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Short Communication

Subcutaneous Recombinant Interleukin-2 Plus Chemotherapy with Cisplatin and Dacarbazine in Metastatic Melanoma

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The aim of our study was to verify the efficacy and tolerability of subcutaneous low doses of interleukin-2 with cisplatin and dacarbazine for malignant melanoma. 24 patients were included. The following schedule was used: cisplatin (CDDP) 100 mg/m^2 day 1; darcarbazine (DTIC) 375 mg/m^2 days 1–5; recombinant interleukin-2 (rIL-2) 4.5 million IU × 2/day days 13–17 and 20–24. The therapy was recycled every 28 days. 10 patients obtained clinical remission (42%), with 2 complete responses (8%) persisting for 12 and 15+ months, and 8 partial responses (35.5%) with a median duration of 5 months. Median survival of all 24 patients was 8 months, 13 months for responders and 6 months for non-responders. Responses were seen predominantly in lymph nodes (48%) and skin-soft tissue (38%), but were also seen in the liver (29%) and lung (14%). Treatment was relatively well tolerated and toxicity was mainly related to chemotherapy.

Key words: metastatic melanoma, CDDP + DTIC + subcutaneous IL-2
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INTRODUCTION

In metastatic malignant melanoma, single agent dacarbazine (DTIC), has been shown to be the most efficacious drug, and yields the highest response rates of about 20% [1]. More recently, combinations including cisplatin (CDDP) with or without DTIC have obtained response rates of over 40% [2], but the majority of these responses were partial and of short duration.

Recombinant interleukin-2 (rIL-2) as single agent, with or without lymphokine-activated killer cells (LAK), has been evaluated in a variety of doses and treatment schedules, and has demonstrated good antitumour activity against malignant melanoma [3, 4]. As the initial intravenous use of this cytokine was associated with severe toxicity requiring intensive care unit support, subcutaneous IL-2 administration was used [5, 6], and its efficacy has been recently demonstrated in metastatic melanoma [7.]

In vitro data and clinical trials suggest that IL-2 immunotherapy and chemotherapeutic agents are not crossresistant [8]. Nevertheless, only a slight improvement in response has been reported for the combination of IL-2 plus DTIC in malignant melanoma patients [9, 10]. Experimental results seem to demonstrate a particular activity for the association of CDDP with IL-2 in melanoma [11]. Therefore, the aim of this study was to verify the efficacy of the triple combination of subcutaneous rIL-2, CDDP and DTIC in patients with malignant melanoma.

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PATIENTS AND METHODS

Patients

Between January 1992 and December 1994, 24 adult patients with metastatic IV stage disease were treated in the Medical Oncology Division of the Oncology Institute in Bari. Eligibility criteria included histologically confirmed, bidimensionally measurable metastatic lesions, performance status ≤2 (ECOG scale), and a life expectancy of at least 3 months. Previous surgery, radiotherapy and chemo-immunotherapy including the drugs used in this protocol, but as single agents only, were permitted, provided that they had been completed at least 4 weeks before entry into the study. Moreover, patients with a history of significant cardiovascular disease or brain metastases were excluded.

Pretreatment evaluation included medical history, physical examination, complete blood, renal and liver function. Chest and skeletal radiograph, electrocardiography and echocardiogram, and tumour measurements (including computed tomography scans if required) were also performed.

The patient characteristics are listed in Table 1. 2 patients had failed prior chemotherapy with DTIC, and 6 patients

Table 1. Patient characteristics

Characteristics	No. (%)
Sex M/F	11/13
Median age (years)	58
Range	34–72
ECOG performance status 0/1/2	6/16/2
No. of metastatic sites 1/2/3/≥4	4/9/8/3
Disease sites*	
Visceral disease	14 (59)
Non-visceral disease	10 (41)
Lymph nodes	21 (87.5)
Skin/soft tissues	16 (67)
Lung	7 (29)
Liver	7 (29)
Bone	3 (12.5)
Other†	3 (12.5)
Previous treatments‡	
Surgery	23 (96)
Radiotherapy	2 (4)
Chemotherapy	2 (4)
Immunotherapy	
IFN alpha adjuvant	6 (25)
metastatic	2 (4)
rIL-2 adjuvant	0
metastatic	4 (17)
No systemic treatment	15 (63)

*Some patients had more than one site of disease. †1 case of abdominal disease, 1 case of adrenal gland and 1 case of neoplastic pericardial effusion. ‡Some patients had more than one systemic treatment.

progressed after a first immunotherapy including rIL-2 (4 patients) and alpha Interferon (2 patients).

Treatment regimen

Treatment consisted of cisplatin on day 1 at 100 mg/m^2 (administered with usual hydration modalities), DTIC at a dose of 375 mg/m^2 in 500 ml of 5% dextrose from days 1 to 5 and rIL-2 (Proleukin, Chiron, Amsterdam, The Netherlands), with a specific activity of 18×10^9 IU/mg of protein equalling 3×10^9 Cetus units, administered subcutaneously at a dose of 4.5 million IU twice a day from days 13 to 17 and from days 20 to 24. The twice daily rIL-2 subcutaneous administration was preferred in order to maintain more constant serum IL-2 levels [7]. The cycle was repeated every 28 days if haematological and renal recovery were complete.

When needed, acetaminophen was administered to reduce fever and systemic 'flu'-like side-effects. The use of intravenous fluids and vasopressor agents was permitted for important hypotension. Furosemide was administered to expedite the mobilisation of retained fluids during and after treatment.

Dose modification

The chemotherapeutical dosage was decreased by 25–50% if grade 4 haematological toxicity or significant infections occurred. If myelosuppression persisted up to the time of the next cycle, chemotherapy was withheld until the neutrophil count recovered to at least 1500/ml and platelets to 100000/ml. G-CSF administration was permitted when neutropenia was less than 500/ml and was continued until the neutrophil level increased to at least 1500/ml. If the recovery of renal function was not complete, CDDP was reduced and/or fractionated.

Evaluation of response and toxicity

Patients were assessed for disease response every 4 weeks by clinical and radiological examination of the disease sites. Response and toxicity were classified according to WHO criteria [12].

The complete response (CR) duration was measured from the onset of CR to the date of disease progression, and that of partial response (PR) from the first day of treatment until disease progression. Duration of survival was calculated from the first day of treatment until the date of death. The time to progression, duration of response and survival were determined by the Kaplan–Meier method. The data pertaining to time to progression, duration of response and survival were updated on May 1995.

RESULTS

Response

Patients received a median of four cycles of treatment (range: 2–6). 10 patients achieved an objective response (42%); 2 patients obtained a CR (8%) after two and three cycles of therapy, which persisted for 12 and 15+ months, respectively. 8 patients obtained PR (33%) with a duration of 9+, 7, 5+, 5+, 4, 3, 3 and 2 months; 9 patients (38%) had stable disease for 3–6 months (median 4 months). Seventy per cent of responses were observed after two or three cycles.

Median duration of overall response was 5+ months and median survival of patients with CR or PR was 13 months (range: 3–27+); patients with stable disease (SD) and progressive disease (PD) had a median survival of 6 months. For all 24 patients treated, the median time to progression was 4 months, and the median survival was 8 months. The age, performance status, disease-free interval, time from first metastasis and start of therapy, and the number of metastatic sites did not influence the overall response, even though a complete response was obtained in 1 patient with two disease sites at the latero-cervical lymph nodes and soft tissues, and in 1 patient with liver disease only. The first of these 2 patients, after six cycles of CDDP + DTIC + IL-2, was given rIL-2 maintenance therapy for 6 months at a dose of 3 million IU/day three times a week; the patient is free of disease at 15 months from the start of therapy.

The response at individual metastatic sites is shown in Table 2. Responses were also seen in pretreated patients, with 2 of the 4 patients pretreated with IL-2 achieving a partial response, and 1 of the 2 patients pretreated with DTIC obtaining a partial response. Among the patients pretreated with interferon, 1 obtained a complete response and 1 a partial response.

Toxicity

The therapy was relatively well tolerated and toxicity was mainly related to chemotherapy. The most relevant side-effect was myelosuppression (neutropenia and thrombocytopenia WHO grade 3–4 in 7 patients), which represented a dose-limiting toxicity in 25% of patients. 6 of these 7 patients required use of recombinant G-CSF because of granulocytopenia less than 500/ml. 2 patients required platelet transfusions for platelet counts less than 20000/ml. 6 patients (25%) had delayed treatment owing to slow recovery of the

Table 2. Response characteristics

Characteristics	No. of patients	CR	PR	(CR + PR) (%)	SD	PD
Disease sites						
Lymph nodes	21	1	9	(48)	7	4
Skin/soft tissues	16	1	5	(38)	8	2
Liver	7	1	1	(29)	3	2
Lung	7	—	1	(14)	4	2
Skeleton	3	—	—	—	2	
Other	3	—	—	—	3	—
No. of disease sites						
≤2	13	2	3	(38)	5	3
>2	11	—	5	(45)	4	2
ECOG performance status						
0–1	22	1	8	(41)	8	5
2	2	—	1	(50)	—	1
Previous systemic treatments						
Yes	9	1	3	(44)	4	1
No	15	1	5	(40)	6	3

CR, complete response; PR, partial response; SD, stable disease, PD, progressive disease.

neutrophil and/or platelet count. 3 patients required red blood cell transfusions for symptomatic anaemia (haemoglobin less than 7 g %).

Nausea and vomiting were generally well controlled by ondansetron and dexamethasone. 4 patients had a reduction of creatinine clearance to less than 60 ml/m which persisted for approximately 1 week in spite of prolonged hydration and furosemide administration. Because of their slow and incomplete renal recovery, further CDDP administration was fractionated in these patients. One patient complained of a persistent bilateral hypoacusia.

The IL-2-related toxicity was very low and, after the first days of treatment as inpatients with the purpose of testing eventual reactivity of each patient to IL-2, the treatment was continued as home therapy. The most frequent side-effects included erythema and induration at injection site (100%), 'flu'-like syndrome (80%), mild hypotension (30%) not requiring the use of fluid or vasopressor agents, nausea and vomiting (30%), itching and skin rash, myalgias, oliguria, and temporary increase of transaminase (10%). One patient developed pulmonary oedema after the second day of IL-2 administration and thus continued treatment with chemotherapy alone. Nevertheless, a more precise clinical history of this patient showed that he was affected by an asymptomatic mitral valve insufficiency. This patient obtained a partial response of 5 months. All IL-2 side-effects regressed when therapy ceased. About 70% of rIL-2 was administered as home therapy.

DISCUSSION

The chemo-immunotherapeutic regimen used in this study, comprising CDDP, DTIC and low doses of rIL-2 given subcutaneously, proved to be efficacious in metastatic melanoma patients. In fact, we obtained a 42% overall response with a median response duration of more than 5 months and a median responder survival of 13 months. Moreover, responses were also noted in visceral sites including lung and liver, and in patients with multiple metastatic sites. These results are much better than those obtained when these drugs were used as single agents and better than those observed with a IL-2–DTIC combination for which the response rate was generally less than 30% [9, 10]. The use of CDDP in association with IL-2 [13] or the introduction of CDDP in the IL-2–DTIC combination, seems to increase significantly clinical results, as demonstrated by several authors [14, 15]. However, these results are difficult to compare because of the different IL-2 doses and schedules used and because other drugs (carmustine, interferon or tamoxifen) were also employed.

In the published results on the combination of CDDP, DTIC and IL-2, the latter has been administered at intravenous doses 10-fold higher than our regimen. As a consequence, toxicity was higher than in our series, whereas the therapeutic results were similar. In fact, in our study, no patient required a dose reduction and all symptoms resolved after ceasing treatment.

In conclusion, the regimen utilised in this study is a valid therapeutic option for the design of future phase III trial in malignant melanoma.

1. Legha SS. Current therapy for malignant melanomas. *Semin Oncol* 1989, **16** (Suppl. 1), 34–44.
2. De Prete SA, Maurer LH, O'Donnel J, *et al.* Combination chemotherapy with cisplatin, carmustine, dacarbazine and tamoxifen in metastatic melanoma. *Cancer Treat Rep* 1984, **68**, 1403–1405.
3. De Lena M, Lorusso V, Guida M. *Interleukin-2: Biological, Pharmacological, and Clinical Aspects.* Milano, Masson, 1992.
4. Rosenberg SA. The immunotherapy and gene therapy of cancer. *J Clin Oncol* 1992, **10**, 180–199.
5. Atzpodien MJ, Korfen A, Franks CR, *et al.* Home therapy with recombinant interleukin-2 and interferon-2b in advanced human malignancies. *Lancet* 1990, **335**, 1509–1512.
6. Guida M, Latorre A, Casamassima A, *et al.* Subcutaneous rIL-2 in advanced melanoma and kidney carcinoma: clinical and biological aspects. In Bergmann L, Mitron PS, eds. *Contributions in Oncology Cytokines in Cancer Therapy.* Basel, Karger, 1994, 182–190.
7. De Lena M, Guida M, Casamassima A, *et al.* Subcutaneous rIL-2 in advanced melanoma and kidney carcinoma. *Int J Oncol* 1992, **1**, 181–189.
8. Richards JM, Gilewski TA, Ramming K, *et al.* Effective chemo-

therapy for melanoma after treatment with interleukin-2. *Cancer* 1992, **69**, 427–429.
9. Flaherty LE, Redman BG, Chabot GG, *et al.* A phase I–II study of dacarbazine in combination with out patient interleukin-2 in metastatic malignant melanoma. *Cancer* 1990, **65**, 2471–2477.
10. Stoter G, Ammdal S, Kodenhuis S, *et al.* Sequential administration of recombinant human Interleukin-2 and dacarbazine in metastatic melanoma: a multicenter phase II study. *J Clin Oncol* 1991, **9**, 1687–1691.
11. Allavena P, Pirovano P, Bonazzi C, *et al. In vitro* and *in vivo* effects of cisplatin on the generation of lymphokine activated killer cells. *J Natl Cancer Inst* 1990, **82**, 139–142.
12. Miller AB, Hoogstraten B, Staquet M, *et al.* Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
13. Demchak PA, Mier JW, Robert NJ, *et al.* Interleukin-2 and high-dose cisplatin in patients with metastatic melanoma. A pilot study. *J Clin Oncol* 1991, **9**, 1821–1830.
14. Legha S, Ring S, Bedikian A, *et al.* Biochemotherapy using Interleukin-2 + Interferon Alpha-2a in combination with Cisplatin, Vinblastine and DTIC in patients with metastatic melanoma. *Melanoma Res* 1993, **3**, 32–36.
15. Khayat D, Borel C, Tourani JM, *et al.* Sequential chemoimmunotherapy with cisplatin, interleukin-2, and interferon alfa-2a for metastatic melanoma. *J Clin Oncol* 1993, **11**, 2173–2180.

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