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Cisplatin and Vindesine Combination Chemotherapy in Advanced Malignant Melanoma: an EORTC Phase II Study*

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Abstract—*Sixty-one evaluable patients with measurable advanced malignant melanoma received 4-week courses of a combination of cisplatin* 100 mg/m² *as a* 24-*hr i.v. infusion on day* 1 *and vindesine* 3 mg/m² *as an i.v. bolus on days* 1, 8, 15 *for two courses and every other week thereafter. Two patients achieved complete response for* 46 *and* 81+ weeks *respectively, eleven patients achieved partial response for a median of* 17 weeks *(range* 8–26*) and three patients had no change for* 24 *weeks or more. The overall response rate of* 21% *did not seem to be affected by prior chemotherapy or site of indicator lesions, soft tissue vs visceral. Myelosuppression, consisting essentially of leucopenia, required dose schedule modifications in* 41% *of the first two courses and* 12% *of the remaining courses, but never produced major complications. Non-hematologic toxic effects were prominent, especially nausea and vomiting, which were universal. Alopecia was seen in* 71% *of the patients, neuromuscular manifestations in* 39%, *diarrhea in* 30%, *renal impairment in* 25%, *mucositis in* 12%, *ototoxicity in* 7% *and phlebitis in* 3%. *These results do not suggest striking additive or synergistic antitumor activity of cisplatin and vindesine in advanced malignant melanoma, at least with the method of drug administration selected for this trial.*

INTRODUCTION

CHEMOTHERAPEUTIC agents have usually been of limited clinical benefit in malignant melanoma [1, 2]. DTIC is still widely considered as standard first-line chemotherapy; however, the overall response rate that may be obtained with this compound approximates 20% and response duration is usually short-lasting [3]. Minor efficacy of current systemic treatments in patients with malignant melanoma points to the crucial need for new drug investigations in this disease.

Cisplatin is a new anticancer agent that has shown antitumor activity in a broad spectrum of tumor types [4]. Hints of activity of this compound in malignant melanoma were initially described in a small series of patients [5, 6] and, more recently, a response rate of 11% was found among patients with prior chemotherapy in a large-scale trial of the Southwest Oncology Group [7]. Vindesine is a new vinca alkaloid derivative that has been reported to achieve a 10–22% response rate in advanced malignant melanoma [8–12]. However, no evidence of activity could be detected with this agent in a phase II study of the EORTC Malignant

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Melanoma Cooperative Group [13] as well as in a recently reported series of 12 patients [14].

In non-small cell carcinoma of the lung, it has been suggested that the combination of cisplatin and vindesine might yield an additive and perhaps synergistic antitumor effect [15]. This possible synergism, as well as the individual therapeutic potential of these drugs in advanced malignant melanoma, prompted our group to embark on a phase II study with a combination of these agents. This paper reports the final evaluation of this trial.

MATERIALS AND METHODS

Eligibility criteria included histologic proof of advanced malignant melanoma, measurable lesions, recovery from prior drug-induced toxic effects, progressive disease, age ≤ 75 yr, performance status ≥ 50 (Karnofsky scale), leucocyte counts $\geq 4{,}000/mm^3$, platelet counts $\geq 100{,}000/mm^3$ and normal serum creatinine and bilirubin levels. Patients with active metastatic involvement of the central nervous system, uncontrolled infection, overt psychosis, marked senility or additional malignancies were not eligible.

The chemotherapy regimen was given in 4-week courses. Cisplatin was administered on day 1 at a dose of 100 mg/m^2 as a 24-hr i.v. infusion with mannitol. Furosemide was added as indicated. Patients were prehydrated and cisplatin administration was followed by a 24-hr hydration program. Vindesine was given at a dose of 3 mg/m^2 as a rapid i.v. injection on days 1, 8 and 15 for the first two courses and every other week thereafter. Courses were postponed if there was no complete recovery from bone marrow- or renal toxicity at scheduled re-treatment. The study protocol called for dose reductions of cisplatin if severe myelosuppression or significant serum creatinine elevation were encountered in the previous course. On days 8 and 15 the dose of vindesine was reduced by 50% if white blood cells (WBC) were between 2000 and 3000/mm^3 and/or platelets were between 50,000 and 75,000/mm^3; the drug was withheld with lower values.

Complete response denotes total clinical disappearance of all known disease. Partial response indicates a 50% or more decrease in the sum of the products of the diameters of all lesions. No change is an estimated decrease of less than 50% or increase of less than 25%. Progressive disease is an estimated increase of 25% or more or appearance of any new lesions. In patients with more than one indicator lesion the poorest response designation prevails. Response duration is calculated from initiation of therapy.

RESULTS

Seventy-six patients were entered into the study by 16 institutions. Eight were not eligible because of serum creatinine elevation (3 cases), expected difficulties of follow-up (2 cases), cerebral metastases, age above 75 and leucopenia (1 case each). Seven patients were not evaluable because of loss to follow-up after days 1, 15 and 23 (3 cases), death on day 15, inadequate documentation, inter-current disease complication on day 7 and treatment refusal after one course of therapy with no evidence of progression or excessive toxicity (1 case each). Of note, two non-eligible patients attained a partial response and one patient lost to follow-up after day 15 had achieved a 50% shrinkage in tumor lesions when treatment was stopped. A total of 5 institutions accrued five or more patients in the study and contributed 77% of the 61 evaluable patients. Among these institutions the ratio of the number of evaluable patients to the number of entries was 86% (47/55) vs 67% (14/21) for the others ($P > 0.05$).

Pretreatment characteristics of the 61 evaluable patients are summarized in Table 1. The primary site was the trunk in 20 out of 32 men and the extremities in 17 out of 29 women. Prior chemotherapy consisted of one single-agent treatment with DTIC in 15 patients. Nine of the remaining patients had previously received multiple single-drug programs or combination chemotherapy that included DTIC.

The median number of courses was 3 (range 1–8). One patient received one course, 27 received two courses, 13 received three courses, 10 received four courses and 10 received 5–8 courses for a total of 194 courses.

The overall response rate was 21% (Table 2). Two women with soft tissue and pulmonary

Table 1. Characteristics of the 61 evaluable patients

Men/women	32/29
Median age (range)	53 (22–71)
Median Karnofsky (range)	90 (60–100)
Site of primary:	
trunk	26
extremities	24
head and neck	6
unknown	5
Prior cytotoxic therapy:	
none	25
chemotherapy	24
radiotherapy	7
chemo- and radiotherapy	5
Indicator lesions:	
soft tissue	27
visceral (lung)	15 (13)
soft tissue and visceral (lung)	19 (14)

Table 2. Response data

	No. of patients	Response rate, %	Median response duration in weeks (range)
Complete response	2	3	64+ (46 - 81+)
Partial response	11	18	17 (8 - 26)
No change	3	5	
Progression	45	74	
Total	61		

metastases achieved complete response. One of these had no prior chemotherapy and relapsed in the brain after 46 weeks. The other patient who had shown progressive disease under prior DTIC and who received only 4 courses of cisplatin and vindesine is still in complete remission after 81+ weeks. Partial response was obtained in 11 patients for a median of 17 weeks (range 8–26 weeks). Two of these patients who were administered another therapy while still responding after 14 and 21 weeks are not fully evaluable for response duration. Six of the partial responders had prior chemotherapy and six had visceral indicator lesions. Finally, three patients had stable disease for 24, 24 and 32 weeks respectively; all had received prior chemotherapy and indicator lesions were in soft tissues, visceral sites or both.

Among all responders the median time to partial response was 4 weeks (range 1–13 weeks). In the 2 patients who attained complete remission a 50% tumor shrinkage was apparent after 4 weeks and lesions disappeared after 10 and 13 weeks respectively. Among the 5 responders with indicator lesions limited to soft tissues the median time to response was 4 weeks (range 1–8 weeks), whereas the corresponding figure in the remaining 8 responders was 6 weeks (range 2–13 weeks). There was no apparent correlation between time to response and response duration in individual patients.

Response rates were analyzed by several variables of potential prognostic value. The overall response rate in patients with and without prior chemotherapy was 24 and 19% respectively. For prior and no prior radiation therapy the corresponding figures were 8 and 25% respectively. In 27 patients with measurable disease in soft tissues only the response rate was 19%, whereas in 34 patients with other types of indicator lesions this rate was 24%. Age, sex, site of primary disease and performance status did not seem to influence response rate either. Of interest, among the 47 evaluable patients treated in the five institutions with the largest accrual 12 (26%) achieved partial or complete response, whereas a single partial responder was seen in the remaining 14 patients (7%).

Of 194 courses given 42% were modified for toxicity per protocol. Myelosuppression was the main cause of dose schedule changes. Of 121 courses given as first or second course 49 (41%) were modified for myelosuppression, i.e. 47 for leucopenia, one for thrombocytopenia and one for leucopenia and mucositis. Non-hematologic toxic effects necessitated treatment modifications in 5 additional early courses, i.e. gastrointestinal distress (2), neurotoxicity (2) and renal impairment (1). It must be pointed out that changes for toxicity in the first and/or the second course were made in 6 out of 13 (46%) responders and in 32 out of 48 (67%) non-responders ($P > 0.05$). Of the 73 courses given as third or subsequent courses only 9 (12%) were modified for myelosuppression and 1 for vomiting, but 11 were modified for neurologic manifestations and 7 for kidney damages. At least 8 patients went off-study because of poor tolerance to this regimen.

Myelosuppression consisted mainly of leucopenia and to a lesser extent of thrombocytopenia. Considering all courses, 24% of the patients had no leucopenia and 51 had WBC between 2000 and 3999/mm^3. The remaining patients had lower counts but only 3% had WBC below 1000/mm^3. The median WBC count was 2400/mm^3 and the lowest value was 600/mm^3. The majority of the patients (77%) did not experience thrombocytopenia and only one had platelet counts below 50,000/mm^3 (36,000/mm^3). None of the patients had evidence of infection of hemorrhage related to bone marrow impairment.

Non-hematological toxic effects consisted chiefly of nausea and vomiting (Table 3). This gastrointestinal intolerance was encountered in all patients and was severe in about one-half of these. Alopecia was the second most frequent toxic effect and was experienced by 71% of the patients. Neuromuscular manifestations, including primarily parasthesia, myalgia, muscle weakness and obstipation, were common and occasionally severe. Diarrhea occurred mainly during cisplatin administration or during the hydration procedure.

Table 3. Non-hematological toxic effects

Toxic effect	Number of toxic patients		
	Total (%)	Mild to moderate	Severe
Nausea/vomiting	61 (100)	33	28
Alopecia	43 (71)	21	22
Neurological	24 (39)	20	4
Diarrhea	18 (30)	12	6
Renal	15 (25)	15	
Mucositis	7 (12)	7	
Ototoxicity	4 (7)	4	
Phlebitis	2 (3)	2	

Renal function impairment (creatinine ≥ 1.5 mg/100 ml) was found in 15 patients, but only 6 had creatinine elevations to 2 mg/100 ml or more, with a maximum of 2.8 mg/100 ml. Other toxic effects consisted of mild to moderate mucositis, ototoxicity with hearing loss and/or tinnitus and phlebitis.

DISCUSSION

The overall response rate of 21% is somewhat higher than that reported in most large series with cisplatin and vindesine used as single agents. Results of this cooperative non-randomized trial do not suggest major additive or synergistic antitumor activity of these agents in advanced malignant melanoma. It is noteworthy that apparently minor alterations were introduced in this 2-drug program as compared to the regimen that proved successful in lung cancer [15].

This final analysis does not confirm the favorable results initially reported with this combination of cisplatin and vindesine in previous interim reports [16, 17], pointing to the need for sizeable series of patients before drawing firm conclusions [18]. This has already been strikingly illustrated in a single institution trial of a combination of CCNU, vincristine and bleomycin against malignant melanoma [19, 20]. Thus a 42% response rate was reported in an initial series of 42 patients [19], but no additional response could be obtained with this combination in a subsequent series of 25 patients [20]; a multivariate analysis of 13 variables of potential prognostic value failed to explain this puzzling and highly significant difference in response rate ($P < 0.001$).

In the present EORTC study a careful analysis of the data could not identify variables of significant prognostic value for the response to chemotherapy. This might be related to the relatively small number of patients included in various prognostic categories. Results were encouraging against visceral disease and, of particular interest, the data seem to indicate that response rate might be independent of prior chemotherapy, which consisted of DTIC regimens in the vast majority of our patients. On these grounds the EORTC Malignant Melanoma Cooperative Group is currently evaluating a three-drug combination with cisplatin, vindesine and DTIC.

Overall, toxic effects encountered with this combination were fairly acceptable, although treatment withdrawal in more than 10% of the patients resulted from excessive toxicity. Cisplatin-induced gastrointestinal intolerance was particularly significant but none of the patients received high-dose metoclopramide [21]. It would appear from this trial with 24-hr infusions of cisplatin that this mode of drug administration does not reduce emesis as compared to bolus injections. Neuromuscular effects were also prominent and possible compounding of these toxic manifestations cannot be excluded in a combination of drugs with individual potential for neurotoxicity. Myelosuppression required dose-schedule modifications in nearly one-third of the total number of courses administered but did not produce major complications. These modifications occurred in 41% of the two first courses vs 12% of the subsequent courses; this difference may be ascribed to the variation per protocol in the frequency of vindesine therapy. The possible relationship found in this trial between early tolerance to chemotherapy or full dose administration and likelihood of response remains to be substantiated.

In conclusion, our combination of cisplatin and vindesine has shown therapeutic effectiveness in patients with unfavorable prognostic features. However, the overall response rate is disappointingly low, response duration does not exceed 6 months in partial responders and prolonged therapy often results in dose-limiting non-hematologic toxic effects. These findings further emphasize the high priority of clinical trials aimed at identifying new active compounds against malignant melanoma.

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