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Evaluation of Merbarone (NSC 336628) in Disseminated Malignant Melanoma

A Southwest Oncology Group study

Milan Slavik[1], P.Y. Liu[2], Eric H. Kraut[3], Ronald B. Natale[4], Lawrence E. Flaherty[5], and Vernon K. Sondak[6]

[1]*Wichita CCOP, University of Kansas School of Medicine-Wichita and Department of Veterans Affairs Medical Center, Wichita, Kansas;* [2]*Southwest Oncology Group Statistical Center and Fred Hutchinson Cancer Research Center, Seattle, Washington;* [3]*Ohio State University School of Medicine, Columbus, Ohio;* [4]*University of Southern California School of Medicine, Los Angeles, California;* [5]*Wayne State University School of Medicine, Detroit, Michigan;* [6]*University of Michigan School of Medicine, Ann Arbor, Michigan, USA*

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Abstract

Merbarone, NSC 336628, is an investigational anticancer drug with activity against experimental animal tumors including melanoma. This paper presents results of a Phase II clinical study of merbarone in patients with biopsy proven stage IV malignant melanoma without prior chemotherapy and with no evidence of CNS involvement. Thirty-five patients with median age 58 (range 27–81), with performance status 0–2 were treated with merbarone 1000 mg/m^2/day for five days by intravenous continuous infusion repeated every 3 weeks. All patients (21 males and 14 females) were evaluable for toxicity. Two patients were not evaluable for response having been removed from protocol treatment due to toxicity and received other treatment during the first course of chemotherapy. Among the evaluable patients there was one complete response in a supraclavicular lymph node lasting four months and one partial liver response lasting three months. The remaining thirty-one patients were non-reponders. Of these one had a stable disease lasting 21 months. The overall objective response rate was 6% (2/35) with a 95% confidence interval of 1%–19%. Twenty-six of the 35 patients have died. The estimated median survival of the entire group was 9 months with a 95% confidence interval of six to eleven months. Renal toxicity was dose-limiting and manifested as increasing serum creatinine (54% of patients), proteinuria (51%) and hematuria (9%). One patient experienced grade 4 creatinine increase, proteinuria and acute renal failure. Other toxicities included nausea (71%), vomiting (51%), malaise (23%), weakness (20%), alopecia (17%), diarrhea (17%), anorexia (14%), transaminase (SGOT, SGPT) increase (14%), constipation (14%), alkaline phosphatase or 5'nucleotidase increase (9%), and fever (9%). Hematologic toxicity (granulocytopenia, leukopenia, and anemia) was generally mild and infrequent (29%, only one patient had grade 4 granulocytopenia). Overall 9 patients (26%) had at least one grade 3 toxicity. We conclude that merbarone at this dose and schedule has detectable but minimal activity in the treatment of metastatic malignant melanoma and given the significant renal toxicity this schedule does not merit further evaluation in this disease.

Introduction

Merbarone (5-[N-phenylcarboxamido]-2-thiobarbituric acid, NSC 336628) is a new investigational anticancer drug of novel structure and mode of action. It was synthesized in the Uniroyal Research Laboratories (Uniroyal Ltd, Guelph, Ontario, Canada) as a conjugate of thiobarbituric acid and aniline joined by an amide linkage and subsequently screened for antitumor activity by the

Division of Cancer Treatment, National Cancer Institute (NCI) [1]. While none of 700 barbiturate analogues examined by the NCI screening program revealed any significant antitumor activity in any murine tumor systems [2], merbarone demonstrated remarkable experimental antitumor activity with "curative effects" against several implanted tumors, including L1210 and P388 leukemia, M5076 sarcoma and B16 melanoma in mice [1,3].

Although its exact mode of action has not yet been fully elucidated [3–5], an increasing body of evidence indicates that merbarone inhibits topoisomerase II [6–10] and may represent a novel class of inhibitor for this enzyme [10]. Because of all of these unique features and particularly because of its curative experimental antitumor activity merbarone was selected for clinical development [3] and introduced into clinical studies. A single repeated dose schedule (daily × 5) was found to be the most active one in the experimental murine tumors and since a substantially greater amount of drug was tolerated when the dose was delivered over a five day period in beagle dogs preclinical toxicity studies [3], two daily × 5 I.V. infusional regimen were explored in the phase I clinical studies [3,11,12]. Of these, the daily × 5 continuous intravenous infusion regimen via central catheter at a dose of 1000 mg/m^2/day was recommended for phase II clinical studies [11,12]. This schedule was also selected for a phase II clinical study of merbarone in patients with disseminated malignant melanoma conducted by the Southwest Oncology Group (SWOG) as part of its ongoing search for new active cytotoxic agents in the treatment of this disease (SWOG-8913).

Material and methods

Patients with bidimensionally measurable stage IV malignant melanoma were eligible for the study. The eligibility criteria included pathological verification of malignant melanoma, no history of recent (within one year) myocardial infarction or evidence of congestive heart failure, adequate bone marrow reserve defined as an absolute granulocyte count ≥ 2000/μl and platelet count ≥ institutional lower limit of normal and adequate renal and liver functions defined as serum creatinine ≤ institutional upper limit of normal or a measured creatinine clearance ≥ 60 mL/min; serum bilirubin ≤ institutional upper limit of normal and SGOT ≤ 2× 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 surgical or radiation treatment. If all known sites of disease had been previously radiated, objective evidence of progression prior to registration was required. While no prior chemotherapy was allowed, one prior biologic regimen and prior hormonal therapy were acceptable. Full recovery from all side effects of any prior treatment, MRI or CT scan of the head negative for brain metastases within 28 days prior to registration, and no prior malignancy (within five years) were among additional requirements of this study. Pregnant or lactating women were excluded and women and men of reproductive potential could not participate unless they had agreed to use an effective contraceptive method. 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. Merbarone 1000 mg/m^2 was administered as a 24 hour continuous infusion in at least 1000 mL 5% dextrose for injection USP for five days every 3 weeks. Treatment was continued until progression, occurrence of unacceptable toxicity requiring discontinuation of chemotherapy, patient withdrawal or death. Dose modification or delay in subsequent courses was provided depending upon the toxicity grade observed since the preceding course.

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 from baseline in size of all measurable tumor masses as measured by the sum of products of their greatest perpendicular diameters, no new lesions. The non-responders included stable disease and progression. Stable disease did not qualify for complete response, partial response or progression; progression – 50% increase or an increase of

10 cm^2 (whichever is smaller) in sum of products of measurable lesions over the smallest sum observed or appearance of any new lesion or reappearance of any lesion which had disappeared.

Results

Forty-one patients were entered in this study during two stages of accrual. Five patients were ineligible, four due to prestudy tests or measurement not performed within the specific time frame and one due to brain metastases present at registration. One patient (otherwise eligible for study) received no treatment. Consequently, thirty-five patients were available for statistical analysis and for the evaluation of toxicity and response. Baseline characteristics of the evaluable patients are presented in Table 1.

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%.

Of the 35 patients, response could not be determined for two patients having been removed from treatment due to toxicity and received other treatment during the first course of chemotherapy. These two patients are assumed to be non-responders. There was one complete response lasting four months in a patient with distant metastasis in a supraclavicular lymph node and one partial response in a patient with liver metastases lasting 3 months.

The remaining thirty-one patients evaluable for response were non-responders. Of those one had stable disease lasting 21 months. The overall objective response rate (CR+PR) was 6% (2/35), with a 95% confidence interval of 1%–19%. Twenty-six of the 35 patients have died. The estimated median survival is nine months with a 95% confidence interval of six to eleven months. All 35 patients were evaluated for clinical toxicity. Renal toxicity was dose limiting and manifested as increasing serum creatinine in 54%, proteinuria in 51% and hematuria in 9% of the evaluable patients. One patient experienced grade 4 serum creatinine increase, proteinuria and renal failure. Other clinical toxicities included nausea (71% of patients), vomiting (51%), malaise (23%), weakness (20%), alopecia (17%), diarrhea (17%), transaminase (SGOT, SGPT) increase (14%), anorexia (14%), constipation (14%), alkaline phosphatase or 5'nucleotidase increase (9%) and fever (9%). Hematologic toxicity (granulocytopenia, leukopenia, and anemia) was generally mild and infrequent (29%). Only one patient had grade 4 granulocytopenia. Overall, 9 patients (26%) had at least one grade 3 toxicity.

Table 1. Patient characteristics (n=35).

Median age	58	(27–81 Range)
Sex males/females	21/14	
Race white/black	34/1	
Performance status		
PS 0–1	31	89%
PS 2	4	11%
*Active disease sites**		
Distant nodes	12	34%
Liver	14	40%
Lung	16	46%
Bone	2	6%
Other	19	54%
Prior biological treatment		
Yes	5	14%
No	30	86%

* Sum is greater than 100% as some patients had more than one disease site.

Discussion

The identification of new active cytotoxic agents for the therapy of malignant melanoma is essential. To this end, the Southwest Oncology Group is conducting phase II clinical studies of promising, new investigational anticancer drugs in the treatment of this disease. Merbarone, NSC 336628, was selected for phase II clinical evaluation in malignant melanoma because of several unique features including novel structure, novel mode of action and experimental antitumor activity *in vivo* against murine B16 melanoma. Recognized disadvantages of the drug, however, were the facts that it could be administered only by one schedule (daily × 5 continuous infusion for five days) and its dose limiting nephrotoxicity, both of which could potentially represent problems in integration of this drug into combination chemotherapy regimens. The phase II clinical study conducted by the Southwest Oncology Group (SWOG-8913) was the first clini-

cal study evaluating the activity of merbarone in the treatment of disseminated malignant melanoma and the results presented in this paper are the first ones reported in the treatment of this disease. Our results reveal only minimal activity (6% objective response rate) at the expense of significant renal toxicity, which was life-threatening in one of the thirty-five evaluated patients. Consequently, we cannot recommend further evaluation of this schedule of merbarone for the treatment of metastatic malenoma. However, the fact that even minimal activity of merbarone was detected in the treatment of this disease should not be dismissed since it may represent an important clue for development of new drugs in treatment of malignant melanoma. Similar "hints" of activity were detected in phase II clinical studies of merbarone against other malignant tumors such as soft tissue sarcoma [13], adenocarcinoma of the pancreas [14,15], non-small cell lung cancer [16,17], and squamous cell carcinoma of the uterine cervix [18]. All these results suggest a potential for improvement of the therapeutic index of merbarone through better formulation [19], enabling different dose schedules, or for the development of merbarone analogues [20]. In fact, merbarone would appear to be an ideal drug suitable for analogue development.

In summary, we conclude that merbarone at this dose and schedule has detectable but minimal activity in the treatment of metastatic malignant melanoma. Given the significant renal toxicity, this dose schedule does not merit further evaluation for this disease. However, the development of improved formulations of this drug and synthesis of merbarone analogues represent potential leads for improving upon the low level of activity seen in this trial.

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Address for offprints: Southwest Oncology Group (SWOG-8913), 5430 Fredericksburg Road, Suite 618, San Antonio, Texas 78229, USA

Corresponding author: M. Slavik, Professor of Medicine and Pharmaceutical Chemistry, University of Kansas School of Medicine-Wichita, Medical Service, Department of Veterans Affairs Medical Center, 5500 E. Kellogg, Wichita, Kansas, 67218 USA