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Clinical Trials Summaries

Randomized Phase II Trial of TCNU Versus Mitozolomide in Malignant Melanoma

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INTRODUCTION

It is well recognized that chemotherapy is only of limited clinical benefit in malignant melanoma and there is an obvious need for the development of more active agents than are currently available. Of the latter, the nitrosoureas have shown some activity [1]. In preclinical and phase I studies both the new nitrosourea TCNU and the related compound mitozolomide showed some activity against malignant melanoma [2, 3]. Consequently the Early Clinical Trials Group of the EORTC decided to perform a randomized phase II study of these two new agents, in this disease.

PATIENTS AND METHODS

Patients entering this study all had histologically proven malignant melanoma that was recurrent or metastatic disease. No patients had received prior chemotherapy. All patients had measurable or evaluable lesions with documented progression within 2 months prior to entry into the study. Only patients less than 75 years of age with a performance status of less than or equal to 2 and a life expectancy anticipated to be greater than 3 months were eligible. Informed consent was obtained from all patients. TCNU was given orally at a dose of 130 mg/m^2 every 5 weeks and mitozolomide given intravenously at a dose of 100 mg/m^2 every 6 weeks. The protocol required a minimum of two courses of treatment for patients to be eligible for assessment of response, unless there was clear evidence of disease progression following the first cycle of treatment. Standard criteria for complete and partial response, no change and progressive disease were used according to UICC criteria.

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RESULTS

Seventy-four patients were entered into the trial over a period of 11 months, 11 institutions participating in this multicentre trial. Patient details are identified in Table 1 where it is seen that the majority of patients were asymptomatic or had only minimum symptoms and there was an even distribution between the two treatment options between those with skin/soft tissue disease versus those with visceral involvement. Of the 36 patients receiving mitozolomide 32 are evaluable and of the 38 patients treated with TCNU 34 are evaluable. The eight patients who are considered inevaluable on this protocol all had disease that progressed within 4 weeks from starting treatment. Of patients treated with mitozolomide, only eight patients received more than two cycles of therapy, four receiving three cycles and only two receiving six cycles. Of patients treated with TCNU, 17 patients received more than two cycles of therapy, eight receiving three, six receiving four and three receiving five cycles of treatment. The responses are identified in Table 2 where it is seen that for mitozolomide there were 3/32 responses, including one complete remission and for TCNU 4/34

Table 1. Patients

		Mitozolomide	TCNU
Entered		36	38
Evaluable		32	34
Male/female		16/16	18/16
Age:			
Median		57	61
Range		31–75	24–74
Performance status	0	15	26
	1	13	7
	2	4	1
Sites of disease:			
skin/soft tissue		12	10
visceral		20	24

responses with one complete and three partial responses. Within 95% confidence intervals the response rates are therefore 9% and 12% for mitozolomide and TCNU respectively. Reviewing the individual responses to mitozolomide the patient obtaining a complete remission was a 54-year-old female with metastatic nodes which completely disappeared after two cycles of treatment. The response duration was 26 weeks when following five cycles of therapy there was tumour recurrence. The two partial responses to mitozolomide occurred in a female of 61 years with pulmonary metastases where therapy had to be discontinued after four cycles of treatment because of prolonged myelosuppression, the response lasting for 39 weeks, and a 64-year-old male who also had pulmonary metastases. This patient's chest X-ray showed complete resolution of these lesions which, however, remained positive on CT scan; therapy was discontinued after six cycles of treatment because of prolonged myelosuppression but the response duration continues at 41+ weeks. For patients responding to TCNU the complete remission was seen in a 29-year-old female with pulmonary metastases who remains in complete remission at 52+ weeks. The partial remissions were seen in a 24-year-old male with nodal metastases which responded for 54 weeks, a 66-year-old female with multiple skin and pulmonary metastases whose disease progressed after a partial response lasting 11 weeks, a similar time interval being seen in the 65-year-old female who similarly had multiple skin metastases that demonstrated a partial response.

Toxicity

The major toxicity for both drugs was haematological and this is summarized in Table 3. Thrombocytopenia was more significant than leukopenia where although the median platelet counts were acceptable individual patients showed counts as low as 11,000–13,000/mm^3, nausea and vomiting was the principal non-haematological toxicity where anti-emetic therapy was required for 24/32 patients receiving mitozolomide and 31/34 receiving TCNU, neither drug caused a major problem for patients who were adequately treated with anti-emetics. Minor hair loss was observed in two patients receiving each drug.

DISCUSSION

In this randomized phase II comparison of TCNU and mitozolomide both drugs have shown some activity with response rates of 9 and 12% for

Table 2. Response

	Mitozolomide		TCNU	
CR	1		1	
PR	2		2	
NC	1		7	
PD	19		18	
EPD*	9		6	
Total	32		34	
Response rate:	3/32 9% (0→19%)		4/34 12% (1→23%)	
	CR	PR	CR	PR
Site:				
skin/soft tissue	1	—	—	2
visceral	—	2	1	1
Duration (weeks)	26	39	52+	54
		41+		11
				11

*Early progressive disease (only one treatment).

mitozolomide and TCNU with confidence limits ranging to 19 and 23% respectively. In comparison with other agents used for treating this highly refractory disease, the investigators conclude that both drugs have occasional activity which has benefited patients. Of particular note is the length of response in patients responding to TCNU 2/4 of which have responded for periods in excess of 1 year. Toxicity was for the most part predictable with a high acceptance rate by patients. Thrombocytopenia can be a particular problem in patients with malignant melanoma who are at high risk of central nervous system metastases with the concomitant risk of intra-cranial haemorrhage if platelet counts are low. Nevertheless, given the ease of administration and high patient acceptance of these agents, we believe that the response rates justify consideration of these drugs in combination studies.

Table 3. *Haematological toxicity (median and range of nadir value)*

	Mitozolomide	TCNU
WBC 1st course	4.3 (2.0–8.0)	3.4 (1.2–9.8)
WBC overall	3.4 (2.0–8.0)	2.5 (0.7–9.8)
Platelets 1 course	103 (11–300)	77 (13–198)
Platelets overall	77 (11–300)	60 (13–198)

REFERENCES

1. Carter RD, Krementz ET, Hill GJ. DTIC and combination therapy for melanoma. Studies with DTIC, BCNU, CCNU, vincristine and hydroxyurea. *Cancer Treat Rep* 1976, **60**, 601–609.
2. Smyth JF, Macpherson JS, Warrington PS *et al.* Phase I study of TCNU, a novel nitrosourea. *Eur J Cancer Clin Oncol* 1987, **23**, 1845–1849.
3. Fodstad O, Amdal S, Pihl A. Activity of mitozolomide (NSC 353451), a new imidazotetrazine, against xenografts from human melanomas and lung and colon carcinomas. *Cancer Res* 1985, **45**, 1778–1786.