Investigational New Drugs **11**: 223-226, 1993.

Evaluation of amonafide in disseminated malignant melanoma

A Southwest Oncology Group study

Milan Slavik[1], Kenneth J. Kopecky[2], Vernon Sondak[3], John B. Craig[4] and Michael K. Samson[5]
[1]*University of Kansas School of Medicine and Department of Veterans Affairs Medical Center, Wichita, KS;* [2]*Southwest Oncology Group Statistical Center, Seattle, WA;* [3]*University of Michigan Medical Center, Ann Arbor, MI;* [4]*University of Texas Health Sciences Center, San Antonio TX;* [5]*Wayne State University School of Medicine and Department of Veterans Affairs Medical Center, Dedroit MI, USA*

Key words: amonafide, phase II, melanoma

Abstract

Amonafide (AMF), NSC 308847 is an investigational anticancer drug acting as a DNA intercalating agent. This paper presents results of a phase II clinical study of AMF in disseminated malignant melanoma. Twenty patients, eleven males and nine females, with biopsy proven malignant melanoma, performance status 0–2; median age 59 (range 29–74), and no previous chemotherapy, were treated with AMF 300 mg/m^2/day by 60 min I.V. infusion for five days repeated every three weeks. Fifteen patients had lung (9 patients) and/or liver (8 patients) involvement. None had known brain metastasis at entry. All 20 patients were evaluated for response and toxicity. Six patients had stable disease and fourteen had increasing disease. With 0/20 responses, the upper 95% confidence limit for the response rate was 14%. The median survival time was 5.7 months. Hematologic toxicity was dose limiting with the incidence of leucopenia 45% and thrombocytopenia 20%. The nonhematologic toxicities included nausea and vomiting (60%), alopecia (20%), headaches (15%), diarrhea (10%), and phlebitis (10%). We conclude that AMF administered at this dose and schedule is not active in the treatment of patients with malignant melanoma, previously untreated with chemotherapy.

Introduction

Amonafide (Benzisoquinolinedione, Nafidimide, NSC 308 847) is a new investigational anticancer drug of European origin and novel structure. It was synthesized by Brana and associates [1] from imide derivatives of 3-nitro-$1_1\alpha$ naphtalic acid as a part of a program designed to combine into a single molecule the structural entities responsible for the antitumor activity of aristocholic acid, cycloheximide, tilorone, and 1-(morpholinemethyl)-4-phtalimido-piperidine-2-6 dione [1,2]. The structure activity studies revealed that two methylene groups in the side chain and the presence of the basic terminal nitrogen are essential for cytotoxic activity of this drug [3]. Amonafide appears to function as a DNA intercalating agent [4] and to be cross resistant with other intercalators [5]. Amonafide was selected for clinical development based on its experimental antitumor activity against intraperitoneally implanted L1210 and P388 leukemias, M5076 sarcoma, and B16 melanoma in mice [5].

Phase I evaluation of amonafide exploring various schedules including single I.V. dose repeated every 4 weeks [6] daily × 5 I.V. schedule repeated every 3–4 weeks [7] and daily × 2 I.V. schedule [8] revealed reversible and not cumulative myelosuppression to be the dose limiting toxicity. The nonhematologic toxicities included mild nausea and vomiting, alopecia and maculopapular rash at higher doses, mild phlebitis and infusion rate dependent dizziness and tinnitus [6,7]. Clinical

interest for phase II evaluation of this drug was simulated by the reports of anticancer activity in three patients with solid tumors detected during the phase I evaluation of this drug [6,7]. As part of an ongoing search for new active cytotoxic agents against malignant melanoma, the Southwest Oncology Group (SWOG) conducted a phase II clinical study of amonafide in patients with advanced disease (SWOG 8723). Based on the schedule dependency noted in preclinical studies and the increase in dose intensity, the daily × 5 schedule was selected for the phase II evaluation of this drug.

Materials and methods

Patients with bidimensionally measurable stage IV malignant melanoma were eligible for the study. The eligibility criteria included pathological verification of malignant melanoma, adequate bone marrow defined as pretreatment granulocyte count $\geq 1500/\mu l$ and platelet count $\geq 100{,}000/\mu l$, and adequate renal and liver function defined as serum creatinine $\leq$ 1.5 mg%, serum bilirubin $\leq$ 1.5 mg/DL and SGOT $\leq 2 \times$ the institutional upper limit of normal. Performance status 0–2 (SWOG criteria) was required. Prior surgery and/or radiation therapy were allowed, however, at least four weeks must have elapsed since completing radiation therapy. If all known sites of disease had been previously radiated, objective evidence of progression prior to registration was required. While prior cytotoxic chemotherapy was not allowed, one prior biologic regimen was acceptable. Pretreatment laboratory values must have been obtained within 14 days of patient registration and a written informed consent in accordance with the institutional and FDA guidelines was obtained from the patient before entering this study.

The initial amonafide dose was 300 mg/m^2 in 100 ml 0.9% Sodium Chloride USP administered by intravenous infusion over one hour daily × 5 days repeated every 21 days. Treatment was continued until progression, unacceptable toxicity requiring discontinuation of chemotherapy, patient withdrawal, or death.

Dose modification in subsequent courses was provided, depending on the nadir of the granulocyte and platelet counts during the preceding cycle. Standard SWOG criteria were used for the estimation of performance status and for evaluation of toxicity and response. Response definitions were as follows: complete response – complete disappearance of all measurable and evaluable disease and no new lesions; partial response, at least 50% reduction in size of all measurable tumor masses as measured by the sum of products of their greatest perpendicular diameters, no new lesions; stable disease did not qualify for complete response, partial response or progression; progression – 50% increase in sum of products of measurable lesions over smallest sum observed or appearance of any new lesion or reappearance of any lesion which had disappeared.

Results

Twenty-three patients were entered on this study during two stages of accrual. Three patients were ineligible: two because of missing baseline tests and one because baseline laboratory tests were done more than 14 days prior to registration. Consequently 20 patients are eligible for evaluation of toxicity and response. Baseline patient characteristics are presented in Table 1. All patients were white. Active sites of disease are tabulated as the percent of patients with a specific site of active disease. Any one patient may have multiple sites of active disease and thus the percentages add up to greater than 100%. None of the patients had known brain metastasis at entry.

Twenty patients eligible for evaluation of toxicity and response received 44 cycles of treatment. Of these, six patients received only one cycle, ten patients received two cycles, three patients received four cycles, and one patient received six cycles of treatment. Among the 14 eligible patients, who received more than one cycle, the second cycle's dose was escalated, unchanged or reduced in six, four, and four patients respectively.

All twenty eligible patients were evaluated for toxicity. Bone marrow toxicity was dose limiting with the incidence of leucopenia of 45% and throm-

Table 1. Patient characteristics (n = 20)

Median age	59	(29–74 Range)
Sex males/females	11/9	
Performance status		
PS 0	10	
PS 1	8	
PS 2	2	
Primary site		
Trunk	6	30%
Eye	5	25%
Lower extremity	3	15%
Upper extremity	2	10%
Head & neck	3	15%
Unknown	1	5%
Active disease sites		
Regional nodes	3	15%
Distant nodes	5	25%
Liver	8	40%
Lung	9	45%
Bone	2	10%
GI	2	10%
Other	3	15%

bocytopenia 20%. Severe (Grade 3–4) hematologic toxicity occurred in 35% patients. The nonhematologic toxicities included nausea and vomiting in 60%, alopecia in 20%, headaches in 15%, diarrhea in 10%, phlebitis in 10%, and dizziness in 5% of the patients. In addition, one of the ineligible patients was bedridden for two days after treatment due to fatigue and myalgia.

Of the twenty patients, evaluated for response none achieved complete or partial remission, six patients had stable disease and fourteen had tumor progression. With 0/20 responses, the upper 95% confidence limit for the response rate was 14%. Nineteen of the twenty eligible patients have died and one patient is alive at 27 months. The median survival is 5.7 months (range 23 days–27 months).

We conclude that amonafide administered at this dose and schedule is not active in the treatment of patients with disseminated malignant melanoma, previously untreated with chemotherapy. The negative results reported in this study occurred inspite of the fact that we have selected the dose schedule offering the high dose intensity regimen for this drug. On the other hand, the negative outcome of this study is not surprising, since the majority of the patients had a rapidly progressing disease, allowing only administration of one or two courses of therapy and since malignant melanoma is resistant to other intercalating agents, cross resistant with amonafide. Perhaps studies on the nature of this resistance would result in discoveries of the new drugs active in this disease.

Acknowledgements

This study was conducted by the Southwest Oncology Group (Charles Coltman, M.D., Chairman) and supported by the following PHS Cooperative Agreement grants awarded by the National Cancer Institute: DHHS: CA-12644, CA-37249, CA-27057, CA-22433, CA-14028, CA-46282, CA-42777, CA-35261, CA-35084, CA-35178, CA-27057, CA-46113, CA-28862, CA-35119, CA-13258, CA-35431, CA-32102.

We thank Ms. Sheryl Johnson for secretarial assistance in preparation of this manuscript.

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Address for offprints: Southwest Oncology Group (SWOG-8723), Operations Office, 5430 Fredericksburg Road, Suite #618, San Antonio, TX 78229-6197, USA