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Short Communication

Phase II Study of a Short Course of Weekly High-dose Cisplatin Combined with Long-term Oral Etoposide in Metastatic Malignant Melanoma

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The results of cytostatic therapy in metastatic melanoma are very disappointing. In phase II studies with high-dose cisplatin regimens, a remarkably high response rate was observed. In a phase I study with a short course of weekly cisplatin, combined with oral etoposide, we were able to reach, in most patients, a cisplatin dose intensity of 60 mg/m²/week. We performed a phase II study with this schedule in metastatic malignant melanoma. 15 consecutive patients were entered in the study. Treatment consisted of cisplatin 70 mg/m² on days 1, 8, 15 and days 29, 36, 43 combined with oral etoposide 50 mg daily, days 1–15 and days 29–43. Patients with a response or stable disease continued treatment with oral etoposide 50 mg/m² daily, days 1–21 every 4 weeks. All patients were evaluable for response and toxicity. The majority of the patients received six cycles of cisplatin with the planned cisplatin dose intensity of 60 mg/m²/week. A partial response was observed in 2 patients (13%; 95% confidence interval (CI) 2–44%) of, respectively, 22 and 12 weeks; stable disease was observed in 6 patients. Toxicity consisted mainly of alopecia and bone marrow suppression. 4 patients had tinnitus, one patient had neurotoxicity grade 1. The regimen studied has only limited activity in metastatic melanoma in spite of the high-dose intensity of cisplatin reached with this schedule.

Key words: phase II study, cisplatin, etoposide, melanoma

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INTRODUCTION

DESPITE THE introduction of new cytotoxic drugs and immunotherapy with IL-2 and interferons, the grim prognosis for patients with metastatic malignant melanoma has not improved over the last decade. Since the early 1970s, dacarbazine (DTIC) has been considered the drug of first choice, although response rates in various schedules never exceed 30% and responses are in general of short duration [1]. In combination regimens of DTIC with cisplatin, BCNU and/or vindesine, occasionally response rates of >40% have been reported [2]. Some patients will occasionally reach a durable complete response [3, 4]. Cisplatin as a single agent administered at a conventional dose and schedule yields a response rate of 10–15% [5, 6]. Glover and associates performed a phase II study with high-dose cisplatin in combination with WR-2721 every 3–4 weeks [7]. In this study, 19 out of 36 patients responded (53%). Out of 4 patients treated with cisplatin at a dose ≤100 mg/m² none responded, while 5 out of 6 patients treated with an initial cisplatin dose of 150 mg/m² responded. This suggests that a higher cisplatin dose intensity might be of benefit. In a phase I study with a short course of weekly cisplatin, combined with oral etoposide, we were able to administer cisplatin at a dose intensity of 60 mg/m²/week in most patients [8]. We performed a series of phase II studies with this regimen in solid tumours which, based on the positive results of Glover and associates, also included metastatic melanoma. A response rate of at least 40% was considered of interest as lower response rates can be achieved with less intensive treatment.

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PATIENTS AND METHODS

Patients were required to have histological proof of malignant melanoma with distant metastases, a WHO performance status of 2 or better, white blood cell count $>3.0 \times 10^9$/l, platelet count $>100 \times 10^9$/l, creatinine clearance >60 ml/min and a serum bilirubin <25 μmol/l. All patients had a full medical history and physical examination before start of treatment, an ECG, chest X-ray and CT-scan of the chest and abdomen with and without i.v. contrast and, if appropriate, clinical measurement of pathological lymph nodes or skin metastases. CT-scan of the brain and bone scintigraphy were only performed on indication. All patients had a neurological examination including estimation of the vibration perception threshold before the start, after completion of treatment and 3 months thereafter. All patients gave oral informed consent.

During treatment, patients had a weekly physical examination, assessment of toxicity, full blood counts and estimation of serum electrolytes, calcium, magnesium, creatinine and liver function tests as well as a creatinine clearance.

Response to treatment was assessed 2 weeks after the last cisplatin administration and every 8 weeks thereafter. The standard WHO criteria were used for evaluation of response and toxicity [9].

Treatment schedule

Cisplatin was administered at a dose of 70 mg/m^2 on days 1, 8, 15 and days 29, 36, 43; oral etoposide was administered at a dose of 50 mg daily, days 1–15, and days 29–43. During cisplatin administration, patients were hospitalised for 24 h. The treatment regimen consisted of prehydration with 1000 ml dextrose-saline, 20 mmol KCl and 1 gram $MgSO_4$ in 4 h; cisplatin powder was dissolved in 250 ml 3% NaCl and administered over 3 h followed by posthydration with 2 litres of dextrose-saline, 40 mmol KCl and 2 grams $MgSO_4$ in 8 h. As anti-emetic treatment, 8 mg ondansetron was given as a slow i.v. bolus directly before starting the cisplatin administration and was repeated, if necessary, after 12 h. In case of delayed nausea and vomiting, metoclopramide 20 mg three times daily was given orally or per suppository.

Dose reductions were not allowed. If at the day of planned cisplatin administration WBC were $<2.5 \times 10^9$/l and/or platelets were $<75 \times 10^9$/l, treatment was postponed until recovery above these values with a maximum delay of 2 weeks. In case of a delay of >2 weeks or in case of neuro- or nephrotoxicity grade 2, patients were taken off study. Patients responding to treatment, or with stable disease at first response evaluation, continued treatment with oral etoposide at a dose of 50 mg/m^2 daily, days 1–21, every 28 days for a maximum of four cycles. Etoposide was administered as 50 mg gelatin capsules and the dosage was adjusted such that the administered dose deviated <5% from the total planned dose of etoposide. Etoposide cycles were postponed in case of WBC $<2.5 \times 10^9$/l and/or platelets $<75 \times 10^9$/l until recovery above these values. During treatment with oral etoposide, full blood counts were made every 2 weeks and serum electrolytes, liver and renal function tests were carried out every 4 weeks.

RESULTS

15 consecutive patients who met the eligibility criteria were entered into the study. The patient characteristics are given in Table 1. One patient was pretreated with DTIC for skin metastases on which treatment she had a short lasting complete response. 9 patients were pretreated with immunotherapy consisting of systemic IL-2 plus α-interferon on which treatment one patient had a partial response.

Table 1. Patient characteristics

No. of patients entered	15
Male:female	9:6
Median age, years (range)	44 (34–55)
Median PS (range)	1 (0–1)
Previous treatment	
Immunotherapy (IL-2 + α IFN)	9
Chemotherapy	1
None	5
Dominant site of metastases	
Visceral	13
Lymph nodes	2

All 15 patients were evaluable for response and toxicity. The side-effects, reported as worst toxicity observed during the whole treatment period, are shown in Table 2. All patients developed anaemia, 6 patients required packed cell transfusions for a total of 31 units. Leucocytopenia grade 3 was observed in only 4 patients, thrombocytopenia grade 3 in one and grade 4 in one patient. None of the patients required a platelet transfusion and there were no eposides of neutropenic fever.

Non-haematological toxicities observed were: alopecia in all patients, neurotoxicity grade 1 was observed in only one patient. Nephrotoxicity was not observed in this study. 4 patients had ototoxicity grade 2 (tinnitus) according to the NCI-Common Toxicity Criteria. The median weight loss during therapy was 4 kg (range 1–10 kg).

In total, 80 cycles of cisplatin were administered, median six per patient (range 3–6). 9 patients completed the treatment without any delay and reached the planned cisplatin dose intensity of 60 mg/m^2/week. In 5 patients, a delay of 1 week and in one patient a delay of 2 weeks was necessary because of slow bone marrow recovery.

2 patients had a partial response: the woman previously responding to DTIC had a partial response of skin and a renal metastasis lasting 22 weeks; the second patient, a man with skin and lymph node metastases, had a partial response of 12 weeks duration. The overall response rate is 13% (95% CI 2–44%). 6 patients had stable disease with a median duration of 26 weeks (range 12–50 weeks). 7 patients had progressive disease.

Table 2. Worst toxicity per patient

WHO grade	0	1	2	3	4
Haemoglobin	0	6	8	1	0
Leucocytes	3	2	6	4	0
Platelets	11	2	0	1	1
Nausea/vomiting	0	2	4	9	0
Neurotoxicity	14	1	0	0	0
Ototoxicity	11	0	4	0	0
Nephrotoxicity	15	0	0	0	0

8 patients continued oral etoposide after response evaluation for a median of two cycles per patient (range 1–4 cycles). Reasons not to complete the four planned etoposide cycles were progressive disease in 3 patients and refusal in one patient. Only one patient with stable disease after the 'induction' phase had a decrease in size of the metastases during oral etoposide but did not meet the criteria for partial response. In all other patients, the response status did not improve during the treatment with oral etoposide. After entrance of 15 patients, the study was closed according to protocol in view of the low response rate observed.

DISCUSSION

The treatment of patients with metastatic melanoma remains unrewarding. Only a few treatment schedules with minor activity are available. The role of cisplatin in the treatment of these patients is still a matter of debate. We previously reported a response rate of 40% with conventional doses of cisplatin in combination with ifosfamide [10]. Glover and colleagues reported a high response rate of 53% with high dose cisplatin in combination with the cytoprotector WR-2721 [7]. Only patients treated with cisplatin at a dose >100 mg/m^2 responded. A different high-dose schedule of cisplatin 100 mg/m^2 days 1 and 8 in combination with WR-2721 was explored by Buzaid and colleagues [11] but they did not observe any response in 9 patients. In both studies, the projected cisplatin dose intensity was 50 mg/m^2/week. Another high-dose cisplatin schedule was published by Murren and associates [12]. Their original schedule consisted of cisplatin 100 mg/m^2 days 1 and 8 combined with DTIC 300 mg/m^2 days 1 and 2 and day 8 and 9, but it had to be modified to cisplatin 50 mg/m^2 plus DTIC 350 mg/m^2 days 1–3 every 4 weeks mainly because of renal toxicity. The latter regimen was better tolerated and 7 out of 14 patients on this regimen responded to treatment. This positive result could, however, not be confirmed by others using the same regimen: Steffens and associates observed a response rate of only 17% while Buzaid and associates, applying the same regimen in combination with tamoxifen, observed a response rate of only 13% [13, 14]. In these regimens, the projected cisplatin dose intensity was 37.5 mg/m^2/week. In our study, with a projected cisplatin dose intensity of 60 mg/m^2/week, which was reached in most patients, we observed a response in only 2 out of 15 patients. These data taken together suggest that the overall dose intensity of the course might be less important than a high cisplatin dose per administration. The experience with single agent etoposide in malignant melanoma is very limited and disappointing [15, 16]. The combination of cisplatin with etoposide has been tested in the subcapsular renal assay on human metastatic melanoma. In these studies, 15% of the implants were sensitive to the combination of cisplatin/etoposide which corresponds to our clinical observation [17]. In our study, continuous oral etoposide was administered for reasons of clinical synergy of both drugs in other solid tumours and the schedule was used in a broad phase II programme. Since we did not observe further response improvements during continuation with oral etoposide after the 'induction' phase with cisplatin, we feel that there are no arguments left to explore etoposide further in the treatment of melanoma. We conclude that the presently studied regimen has only limited activity in melanoma and cannot be recommended in this disease.

1. Comis RL, Carter SK. Integration of chemotherapy into combined modality therapy of solid tumors. IV. Malignant melanoma. *Cancer Treat Rev* 1974, **1**, 285–304.
2. McClay E, Mastrangelo MJ. Systemic chemotherapy for metastatic melanoma. *Semin Oncol* 1988, **15**, 569–577.
3. Hill GJ, Krementz ET, Hill HZ. Dimethyl triazeno imidazole carboxamide and combination therapy for melanoma. *Cancer* 1984, **53**, 1299–1305.
4. Ahmann DL, Creagan ET, Hahn RG, Edmonson JH, Bisel HF, Schaid DJ. Complete responses and long-term survivals after systemic chemotherapy for patients with advanced malignant melanoma. *Cancer* 1989, **63**, 224–227.
5. Goodnight JE, Stephens Moseley H, Eilber FR, Sarna G, Morton DL. *cis*-Dichloro-diammineplatinum(II) alone and combined with DTIC for treatment of disseminated malignant melanoma. *Cancer Treat Rep* 1979, **63**, 2005–2007.
6. Al-Sarraf M, Fletcher W, Oishi N, *et al.* Cisplatin hydration with and without mannitol diuresis in refractory disseminated malignant melanoma: a Southwest Oncology Group Study. *Cancer Treat Rep* 1982, **66**, 31–35.
7. Glover D, Glick JH, Weiler C, *et al.* WR-2721 and high-dose cisplatin: an active combination in the treatment of metastatic melanoma. *J Clin Oncol* 1987, **5**, 574–578.
8. Planting AST, van der Burg MEL, de Boer-Dennert M, *et al.* Phase I study of weekly high-dose cisplatin combined with long term oral etoposide in advanced solid tumors. *Ann Oncol* 1995, **6**, 190–192.
9. WHO Handbook for Reporting Results of Cancer Treatment. *WHO Offset Publication* no. 48 Geneva, WHO, 1979.
10. Verweij J, Planting AST, van der Gaast A, Stoter G. Phase II study of cisplatin plus 24-hour infusion of ifosfamide in advanced malignant melanoma. *Ann Oncol* 1990, **1**, 77–78.
11. Buzaid AC, Murren J, Durivage HJ. High-dose cisplatin plus WR-2721 in a split course in metastatic melanoma. *Am J Clin Oncol* 1991, **14**, 203–207.
12. Murren JR, DeRosa W, Durivage HJ, Davis C, Makuch R, Portlock CS. High-dose cisplatin plus dacarbazine in the treatment of metastatic melanoma. *Cancer* 1991, **67**, 1514–1517.
13. Steffens TA, Bajorin DF, Chapman PB, *et al.* A phase II trial of high-dose cisplatin and dacarbazine. *Cancer* 1991, **68**, 1230–1237.
14. Buzaid AC, Murren JR, Durivage HJ. High-dose cisplatin with dacarbazine and tamoxifen in the treatment of metastatic melanoma. *Cancer* 1991, **68**, 1238–1241.
15. European Organization for Research on the Treatment of Cancer, Clinical Screening Group. Epipodophyllotoxin VP 16213 in the treatment of acute leukaemias, haematosarcomas, and solid tumours. *Br Med J* 1973, **3**, 199–202.
16. Cecil JW, Quagliana JM, Coltman CA, *et al.* Evaluation of VP-16-213 in malignant lymphoma and melanoma. *Cancer Treat Rep* 1978, **62**, 801–803.
17. Muhonen T, Pyrhönen S, Laasonen A, *et al.* Mouse subrenal capsule assay chemosensitivity and DNA flow cytometry parameters of human melanoma metastases. *Acta Oncologica* 1994, **33**, 431–437.