Phase II Trial of Cisplatin and α-Interferon in Advanced Malignant Melanoma

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Purpose: **To evaluate the antitumor activity of combination cisplatin (CDDP) and α-interferon (α-IFN) in advanced, measurable metastatic melanoma.**

Patients and Methods: **Adult patients with metastatic melanoma were required to have bidimensionally measurable lesions and a Karnofsky performance status ≥ 60%. Serum creatinine ≤ 1.5 mg/dL, creatinine clearance ≥ 60 mL/min, adequate organ and bone marrow function, and radiologic proof of the absence of brain metastases were required. CDDP 40 mg/m² intravenously (IV) on day 1 and day 8, and α-IFN 3 million units/m² subcutaneously on days 1 to 5 and 8 to 12 were administered every 3 to 4 weeks.**

Results: **Forty-two patients were entered onto this phase II trial and were assessable for response and toxicity. Three patients achieved complete responses (CRs) that lasted 31+, 5, and 8+ months. Seven patients had partial responses (PRs) and a median response duration of 4.4 months. The overall objective response rate was 24% (95% confidence interval, 12% to 39%). Toxicities were mild. Only 11% of the courses required dose reduction of α-IFN, and three of 128 courses required CDDP dose reduction for reversible nephrotoxicity.**

Conclusion: **The combination of moderate-dose CDDP and α-IFN as administered in this schedule is well tolerated and possesses encouraging activity in metastatic melanoma.**

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THE TREATMENT OF disseminated melanoma remains unsatisfactory. The most active single agents provide brief objective responses in only 20% of patients. Combination chemotherapy has yielded slightly higher rates of objective response, but complete remissions are rare, and response durations average no longer than a few months. High-dose regimens that require bone marrow support have produced more frequent objective responses, but response durations have also been short and without apparent survival benefit.

The recent elucidation of various mechanisms of resistance to antineoplastic agents and the successful modulation of resistance by other drugs or biologic agents such as interferons (IFNs) have led to the development of treatment protocols that incorporate these combinations into front-line therapy. One such regimen, which has produced up to 50% objective remissions in metastatic melanoma, consists of the combination of carmustine (BCNU), dacarbazine (DTIC), cisplatin (CDDP), and tamoxifen. The rationale for this combination involves the modulation of resistance to CDDP and its analog by tamoxifen.[1-3]

The mechanisms of antitumor activity by the IFNs are not fully understood, but these agents are known to produce a multitude of effects that included changes in the control of gene expression and alterations in nucleotide biosynthetic pathways. IFNs may also protect against the myelotoxicity of antineoplastic agents.[4] The data from in vitro studies suggest that IFN-α, -β, and -γ modulate the antineoplastic activity of selected drugs with single-agent activity against certain tumors.[5] These interactions have been exploited successfully in colorectal cancer protocols in which the combination of α-IFN and fluorouracil (5-FU) has been associated with an approximate doubling of the response rates compared with 5-FU alone.[6]

The optimal dose and schedule of α-IFN for this modulation remains largely unanswered; published clinical trials have contained a wide range of IFN doses, some of which reflect the approach of maximizing dose-intensity rather than attempting to identify the optimum modulatory dose. Although the lack of overlapping toxicities of these agents would allow for potential dose escalation, we designed a trial specifically to explore the activity of this combination in metastatic melanoma at doses expected to cause only modest toxicity, which would thus be feasible for administration in the outpatient setting.

PATIENTS AND METHODS

Eligibility Criteria

Forty-two patients with biopsy-proven, bidimensionally measurable metastatic melanoma were entered onto this study. All patients were required to have a Karnofsky performance status of at least 60%, an estimated survival of at least 4 months, leukocyte count ≥ 3500/μL, platelet count ≥ 150,000/μL, hemoglobin level ≥ 10 g/dL, creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60

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mL/min, alanineaminotransferase (ALT) ≤ 100 U/mL, and total bilirubin ≤ 1.6 mg/mL. After the discovery of previously unsuspected brain metastases in three of the first 12 patients enrolled onto the study, a requirement for negative brain computed tomographic or magnetic resonance imaging scan was added to the eligibility criteria. Any prior radiotherapy, chemotherapy, or immunotherapy must have been completed at least 4 weeks before entry onto the study, and patients must not have received either of the protocol drugs previously. Patients who required or were expected to require corticosteroid therapy, those with active cardiopulmonary disease or poorly controlled diabetes mellitus, pregnant or lactating women, and those with a history of another invasive malignancy were excluded. The protocol was approved by the institutional review board of the City of Hope National Medical Center; all patients gave their written, voluntary informed consent before treatment began.

Treatment

Before the initiation of therapy, all patients underwent a complete medical history and physical examination; laboratory studies included a complete blood cell count with differential WBC count, prothrombin and partial thromboplastin time, 18-function biochemistry panel, creatinine clearance, magnesium level, chest radiograph, ECG, and urinalysis.

Therapy consisted of CDDP, 40 mg/m^2 given by rapid intravenous (IV) infusion in 200 mL of 0.9% saline, days 1 and 8, and α-IFN, 3 million units/m^2 subcutaneously, days 1 to 5 and 8 to 12 of each 21-day cycle. All patients received at least 1 L of IV fluid before CDDP administration and were discharged from the hospital or clinic only after the assurance of adequate oral fluid intake. The choice of antiemetics was discretionary but excluded glucocorticoids. The first dose of α-IFN was given subcutaneously immediately after CDDP, and subsequent doses were self-administered at approximately 24-hour intervals. All patients were administered acetaminophen 650 to 1,000 mg orally as a premedication and 4 hours after each dose of α-IFN, and subsequently as needed to control fever and myalgias. Treatment cycles were to be repeated every 3 to 4 weeks, which depended on the time required for resolution of the constitutional effects of therapy.

Follow-up required by the protocol included physical examinations and 18-function biochemistry panels on days 1 and 8, complete blood cell counts and 6-function biochemistry panels on days 1, 5, 8, and 12, and urinalysis on day 1 and 12 of each cycle. Chest radiographs and ECGs were required before each cycle, and tumor measurements that required scans were repeated after every two cycles.

The Southwest Oncology Group toxicity grading scale was used for assessment of α-IFN toxicities (Table 1). Patients who experienced no grade A or higher toxicity were eligible to increase the α-IFN dose by 2 million units/m^2/d on the next full cycle. For any grade A toxicity, α-IFN was continued without dose adjustment. For any grade B or C toxicity, α-IFN was withheld until the toxicity had resolved to grade A or less; then treatment was restarted at 50% of the initial dose for that cycle. For any grade D or recurrent grade B or C toxicity at the reduced dose, the patient was taken off of protocol therapy.

CDDP dose adjustments for nephrotoxicity consisted of a reduction of the initial dose by one or two levels, which depended on the maximum degree of creatinine elevation during the prior treatment cycle and the serum creatinine on the day of therapy (Table 1).

Definitions of Response

Complete response (CR) was defined as the complete disappearance of all objective evidence of disease on two separate measurements at least 4 weeks apart. Partial response (PR) required a 50% or greater reduction in the products of the diameters of all measurable bidimensional lesions without a CR and with no new lesion that lasted at least 4 weeks. Stable disease was defined as less than PR but no new lesion or progression of existing lesions; disease progression was defined as a ≥ 25% increase in the product of perpendicular diameters of the measurable lesions. The duration of response was measured from the onset of best response (including CRs) to the date of disease progression; duration of survival was measured from the time of study entry until the date of death. All tumor measurements in patients who responded were confirmed by the principal investigator and a member of the

Table 1. Dose Levels and Adjustments for Toxicity

	Dose Levels				
	−2	−1	0	+1	+2
α-IFN (million units/m^2 days 1-5, 8-12)	.75	1.5	3	5	7
CDDP (mg/m^2 days 1 and 8)	15	25	40	—	—

Toxicity	Grade A (minimal)	Grade B (moderate)	Grade C (severe)	Grade D (life-threatening)
Hematologic				
Granulocytes (per μL)	1,000-1,500	500-999	250-499	< 250
Platelets (per μL)	75,000-100,000	50,000-74,999	25,000-49,999	< 25,000
Hepatic				
Bilirubin (mg/dL)	1.5-2.0	2.1-2.5	2.6-3.0	> 3.0
SGOT (IU/L)	50-150	151-300	301-600	> 600

Maximum Creatinine (mg/dL)	Treatment Day Creatinine (mg/dL)	CDDP Dose Reduction
≤ 3.0	≤ 1.5	None
3.1-4.5	≤ 1.5	1 level
4.6-6.0	≤ 1.5	2 levels

NOTE. Dose adjustments of α-IFN for grade A to grade D levels of toxicity are provided in the text.

Department of Biostatistics. The response rates were calculated using the exact formula for binomial proportions.

RESULTS

Patient Characteristics

Forty-two patients with measurable metastatic melanoma were entered onto this trial and were assessable for response and toxicity. The median age was 52 years (range, 21 to 75); there were 28 male and 14 female patients. The median performance status was 90% (range, 60% to 100%). The sites of metastatic disease are listed in Table 2. Most patients had received no prior therapy; six had failed high-dose interleukin-2 (IL-2), three had received tumor vaccines, and one each had received Isoprinosine (methisoprinol) an investigational immunomodulator, CI-921 (an investigational acridine analog), and tamoxifen. One patient had been administered tumor vaccine followed by BCNU and DTIC-containing combination chemotherapy and subsequent high-dose IL-2.

Response

All 42 patients were considered assessable for response. Three patients had CRs, that lasted 31+, 5, and 8+ months. Seven patients achieved PRs, with a median response duration of 4.4 months (range, 1.5 to 9.5 months). The overall objective response rate was 24% (95% confidence interval, 12% to 39%). Among the 41 patients who remained assessable for long-term follow-up (one patient, who refused further therapy after only one-half cycle because of subjectively intolerable constitutional side effects, was subsequently lost to follow-up), the median time to progression was 2.9 months, and the median survival of the entire group was 7.4 months (range, 1.8 to 28+ months). The sites of metastatic disease for the entire group are given in Table 2. The sites of disease in those patients who achieved CR were pulmonary and lymph node; PRs were observed in one of seven patients with bone metastases, five of 16 with liver and/or other visceral sites, and one with metastatic disease that was limited to soft tissue.

Table 2. Sites of Metastatic Disease

Sites of Disease	Total	PR	CR
A. Skin and/or soft tissue only	7	1	
B. Lymph nodes ± (A)	2		1
C. Pulmonary ± (A) and/or (B)	10		2
Liver and/or visceral ± any among (A, B, C)	16	5	
Bone ± any other	7	1	

Table 3. Treatment Toxicities

	Cycles (N = 126)	
	No.	%
Creatinine elevation ≥ 1.6 mg/dL	3	2
Granulocytopenia		
500-999/μL	10	8
Thrombocytopenia		
50,000-75,000/μL	4	3
25,000-49,000/μL	1	1
IFN dose reduction 1 level	14	11

Protocol Therapy Administered and Toxicities of Treatment

The median number of treatment cycles administered was two (range, one to nine). Toxicities of treatment are shown in Table 3. Only three patients required a one-level dose adjustment of CDDP for nephrotoxicity; the maximum creatinine was 2.1 mg%. IFN doses were reduced to 50% of the initial dose in 11% of cycles (14 of the 128 total cycles administered) and to 1 million units/m^2 in only two cycles. Half of the patients who required a dose reduction of α-IFN were able to tolerate a reescalation of the dose from 1.5 million units/m^2/d to 2.5 million units/m^2/d without the recurrence of dose-limiting toxicities. Ten percent (12 of 126 cycles) of the α-IFN doses were escalated to the 5 million units/m^2/d dose level because of the lack of toxicity at the lower dose, and five (42%) of these patients subsequently required a 50% dose reduction because of an intolerance of the higher dose. The most frequent indication for a dose reduction of α-IFN was granulocytopenia, which occurred at a grade B level (nadir, 500 to 999/μL) in 10 (8%) cycles at the initial dose. Grade B thrombocytopenia (50,000 to 75,000/μL) occurred in four cycles (3%), and grade C (25,000 to 49,000/μL) occurred in only one. Although mild to moderate fatigue, anorexia, myalgias, and malaise were experienced by most patients, these symptoms were never the sole indication for a dose reduction of either agent.

Seven patients withdrew from treatment without developing medical indications for the discontinuation of protocol therapy; in most cases, these patients experienced grade B fatigue and malaise that did not improve off therapy and later was attributable to the constitutional symptoms of progressive tumor.

DISCUSSION

We designed the present therapeutic regimen to take advantage of the potential in vivo modulation of CDDP by α-IFN. CDDP as a single agent provides an objective response in approximately 10% of patients with meta-

static melanoma.[7,8] The schedule used in our protocol was chosen to provide prolonged exposure to α-IFN after intermittent exposure to CDDP. The doses of both agents were expected to be well tolerated and thus available to a more representative patient group than has been studied in trials of more intense therapies, ie, high-dose combination chemotherapy or IL-2.

Preclinical studies of the interactions between α-IFN and a number of chemotherapeutic agents have shown synergy or additivity in either clonogenic or xenograft assays.[9-15] The dose, route, and schedule requirements for optimum therapeutic interaction between chemotherapeutic agents and α-IFN have not yet been defined clearly. However, the data from most of these studies suggest that the drug must possess single-agent activity to be modulated effectively by α-IFN, and these interactions are limited to certain drug combinations and tumor histologies.[5] The specific biochemical and/or immunologic interactions between these two agents differ among those model systems in which they have been studied. Among the proposed mechanisms of interaction are alterations by α-IFN of nucleotide biosynthetic pathways,[14] metabolic effects that may reduce various aspects of host sensitivity to the chemotherapeutic agent,[4,15] and a variety of immunologic effects based on the interactions between tumor, host, and drug.[5]

The interaction of CDDP with α-IFN has been of great interest because of the wide range of malignancies responsive to CDDP and its analogs. Preclinical data suggest that these agents could be combined to advantage in malignancies with some degree of sensitivity to CDDP. Increased lifespan has been reported with the addition of murine IFN to CDDP in mice that have P388 leukemia.[9] In murine xenografts of three human non–small-cell lung cancer lines (NX002, CX117, and CX143), human lymphoblastoid IFN potentiated the activity of CDDP.[10] A similar effect was observed in a murine xenograft of a human mesothelioma line (BG), that used recombinant human α-IFN with CDDP.[11] CDDP and human recombinant α-IFN also showed synergistic activity that was schedule-dependent (requiring prolonged simultaneous exposure to both agents) against a human myeloma in an in vitro drug-sensitivity assay.[12] In a similar assay system, recombinant human α-IFN and CDDP had synergistic activity against the ovarian cancer cell line BG-1 and additive effects against four of five fresh human tumor specimens tested.[13]

A recent phase I study of the combination of CDDP with α-IFN suggested that the maximum-tolerated dose (MTD) of CDDP was only 25 mg/m^2 every 5 weeks with a dose and schedule of α-IFN (5 million units/m^2 subcutaneously 3 days per week, 3 of every 5 weeks) similar to those we used.[16] In a preliminary report of the phase II trial performed by the same investigators in 15 patients with metastatic melanoma, the majority of toxicities seemed attributable to α-IFN; however, because of grade 2 nephrotoxicity, the investigators concluded that further CDDP dose-escalation would probably not be tolerated.[17] Because patients in that trial were allowed up to 120 mg/m^2 of prior CDDP, it is difficult to determine whether the modest CDDP dose used represented the true MTD in combination with α-IFN, because CDDP may be limited by cumulative effects as well as acute toxicities. In another recent report, 15 patients with metastatic melanoma, were treated with α-IFN (10 million units) subcutaneously daily and CDDP 50 mg/m^2 on days 8 and 9 every 28 days. In this group, one CR and three PRs, all of brief duration, were reported.[18] A similar level of activity was reported in a separate study of 15 patients with metastatic melanoma who were treated with α-IFN 5 million units/m^2 IV with CDDP 20 mg/m^2 both daily for 4 days every 3 weeks. One CR and three PRs of brief duration were observed in this group; grade 3 or 4 leukopenia occurred in half of the patients.[19]

The dose-intensity of α-IFN and CDDP in our study was similar to that used in the phase I and II studies previously described. We observed predominantly constitutional and mild asymptomatic laboratory toxicities and almost no CDDP-related nephrotoxicity or neurotoxicity in this patient population with no prior CDDP exposure. Although this combination of CDDP and α-IFN produced a modest objective response rate, the achievement of two durable CRs and seven PRs in this group of patients with relatively unfavorable sites of disease confirms its promising clinical activity.

Two recent studies of CDDP at higher doses in combination with DTIC (and, in one trial, with the addition of tamoxifen) failed to suggest an advantage of higher doses of CDDP (150 mg/m^2) in metastatic melanoma.[20,21] We do not believe that further dose intensification of CDDP is likely to produce markedly enhanced antitumor activity unless it can be modulated by other agents that currently are under investigation.

We believe that the results of our study show encouraging activity for this well-tolerated combination of α-IFN and CDDP in metastatic melanoma. Future protocol designs should be based on the nonoverlapping toxicities of these modulating agents and the evolving information about the important interactions among chemotherapeutic drugs and biologic agents.

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