Anti-Cancer Drugs 1999, **10**, pp. 735–739

Clinical study

Phase II trial of escalated dose of tirapazamine combined with cisplatin in advanced malignant melanoma

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A phase II study was undertaken to determine the efficacy of tirapazamine combined with cisplatin in patients with metastatic melanoma between April 1996 and April 1997. Tirapazamine 390 mg/m^2, administered i.v. over 2 h, followed in 1 h by cisplatin 75 mg/m^2 over 1 h, were used every 21 days to treat chemotherapy-naive patients with metastatic melanoma. Objective tumor measurements were used to assess efficacy of the regimen. NCI common toxicity criteria were used to grade toxicities. Forty-eight patients with metastatic melanoma of cutaneous or mucosal origin, none with symptomatic brain metastasis, were treated. Nine patients had a partial response, with an overall response rate of 20% (95% confidence interval: 9–33%). The median duration of response was 6 months. Grade 3 nausea, vomiting, anorexia, muscle cramps and fatigue occurred in fewer than 10% of patients. Neutropenia and thrombocytopenia were rare. This outpatient single-day administered tirapazamine–cisplatin regimen has definite activity in chemotherapy-naive patients with metastatic melanoma. Further studies in combination with other agents active against this disease are warranted.

Key words: Chemotherapy, cisplatin, melanoma, tirapazamine.

Introduction

Tirapazamine is the lead compound in a novel class of bioreductive agents that under hypoxic conditions are bioreduced to a nitroxide-based free radical that causes DNA breaks by abstracting hydrogen from it.[1,2] Damage induced by the free radicals may enhance the effects of chemotherapy or radiotherapy.[1,2] Tirapazamine has been shown to enhance cisplatin activity in a schedule-dependent fashion, especially when tirapazamine is given i.v. between 1 and 3 h before cisplatin.[3]

In our previous clinical study using 260 mg/m^2 tirapazamine plus 75 mg/m^2 cisplatin in patients with metastatic melanoma, we observed partial responses in eight (33%) of 24 chemotherapy-naive patients with metastatic melanoma of skin origin.[4] This response rate was superior to that observed with cisplatin alone as reported in the published medical literature.[4] Subsequent phase I–II clinical studies with escalating doses of tirapazamine in lung cancer indicated that 390 mg/m^2 tirapazamine in combination with 75 mg/m^2 cisplatin was well tolerated.[5] Moreover, early results of a phase III randomized study in patients with metastatic non-small cell lung cancer (NSCLC) suggested that 390 mg/m^2 tirapazamine plus cisplatin may be more effective than cisplatin alone (response rate 27.5 versus 13.7%; $p<0.001$) and median survival of 34.6 versus 27.7 weeks; $p=0.008$).[6] The 27.5% response rate in patients with NSCLC with escalated tirapazamine was slightly higher than that observed in patients with NSCLC treated with 260 mg/m^2 tirapazamine and the same dose of cisplatin (24%) suggesting a possible dose-response relationship. Here, we report the results of a phase II trial in patients with previously untreated metastatic melanoma using cisplatin 75 mg/m^2 and tirapazamine 390 mg/m^2 as a single-day, i.v. therapy every 21 days.

Materials and methods

Forty-eight consecutive patients with histologically confirmed, previously untreated metastatic melanoma

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of skin or mucosal origin, who were not eligible for, or who chose not to be treated on a higher priority interleukin-2-based biochemotherapy protocol, were treated with tirapazamine–cisplatin combination between April 1996 and April 1997. Patients were required to be over 18 years old, and have a Karnofsky performance status of 70% or better, measurable disease and an anticipated survival of at least 8 weeks. Patients with symptomatic brain metastases were excluded. In addition, all patients had a white blood cell count of at least 4.0×10^9/l, platelet count over 100×10^9/l, serum creatinine level less than 1.3 mg/dl and serum bilirubin level 1.5 mg/dl or less.

Patients were not permitted to have had prior chemotherapy, but were permitted to have received adjuvant therapy with melanoma vaccine or interferon. Patients with metastatic choroidal melanoma were not eligible. Patients who had received prior radiation therapy were eligible provided they had at least one site of measurable disease outside the radiation field. Written informed consent was obtained from all patients before entry into the study, per institutional policy.

Tirapazamine was provided by Sanofi Winthrop (Malvern, PA) as a sterile solution (0.7 mg/ml) in glass ampules containing 20 ml tirapazamine in an isotonic citrate buffer with a pH between 3.7 and 4.3. The starting dose of tirapazamine was 390 mg/m^2. The total tirapazamine dose for each treatment was transferred using a filter needle from the ampules into a chemotherapy bag and administered by infusion pump over 2 h. One hour after completion of tirapazamine, the patient was given cisplatin at a dose of 75 mg/m^2 in 250 ml of normal saline over 1 h. Intravenous hydration with 5% dextrose in 0.5 normal saline was given before tirapazamine was administered and after completion of cisplatin dose. Antiemetics were prescribed prophylactically at the discretion of the treating physician; most patients received dexamethasone and ondansetron. The treatment was repeated every 3 weeks. Doses of tirapazamine were modified during the study to maintain a tolerable degree of non-hematologic toxicity. Grade 2 ototoxicity required a 25% reduction in the tirapazamine dose. A grade 3 or 4 tirapazamine-related toxic effect required cessation of tirapazamine administration.

Patients were evaluable for safety of tirapazamine if they received any of the drug. They were assessable for response if at least one course of tirapazamine–cisplatin chemotherapy was completed. Response to treatment was assessed at 6-week intervals. A complete response was defined as the disappearance of all evidence of disease for at least 4 weeks. Partial response was defined as a 50% or greater reduction in the sum of the products of all measurable indicator lesions for at least 4 weeks without the appearance of new lesions. No response (including stable disease and minor response) was defined as a less than 25% increase or decrease in measurable disease without the appearance of new lesions. Progressive disease was defined as a greater than 25% increase in measurable disease or the appearance of new lesions.

Before the start of chemotherapy, all patients were evaluated with a history and physical examination, complete blood count, urinalysis, measurement of serum electrolytes and creatinine levels, and chemistry profile including alkaline phosphatase, bilirubin, glutamic-oxaloacetic transaminase and lactic dehydrogenase. Patients underwent baseline electrodiography, audiometry and detailed vision testing consisting of complete ophthalmologic evaluation with a slitlamp examination, fundus photographs, color vision testing and electro-oculography.

Evaluation during therapy included weekly complete blood counts, urinalysis, serum electrolyte measurements and chemistry profile on day 7 of each course and before the start of the next course of chemotherapy. Follow-up audiometry was performed before every other course of therapy. Ophthalmologic evaluation was performed after course 2 and upon discontinuation of therapy. Tumors were measured before each course when palpable or at 6 week intervals using appropriate radiologic examinations. The duration of response was measured from the date of start of treatment with tirapazamine–cisplatin to the time of disease progression.

Results

Forty-eight patients with a median age of 52 years were entered in the trial. Their characteristics are summarized in Table 1. Forty-six patients were assessable for response and all were assessable for toxicity.

Tirapazamine–cisplatin therapy produced nine partial responses for an overall objective tumor response rate of 20% (95% confidence interval: 9–33%). The median duration of response was 6 months (range 2–13 months). Two of the responders with surgically unresectable advanced regional disease had major responses after tirapazamine–cisplatin therapy. Both patients remain free of disease more than 24 and 28 months after subsequent surgical resection of residual residual. In two patients, scans confirming response were delayed until 8 weeks from observation of greater than 50% tumor regression, by then the tumor had progressed as evidenced by appearance of new

Table 1. Patient characteristics

No. of patients registered	48
Assessable for toxic effects	48
Assessable for response	46
Median (range): age; years	52 (22–76)
male	34 (71%)
female	14 (29%)
Race	
White	42
Hispanic	4
Black	1
other	1
Performance status	
100%	13 (27%)
90%	26 (54%)
80%	9 (19%)
Prior therapy for melanoma	
radiotherapy	17
interferon/interleukin-2	13
melanoma vaccine	5

CNS metastasis in one and regrowth of known pulmonary disease in the other. Responses were observed at all sites including the adrenal gland (33% of patients with adrenal metastases), lymph nodes (16%), lung (16%), liver (13%), and skin and/or soft tissues (8%). Disease was stabilized in 11 patients and progressed despite therapy in 26 others. The median duration of survival for all patients was 6 months. The median survival of the nine patients who had partial response was more than 24 months.

The hematologic toxicity associated with tirapazamine-cisplatin was minimal. Neutropenia and thrombocytopenia were mild and infrequent. No cases of grade 4 neutropenia or thrombocytopenia occurred. Grade 3 neutropenia was seen in six courses and thrombocytopenia in two courses. Nonhematologic side effects were the most common but were rarely severe. Muscle cramping and gastrointestinal disturbances occurred in over 70% of patients but were grade 3 or 4 in fewer than 15% of patients. Anorexia, nausea and vomiting occurred in more than 80% of patients, and were mostly grade 1 or 2. Diarrhea occurred in 70% of patients and primarily on the day of chemotherapy administration. Fatigue was common and profound (grade 3 or 4) in 23% of the patients, mostly during the week following the administration of treatment. Peripheral neuropathy with neurosensory manifestations including paresthesia and visual and auditory symptoms occurred in about half of the patients, mainly in those who received four or more courses of therapy. Paresthesia occurred in a third of patients. About half of the patients had auditory complaints, including tinnitus (38%) and decreased hearing (17%). Decreased hearing occurred in eight patients. In two patients, there was acute hearing loss following chemotherapy administration, with full resolution of symptoms within 24 h. Visual side effects occurred in 63% of patients and included blurring of vision (29%), floaters (29%), dim vision (6%), and photosensitivity and conjunctival irritation (4%). The result of detailed vision testing has been published separately.[7] Maculopapular skin rash occurred in 27% of patients. The chemotherapy dose was reduced in six courses because of treatment-related toxic effects. No patient suffered renal failure requiring discontinuation of therapy, but six patients had a transient elevation of 1.5 mg/dl or greater. This level increased to 3.5 mg/dl in one patient. Renal function returned to normal in all patients following adequate hydration. Hypomagnesemia, with a serum magnesium level less than 1.2 mg/dl, most likely due to cisplatin, occurred in five patients and this was resolved with the administration of a magnesium supplement.

Discussion

In this trial, we attempted to enhance the potency of tirapazamine-cisplatin combination by increasing the dose of tirapazamine from 260 mg/m^2, used in the previous study, to 390 mg/m^2 while maintaining the dose of cisplatin at 75 mg/m^2. The increase of the tirapazamine dose was not associated with an improved response rate. Table 2 compares the characteristics of patients in the current study with those of the 24 previously untreated patients with metastatic cutaneous melanoma from the first study. The patients in the first study had more favorable performance status and lesser tumor burden based on number of metastatic sites and incidence of visceral versus soft tissue metastases. In addition, the 24 patients in the first study had indolent disease with none having tumor progression during the first course of therapy. In contrast, five patients in the second study had tumor progression during the first course of therapy and were taken off the study before receiving the second course of therapy. Despite the higher dose of tirapazamine administered in this study, the severity of treatment-related toxicities was less than the earlier study because of more effective use of palliative measures (Table 3). Increase of tirapazamine dose was not associated with more severe myelosuppression.

These results indicate that combination tirapazamine-cisplatin administered on a single-day intermittent schedule in the two studies has definite activity against metastatic cutaneous or mucosal melanoma in

Table 2. Clinical information of previously untreated patients with cutaneous or mucosal melanoma entered in the two phase II tirapazamine–cisplatin trials

	Low dose	Escalated dose
No. of patients registered	24	48
Age (years): median	64	52
Sex: male	16 (62%)	34 (71%)
Performance status		
90–100%	23 (96%)	39 (81%)
70–80%	1 (4%)	9 (19%)
Prior radiotherapy	6 (25%)	17 (35%)
No. of metastatic sites		
one	5 (21%)	6 (13%)
three or more	10 (42%)	28 (58%)
Sites of metastases		
viscera (GI/lung/liver/brain)	17 (71%)	39 (81%)
node/soft tissue/skin only	7 (29%)	9 (19%)
lung	11 (46%)	31 (65%)
liver	7 (29%)	16 (33%)
Tumor progression after one course of therapy	0 (0%)	5 (10%)

Table 3. Tirapazamine with cisplatin: comparison of two studies—side effects and toxicity grade

	Toxicity					
	Low dose (48 patients)			Escalated dose (48 patients)		
	Overall	Grade 3	Grade 4	Overall	Grade 3	Grade 4
Fatigue (%)	94	27	–	90	21	2
Muscle cramps (%)	92	17	–	84	6	–
Nausea (%)	88	21	–	92	10	–
Anorexia (%)	75	15	–	82	4	–
Diarrhea (%)	62	–	–	70	–	–
Vomiting (%)	60	8	10	84	12.5	2
Constipation (%)	60	6	–	90	4	–

chemotherapy-naive patients. The response rate of about 24% (17 of 72 patients) in untreated patients with non-choroidal melanoma appears to be superior to the historical data with cisplatin alone. The lack of therapy-related myelosuppression and manageable toxicity makes tirapazamine-cisplatin combination a potential candidate for front-line therapy of metastatic melanoma. Preclinical studies with tirapazamine plus dacarbazine showed that tirapazamine enhances the antitumor activity of dacarbazine.[8] Other similar studies have shown that combining tirapazamine with conventional cytotoxic drugs, including alkylating agents, doxurubicin and tubulin toxins such as taxanes, may enhance the efficacy of these drugs as well.[9] Clinical studies in patients with non-small cell lung cancer as well as patients with head and neck cancer showed that full doses of tirapazamine plus cisplatin combined with full doses of anticancer agents such as paclitaxel and 5-fluorouracil are well-tolerated combination chemotherapy regimens.[10,11] The role of tirapazamine should next be evaluated in widely used combinations such as the cisplatin-vinblastine-dacarbazine (CVD) and the carmustine-cisplatin-dacarbazine-tamoxifen (Dartmouth or BCDT) chemotherapy regimens.

Conclusion

The tirapazamine-cisplatin combination is active against metastatic cutaneous or mucosal melanoma in chemotherapy-naive patients. The escalated dose of tirapazamine (390 mg/m^2) is not more effective than the previously studied lower dose (260 mg/m^2) when given in combination with cisplatin. The tirapazamine-cisplatin combination is well tolerated with

manageable side effects. Further studies of tirapazamine-cisplatin combined with dacarbazine and biological agents such as interferon and interleukin-2 are warranted to clearly delineate the role of tirapazamine in the management of metastatic melanoma.

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(Received 15 June 1999; accepted 24 June 1999)