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A Phase II Study of m-AMSA in Patients with Malignant Mesothelioma

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Summary. *Nineteen patients with histologically confirmed malignant mesothelioma were treated with m-AMSA at the University of Pretoria. All patients had evaluable disease and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3. m-AMSA 120 mg/m² was given IV every 3 weeks. Hematopoietic suppression was the major side-effect. Eleven patients developed leukopenia. There was one partial response (16 weeks), and a no change status was documented in 12 patients (median duration of 20 weeks). The median survival time of patients was 27 weeks from entry on study. Radionuclide ventricular ejection fraction tests were performed to evaluate cardiac function.*

Introduction

No satisfactory treatment has been described for patients with malignant mesothelioma. The roles of surgery, chemotherapy, and radiotherapy are not well defined, and the lack of a uniform method of clinical staging complicates the interpretation of results. Cooperative Oncology Groups have generally studied malignant mesothelioma as a subtype of soft-tissue sarcoma and not as a distinct entity whose clinical behavior differs from that of other tumors of mesodermal origin. From 1972 to 1980 the Eastern Cooperative Oncology Group treated patients with malignant mesothelioma according to four sequential chemotherapy protocols for advanced sarcoma. Of the 96 patients, 32 were diagnosed and treated in South Africa. The responses were seven of 51 with adriamycin, including two complete remissions (CR); two of 24 with adriamycin combinations, and two of seven with cycloleucine. The median survival for patients responding to treatment was 29.9 months, as against 6.3 months in non-responders. The median survival for seven patients with abdominal mesothelioma was 12 weeks [7]. A feasibility study was carried out to investigate combined doxorubicin and radiotherapy in pleural mesothelioma; although this treatment combination was relatively well tolerated, this was not considered sufficient to justify extending that study (survival ranged from 19 to 108 weeks, with a median of 46 weeks) [8]. It is therefore clear that phase II studies of new agents constitute the best approach to patients with this disease who cannot be cured by surgery.

The present study was therefore undertaken to assess the effectiveness of m-AMSA in patients with unresectable malignant mesothelioma of the pleural or peritoneal cavity.

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m-AMSA [4′-(9-acridinylamino)-methan sulfon-m-anisidide; NSC 249992] is one of many acridine derivatives prepared by Cain et al. [1, 3, 4]. The mechanism of the drug has not been entirely elucidated. The hypothesis is that m-AMSA binds to DNA through intercalation. Several phase I and II studies have been completed without showing activity in solid tumors [2,5]. Leukopenia was the major dose-limiting toxicity. Other side-effects include thrombocytopenia, nausea, vomiting, and cardiotoxicity [6, 9–11]. Phase II trials were recommended at a dose of 120 mg/m² given 3- to 4-weekly.

Materials and Methods

Twenty patients (15 males and 5 females) ranging in age from 29 to 71 years (median 53 years) with advanced malignant mesothelioma of the pleura (17 patients) or abdomen (3 patients) were entered on this ECOG study (P-A 380). All patients had histologically confirmed malignant mesothelioma beyond hope of surgical cure. All patients had evaluable disease, although none of the patients had bidimensionally measurable disease.

Thoracotomy or laparotomy had been performed in all patients entered on study. In all patients the disease was too advanced to permit surgical resection. An estimate of the degree of pleural or peritoneal involvement (from fine nodulation to massive tumor) obtained at surgery was combined with the radiological findings to assess tumor load in each patient. It was not possible to estimate all areas of tumor thickening in the presence of massive pleural effusion. Patients with pleural mesothelioma were therefore evaluated following thoracocentesis. Extent of disease within the hemithorax was defined as follows: *moderate,* loss of one-third of radiographically visible lung tissue; *marked,* loss of between one-third and two-thirds of radiographically visible lung tissue; and *extensive,* loss of two-thirds of radiographically visible lung tissue. This classification was used irrespective of whether or not the lung was compressed by tumor, infiltrated by tumor, or considered to contain metastatic mesothelioma within the lung tissue. All patients with pleural involvement were referred from thoracic surgery and those with abdominal mesothelioma were referred from general surgery. Because of the difficulties in objectively evaluating response in patients with malignant mesothelioma, survival was a major end-point for evaluation in this study. In patients with thoracic mesothelioma special attention was paid to respiratory reserve and radiological changes, while in patients with abdominal mesothelioma

special attention was paid to abdominal ultrasound and abdominal CAT scan.

All patients had normal hematologic, liver, heart, and kidney function tests prior to the start of treatment. Baseline and follow-up electrocardiograms (ECG) were obtained in all patients. A baseline radionuclide ventricular ejection fraction test was performed in 14 patients. In six patients who continued long enough with the treatment, follow-up ejection fraction tests were also obtained.

Table 1. History of asbestos exposure

	Exposure	Probable exposure	No exposure
Pleural mesothelioma	13	2	2
Abdominal mesothelioma	1	2	–

Table 2. Symptoms in patients with malignant mesothelioma

A) Primary disease symptoms	
Abdominal mesothelioma	(3 patients)
Abdominal pain	3
Abdominal swelling	2
Nausea and vomiting	1
Pleural mesothelioma	(16 patients)
Dyspnea	15
Chest pain	9
Coughing	9
B) Systemic symptoms	
Weight loss	10 patients
Night sweats	5 patients
Weakness	3 patients
Loss of appetite	2 patients

The ECOG performance status (PS) is defined as follows: 0, normal activity; 1, symptoms but ambulatory; 2, in bed < 50% of time; 3, in bed > 50% of time; and 4, 100% bedridden. PS was 0 in five patients; 1 in three patients; 2 in five patients; and 3 in six patients.

A history of definite asbestos exposure was obtained in 14 of the 20 patients; two further patients had a history of probable exposure, while in four patients there was no history of asbestos exposure (see Table 1). Six of the patients had received chemotherapy or radiotherapy prior to entry on this study.

The patients' symptoms are shown in Table 2. Systemic symptoms, including weight loss and night sweats, were present in 12 of the patients.

A dose of m-AMSA 120 mg/m^2 was given IV every 3 weeks. In patients who had received prior chemotherapy or radiotherapy, the dose was reduced to 90 mg/m^2 IV every 3 weeks. The drug was dissolved in 500 ml 5% dextrose in water, and was administered as an IV infusion over 1 h. If phlebitis (due to the drug administration) occurred, a larger volume of dextrose 5% in water was given.

The dose of m-AMSA was adjusted according to nadir counts, as follows:

WBC	Platelets	Dose of m-AMSA
> 4,000	> 150,000	120 mg/m^2
2,500–3,999	75,000–149,000	90 mg/m^2
1,500–2,499	40,000– 74,900	70 mg/m^2
< 1,500	< 40,000	0

The total dose given ranged from 180 mg to 3,080 mg. Three patients are still receiving m-AMSA at the time of writing.

Table 3. Toxicity of m-AMSA in patients with malignant mesothelioma

Toxicity grade[a]	Leukopenia	Anemia	Nausea and vomiting	Allergy	Local toxicity
1	4	2	5	2	0
2	5	0	6	0	1
3	2	0	2	0	0

[a] Toxicity criteria

		Grade			
		0	1	2	3
Leukopenia	WBC× 10^3	≥ 4.5	3.0–< 4.5	2.0–< 3.0	1.0–< 2.0
	Neut × 10^3	≥ 1.9	1.5–< 1.9	1.0–< 1.5	0.5–< 1.0
Anemia	Hgb gm%	≥ 11	9.5– 10.9	< 9.5	Req transfusion
	Hct %	≥ 32	28 – 31.9	< 28	
	Clinical			Sx of anemia	
Nausea and vomiting		None	Nausea	Nausea and vomiting controllable	Vomiting intractable
Allergy		None	Transient rash Drug fever ≤ 38° C (≤ 100.4° F)	Urticaria Drug fever > 38° C (> 100.4° F) Mild bronchospasm	Serum sickness; bronchospasm-requiring parenteral medication
Local toxicity		None	Pain	Pain + phlebitis	Ulceration

Results

Toxic Effects

The toxic effects documented included nausea and vomiting in 13 patients (65%) and leukopenia in 11 patients (55%) (nadir count). In one patient painful phlebitis was observed although no extravasation of the drug occurred. In two patients mild pruritus attributed to the m-AMSA occurred. The toxic effects are shown in Table 3. No grade 4 toxicity was encountered.

Changes documented in liver function tests and possibly attributable to m-AMSA were as follows: increase in the alkaline phosphatase value in four patients and increase of SGOT or γ-GT in three patients. It was not definite that these enzyme changes were drug-related. In nine of the patients an increase of the bilirubin above normal was observed.

None of the patients had evidence of cardiac disease at the start of treatment. Radionuclide ventricular ejection fraction tests were performed to obtain baseline values in 14 patients; but only six patients remained on study long enough to justify serial follow-up with the radionuclide ejection fraction tests. This test has become an accepted method for non-invasive evaluation of left-ventricular function and motion in patients receiving potentially cardiotoxic chemotherapy. Serial assessment of left-ventricular performance allows identification of patients at risk for the development of cardiotoxicity and of those who could receive therapy safely at substantially higher cumulative doses than those conventionally recommended. Table 4 shows the baseline and follow-up test values and the total dose of m-AMSA for those patients in whom serial ventricular ejection fraction studies were performed. As can be seen there was no significant decrease in the ejection fraction values of four patients receiving up to 920 mg m-AMSA. One patient, who received 1,000 mg m-AMSA, showed a 22% decrease in the ventricular ejection fraction, while an other patient, who received 1,460 mg m-AMSA, showed a decrease of 27% in his ventricular ejection fraction value.

Therapeutic Effects

Among the 19 evaluable patients only 1 met the criteria for partial response (PR). This patient, a 64-year-old man, complained of dyspnea and productive cough which started a month prior to the diagnosis of pleural malignant mesothelioma. He had previously been exposed to asbestos (as a boilermaker) and was a heavy smoker. His previous treatment consisted of, first, radiotherapy and adriamycin given concomitantly, and on relapse procarbazine given by mouth. The procarbazine was stopped 6 weeks prior to treatment with m-AMSA. At the start of treatment with m-AMSA examination showed a right pleural effusion. Chest X-rays showed the effusion and marked pleural thickening. His PS was 3. Following the administration of two courses of m-AMSA the patient felt subjectively better. His PS improved to one and chest X-rays showed a marked reduction of the pleural effusion and a moderate reduction of the pleural thickening. This response lasted for 16 weeks.

In the remaining six patients progressive disease was documented in spite of the treatment. In 12 patients the best response was evaluated as no change lasting from 4 weeks to 64 weeks (median 20 weeks).

Table 4. Radionuclide ventricular ejection fraction tests in patients with malignant mesothelioma treated with m-AMSA

Patient no.	Baseline test	Follow-up test	Total dose of m-AMSA
1	64%	71%	600 mg
2	61%	60%	600 mg
3	61%	52%	740 mg
4	56%	58%	920 mg
5	64%	42%	1,000 mg
6	69%	42%	1,460 mg

Survival

The median survival time from first symptoms was 60 weeks (12–160 weeks). The median survival time from tissue diagnosis of malignant mesothelioma was 39 weeks (6–123 weeks). The median survival time from the start of treatment with m-AMSA was 27 weeks (3 – > 98 weeks).

Discussion

Although the present series is too small to allow a definite conclusion on the value of m-AMSA in the treatment of malignant mesothelioma, it is nevertheless adequate to allow the conclusion that as given in this study the drug does not offer significant hope for patients with this disease. The results obtained did not warrant any further extension of the study.

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