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Clinical Trials Summaries

A Phase II Study of Mitozolomide in Metastatic Transitional Cell Carcinoma of the Bladder

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INTRODUCTION

A NUMBER of cytotoxic drugs have shown some activity in the systemic treatment of advanced bladder cancer, with methotrexate and *cis*-platinum the most active single agents [1, 2]. Because of the poor results of local treatment alone, these agents are currently being incorporated into experimental studies of the initial treatment of the disease. The results of treatment for metastatic disease, however, even with these relatively active agents, are disappointing, with response rates for single agents rarely rising above 30% and little evidence that such treatment prolongs survival. Additionally the patient population may be old and frail and the toxicity associated with many cytotoxic agents is unacceptable in this group. There is therefore a continuing need to evaluate new drugs in this disease.

Mitozolomide (NSC 353451; CCRG 81010; M & B 39565) is a novel agent with structural similarities to the chloroethyl nitrosoureas [3]. The drug was highly active in pre-clinical studies and during Phase I assessment some evidence of activity was seen in ovarian cancer, lymphoma, testicular teratoma and nasopharyngeal carcinoma [4]. Subjective toxicity with Mitozolomide was minimal with the dose limiting toxicity being myelosuppression.

In view of this lack of subjective toxicity this group conducted a Phase II study of Mitozolomide in advanced bladder cancer.

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PATIENTS AND METHODS

Eighteen patients were registered in this study between November 1985 and June 1987. Three patients were not eligible; two patients rapidly progressed and died before receiving the drug and one patient vomited soon after receiving the medication and therefore was not considered to have received treatment.

Patients were eligible for entry to the study if they had biopsy proven, urothelial transitional cell carcinoma with measurable metastatic disease. Tumour in the bladder did not exclude from the study but was not used as an indicator lesion. Patients had received no previous chemotherapy within the past 3 weeks (6 weeks for nitrosoureas and mitomycin C) and any palliative radiotherapy that had been given should have been a minimum of 6 weeks before. Radiotherapy to the indicator lesions was not permitted.

The plan of the protocol was for patients to receive two courses of Mitozolomide at a dose of 90 mg/m^2 orally and their response assessed at 12 weeks (i.e. after two courses of treatment). If progression had occurred or there was no change the patient went off study. If patients showed evidence of response, three further courses could be given as clinically indicated.

Response was to be assessed using UICC criteria and any responses were to be reviewed by an independent panel.

RESULTS

Fifteen patients received treatment. Nine patients received only one cycle and six patients two cycles. Patient characteristics and responses to

treatment are summarized in Table 1.

The patients who received only one cycle did not receive a second cycle for the following reasons: five patients died from rapidly progressive disease, one patient died from a pulmonary embolus, two patients developed myelosuppression of a severity sufficient to prevent further treatment and one patient developed myelosuppression and septicaemia.

Six patients received two cycles of treatment, five of these patients showed signs of progressive disease at the 12 week assessment and one patient showed evidence of no change in his disease. No responses were seen.

Toxicity

Myelotoxicity was severe. In only five of 21 courses administered was there no platelet toxicity and in only nine of the 21 courses administered was there no leucopenia. Three patients had WHO grade 3/4 leucopenia and four patients had WHO grade 3 thrombocytopenia during the first cycle. In three patients this toxicity precluded further treatment.

There was little subjective toxicity. Some patients experienced nausea and vomiting in the first 24 h after treatment; in most cases this was mild, but on four occasions WHO Grade 2 nausea and vomiting was observed, and on one occasion WHO Grade 3.

DISCUSSION

Mitozolomide was chosen for Phase II assessment in bladder cancer because of its encouraging results *in vitro* and in animal models and because of its low level of subjective toxicity in Phase I assessment. This study demonstrates that in this population of patients with assessable metastatic bladder cancer no responses were seen and also that myelotoxicity was unacceptable. Mitozolomide has shown similar toxicity in other Phase II studies [5]. Responses to Mitozolomide have been seen in lung cancer and melanoma but other tumour types appear to be resistant to the doses that can be reasonably administered [6]. In summary, therefore, it must be concluded that Mitozolomide has no significant activity in advanced bladder cancer and in view of the considerable toxicity seen, doubt must be cast on whether this drug should be investigated further in human cancer.

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Table 1. Patient characteristics and response

Median age in years (range) 70 (53–80)
Male:female 12:3

	1 course	*2 courses*	*NC**	*Prog*	*ETD*	*ENTD*	*Total*
Total	9	6	3	8	0	4	15
Disease (predominant metastatic site)							
Nodes	3	3	0	6	0	0	6
Liver	1	0	0	0	0	1	1
Lung	5	3	3	2	0	3	8
Performance score							
0	2	4	1	5	0	0	6
1	4	2	2	3	0	1	6
2	3	0	0	0	0	3	3

*NC = no change, Prog = progressive disease, ETD = early toxic death, ENTD = ealy non-toxic death.

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