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ORIGINAL ARTICLE

A phase II study of oxaliplatin, docetaxel, and GM-CSF in patients with previously treated advanced melanoma

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Abstract
Purpose Although much focus has been placed on immunotherapy for melanoma, further development of chemotherapy approaches is needed. Melanoma is responsive to platinum compounds and taxanes, but there is limited experience with combinations of these agents. Oxaliplatin has been reported to have detectable activity in melanoma, and a phase I study has identified a tolerable dose and schedule of oxaliplatin in combination with docetaxel and hematopoietic growth factor support. GM-CSF has a theoretical advantage of immune potentiation. These considerations supported the study of oxaliplatin, docetaxel, and GM-CSF in patients with advanced melanoma.
Methods Eligibility included adequate organ function, PS ≤ 2, at most one prior chemotherapy and one prior immunotherapy, no prior treatment with oxaliplatin or taxanes and no chremophor allergy. After premedication, docetaxel was administered day 1 at 75 mg/m^2, then oxaliplatin on day 2 at 85 mg/m^2. GM-CSF (250 mcg/m^2) was administered s.c. days 3–12. Cycles were 21 days in length, and disease reevaluation was performed every two cycles by RECIST criteria.
Results Nineteen patients received at least one cycle, eight with one prior systemic therapy, five with two prior systemic therapies. Five patients did not complete two cycles and were not formally evaluable for response. Five patients had stable disease (SD), including one who failed two prior therapies and went on to receive ten cycles. The remaining nine patients displayed progressive disease (PD) after two cycles. Notable toxicities included seven cases (37%) of grade III/IV neutropenia and two (11%) hypersensitivity reactions.
Conclusions This combination of oxaliplatin, docetaxel, and GM-CSF has limited clinical activity in previously treated patients with advanced melanoma. Exploration in treatment-naïve patients may still be warranted.

Keywords Melanoma · Metastatic · Oxaliplatin · Docetaxel · GM-CSF · Chemotherapy

Introduction

Melanoma is the most aggressive skin cancer and is often curable when treated early with surgical resection. Unfortunately, current treatment strategies for non-resectable stage III or IV disease (metastatic melanoma) rarely lead to prolonged disease-free survival with an approximate median survival of 9 months. Two agents are approved by the FDA for this setting: the chemotherapeutic dacarbazine (DTIC) and the immunoregulatory cytokine IL-2. Either agent gives clinical response rates of 7–15%, with no evidence that overall survival is improved [1–3]. Following front line therapy, a vast majority of patients relapse and require additional chemotherapeutic agents. Despite numerous clinical trials over the last 30 years, no chemotherapeutic approach has proved more effective than DTIC alone [4, 5].

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Clearly second and third line treatment options for metastatic melanoma are needed.

Oxaliplatin, a platinum-based chemotherapeutic, and docetaxel, a taxane anti-mitotic drug, both have single agent activity against melanoma in vitro and in vivo. Platinum compounds are active in melanoma, showing response rates in the range of 15% [6]. Cisplatin has long been included in combination chemotherapy regimens [7, 8], although melanoma cell lines are sometimes resistant to this agent [9]. Several observations support oxaliplatin activity in this disease. In vivo mouse models demonstrate that oxaliplatin is active against melanoma. In addition, some melanoma cell lines resistant to cisplatin and carboplatin are sensitive to oxaliplatin in vitro [9, 10]. In a phase I study of oxaliplatin, a clinical response was observed in a patient with melanoma [11]. Further exploration of taxanes, single agent or in combination, as second line therapy for metastatic disease has been proposed [12]. Docetaxel is active against melanoma cell lines and fresh tumor explants in vitro [13, 14] and in mouse xenograft experiments in vivo [15]. Phase II studies of docetaxel in patients with melanoma demonstrated response rates of 12.5 and 17% [16, 17].

Combinations of platinum compounds and taxanes have been additive or synergistic in preclinical models and in clinical trials of several cancers [18]. A phase I study of docetaxel/oxaliplatin was performed in patients with either breast cancer or non-small cell ling cancer [19]. Recommended phase II dosing with hematopoietic growth factor support for the combination was 85 mg/m^2 of docetaxel on day 1 and up to 130 mg/m^2 of oxaliplatin on day 2. G-CSF was used for growth factor support in that study. GM-CSF is an important alternative hematopoietic growth factor. In addition to stimulating hematopoiesis, multiple lines of evidence suggest that GM-CSF plays an immunomodulatory role against cancer via dendritic cell recruitment [20]. Moreover, for melanoma GM-CSF as a single post-surgical adjuvant has been shown to improve overall survival, compared to historical controls when given daily for 14 out of each 28 days [21]. This has prompted an interest in utilizing GM-CSF for hematopoietic support in chemotherapy trials for melanoma [22, 23]. Taken together, these data prompted our investigation of the combination of oxaliplatin, docetaxel, and GM-CSF in the treatment of patients with metastatic melanoma.

Patients and methods

Patient eligibility

Eligible patients had to be ≥18-year-old with histologically confirmed, radiologically measurable melanoma with AJCC Stage IIIc or IV disease. All patients were required to supply signed, written informed consent. Patients were allowed one prior chemotherapy and/or one prior immunotherapy. Biochemotherapy combinations were considered as a single chemotherapy regimen. Prior radiation therapy was allowed if a site of measurable disease existed outside of the radiation port. A "washout" period of 4 weeks (6 weeks for nitrosureas) was required since the last therapy with all toxicities resolved. All patients were required to have an ECOG performance status of 0–2. Adequate organ function was defined by laboratory values as follows: WBC > 3,000/μL, platelets > 100,000/μL, hemoglobin ≥ 10 g/dL, total bilirubin, AST and ALT within institutional normal limits, and serum creatinine ≤1.5 mg/dL or a creatinine clearance of ≥60 mL/min.

Patients who met the following criteria were excluded: untreated brain metastases, pregnant or nursing women, prior therapy with taxanes or oxaliplatin, HIV+, neuropathy ≥grade 2, and history of a severe allergic reaction or anaphylaxis to agents prepared with Cremophor vehicle. Also ineligible were patients with another malignancy within the last 5 years except for curatively treated non-melanomatous skin cancer or carcinoma in situ of any organ without other evidence of disease. Patients with multiple primary melanomas were eligible as were patients who received definitive therapy for brain lesions (surgery or stereotactic radiation) and remained clinically stable 4 weeks later without progression in the brain or need for corticosteroids.

In accordance with the Declaration of Helsinki, this prospective clinical trial was approved by the University of Chicago Clinical Trials Review Committee and the Institutional Review Board. It was likewise approved by the appropriate ethics committee for all participating institutions.

Treatment plan

Treatment was administered on an outpatient basis in 21-day cycles. On day 1, patients received docetaxel 75 mg/m^2 by intravenous (IV) infusion. On day 2, oxaliplatin 85 mg/m^2 was administered by IV infusion over 2–3 h. Patients were premedicated with dexamethasone 20 mg IV on day 1 and ondansetron 12 mg by mouth (PO) on day 2. GM-CSF 250 mcg/m^2 was administered subcutaneously (SQ) daily beginning on day 3 until WBC was >30,000/μL or through day 12, whichever occurred first. Treatment cycles continued until intolerable toxicity or disease progression.

Due to concern for oxaliplatin potentiation of docetaxel toxicity, dose reductions for febrile neutropenia, neutropenia >grade 1 at the time of the next cycle, or grade 3–4 mucositis were as follows: docetaxel was reduced to 60 mg/m^2; if the toxicity recurred then oxaliplatin was reduced to 65 mg/m^2; treatment was discontinued with a

third episode. For grade 4 AST, ALT, or alkaline phosphatase elevation, docetaxel was held until resolution to enrollment requirements. For paresthesias associated with pain or functional impairment, which persisted at the next cycle, oxaliplatin was held until resolution and then resumed with a 20% dose reduction. Oxaliplatin was discontinued if paresthesias persisted beyond 3 weeks.

Evaluation of response and toxicities

Target lesions were identified, measured, and recorded at baseline by physical examination and CT imaging of the head, chest, abdomen, and pelvis. Patients underwent general clinical examination, neurological assessment, laboratory studies (comprehensive metabolic profile, complete blood count with differential, ALT, AST, and alkaline phosphatase) after each cycle. Disease was radiologically re-evaluated every two cycles using RECIST criteria.

Toxicities were assessed by a history, physical examination and laboratory studies after each cycle. Grading was according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3. For toxicity tabulations, the highest grade of a given toxicity was taken for each patient.

Sample size and statistical considerations

The primary endpoint was achievement of clinical response, meaning a complete response (CR) or partial response (PR), every two cycles as defined by RECIST [24]. Secondary objectives were defining overall survival, progression-free survival, and toxicity assessment. The sample size was determined using an optimal two-stage Simon's statistical design seeking to detect a response rate in this pretreated population of 15% [25]. Any clinical response (CR or PR) among the first 16 patients would warrant expansion to the second stage of accrual for a total of 29 patients. Only patients that received two cycles of therapy or came off study due to toxicity were included in the early stopping criteria. This design allowed for a 0.72 probability of stopping early if the true response rate is 2%.

Patients were considered evaluable for safety if they received any study medication. Response analysis was considered on an intention to treat basis for all patients enrolled into the trial regardless of whether they received study medication. Descriptive statistics were used to present the primary endpoint (response rate) and toxicity assessment (number of patients experiencing any particular toxicity). Median progression-free survival and overall survival were calculated using the Kaplan–Meier method.

Results

Patient characteristics

Twenty patients were enrolled in this open label, non-randomized, multi-institutional single arm phase II trial. Patient characteristics are presented in Table 1 and outcomes are summarized in Fig. 1. One patient was deemed ineligible prior to therapy administration due to elevated creatinine, and was not included in additional analysis. One patient had a prior-treated brain metastasis. Thirteen patients had received a prior chemotherapy regimen, previous immunotherapy, or both. Nineteen patients received at least one cycle of the assigned therapy and were evaluable for toxicity. Fourteen patients completed two cycles of chemotherapy and were radiologically evaluable for response.

Table 1 Patient Characteristics

No. of patients enrolled	20
No. of patients evaluable for toxicity	19
Age (years)	
Mean	58
Median	63
Range	19–81
Sex	
Male (%)	12 (63)
Female (%)	7 (37)
Prior systemic therapy	
Chemotherapy only	5
Immunotherapy only	4
Chemotherapy and Immunotherapy	4
None	6

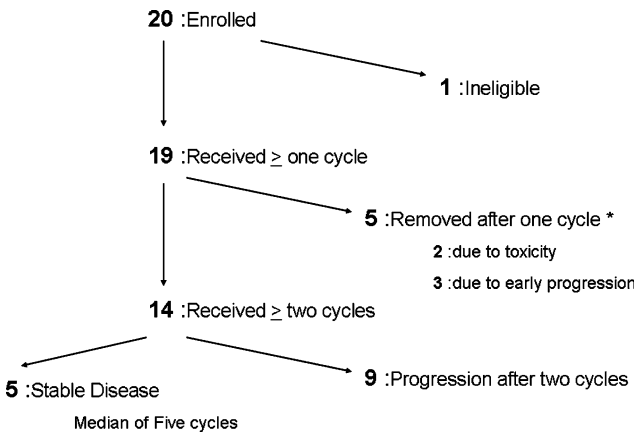

Fig. 1 Summary of patient outcomes numbers indicate the number of patients at each study timepoint.*All five patients removed after one cycle were included in the final intention to treat analysis; however, the three patients removed due to early progression were not included in the stopping criteria analysis

A total of 52 courses of chemotherapy were administered (mean = 2.7 cycles in 19 patients receiving treatment). The study did not advance to the second stage because no responses as defined by RECIST criteria were seen.

Toxicity

The common and notable toxicities are listed in Table 2. The therapy was generally well tolerated. Two patients discontinued therapy after one cycle due to toxicity and there were five dose reductions. One patient had a grade 3 hypersensitivity reaction to oxaliplatin, which was held on the second of two cycles. The oxaliplatin dose was reduced 25% with the second of two cycles in another patient who had grade 3 thrombocytopenia. Grade 2 hypersensitivity and grade 2 exfoliative dermatitis led to docetaxel discontinuation with the second of four cycles in one patient. A patient who had stable disease and received ten cycles experienced grade 2 fatigue and diarrhea prompting a 25% dose reduction of docetaxel beginning with cycle 4. Both docetaxel and oxaliplatin were reduced 25% in the fifth patient with grade 3 thrombocytopenia, grade 4 neutropenia, and grade 1 peripheral neuropathy. Not unexpectedly, significant neutropenia (37% of patients with grade 3 or 4) and thrombocytopenia (32% of patients) were commonly observed. The only grade 3 or 4 toxicities experienced by more than two patients were neutropenia and fatigue. The most common non-hematologic toxicities were fatigue (84%), anorexia (63%), diarrhea (58%), and nausea (47%). Peripheral neuropathy was observed, seven sensory and one sensorimotor events (total 42%), but no grade 3 or 4 neurologic toxicities were seen.

Two patients came off study following the first cycle due to toxicity: one experienced grade 4 leukopenia, grade 3 dehydration, hyponatremia, and small bowel obstruction, the other developed grade 3 diarrhea and hyponatremia.

Table 2 Toxicity

Adverse event	Grade 1–2 (%)	Grade 3–4 (%)	Total (%)
Fatigue	13 (68)	3 (16)	16 (84)
Anorexia	11 (58)	1 (5)	12 (63)
Diarrhea	10 (53)	1 (5)	11 (58)
Anemia	8 (42)	1 (5)	9 (47)
Nausea	7 (37)	2 (11)	9 (47)
Neuropathy	8 (42)	0 (0)	8 (42)
Hypocalcemia	7 (37)	0 (0)	7 (37)
Alopecia	7 (37)	0 (0)	7 (37)
Neutropenia	0 (0)	7 (37)	7 (37)
Thrombocytopenia	4 (21)	2 (11)	6 (32)
Vomiting	3 (16)	2 (11)	5 (26)
Dehydration	3 (16)	2 (11)	5 (26)
Hyponatremia	3 (16)	2 (11)	5 (26)
SGOT/SGPT elevation	3 (16)	1 (5)	4 (21)

Clinical response

Five patients were classified by RECIST criteria as having stable disease and received a median of five (mean 5.8) cycles of chemotherapy. One of these patients, previously treated with adjuvant carboplatin/DTIC/vinblastine/Ara-C and then IFN-α/IL-12 for metastatic disease, had a decrease in tumor size not meeting RECIST for PR (classified as a minor response in Table 3) and went on to receive ten cycles of oxaliplatin/docetaxel/GM-CSF. Nine patients had progressive disease after two cycles. Five patients did not complete the first two cycles; two were removed for toxicity, and the other three patients experienced early progressive disease. Patient responses stratified by prior therapy are presented in Table 3. At the time of data analysis all but one patient were deceased. That patient, who had received four cycles of therapy on study before progressing, was alive at 43 months. Median progression-free survival was 1.4 months (range <1 to 8 months). Median overall survival for all patients was 5.4 months (range for deceased patients <1 to 17 months).

Discussion

Despite over 30 years of melanoma clinical trial efforts, few effective treatments for metastatic melanoma exist [4, 5]. When compared to DTIC monotherapy, no chemotherapy treatment has proved more effective. Combination chemotherapy showed intriguing results in phase II studies [7], but randomized clinical trials revealed similar outcomes compared to DTIC alone [8]. Similarly, a combined immunotherapy and chemotherapy approach demonstrated early promise [26], but randomized studies did not show a clear

Table 3 Outcome of patients by prior therapy

Prior systemic therapy	Progressive disease	Stable disease	Minor response[a]	Not evaluable for response[b]
Chemotherapy	2	1	0	1
Immunotherapy	3	1	0	0
Both	4	0	1	0
Neither	0	2	0	4
Total	9	4	1	5

No patients achieved a PR or CR by RECIST

[a] Minor response refers to a decrease in tumor size not meeting criteria for PR by RECIST criteria. This is considered stable disease by RECIST

[b] Patients did not receive two cycles of therapy and were not radiologically evaluable

improvement in overall survival and toxicities were significant [1, 27–30]. Despite a more recent focus on immunotherapy for melanoma, chemotherapy approaches remain commonly used for patients with advanced disease. For patients failing first line therapies, effective additional chemotherapy treatment options are needed.

Based upon preclinical and clinical data indicating activity of oxaliplatin and docetaxel in melanoma, this multicenter phase II trial was designed to evaluate the efficacy of the combination in melanoma. Because phase I data of the combination indicated that the major toxicity was myelosuppression, growth factor support was necessary [19]. While G-CSF was used in that study we selected the related molecule, GM-CSF, for hematopoietic growth factor support in our study. GM-CSF-based chemoimmunotherapy combinations had shown attractive response rates in phase II studies [31, 32], and GM-CSF alone was suggested to improve survival when administered in the post-surgical adjuvant setting compared to historic controls [21]. Although some data suggest that GM-CSF potentiates anticancer immune responses, our trial included GM-GSF primarily as hematopoietic growth factor support [33–36].

There are no proven therapies beyond DTIC or IL-2 for metastatic melanoma, so accrual to this study was straightforward. Toxicities were generally acceptable with, as expected, neutropenia being the most common grade 3 or 4 toxicity (seen in 35% of patients). No more than two patients experienced any other particular grade 3 or 4 toxicity.

GM-CSF mitigated the hematologic toxicity of this chemotherapy combination fairly well, with only one patient requiring dose reduction due to neutropenia present at the start of next cycle. Therefore, GM-CSF is a reasonable alternative to G-CSF as hematopoietic growth factor support in patients with melanoma being treated with myelosuppressive chemotherapy. No conclusions can be drawn regarding the evaluation of the efficacy of anti-tumor immune potentiation by GM-CSF as this was not a designed endpoint of this study, and also due to the poor response to the oxaliplatin, docetaxel, and GM-CSF combination in these pretreated patients, many of whom (8/19) had progressed following prior immune therapy.

Neurotoxicity was a major concern during the design of the study as both oxaliplatin and docetaxel can be causative agents. In the phase I trial of the combination of docetaxel and oxaliplatin, neurotoxicity was not dose-limiting [19]. Although calcium and magnesium infusions have been employed to reduce the incidence of oxaliplatin nerve toxicity [37], electrolyte infusions were not employed systematically in this trial. Decreased magnesium and calcium as a consequence of therapy were seen at low rates. As expected, neurotoxicity was seen (40% of patients experienced peripheral neuropathy) but was not dose-limiting, with no grade 3 or 4 neurotoxicity events observed.

No patients met RECIST criteria for response. One patient did have prolonged stable disease with minor tumor shrinkage not meeting response criteria and went on to receive ten cycles of therapy. Of the six patients that had not received prior therapy, the two who were able to receive two cycles of treatment both achieved stable disease. However, of the 13 pretreated patients, 12 received two cycles and were radiologically evaluable for response and only 3/12 (25%) achieved stable disease. Therefore, consideration could be given to explore this combination in patients without prior therapy.

In summary, the combination of oxaliplatin, docetaxel, and sargramostim (GM-CSF) has limited clinical activity in patients with previously treated metastatic melanoma. Treatment-naïve patients were not focused upon in this study, and further consideration of this combination could be given in that population. The biologic mechanism of occasional responsiveness to chemotherapy in melanoma remains elusive.

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