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CLINICAL TRIAL REPORT

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Treatment of metastatic malignant melanoma with cisplatin plus tamoxifen

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Abstract A phase II study was performed to assess the efficacy and toxicity of the combination of cisplatin (CDDP) and tamoxifen (TAM) in patients with metastatic malignant melanoma (MM). A total of 31 consecutive previously untreated patients with unresectable measurable MM were given 100 mg/m^2 CDDP every 21 days and 60 mg TAM every 12 h daily. All courses were given on an outpatient basis. A total of 119 courses of treatment were given. In all, 5 of the 31 patients (16%) had an objective response (95% confidence interval 5.3–34%) and 2 (6%) achieved a clinical complete response. The median duration of response was 7 months. The main side effect was gastrointestinal: 13% of the patients experienced grade 3/4 nausea/vomiting. Hematological or neurological toxicities were mild and rare. In conclusion, the combination CDDP-TAM has limited activity in MM, although its toxicity is tolerable. Our results do not allow us to recommend its use for the treatment of MM.

Key words Malignant melanoma · Chemotherapy · Cisplatin · Tamoxifen

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Introduction

In general, chemotherapy has had very limited success in the treatment of metastatic malignant melanoma (MM). Dacarbazine (DTIC), cisplatin (CDDP), nitrosoureas, and vinca alcaloids are the most useful drugs, but the response rate obtained with single-agent therapy varies between 10% and 20% [11]. Taxanes have recently been incorporated into this group of agents [23]. Combination chemotherapy may achieve a 40% response rate, with the median duration of response being 6 months [10]. The median survival of patients with MM is poor (less than 1 year), whatever therapy is used; for this reason the treatment for this condition remains palliative.

In 1976, Fisher et al. [6] reported that tumoral cells had estrogenic receptors in about 50% of patients. However, later studies disclosed that both the concentration of receptors and the percentage of positivity were lower [4, 24]. One trial on the efficacy of TAM for MM showed a response rate of 7% [21]. When combined with chemotherapy in several schemes, TAM obtained a global response rate of about 50% [13]. Although controversy exists as to whether TAM plays a role in these results, some studies suggest synergism between this drug and chemotherapy:

1. A randomized trial showed a significant advantage in terms of response rate and survival for DTIC-TAM versus DTIC alone [3].

2. In a sequential study the response rate decreased from 55% to 10% when TAM was withdrawn from the combination of CDDP-DTIC-carmustine (BCNU)-TAM [13].

3. The addition of TAM to cisplatin in patients with cisplatin-resistant MM achieves a 16% rate of partial responses and a 16% rate of minor responses [17].

4. In vitro studies suggest synergism between CDDP and TAM in the human MM line T-289 [14].

According to these observations, the association CDDP-TAM may be effective for the treatment of MM while avoiding the toxic effects of combination chemotherapy. However, CDDP-TAM has not been studied as front-line therapy for patients with MM. Our objective was to determine the efficacy and toxicity of CDDP-TAM in patients with MM.

Patients and methods

During the period ranging from March 1992 to May 1993, 31 patients with MM were entered into this study. Criteria for patient eligibility included histological confirmation of MM and bidimensionally measurable metastatic disease. All patients had a performance status of 2 or better according to Zubrod's scale (Eastern Cooperative Oncology Group, ECOG) [25]. No prior chemotherapy or prior radiation therapy on the measurable lesion was allowed. Patients were required to have adequate organ function as defined by a granulocyte count of 2×10^9/l or greater and a platelet count of $>100 \times 10^9$/l; normal renal function as defined by a serum creatinine level of <115 μmol/l and a creatinine clearance of >60 ml/min; and normal hepatic function, that is, a serum bilirubin value of <35 μmol/l and serum glutamic oxalacetic transaminase (SGOT) and serum pyruvic transaminase (SGPT) levels of less than 3 times the upper normal limit, unless these alterations were due to metastatic disease.

All patients had measurable disease that was defined as the presence of at least one lesion, clearly bidimensionally measured by physical examination (for cutaneous or lymph node metastases) and computed tomographic (CT) scan or ultrasound examination (for visceral lesions). Patients with bone involvement as the only manifestation of disease were excluded.

CDDP (100 mg/m^2) was given on an outpatient basis over a 45-min period with 3000 cc of glucosaline solution and mannitol. Patients also received oral TAM at 60 mg twice a day for the whole cycle. Cycles were repeated every 21 days.

The toxicity for each course was recorded before the next treatment course and was graded according to WHO scales [20]. If the blood count on the 1st day of a course showed a neutrophil count of $<1.5 \times 10^9$/l or a platelet count of $<100 \times 10^9$/l, treatment was postponed for a maximum of 2 weeks. If the neutrophil count was $1-1.5 \times 10^9$/l or the platelet count was $70-100 \times 10^9$/l by that time, the dose was reduced by 50%. In instances of lower values, treatment was discontinued. In the case of grade 4 toxicity (hematological or non-hematological) the dose of CDDP was reduced by 25% in subsequent courses. When elevated creatinine values did not return to normal before the next cycle, treatment was discontinued.

Response was evaluated (WHO guidelines [20]) in all patients at the end of every third cycle by medical history, physical examination, pretreatment imaging techniques, and laboratory studies. Reevaluation was undertaken sooner if there was clinical evidence of progression. Briefly, a complete response (CR) required the total disappearance of all tumors initially observed, with no evidence of new areas of malignant disease. A partial response (PR) was defined as a reduction of at least 50% in the sums of the products of the longest perpendicular diameters of all clearly measurable tumor masses, with no increase in the size of any lesion and no new area of malignancy. All responses were maintained for a minimum of 2 months. Stable disease was defined as a decrease of less than 50% in the total tumor size or an increase of less than 25% in the size of one or more measurable lesions. Disease progression was defined as a 25% increase in any measurable lesion, the appearance of new areas of malignant disease, or symptomatic deterioration of the performance status by more than one level.

Table 1 Patients' characteristics

Characteristics	Number	%
Median age in years (range)	53 (23–73)	
M/F	16/15	
Premenopausal	5	
Postmenopausal	10	
Pretreatment ECOG performance status:		
0	13	42
1	10	32
2	8	26
Number of disease sites:		
1	15	49
2	16	51
Sites of disease:		
Lung	16	51
Lymph node	12	39
Liver	10	32
Subcutaneous	9	29
Others	5	16

Table 2 Therapeutic results

Complete response	2 (6%)
Partial response	3 (10%)
Stable disease	12 (39%)
Progression	14 (45%)

Table 3 Toxicity encountered in 119 courses

	WHO toxicity grades 1–2		WHO toxicity grades 3–4	
	Per patient	Per cycle	Per patient	Per cycle
Nausea/vomiting	10 (32%)	41 (34%)	4 (13%)	10 (8%)
Anemia	4 (13%)	7 (6%)		
Leukopenia	2 (6%)	4 (3%)		
Thrombocytopenia	2 (6%)	3 (3%)	1 (3%)	1 (1%)
Neurotoxicity	2 (6%)	3 (3%)		
Nephrotoxicity	2 (6%)	2 (2%)		

Death occurring due to disease progression or toxicity before those dates were considered as therapeutic failures. Response duration and survival were calculated from the 1st day of chemotherapy. Complete or partial responders received up to six courses of chemotherapy until disease progression or unacceptable toxicity occurred.

Informed consent was obtained from all patients. The median survival time and the median remission duration were calculated by the Kaplan-Meier method.

Results

Table 1 displays the patients' characteristics. A total of 31 patients were enrolled into this study at the 7 participating institutions. The median age was 53 (range 23–73) years. There were 15 women (48%), 10 of them in a postmenopausal state (32%). The ECOG performance status was 0 in 13 patients (42%), 1 in 10 patients (32%), and 2 in 8 patients (26%). Altogether, 15 patients (48%) had single unresectable metastases, whereas 16 (52%) presented with involvement of 2 or more organs. The distribution of metastases was as follows: the lung in 16 patients (52%),

the lymph nodes in 12 (38%), the liver in 10 (32%), and the skin in 9 cases (29%).

A total of 119 cycles of CDDP-TAM were given to 31 patients (median 3.8 courses/patient; range 2–6). The mean weekly dose was 22.5 mg/m^2 for cisplatin. One patient decided to discontinue therapy after the second course.

In all, 2 patients (6%) achieved a clinical complete remission and 3 (10%) displayed a PR, for an overall response rate of 16% (95% confidence interval 5.3–34%; Table 2). The median duration of response was 7 months. The responders included 3 men and 2 postmenopausal women. When the site of metastasis was considered, the response rate was 25% for the lung, 10% for the liver, and 16% for lymphadenopathies and skin. No difference was detected with regard to the number of metastatic locations (1 versus 2–3). The median overall survival was 8 months for all patients and 13 months for those who responded to chemotherapy.

Table 3 delineates the toxicity encountered. The main toxicity was nausea/vomiting, which was graded 3–4 in 13% of patients and 8% of the courses. Hematological toxicity was modest, with only 1 patient developing thrombocytopenia of grade 3 (3%). There was no grade 3–4 neutropenia or anemia. In all, 2 patients (6%) experienced peripheral neuropathy after 4 and 5 cycles of chemotherapy, respectively. No patient had deep venous thrombosis or pulmonary embolism. A patient who received four courses of CDDP-TAM had an endometrial carcinoma at 8 months after the end of chemotherapy.

Discussion

The response rate achieved in our patients is similar to that reported for CDDP as a single agent, 10–20% [8, 9]; thus, TAM does not seem to potentiate the action of CDDP. Before reexamining the rationale for the CDDP-TAM regimen, we have to comment on some characteristics of our patients that could have affected the results. Multicentric trials usually yield results worse than those attained in single-institution studies. Besides, in our series there was a higher percentage of patients with an ECOG performance status of 2, visceral metastases, and more than one metastatic site as compared with other series [1, 3, 17]; all these characteristics confer a poor prognosis [11]. However, as our population came from different geographical areas, we think that they truly represent the general features of patients with metastatic MM in our environment.

Some authors have suggested that a postmenopausal status in women could increase the efficacy of TAM in MM, as happens in breast cancer [3]. The proportion of postmenopausal patients in our series was similar to or even higher than that reported from other studies in which TAM was supposed to potentiate the activity of dacarbazine [3] or to overcome cisplatin resistance [17]. However, this theoretical advantage did not result in a higher response rate. Thus, we think that our poor results are not due to the patients' characteristics but to a lack of synergism between TAM and CDDP. Other studies associating chemotherapy and TAM have not been capable to improving the results obtained with single-agent chemotherapy [2, 5, 12, 22].

Several mechanisms could account for the theoretical synergism between TAM and CDDP. TAM delays the appearance of cisplatin resistance through an unknown mechanism that seems different from those described to date [18]. The synergism does not depend on the presence of estrogen or progesterone receptors [16] but could be mediated via antiestrogen binding sites. TAM resistance would be secondary to a decrease in the absolute number of these binding sites [19]. Human melanoma T-289 cell-line cultures have shown that the synergism depends on the TAM concentration; the concentration usually needed is >0.1 μmol/l [14], which requires that TAM be given at a dose of 20 mg/day [13]. However, if the tumor cells have a low level of resistance to CDDP, a higher concentration (1 μmol/l) of TAM is required for sinergy [15], which is achieved with a TAM dose of 160 mg/day. This dose is higher than that used in our trial, but it is difficult to believe that such a small difference would account for our poor results.

The toxicity seen with our scheme corresponds to that produced by high-dose cisplatin. One patient developed an endometrial carcinoma 8 months after the end of chemotherapy. Although this complication has been described in patients with breast carcinoma receiving lower doses of TAM [7], no case has been reported in patients with MM, probably due to their short duration of survival. However, this risk should be kept in mind, especially with the use of high doses.

In summary, the data presently available on the CDDP-TAM combination indicate limited activity with tolerable toxicity. However, the lack of synergism does not allow us to recommend the use of this regimen for the treatment of metastatic MM.

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