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A Phase II Study of m-AMSA in Patients with Primary Liver Cancer

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Summary. *Thirty-five evaluable patients with histologically confirmed primary liver cancer (PLC) were treated with m-AMSA. All patients had measurable disease and an Eastern Cooperative Oncology Group (ECOG) performance status of 1, 2, or 3. m-AMSA 120 mg/M² IV was given every 21 days. Hemopoietic suppression was the major side-effect. In 26 of 35 patients (25 with leukopenia and five with thrombocytopenia), this toxic effect was documented. There was only one patient who had a partial remission (PR) of 51 weeks' duration, but a no change (NC) status was maintained in 28 patients for at least 6 weeks. The median survival time of all patients on this study was 13weeks, which compares favorably with most previous studies.*

Introduction

4′-[9-Acridinylamino] methanesulphon-m-anisidide (m-AMSA, NSC 249992), is related to the acridine dyes. The earliest report of antitumor activity of this group of drugs was shown for acriflavin by Mellanby in 1933 [6]. m-AMSA was synthesized in 1974 [1]. A phase I trial with m-AMSA was performed by the National Cancer Institute [7] and the MD Anderson Hospital [5]. Leukopenia was the major dose-limiting toxicity. Other side-effects include thrombocytopenia, mild nausea, and vomiting. Phase II trials were recommended with a dose of 120 mg/m² as a single dose every 3–4 weeks.

Only minor advances have been made in the treatment of primary liver cancer (PLC) in man [2, 4], so that phase II trials of promising agents are appropriate as a first-line treatment attempt.

The aim of the present study was to do a phase II trial of m-AMSA in patients with PLC so as to assess the possible value of the agent for later incorporation into a phase III clinical trial.

Materials and Methods

Patients with histologically confirmed PLC beyond hope of surgical cure were considered eligible for this study if they had a measurable area of known malignant disease to serve as an objective indicator of response to treatment. None of the patients received any prior treatment. Hepatomegaly was utilized in all patients, as in this series the liver (known to contain carcinoma) was always more than 5 cm below the xiphoid process or the costal margin on quiet respiration. Patients who had undergone surgery with resection or anastomosis within the previous 3 weeks were excluded, and the eligibility criteria further included absence of an active infectious process, leukopenia ($< 4{,}000/mm^3$), thrombocytopenia ($< 100{,}000/mm^3$), and renal disease (creatinine > 1.5 mg/100 ml or BUN > 30 mg).

At the start of treatment, the following examinations were performed: Studies obtained prior to initial therapy consisted of HGB, WBC, platelet count, differential count, urinalysis, BUN or creatinine, bilirubin, alkaline phosphatase, SGOT, serum protein, electrophoresis, prothrombin time, α-fetoprotein, gamma-glutamil transpeptidase, and chest x-ray. In 16 of the patients an inferior vena cavagram was performed and in 24 patients the hepatitis B surface antigen was determined. HGB, WBC, and platelet count were repeated at weekly intervals, BUN or creatinine and bilirubin 2 weeks after initiation of each course, and the remaining studies every 3 weeks. Height and weight, symptomatic status, and performance status (PS) were assessed on the first day of therapy, and at regular intervals thereafter.

Thirty-six patients were entered on study. Of these, one was considered ineligible. Of the 35 eligible patients, 33 were from South Africa (SA) and 2 were from the United States of America (USA). Four of the 35 patients were white and 31 were black (30 black SA). The age range of the 35 patients was 24–77 years (median 50). There were 29 males and six females. Performance status (PS) at the start of treatment with m-AMSA was 0 in four, 1 in twelve, 2 in nine, and 3 in ten patients [Eastern Cooperative Oncology Group (ECOG) PS: 0 = fully active; 1 = ambulatory,

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capable of light work; 2 = in bed < 50% of the time, capable of self-care but not work activities; 3 = in bed > 50% of the time, capable of only limited self-care; 4 = bedridden, ineligible for study]. Twelve of the 35 patients had jaundice at the start of treatment. Two patients had lung metastases, two patients had bone metastases, and one had skin metastases at the start of treatment.

In three patients concomitant cirrhosis was documented and nine patients had concomitant siderosis. In two patients the diagnosis of chronic Budd-Chiari syndrome was based on the findings of centrilobular fibrosis in which numerous vascular channels occurred. The adjacent liver sinusoids were congested. Inflammatory cell infiltration was minimal. Inferior vena cavagram was done in 16 patients, and showed obstruction in three of these.

At the start of treatment, 19 had elevated α-fetoprotein, and HB_sAg was positive in nine of the 24 patients in whom this was determined.

The dose of m-AMSA was 120 mg/m^2 IV given in 500 ml 5 DW over 1 h every 21 days. Dose modification was applied for leukopenia when necessary. No dose modification was used for elevation of serum bilirubin. The total dose given varied from 180 mg–1,148 mg.

Results

Toxic Effects

Leukopenia and thrombocytopenia were documented (see Table 1). Two possibly drug-related cardiac deaths occurred [3]. Neither of these patients had clinical findings of previous cardiac disease or had prior anthracycline exposure. One patient collapsed after the infusion had been completed. Death was presumed to be due to acute cardiotoxicity. The second patient developed multiple ventricular extrasystoles following administration of the first dose of m-AMSA, which cleared within 30 min. The patient died the following day after developing hemoperitoneum. The hematopoietic suppression was always rapidly reversible except in one patient, whose leukopenia persisted for 30 weeks. This patient was a 67-year-old man who presented with general body pains.

Physical examination showed massive hepatomegaly (9 cm below the xiphisternum, and 4 cm below the costal margin to both left and right of the midline). PS was 1. Special investigations showed normal bilirubin and alkaline phosphatase moderately elevated at 62 IU (normal 12–34). Eight days after the first dose of m-AMSA, a nadir white cell count of 2,100 was documented. This had recovered to 5,600 by day 22, and a second dose of m-AMSA was given. Three weeks later, when the white cell count was 4,700, a third dose of m-AMSA was given. A week following the third dose, a nadir white cell count of 2,000 was documented. On day 66, a fourth dose was given according to dose modification because the white cell count was still 2,600, and a fifth dose was given at the full dose range when the white cell count had recovered to 3,900 on day 94. A modified dose was given on day 173, when the white cell count was 3,600, and a full dose was given on day 206, when the white cell count was 5,300. A nadir was documented on day 221, when the white cell count fell to 1,300. The platelet count had fallen on day 212–45,000. Both white cell and platelet count recovered, to values of 3,800 and 95,000 respectively, before death. This patient remained anicteric throughout the course of his disease, although the alkaline phosphatase increased moderately, reaching a value of 111 on day 316. The drug was remarkably well tolerated subjectively by the patients. The median white cell nadir of patients with elevated bilirubin was 2,000, while the median white cell nadir for anicteric patients was 3,500. Too few patients developed thrombocytopenia to document any relationship between bilirubin and thrombocytopenia.

Table 1. Toxicity of m-AMSA in patients with PLC

Toxicity grade[a]	Leukopenia	Thrombocytopenia	Nausea and vomiting	Cardiac effects
I	7	2	0	
II	12	1	1	
III	6	2	0	
IV	0	0	0	2

[a] ECOG toxicity grade: 0, none or normal; 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, lethal

Therapeutic Effects

Only one patient met the criteria for partial response (PR). In this patient the measurable lesions were in the liver, which decreased in size by 65% for 51 weeks. The patient's weight and PS remained constant while his symptoms abated.

Twenty-eight patients were considered either to have stable disease or to have shown improvement less than the minimum criteria for PR. The shortest duration of no change (NC) was 6 weeks, the longest duration of stable disease is > 30 weeks (median 8.5 weeks). Of the 28 patients evaluated as NC, 11 showed minor improvement (less than PR) by clinical measurement and radiological examination, without deterioration in liver functions or with improvement in liver functions. There was a good correlation between physical examination throughout the study and special investigations such as liver function tests and ultrasound.

In six patients there was progressive disease despite treatment (see Table 2).

Table 2. Presponse of patients with primary liver cancer treated with m-AMSA

Total	CR	PR	NC	PD
35	0	1	28	6

Survival Times

The median survival time for all patients from the start of treatment with m-AMSA was 13 weeks (range 1–54 weeks). The median survival time by PS at the start of treatment was PS 0, 25 weeks; PS 1, 13 weeks; PS 2, 11 weeks; and PS 3, 10 weeks. The median survival time of 11 patients who showed improvement less than PR was 12 weeks.

Discussion and Conclusion

In this phase II study of m-AMSA in patients with PLC, the drug was well tolerated except by two patients, in whom possible cardiac toxicity was suspected.

There was only one patient who met the criteria for PR, but it is of interest that even in this uncontrolled series the median survival time was 13 weeks. The PS of patients in the previous phase II study of neocarzinostatin [4], was comparable. As this is the most predictable of the patient discriminant factors affecting survival [2], the survival time of 13 weeks with m-AMSA is promising.

The promising median survival time is not enough to motivate a phase III study of m-AMSA in black SA patients, but a phase II–III study is now being performed by ECOG in USA patients in study EST 1280, in which m-AMSA has been compared with neocarzinostatin. Among black SA patients (unlike USA patients) sufficient response was seen with adriamycin (ADR) to motivate randomization of black SA patients to receive either neocarzinostatin or ADR.

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