimen B after further accrual of patients leads us to re-evaluate our previous aim which was to get a useful alternative to our POC protocol [8]. Consequently, our efforts are now, once again, being oriented to investigate, prospectively, in a new phase II study, the precise current value of the POC regimen in a larger number of patients, until new drugs or new combinations or different approaches in immunotherapy are available which can show better results in the treatment of this unpredictable disease.

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