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Short Communication

A Phase II Clinical Study of mAMSA in Small Cell Carcinoma of the Lung

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Summary. *Thirteen patients with small cell carcinoma of the bronchus that had become resistant to conventional chemotherapy were given 4'-(9-acridinylamino)methanesulphon-m-anisidide (mAMSA) at a dose of 90 or 120 mg/m² at 3-week intervals. Twenty percent of the courses at 90 mg/m² produced marked myelosuppression. No responses were observed. Median survival from the start of treatment with mAMSA was 5 weeks.*

Introduction

4'-(9-Acridinylamino)methanesulphon-m-anisidide (mAMSA) is an acridine derivative with antitumour activity against a number of experimental tumours [2]. Clinical studies have shown activity against acute leukaemia [1] and a variety of solid tumours including metastatic breast carcinoma [5], but used in the treatment of non-small cell lung cancer [3] and metastatic hypernephroma [7] there was little if any effect. Reported non-haematological toxicity includes neurological disturbance and abnormalities of cardiac rhythm [6] as well as nausea and vomiting. Small cell carcinoma of the bronchus is a chemosensitive tumour, which frequently metastasises to the liver. Rodent data suggests that mAMSA concentrates in the liver [4]. Small cell carcinoma of the bronchus was therefore selected for a phase II study of mAMSA [8]. Survival of patients with this tumour can be significantly prolonged with conventional chemotherapy. A phase II study of a new single agent in previously untreated patients could not be justified, so only those patients whose disease had become resistant to conventional chemotherapy were studied.

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Patients and Methods

Thirteen patients, twelve male and one female, entered the study. Ages ranged from 46–73 years (mean 63 years, median 65 years). All had small cell carcinoma of the bronchus, diagnosed by histological examination of biopsy material (10 patients) or by sputum cytology (three patients). Assessment before and after each course of treatment consisted of full history and clinical examination with estimation of Karnofsky performance status, full blood count, biochemical profile including liver function tests, and chest radiograph. Bone marrow biopsy and liver ultrasound were performed before treatment and on completion of three courses of treatment. Electrocardiographs were recorded before and at the end of mAMSA infusions. The sites of evaluable disease were intrathoracic alone in four patients and in the liver alone in two; while seven patients had disease in the chest and in one or more of the following sites: liver, lymph nodes, skin, and bone marrow. Pretreatment Karnofsky performance scores were as follows: 30% and 40%, five patients; 50% and 60%, four patients; 70% and 80%, four patients. Criteria for eligibility included leucocyte count > 3.0 and platelets $> 100 \times 10^9/l$, measurable lesions and no evidence of renal dysfunction. Hyperbilirubinaemic patients were excluded, but those with abnormalities of plasma alkaline phosphatase or alanine transaminase were not. Complete remission was defined as complete disappearance of all measurable disease, and partial remission as $>$ 50% reduction in the products of the diameters of measurable lesions. All patients had been previously treated, 10 with a combination of methotrexate, CCNU, and cyclophosphamide (MCC), one with single-agent iphosphamide, one with single-agent cyclophosphamide, and one with MCC and iphosphamide.

mAMSA was infused IV in 500 ml 5% Dextrose in water over 1 h at a dose of 90 mg/m² (10 patients) or 120 mg/m² (last three patients in the study). Courses were repeated at 3-week intervals.

Results

A total of 23 couses were given, a mean of 1.8 per patient. Twenty were at a dose of 90 mg/m² and three at 120 mg/m². Two patients died of progressive disease whilst receiving treatment, the other 11 had treatment stopped when in became obvious that they

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were dying of progressive disease. None of the three courses at 120 mg/m^2 produced haematological toxicity. Four at 90 mg/m^2 produced marked myelosuppression (leucocyte counts $< 1.0 \times 10^9$/l and/or platelet counts $< 50 \times 10^9$/l), and a further two courses at this dose depressed the leucocyte count to $< 3.0 > 1.0 \times 10^9$/l and the platelet count to $< 100 > 50 \times 10^9$/l. Three patients became jaundiced during treatment and died within 17 days of receiving the first course of mAMSA. Liver metastases had been demonstrated in all three patients before treatment was started and post mortem examination of two cases confirmed that the liver was almost totally replaced by tumour. Two pretreatment electrocardiographs were abnormal, one with atrial ectopic beats and one with atrial fibrillation and myocardial ischaemia; none changed during treatment. No neurological complications were seen. Two patients complained of nausea and vomiting for 1 day after mAMSA administration.

One patient had a documented inappropriate ADH syndrome, which had previously improved with successful antitumour treatment and recurred when the tumour relapsed in lung and liver. During treatment with mAMSA, plasma sodium returned to normal, although there was no change in the measurable disease. There were no complete or partial remissions and all patients in the study are now dead. Survival from starting mAMSA ranged from 2–17 weeks (mean 6.6 weeks, median 5 weeks).

Discussion

The prognosis for patients with relapsed small cell carcinoma of the bronchus is poor, and in eight cases it was only possible to give a single course of mAMSA before the patient died. The complete absence of response indicated that mAMSA as used in this study is unlikely to be effective in the treatment of small cell lung carcinoma, and the study has been discontinued. Despite the marked myelosuppression seen in four patients, we were impessed at how well most patients tolerated treatment. This appears to be an advantage for the drug in the treatment of tumours which may prove to be chemosensitive to it.

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