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Phase II Study of Tauromustine in Disseminated Malignant Melanoma

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Abstract—*Forty-seven patients with metastatic malignant melanoma took part in a phase II trial of tauromustine (TCNU), a new chlorethylnitrosourea based on the endogenous amino acid taurine. TCNU was given orally at a dosage of* 130 mg/m^2 *every fifth week. No patient had previously received cytotoxic therapy. Among* 37 *evaluable patients,* 26 *patients experienced progressive disease including seven patients with early death, five showed no change, and six partial responses, yielding an objective response rate of* 16%. *Responses were limited to subcutaneous, lymph node, bone and lung metastases. Median time to progression was* 26 *weeks for responders. The treatment schedule was well tolerated with a median dose of* 88% *of the predicted dose given during all cycles. Dose-limiting toxicity was thrombocytopenia. It appears that TCNU is active in disseminated malignant melanoma with a response rate similar to other nitrosoureas.*

INTRODUCTION

TAUROMUSTINE (TCNU) is a newly developed water soluble nitrosourea compound in which the nitrogen group of taurine constitutes one of the nitrogens, and the sulphonic acid group of taurine is replaced by a dimethylaminosulphonoyl group. TCNU remains unchanged in plasma for 8 h after oral administration, a unique pharmacokinetic property compared to other nitrosoureas [1].

In preclinical screens antitumour activity was found in five experimental murine tumors with an activity similar or better than other nitrosoureas [1]. Against Harding-Passey melanoma, TCNU had activity comparable to BCNU, CCNU, and better than MeCCNU and chlorozotozin. The therapeutic activity of TCNU against melanoma has been observed in one Phase I study [2]. The present study evaluates the clinical effects of TCNU administered as a first-line cytotoxic therapy to patients with advanced malignant melanoma (MM).

MATERIALS AND METHODS

Patients aged 18–70 with histologically confirmed MM with measurable or evaluable disease that could not be treated with surgery or radiotherapy were included in the study. Other criteria of eligibility included performance status ≤3 (WHO scale), no prior chemotherapy, no second malignancies, and normal renal and bone marrow functions. All patients gave informed consent to their participation in the study.

TCNU was administered orally every 5 weeks at a dose of 130 mg/m^2. The initial dose was reduced to 80 mg/m^2 for patients who received extended irradiation to the axial skeleton. If no haematological toxicity was registered during the previous course the dose was increased to 120% of the initial dose. The dose of TCNU was adjusted according to platelet and WBC counts. Treatment was continued for a minimum of 10 weeks unless the disease progressed or severe side-effects occurred. All patients were evaluated prior to treatment and at the end of every second cycle. Each patient was scheduled to receive at least two courses of therapy. In the case of progressive disease (PD) the treatment was discontinued whereas no change (NC) or regression [partial response (PR) and complete response (CR)] after two courses led to continuation of therapy until PD was noticed. Assessment of response, duration of response, time to treatment failure and toxic effects were graded according to the World Health Organization (WHO) criteria [3].

TCNU was supplied, by the LEO Company, Helsingborg, Sweden, in tablets of 25 and 50 mg.

RESULTS

Between May 1986 and September 1987, 47 consecutive patients with MM entered into the

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Table 1. Responses to tauromustine

	CR	PR	NC	PD	ED	Total
Evaluable	0	6	5	19	7	37

Percentage objective response: 16.

Table 2. Haematological toxicity in 45 patients

	WHO grade					Total
	0	1	2	3	4	
Leukocytes	13	7	15	8	2	45
Thrombocytes	16	8	11	4	6	45
Haemoglobin	23	11	8	2	1	45

study. Three patients were lost to follow-up. Seven patients were non-eligible due to: other malignancy (3), age >70 (1), abnormal renal function (2) and psychiatric disorder (1). Among the 37 patients eligible and evaluable for response, 26 were males and 11 females. The median age was 56 (range: 25–70). All patients had a performance status ≤3 (median: 1). Dominant site was visceral, 25; soft tissue, 10; bone, 2. Nineteen patients experienced PD, seven early death (ED), five NC, and six PR, yielding an objective response rate of 16% (Table 1). Responses were only observed in bone, lung, skin and lymph nodes. Median time to progression by life table analysis was 24 (range 21–36) weeks for responders and 24 (13–42) weeks for NC and responders. In April 1988, four patients were still in treatment and 34 patients had left the study due to PD with a median time to PD of 10 weeks.

A median dose of 88% of the scheduled dose per cycle was given, and only two patients received an initial dose of 80 mg/m^2 of TCNU. Toxicity could be evaluated for 119 courses of TCNU given to 45 patients (Table 2). Dose-limiting toxicity was WHO grade 2–3 thrombocytopenia (nadir day 28, recovery day 35). In six patients a grade 4 thrombocytopenia was observed. Leukocyte nadirs (day 35, recovery day 42) were of grade 2 toxicity in 15 patients and grade 3 in eight patients.

The non-haematological toxicity was predominately gastrointestinal, WHO grade 1–3 (Table 3). Eighteen patients experienced tumour pain and 14 patients episodes of sweating. Alopecia, cardiac, renal and hepatic toxicity, allergy or drug fever were not observed.

CONCLUSION

The present study reveals that TCNU has some activity in disseminated malignant melanoma with a response rate of 16% in previously untreated patients. TCNU is similar to other nitrosoureas with respect to haematologic toxicity, especially thrombocytopenia, which is a dose-limiting factor. Previous studies with DTIC and nitrosourea derivatives have produced response rates of 20–30% in patients with MM [4, 5]. The efficacy of TCNU is comparable to BCNU and CCNU, but the major advantage of the drug is that it can readily be given on an out-patient basis with acceptable side-effects and lower toxicity than DTIC.

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Table 3. Non-haematological adverse reactions in 45 patients

	WHO grade					Total
	0	1	2	3	4	
Nausea/vomiting	13	5	20	7	0	45
Diarrhoea	37	6	1	1	0	45
Oral	44	0	0	1	0	45
Pulmonary (dyspnoea)	31	7	4	1	0	43*
Cutaneous	44	0	0	1	0	45
Infection	42	0	2	1	0	45
Haemorrhage	44	0	1	0	0	45

*Two patients had pre-existing symptoms.

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