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High-dose cisplatin in disseminated melanoma: a comparison of two schedules*

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Summary. A total of 38 patients with metastatic melanoma received monthly chemotherapy with cisplatin at a dose of 200 mg/m^2, per cycle; 14 received 20 mg/m^2 cisplatin i.v. on days 1–5 and 24 were given 100 mg/m^2 i.v. on days 1 and 8. Objective responses were seen in 2/14 treated on days 1–5 and in 5 of 22 evaluable subjects receiving cisplatin on days 1 and 8, for an overall response rate of 22%. The median survival of all patients was 6 months, with no significant difference observed between the two schedules. Severe neurotoxicity and myelosuppression were more common in patients treated on days 1–5. Two patients treated in this manner were bedridden due to neurotoxicity and four developed grade 4 leukopenia after the first cycle of chemotherapy. Only one patient treated with the divided-dose schedule became leukopenic during the first cycle, and none of the patients were debilitated by neurotoxicity. Thrombocytopenia was statistically more severe. Nausea and vomiting, fatigue, ototoxicity, and paresthesia were seen with equal frequency. Very high doses of cisplatin can be delivered with acceptable toxicity using a divided-dose schedule. As the response rate on this schedule appeared to be comparable with that achieved on the more toxic consecutive 5-day schedule, the former deserves to be tested in diseases known to show a dose response to cisplatin. However, in melanoma, administration of 200 mg/m^2 per course did not appear to be associated with a markedly improved response rate, compared with cisplatin alone at "standard" doses.

Introduction

Conventional chemotherapy results in tumor regression in 15%–20% of patients with disseminated malignant melanoma. Combination chemotherapy has not improved the response rate or the duration of response in this disease [5, 13].

Three previous series using conventional-dose cisplatin reported responses in 10%–28% of patients, with an overall response rate of 13.4% in 89 patients [3, 4, 17]. Preliminary reports of intra-arterial cisplatin in melanoma suggest that the former appears to be superior to systemic cisplatin, possibly due to the higher regional concentrations of active agent attained with intra-arterial administration [14, 15]. That a dose response exists for cisplatin has also been suggested in a dose-escalation study of cisplatin in combination with the radioprotector WR-2721 at the University of Pennsylvania; the response rate increased as the monthly dose of cisplatin exceeded 100 mg/m^2 [8].

Tumor regression has been reported in patients with cisplatin-refractory germ-cell cancers of the testes as well as ovarian cancers when 40 mg/m^2 cisplatin was given daily for 5 days [13]. Using the same dose schedule, we undertook a study of very high-dose cisplatin in metastatic melanoma. Initially, patients received a total of 200 mg/m^2 at doses of 40 mg/m^2 on days 1–5; because of unacceptable toxicity on this schedule, subsequent patients received 100 mg/m^2 on days 1 and 8 of a 28-day cycle. We report the efficacy and toxicity of high-dose cisplatin given on two separate schedules in patients with metastatic melanoma.

Materials and methods

Patients with pathologic evidence of metastatic melanoma were eligible if they were previously untreated and had measurable disease, an ECOG performance status of 0–3, a creatinine clearance of >60 cm^3/min, and a serum creatinine value of <1.5 mg%. Patients with detectable abnormalities at 2,000 Hz on the pretreatment audiogram were excluded. This study was begun by the Puget Sound Oncology Consortium and was subsequently opened to other Southwest Oncology Group members.

Consecutive-day schedule. Hydration with normal saline was initiated 12 h before the first dose of cisplatin at a rate of 250 cm^3/h and continued until 12 h after the last dose. At 20–30 min prior to each dose of cisplatin, 20 mg furosemide was given i.v. A dose of 40 mg/m^2 cisplatin was reconstituted in 250 cc 3% saline and was given over 30 min on 5 consecutive days. Daily serum electrolyte, calcium, magnesium, blood urea nitrogen (BUN), and creatinine values were determined both during therapy and for 1 week after its completion.

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Divided-dose schedule. Hydration with normal saline was initiated prior to cisplatin administration; 1 l hydration was given before and after the chemotherapy. A dose of 100 mg/m^2 cisplatin was reconstituted in 3% saline and was given over 30 min. Patients were seen on day 8, at which time a complete blood count was done and calcium, magnesium, BUN, and creatinine levels were checked.

Subsequent courses were repeated at 28-day intervals. Prior to each cycle, a physical examination was carried out and a complete blood count, measurements of serum calcium, magnesium, BUN, and creatinine levels, liver function studies, a chest X-ray and an audiogram were repeated. Tumor measurements were rechecked.

Toxicity and dose adjustment. Dose modifications were required for myelosuppression, renal insufficiency, and neurotoxicity. Modifications for myelosuppression were made according to the nadir counts. Grade 1 toxicity (WBC = 3,000–3,999 cells/mm^3 or platelets = 75,000–99,999) necessitated a 25% dose reduction, and grade 2 toxicity (WBC = 2,000–2,999 cells/mm^3 or platelets = 50,000–74,999) required a 50% dose reduction. When grade 3 (WBC = 1,000–1,999 cells/mm^3 or platelets = 25,000–49,000) or grade 4 (WBC <1,000/mm^3 or platelets <25,000) myelosuppression developed, chemotherapy was withheld until marrow recovery and the dose of cisplatin was reinstituted at a 50% dose reduction. If renal impairment developed, cisplatin chemotherapy was withheld until the pretreatment serum creatinine values fell to <1.5% mg% and the estimated creatinine clearance exceeded 60 cm^3/min.

Chemotherapy was discontinued in patients whose audiogram demonstrated abnormalities at 2,000 Hz. Ototoxicity was considered to be mild if only tinnitus developed, moderate if the patient noted a functional hearing deficit, and severe if the patient developed deafness. Mild paresthesias and loss of deep tendon reflexes were not an indication for discontinuation of therapy. However, loss of motor strength or position sense, gait disturbance, or the inability to perform fine motor movements were indications for discontinuing therapy. Patients with disease progression were removed from the study.

All patients received antiemetic therapy that included high-dose metoclopramide and dexamethasone; additional antiemetic agents were given on an individual basis. All patients received magnesium supplementation of 16 mEq $MgSO_4$ per liter of hydration fluid.

Results

A total of 38 patients received high-dose cisplatin therapy (200 mg/m^2 per 28 days), 14 on days 1–5 and 24 on days 1 and 8. The patient characteristics for these two schedules are given in Table 1. These two groups were comparable with respect to age, disease-free interval, and sites of disease. A median of two cycles were given on the divided-dose schedule vs a median of one cycle on the daily schedule. One patient on the daily schedule required discontinuation of therapy because of neurotoxicity; the remainder demonstrated disease progression.

The response to therapy was evaluable in all 14 patients treated on the daily ×5 schedule. Two responses (14%) were observed: one was complete, lasting 9 months, and one was partial, lasting 11 months. Three patients experienced disease stabilization. In all, 12 patients died of their disease and 2 are alive with progressive disease. The median survival for patients treated daily was 7 months. Of the 24 patients treated on the divided-dose schedule, 23 were evaluable for response, as 1 patient refused therapy on day 8 of the first cycle. One patient achieved a complete response and five experienced partial responses, for an overall response rate of 26%. A total of 18 patients died of their disease, 5 are alive with progressive disease, and 1 patient is in complete remission 3+ months after beginning therapy. The latter patient underwent partial remission of an abdominal mass after three cycles of cisplatin; as this was the sole site of disease, debulking was carried out and the surgical specimen contained only necrotic tumor. The median survival for this group was 4.5 months.

Table 1. Patient characteristics

	Days 1–5	Days 1, 8
Patients (*n*)	14	24
Men: women	6:8	14:10
Median age (range) in years	47 (27–73)	52.5 (26–64)
Disease-free interval (range)	9 months (0–101)	14 months (0–97)
Metastatic at diagnosis	2	4
Sites of disease:		
Liver	5 (36%)	11 (46%)
Non-liver	8 (64%)	13 (54%)
Solitary site	5 (36%)	8 (33%)
2 sites of disease	4 (29%)	10 (42%)
>2 sites of disease	4 (29%)	6 (25%)
Median number of cycles (range)	1 (1–3)	2 (1–3.5)

Table 2. Toxicity of cisplatin by schedule

	Days 1–5	Days 1, 8
Patients treated (*n*)	14	24
Nausea and vomiting grade 1+	2	14
Nausea and vomiting grade 2+	6	6
Nausea and vomiting grade 3+	3	1
a:		
<500	3	1
500–1,000	0	0
1,000–1,500	1	1
Platelets:		
<20,000	2	0
20,000–50,000	0	0
50,000–75,000	1	0
75,000–100,000	2	1
Neurologic toxicity:		
Numbness	2	1
Weakness	2	2
Fatigue	1	3
Ototoxicity grade 1+	2	2
Ototoxicity grade 2+	2	5
Tinnitus	1	2
Tremors	1	0
Mucositis	1	0
Hot Flashes	1	1
Edema	1	1
Diarrhea grade 1+	1	0
Diarrhea grade 2+	3	0
Poor quality of life	1	

Table 3. Response and survival

	Days 1–5	Days 1, 8
Patients treated (*n*)	14	24
Not evaluable	0	1
Response evaluable	14	23
Complete response	1 (7%)	1 (4%)
Partial response	1 (7%)	5 (21%)
Stable disease	3 (21%)	0
No response	9 (64%)	17 (74%)
Median survival	7 months	4.5 months

A comparison of the two different schedules is summarized in Table 2. Nausea and vomiting was the most common toxicity, experienced by 11 patients (79%) treated on days 1–5 and 21 (88%) treated on the divided-dose schedule. Marrow toxicity was more severe on the 5-day schedule. Four patients (28%) developed leukopenia during the first cycle – three had grade 3 and one, grade 1 leukopenia; three of these patients required hospitalization for antibiotics treatment while febrile. In contrast, only two patients (8%) treated on the divided-dose schedule experienced leukopenia, one during the first cycle and one during the third; one of these patients required hospitalization for fever. Likewise, thrombocytopenia was more common on the 5-day schedule (36% vs 4%). Neurologic complications occurred with equal frequency on both schedules and was not correlated to the level of serum magnesium. However, although two patients in each treatment group complained of "weakness", severe weakness resulting in the patient's being bedridden developed in two patients treated on days 1–5 but was not observed in those given the divided dose. The cumulative cisplatin dose for these two patients was 200 mg/m^2. Fatigue, ototoxicity, and numbness occurred equally in both groups. The survival for all patients on study is illustrated in Table 3; the median survival for all patients was 6.0 months.

Discussion

Aggressive hydration has shifted the dose-limiting toxicity of cisplatin from nephrotoxicity to neurotoxicity. With conventional-dose cisplatin in gynecologic malignancies, the development of peripheral neuropathy has been correlated with the development of hypomagnesemia as well as with the cumulative dose of cisplatin. The importance of maintaining a normal serum magnesium level is uncertain, as the development of hypomagnesemia is directly related to the cumulative dose of cisplatin. In all, 70% of patients receiving cumulative doses of cisplatin in excess of 600 mg at "standard" doses per individual course developed neuropathy [2]. Ozols et al. [13] initially reported a severe sensory neuropathy resulting in ataxia in women with ovarian cancer who were treated with cisplatin at 40 mg/m^2 on days 1–5. Most had received high cumulative doses of cisplatin during prior treatment. Severe neurotoxicity was not seen in men with cisplatin-refractory germ-cell cancers treated in the same manner [13]. It was postulated that severe neurotoxicity was unique to an older group of women who received high cumulative cisplatin doses.

Since Ozol's initial report, severe neuropathy has been reported in the majority of men treated on the 5-day schedule [11, 12]. The two patients in the present series who developed ataxia shortly after the first cycle of cisplatin had not previously received cisplatin. The plasma pharmacokinetics of cisplatin have been determined in patients with non-small-cell lung cancer who were treated on the 5-day schedule of very high-dose cisplatin as well as in those treated on days 1 and 8 (divided-dose schedule). As the terminal half-life of the plasma ultrafiltrate of cisplatin is 40 h, a daily schedule for 5 days results in the accumulation of ultrafiltrate platinum, which is avoided on the divided-dose schedule [7]. Neurotoxicity appears to be related to the cumulative dose of cisplatin as well as the cumulative levels of ultrafiltrate platinum.

Life-threatening myelosuppression is rarely observed with conventional-dose cisplatin. In contrast, the very high-dose, daily schedule results in grade 4 leukopenia in 29%–89% of patients and in grade 4 thrombocytopenia in 50%–90% [11, 13]. Marrow toxicity develops after chronic cisplatin administration; that myelosuppression was seen in patients on the daily schedule but not in those receiving the divided dose suggests that ultrafiltrate platinum levels are also important.

A dose response to cisplatin has been established for germ-cell cancers of the testes and ovarian and, possibly, head and neck cancers [4, 6, 17]. The response rates achieved on both of the present schedules of very high-dose cisplatin appeared similar to those reported for standard-dose cisplatin in disseminated melanoma. This study was not designed to compare the efficacy of "high-" and "standard-" dose schedules and the numbers are too small for any firm conclusions to be drawn. In non-small-cell lung cancer, the response rate to very high-dose cisplatin is considerably higher than that reported for conventional-dose cisplatin given as a single agent (35% vs 13%) [15]. Again, although a direct comparison of the two schedules was not attempted in lung cancer the response rates to high-dose cisplatin on the divided-dose schedule were comparable with those seen on the 5-day schedule, with much less myelosuppression and severe neuropathy. Because the divided-dose schedule is as dose-intensive as the daily schedule, we are investigating the former in settings where a dose response to cisplatin appears to exist.

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