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Phase II trial of CI-980 in patients with disseminated malignant melanoma and no prior chemotherapy

A Southwest Oncology Group study

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Summary

Malignant melanoma is increasing in frequency at a rapid rate in the United States. Metastatic disease is chemoresistant with DTIC considered the most active single agent. CI-980 is a synthetic mitotic inhibitor that blocks the assembly of tubulin and microtubules. It has shown cytotoxic activity against a broad spectrum of murine and human tumor cell tines. CI-980 can cross the blood brain barrier, is effective when given orally or parenterally, and is active against multidrug resistant cell lines overexpressing P-glycoprotein. In this trial, patients with disseminated melanoma with measurable disease, SWOG performance status of 0–1, no prior chemotherapy or immunotherapy for metastatic disease, and adequate hepatic and renal function, were enrolled. Treatment with CI-980 was given by 72 h continuous IV infusion at a dose of 4.5 mg/m^2/day, days 1–3 every 21 days. Twenty-four patients were registered on this study with no patients ineligible. They ranged in age from 33–78 with performance status of 0 in 15 patients and 1 in 9 patients. Nineteen patients had visceral disease with 12 having liver involvement. There were no confirmed responses. The overall response rate was 0% (95% CI 0% –14%). The median overall survival is eleven months (95% CI 4–14 months). The most common toxicities were hematologic and consisted of leukopenia/granulocytopenia and anemia, with nausea/vomiting and malaise/fatigue/weakness also frequent. CI-980 administered at this dose and schedule has insufficient activity in the treatment of disseminated malignant melanoma to warrant further investigation.

Introduction

Malignant melanoma is a common problem in the United States with almost 40,000 new cases and over 7000 deaths annually [1]. Its frequency is increasing, perhaps due to increased recreational exposure to sunlight, with a doubling of the death rate in the last 35 years and increases of approximately 5% per year in the older Caucasian population [1]. Chemotherapy is relatively ineffective for metastatic disease with only 2 out of 30 drugs tested, DTIC and nitrosourea, producing response rates of 10% or better [1]. Complete responses are rare. There is no convincing evidence that combination chemotherapy is significantly better than DTIC alone [1,2]. CI-980, (NSC 635370 [ethyl (S)-(5-amino-1,2-dihydro-2-methyl-3-phenylpyrido (3, 4-b) pyrazin–7-yl) carbamate 2-hydroxyethane sulfonate]) is a synthetic mitotic inhibitor which binds to the colchicine binding site on tubulin but at a site distinct from that of the vinca alkaloids, inhibiting the assembly of purified tubulin and microtubules [3–5]. This disrupts structural components of the cell and blocks formation of the mitotic spindle. Treated cells accumulate in M phase of the cell cycle and die.

CI-980 has demonstrated profound cytotoxic activity against a broad spectrum of both murine and human

tumors *in vivo*, including P388 leukemia, L1210 leukemia, B16 melanoma, M5076 sarcoma, mammary adenocarcinoma 16c, and colon adenocarcinoma 36, 11a, and 26 [6,7,8]. It is twice as potent as vincristine against P388 leukemia [6]. Multidrug resistance due to P-glycoprotein overexpression does not seem to confer resistance to CI-980 in contrast to other agents [6,7,8]. CI-980 showed activity in intracranial tumor implants, and tissue distribution studies confirmed that it could cross the blood brain barrier, a characteristic potentially useful in melanoma patients. It retained full activity when given PO as well as IM or IV [6,7].

Phase I trials of the drug resulted in severe CNS toxicity consisting of loss of consciousness, confusion, tremors and coma when it was given by 1 to 24 h infusion [9]. However when given over 72 h, CNS effects were mild to moderate with leukopenia the principal dose limiting toxicity [9]. This trial reports the effects of CI 980 in previously untreated patients with disseminated melanoma when given as a 72 h infusion.

Materials and methods

Patient population. All patients were required to have a histologically proven diagnosis of malignant melanoma that was Stage IV and not surgically curable, with bidimensionally measurable disease. Patients had to have no evidence of brain metastases by CT or MRI; if they had a history of brain metastasis, they had to be resected completely free of disease followed by a course of whole brain radiation therapy. They had to have a Southwest Oncology Group performance status of 0 or 1 ($\geq$70 Karnofsky), thus ambulatory and able to carry out light work. Patients may have received prior biologic or immunotherapeutic regimens given in an adjuvant fashion, but no adjuvant chemotherapy and no prior chemotherapy or immunotherapy for metastatic disease. Prior surgery, hormonal therapy or isolated limb perfusion was allowed provided it was completed at least 28 days before registration and patients had recovered from all adverse effects. Prior radiation therapy was allowed provided there was objective evidence of progression of disease or measurable unirradiated disease sites. Patients had to have a pretreatment granulocyte count of $\geq$1500 cells/μl, a platelet count $\geq$100,000 cells/μl, and hemoglobin $\geq$10 gm/dl. Serum creatine and serum bilirubin had to be less than or equal to the institutional upper limit of normal and serum glutamic – oxaloacetic transaminase level (SGOT) had to be $\leq$2.5 times the institutional upper limit of normal or $\leq$5 times the institutional upper limit of normal if the liver was involved by tumor. Patients with other serious illnesses, active infections, and those requiring therapy with other investigational drugs, corticosteroids, or antibiotics were not eligible. Patients with AIDS or known to be human immunodeficiency virus antibody seropositive as well as pregnant or nursing women were not eligible. Patients with a second malignancy were not eligible unless it was an adequately treated basal or squamous cell skin cancer, in situ cervical cancer, adequately treated stage I or II cancer from which the patient was currently disease-free, or any other cancer for which the patient had been disease-free for at least 5 years. Women and men of reproductive potential had to agree to use an effective contraceptive method. No type of concomitant therapy for the patient's melanoma was allowed.

CI-980. CI-980 was supplied by the National Cancer Institute as a sterile lyophilized powder in 6 ml amber glass vials containing 10 mg CI-980 base equivalent. It was reconstituted with 5 ml of Water for Injection, USP, resulting in a concentration of 2 mg/ml. It was further diluted in D5W for IV infusion. Solutions of CI-980 could only be administered through peripheral IV lines (not recommended due to the risk of phlebitis) or through subclavian central venous catheters made of silicone.

Treatment plan. CI-980 was given by a 72 h continuous IV infusion at a dose of 4.5 mg/m^2/day, days 1–3 of each 21 day treatment cycle. Inpatient administration was required during the first cycle and was optional thereafter. Pretreatment with antiemetics capable of preventing mild to moderate nausea and vomiting was recommended. Because of sterility and stability considerations, each prepared dose of drug was infused over 24 h after which a fresh dose was started. Dose reduction of 25% was required for the development of grade 2 or higher disorientation for greater than 24 h, or grade 3 or higher other neurotoxicity. If after 2 dose reductions, the patient again developed a similar level of neurotoxicity, they were removed from treatment. Weekly CBC and platelet counts were required during the first 3 week cycle and if grade 3 or 4 levels of granulocytopenia or thrombocytopenia were seen, then weekly counts were required in all subsequent cycles. At a minimum, a CBC was required the week of treatment and on day 8 of each cycle. A grade 4 level of absolute granulocyte count ($<$500 cells/μl) at any time during treatment

required a 25% dose reduction from baseline in subsequent cycles and allowed optional use of G-CSF. Once a dose reduction occurred for hematologic toxicity, there was no re-escalation of dose allowed, even if G-CSF was used. If after 2 dose reductions grade 4 toxicity recurred, the patient was removed from treatment. Other toxicities of grade 4 level required similar dose reductions and treatment discontinuation.

Definition of response. Standard SWOG response criteria were used to define the antitumor effects that were observed. A complete response required the disappearance of all measurable and evaluable disease in all disease sites including normalization of abnormal disease-related laboratory values and disease-related symptoms with no new lesions. A partial response required $\geq$50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions, with no new lesions or progression of evaluable disease with all measurable and evaluable lesions and sites assessed. Progressive disease was defined as (a) a 50% increase or an increase of 10 cm^2 (whichever is smaller) in the sum of the products of measurable lesions over the smallest sum observed or clear worsening of any evaluable disease, or (b) the appearance of any new lesion or the reappearance of any lesion that had disappeared, or (c) failure to return for evaluation due to deteriorating condition (unless deterioration was clearly unrelated to the cancer). Stable disease was disease that did not meet the criteria for either a complete or partial response or progression. Tumor assessment was requested at the end of every two cycles. After first documentation of a complete or partial response, a second assessment was required after a minimum of 3 weeks to confirm the response.

Results

Patient population. Twenty four patients from 17 different institutions were registered on this study. No patients were ineligible. The characteristics of all 24 eligible patients are listed in Table 1. They ranged in age from 33–78 and 12 (50%) were male. Fifteen (63%) had a performance status of 0 while 9 (38%) had a performance status of 1. Seven (29%) had prior adjuvant biologic therapy and 3 (13%) prior radiation treatment. Nineteen patients (79%) were M1b, thus having some site of visceral metastases. The liver was involved with tumor in 12 patients (50%). One patient had had previous resection and radiation of a brain lesion.

Table 1. Patient characteristics – N = 24

Age, years		
Median	57.5	
Range	33–78	
	No.	Percent
Gender		
Male	12	50%
Female	12	50%
Performance status		
0	15	63%
1	9	38%
TNM classification		
M 1a	5	21%
M 1b	19	79%
Liver involvement		
Yes	12	50%
No	12	50%
Prior adjuvant biologics		
Yes	7	29%
No	17	71%
Prior radiation therapy		
Yes	3	13%
No	21	88%

Response and survival. Response data are listed in Table 2. All 24 eligible patients were evaluated for response. There were no confirmed responses. There was one unconfirmed response in a patient with a liver lesion that decreased by more than 50% at first evaluation 6 weeks after beginning therapy, but new liver and lung lesions developed by the next evaluation 4 weeks later. Because of the transient, unconfirmed nature of the response, this patient is considered to be a non-responder. Hence, the overall response rate was 0% with a 95% confidence interval of 0 to 14%. Twenty-one patients came off treatment because of progression, one came off because of toxicity, one refused treatment unrelated to toxicity, and one patient was off treatment because of death due to disease related causes prior to first assessment. There were no major protocol deviations. Twenty-two of the 24 patients have died. The median overall survival is 11 months with a 95% confidence interval of 4 months to 14 months.

Toxicity. All 24 patients were evaluated for toxicity (see Table 3). The most common toxicities were hematologic and consisted of leukopenia/granulocytopenia (67%) and anemia (58%). Thrombocytopenia was not as prominent. Malaise/fatigue/weakness was also fre-

Table 2. Response – N = 24

	Number	Percent
Complete response	0	0%
Partial response	0	0%
Unconfirmed response	1	4%
Stable/no response	7	29%
Increasing disease	16	67%
Total	24	100%

Table 3. Toxicity – N = 24

Toxicity	Any grade No.	%	Grade 3 No.	Grade 4 No.
1. Leukopenia/granulocytopenia	16	67%	5	5
2. Anemia	14	58%	1	0
3. Nausea/vomiting	12	50%	2	0
4. Malaise/fatigue/weakness	10	42%	2	0
5. Local/phlebitis/thrombosis	6	25%	1	0
6. Fever without infection	6	25%	0	0
7. Neurologic	5	21%	0	0
8. Thrombocytopenia	4	17%	1	0
9. Lymphopenia	4	17%	0	0
10. GI-other	4	17%	0	0
11. Pain	3	13%	0	0
12. Weight gain/loss	3	13%	0	0
13. Infection	2	8%	0	0
14. Respiratory	2	8%	0	0
15. Cardiac	1	4%	0	0
16. Diarrhea	1	4%	0	0
17. Miscellaneous	8	33%	0	1

quent. Nausea and vomiting was occasionally severe but mostly controlled. The grade 4 miscellaneous toxicity was hypoxia from probable oversedation.

Discussion

CI-890 is a very potent mitotic and microtubule inhibitor with *in vitro* activity superior to vincristine that is fully active against vincristine-resistant tumors [10]. It is widely and uniformly distributed in mice thus indicating that it has the ability to cross physiologic barriers and penetrate tumor masses [6]. Because of this it is fully active whether given IV, IM, or PO, making it a suitable drug for outpatient therapy [9]. Phase I trials have shown that in the doses and schedule used here, blood levels are achieved which show activity against most human leukemias and solid tumors *in vitro* [9]. In addition, the 72 h infusion schedule produces prolonged exposure to drug which also enhances cytotoxicity [9].

Thus this phase II trial in patients with disseminated melanoma was undertaken with hope that there might be significant benefit to patients. Unfortunately, no beneficial antitumor actively was found, and further testing of CI-980 in melanoma patients at this dose and schedule is not recommended. A similar lack of activity was seen in phase II trials of CI-980 in colorectal cancer and soft tissue sarcoma patients in which it was given by the same dose and schedule used here [11,12]. One out of sixteen patients with platinum refractory ovarian cancer responded to CI-980 given as in this trial [13].

It is possible that alternative dosing schedules, such as infusions of longer duration, might be useful. In addition, CI-980 has shown synergy with cisplatin and BCNU in tumor model systems [14]. Thus trials of combinations with other agents or evaluation in other tumor types such as leukemia and lymphoma may ultimately prove worthy of investigation.

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References

1. Balch CM, Reintgen DS, Kirkwood JM, Houghton A, Peters L, Ang KK: Cutaneous Melanoma. Ch. 41.2. In: DeVita VT Jr, Hellman S, Rosenberg SA (Eds) Cancer: Principles and Practice of Oncology. 5th Edn. Lippincott-Raven Publishers, Philadelphia, 1997
2. Chapman PB, Einhorn LH, Meyers ML, Saxman S, Destro AN, Panageas KS, Begg CB, Agarwalla SS, Schuchter LM, Ernstoff MS, Houghton AN, Kirkwood JM: Phase III multicenter randomized trial of the Dartmouth Regimen versus Dacarbazine in patients with metastatic melanoma. J Clin Oncol 17: 2745–2751, 1999
3. Wheeler GP, Bowdon BJ, Werline JA, Adamson DJ, Temple CG: Inhibition of mitosis and anticancer activity against experimental neoplasms by ethyl 5-amino-1,2-dihydro-3-[(N-

methylanilino)methyl]-pyridol [3,4-b] pyrazin-7-ylcarbamate (NSC 181928). Cancer Res 42: 791–798, 1982
4. Wheeler GP, Bowdon BJ, Temple C Jr, Adamson DJ, Webster J: Biological effects and structure – activity relationships of 1,2-dihydropyrido [3,4-b] pyrazines. Cancer Res 43: 3567–3575, 1983
5. Bowdon BJ, Waud WR, Wheeler GP, Hain RH, Dansby L, Temple CG: Comparison of 1,2-dihydropyrido [3,4-b] pyrazines (1-deaza-7,8-dihydropteridines) with several other inhibitors of mitosis. Cancer Res 47: 1621–1626, 1987
6. Park-Davis Pharmaceutical Research Division, Warner-Lambert Company, Investigator's Brochure, 1990
7. Waud WR, Leopold WR, Elliot WL, Dykes DJ, Laster WR Jr, Temple CG Jr, Harrison SD Jr, Griswold DP Jr: Antitumor activity of ethyl 5-amino-1,2-dihydro-2-methyl-3-phenylpyridol [3,4-b] pyrazin-7-ylcarbamate, 2 hydroxyethanesulfonate hydrate (NSC 370147) against selected tumor systems in culture and in mice. Cancer Res 50: 3239–3244, 1990
8. Griswold DP Jr, Temple CG Jr, Trader MW, Leopold WR III, Laster WR Jr, Dykes DJ: Antitumor activity of novel 1,2-dihydropyrido [3,4-b]-pyrazine in preclinical drug-sensitive and resistant tumors. Proc Am Ass Cancer Res 27: 306, 1986
9. Rowinsky EK, Long GS, Noe DA, Grochow LB, Bowling MK, Sartorius SE, Donehower RC: Phase I and pharmacological study of CI-980, a novel synthetic antimicrotubule agent. Clin Cancer Res 3: 401–407, 1997
10. de Ines C, Leynadier D, Barasoain I, Peyrot V, Garcia P, Briand C, Rener GA, Temple C Jr: Inhibition of microtubules and cell cycle arrest by a new 1-deaza-7,8-dihydropteridine antitumor drug, CI 980, and by its chiral isomer, NSC 613863. Cancer Res 54: 75–84, 1994
11. Pazdur R, Meyers C, Diaz-Canton E, Abbruzzese JL, Patt Y, Grove W, Ajani J: Phase II trial of intravenous CI-980 (NSC 370147) in patients with metastatic colorectal carcinoma. Model for prospective evaluation of neurotoxicity. Am J Clin Oncol 20: 573–576, 1997
12. Patel SR, Burgess MA, Papadopolous NE, Sidhu G, Gray R, Plager C, Jenkins J, Benjamin RS: Phase II study of CI-980 (NSC 635370) in patients with previously treated advanced soft-tissue sarcomas. Invest New Drugs 16: 87–92, 1998
13. Kudelka AP, Hasenburg A, Verschraegen CF, Edwards CL, Meyers CA, Varma D, Freedman RS, Forman A, Conrad CA, Grove W, Grothey A, Kavanagh JJ: Phase II study of i.v. CI-980 in patients with advanced platinum refractory epithelial ovarian carcinoma. Anti-Cancer Drugs 9: 405–409, 1998
14. Leopold WR, Elliott WL, Pryzbranowski SA, Waud WR: *In vivo* evaluation of the potential for therapeutic synergy between CI-980 and standard chemotherapeutic agents. Proceedings AACR 34: 296, 1993 (abstract)

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