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Phase I Study of Tauromustine Administered in a Weekly Schedule

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Tauromustine was administered orally in weekly doses with interindividual dose escalation to patients with disseminated malignant melanoma. The dose in the first cohort of 6 patients was 20 mg/m²/week. The dose escalation was 5 mg/m²/week. The limit of tolerance was 55 mg/m²/week. 99 patients completed at least 8 weeks of treatment and eight dose levels were evaluated for toxicity. Reversible thrombocytopenia, and to a lesser degree leukopenia, were dose limiting. From a starting dose of 40 mg/m²/week, the long-term tolerated dose was 35 mg/m²/week, thus achieving a considerable increase of dose intensity without a significant increase of toxicity by employing this weekly schedule of tauromustine.
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INTRODUCTION

Traditionally, anticancer agents are administered in doses and at intervals close to the maximally tolerated dose, as this is believed to reduce the tumour burden most effectively. Few attempts have been made to increase the dose intensity by exploring different schedules. For the nitrosourea compounds this approach might be of particular value because of their delayed and cumulative haematological toxicity [1, 2]. De Vita *et al.* [3] investigated three different doses and schedules of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) some years ago. They found that the dose intensity could be increased 2-fold by using weekly instead of 6-weekly administration. Koller *et al.* [4] demonstrated a reduction of the subjective toxicity of methyl-CCNU (*N*-(2-chloroethyl)-*N'*-cyclohexyl-*N*-nitrosourea) employing a split dose schedule; the dose intensity, however, was constant. Recent animal studies have shown that an increased therapeutic index can be obtained by using fractionated administration of tauromustine (Kabi Pharmacia Laboratories, Helsingborg, Sweden). These findings, together with the current knowledge of tumour cell kinetics, make it relevant to investigate the effect of a more frequent administration of nitrosourea compounds.

The objectives of this study were to examine if the dose intensity of tauromustine could be increased without increasing the toxicity by giving weekly doses, and to define the maximal long-term tolerated dose and describe the toxicity pattern when the drug was administered to patients with disseminated malignant melanoma.

PATIENTS AND METHODS

Patients with histologically proven malignant melanoma and measurable or evaluable disease not amenable to curative surgery were included in the study. Other inclusion criteria were progressive disease, performance status 2 or less, a life expectancy of at least 3 months and normal liver, renal and bone marrow function. All patients gave their informed consent to participate in the study which was an open non-randomised investigation approved by national Health Boards and ethics committees.

The initial dose was 20 mg/m²/week and dose escalation was performed as follows. When 6 patients had been treated for a minimum of 8 weeks with a tolerability of at least 75% of the intended dose, the next cohort of patients could receive a dose increase of 5 mg/m²/week and so forth. The number of patients and the intervals for dose increase were selected due to the well-known delayed and cumulative myelosuppression of tauromustine. The patients were seen on an out-patient basis and blood counts were monitored weekly. Effect and non-haematological adverse reactions were scored every 4 weeks according to the WHO recommendations [5].

Tauromustine was supplied by Kabi Pharmacia in tablets of 10, 20 and 50 mg.

RESULTS

Between May 1988 and October 1990, 140 patients entered the study. 5 patients were non-eligible, because of performance status 3 (2 patients), elevated serum creatinine (1 patient), prior malignancy (1 patient) and non-evaluable disease (1 patient). 36 patients were treated for less than 8 weeks due to rapidly progressing disease (35 patients) and toxicity (1 patient). Among 99 evaluable patients, 52 were males and 47 females. The median age was 55 (range 24–79). Prior treatments were surgery (95 patients), chemotherapy (4 patients), hormone therapy (1 patient) and radiotherapy (20 patients). Dominant sites of disease were visceral (65 patients), soft tissue (33 patients), and bone (1 patient).

Dose escalation was stopped at 55 mg/m²/week. The maximally tolerated dose for long-term treatment was 35 mg/m²/week at a projected dose of 40 mg/m²/week.

Reversible thrombocytopenia and leukopenia were dose limiting (Table 1). 1 patient with grade 4 thrombocytopenia and leukopenia at the highest dose level died of diathesis haemorrhagica and bronchopneumonia 16 days after withdrawal of the drug. 2 thrombocytopenic patients had a mild blood loss and 4 patients developed petechiae at some point during treatment.

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Table 1. Maximal haematological toxicity in relation to dose and duration of treatment

			Tauromustine 20–30 mg/m² (No. of patients)	35–40 mg/m² (No. of patients)	45–55 mg/m² (No. of patients)
8–12 weeks treatment					
Total no. of patients			14	12	28
WBC	WHO grade	0	9	4	5
		1	1	4	8
		2	3	3	7
		3	1	1	6
		4	0	0	2
Platelets	WHO grade	0	12	9	13
		1	0	2	3
		2	2	1	6
		3	0	0	3
		4	0	0	3
> 12 weeks treatment					
Total no. of patients			17	13	15
WBC	WHO grade	0	6	1	3
		1	4	4	1
		2	6	4	4
		3	1	4	6
		4	0	0	1
Platelets	WHO grade	0	10	4	2
		1	0	0	3
		2	3	1	3
		3	4	6	3
		4	0	2	4
Mean duration of treatment			21 weeks	19 weeks	14 weeks

Table 2. Non-haematological adverse reactions in relation to dose

		Tauromustine 20–30 mg/m² (No. of patients)	35–40 mg/m² (No. of patients)	45–55 mg/m² (No. of patients)
Total number of patients		31	25	43
Nausea/vomiting				
WHO grade	0	10	3	14
	1	7	10	7
	2	7	6	14
	3	6	4	7
	4	1	1	0
No recording		0	1	1
Tumour pain				
WHO grade	0	14	15	26
	1	6	4	7
	2	6	2	1
	3	4	3	7
	4	1	0	1
No recording		0	1	1
Diarrhoea				
WHO grade	0	25	20	36
	1	4	4	5
	2	2	0	0
No recording		0	1	2
Pulmonary				
WHO grade	0	2	19	31
	1	5	4	5
	2	2	1	5
	3	0	0	1
No recording		0	1	1
Infection				
WHO grade	0	27	20	36
	1	2	4	4
	2	2	0	0
	3	0	0	2
No recording		0	1	1

Among non-haematological adverse effects, gastrointestinal events were most frequently reported. Table 2 show the most common adverse reactions in relation to the various dose levels. There was no statistically significant difference between the dose groups (Spearman's rank correlation test) but a tendency for a higher rating in the higher dose groups. Except for a 6% frequency of alopecia (grades 1 and 2), other adverse reactions were of less than a 4% frequency.

DISCUSSION

The study was designed to reach the maximally obtainable dose intensity of tauromustine employing a weekly schedule, to investigate the long-term tolerable dose and to describe the corresponding toxicity pattern when the drug was administered to patients with disseminated malignant melanoma.

As nitrosourea compounds have a delayed and cumulative toxicity the following precautions were taken: a low starting dose (20 mg/m²/week), modest dose increments (5 mg/m²/week) and an escalation of dose based on an 8-week toxicity profile. To follow these rules and to maintain the continuity of patient recruitment to the study, a large number of patients were required. In a previous study, a 5-week schedule of tauromustine was investigated in the same category of patients. The intended dose was 130 mg/m²/5 weeks. Due to haematological toxicity the long-term median dose, however, was reduced to 88% of the intended dose, resulting in a dose equivalent to 23 mg/m²/week [6]. In this study, the long-term tolerated dose was 35 mg/m²/week, at a projected dose of 40 mg/m²/week which represents a significant dose increase compared to most standard nitrosourea regimens. The dose increments were possible without a significant increase of toxicity. The antitumour effect of the weekly tauromustine schedule in patients with disseminated malignant melanoma is presently being analysed in a phase II trial.

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