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# Phase II Trial of *m*-AMSA in Gallbladder and Cholangiocarcinoma: a Southwest Oncology Group Study*†

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**Abstract**—*Twenty-three patients with gallbladder and cholangiocarcinoma were treated with* m-*AMSA at doses of* 60–120 mg/m$^2$ *i.v. repeated at* 4-*week intervals. Toxicity was primarily hematologic. Partial responses occurred in* 1/12 *patients with gallbladder cancer and* 1/11 *patients with cholangiocarcinoma. The activity of* m-*AMSA in these neoplasms appears similar to that seen in hepatomas.*

## INTRODUCTION

*m*-AMSA (NSC-249992; 4′(9-acridinylamino) methanesulfon-*m*-anisidide) is one compound in a large family of amino acridines synthesized by Cain and Atwell [1]. The drug was selected for further study because of a broad spectrum of experimental antitumor activity in a number of murine tumors, including L1210, P388 leukemia, Lewis lung carcinoma, CD8F1 mammary cancer and B16 melanoma [2]. The mechanism of action of *m*-AMSA has not been entirely elucidated. In preclinical studies it appeared to inhibit DNA synthesis by virtue of its property of intercalation with the DNA molecule [3].

Phase I clinical trials of *m*-AMSA were initiated in 1977 and several dose schedules with acceptable toxicity were identified [4, 5]. These studies demonstrated leukopenia to be the major toxicity. The effect was dose-related and the median time to nadir count was 10 days, with recovery by 21–25 days after injection. Other toxicities observed included nausea, vomiting, alopecia, stomatitis, local tissue necrosis and phlebitis. Liver function tests showed abnormalities of serum bilirubin, serum enzymes and alkaline phosphatase, particularly at higher dose levels. In animal studies *m*-AMSA has been shown to be metabolized to a thioether of acridine and glutothione in the liver and excreted principally via the biliary system [6]. Hepatic dysfunction may prolong biliary excretion and dose reduction in this setting is thus employed [7]. In 1978 the Southwest Oncology Group initiated a phase II study of *m*-AMSA in patients with gallbladder and cholangiocarcinoma. The purpose of the present paper is to report this experience.

## MATERIALS AND METHODS

Patients with histologically confirmed carcinoma not amenable to surgical resection were eligible for the study. All patients had measurable disease, and prior therapy with either chemotherapy or radiation was allowable. Patients were divided into good and poor risk status, with the former group defined as age ≤65 yr, no prior radiotherapy, normal tolerance to prior chemotherapy (if any) and a bilirubin <1.2 mg%. In good risk patients *m*-AMSA was given at a dose of 120 mg/m$^2$ and in poor risk patients at a dose of 90 mg/m$^2$. In patients with markedly abnormal liver function (bilirubin ≥3.0 mg% and/or SGOT >3× normal) the starting dose was 60 mg/m$^2$. *m*-AMSA was administered intravenously in 500 ml of dextrose and water over 1 hr. Courses were repeated at intervals of 4 weeks, and dose adjustments for subsequent courses were

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made, based on nadir blood counts. Dose levels were: 40, 60, 90, 120, 140, 160 and 180 mg/m$^2$. Doses were altered as follows: white blood count $\geq$3000/mm$^3$ and/or platelets $\geq$100,000/mm$^3$, increase 1 dose level; white blood count $<$2000/mm$^3$ and/or platelets $<$75,000/mm$^3$, decrease 2 dose levels; intermediate nadir counts, no change. Complete blood counts with a platelet count, LDH, SGOT, alkaline phosphatase and bilirubin were obtained on pretreatment day 10 of each course and before each subsequent course. Lesions were measured prior to each course, and BUN and creatinine were obtained prior to each treatment.

An adequate trial of therapy consisted of 1 course of *m*-AMSA, with a subsequent follow-up of 4 weeks (standard SWOG response criteria were employed). A complete response was defined as complete disappearance of all measurable disease for $\geq$4 weeks. A partial response was defined as a decrease by 50% or more in the product of two diameters of all measurable lesions or a 30% or greater decrease in the sum of the liver measurements below both mid-clavicular lines and the xiphoid process lasting $\geq$4 weeks. Progressive disease was defined as either the appearance of new lesions, an increase of 50% or more in the sum of the products of two diameters of all measurable lesions or a 30% or greater increase in liver measurements.

Twenty-three patients were registered and all were eligible. Eleven patients had gallbladder carcinoma and 12 had cholangiocarcinoma.

## RESULTS

Clinical and response data for the 23 patients are outlined in Table 1. The majority of patients had received no previous chemotherapy and 20 had measurable disease in the liver. Most patients were symptomatic, with 19/23 having a performance status of 1 or greater. Two patients responded, one having gallbladder carcinoma and one cholangiocarcinoma. Both were partial responses and received 90 and 60 mg/m$^2$ of *m*-AMSA respectively. The site of measurable disease in both of these patients was palpable hepatomegaly. The median number of courses administered was 2, with the range being 1–18+. The observed responses were brief in one instance (2.5 months) and in the patient with cholangiocarcinoma lasted 13+ months. Previous treatment status did not influence response, with 1/10 previously treated and 1/13 previously untreated patients responding. The previous chemotherapy in this latter instance consisted of 5-fluorouracil.

Toxicity was moderate and was predominantly myelosuppression. Leukopenia ($\leq$3000 cells/mm$^3$) occurred in 8/10 previously treated and 3/13 previously untreated patients. Hematologic toxicity and its relationship to the AMSA dose level and previous therapy is outlined in Table 2. It was life-threatening ($<$1000 cells/mm$^3$) in two instances, but no drug-related deaths were recorded. Thrombocytopenia was milder, with only 5/23 having nadir platelet counts of 100,000/mm$^3$ or less. Hematologic toxicity was more severe in patients classified as poor risk and receiving either 60 or 90 mg/m$^2$ of *m*-AMSA.

*Table* 1. *Patient data*

| | Disease | |
|---|---|---|
| | Gallbladder carcinoma | Cholangiocarcinoma |
| No. of patients | 12 | 11 |
| Treatment status: | | |
| No previous therapy | 6 | 7 |
| Previous XRT | 1* | 0 |
| Previous chemotherapy | 6* | 4 |
| M/F | 5/7 | 5/6 |
| Median age | 63.5 | 52 |
| (range) | (52–79) | (39–70) |
| Dose levels: | | |
| 60 mg/m$^2$ | 2 | 7 |
| 90 mg/m$^2$ | 7 | 3 |
| 120 mg/m$^2$ | 3 | 1 |
| Site of measurable disease: | | |
| Liver: hepatomegaly | 5 | 2 |
| L/S scan, CAT liver | 4 | 9 |
| Lung | 1 | — |
| Lymph node | 2 | — |
| Median survival (months) | 2.75 | 2.0 |
| (range) | (2–7.0) | (1–18+) |
| Response data: | | |
| CR | 0 | 0 |
| PR | 1 | 1 |
| NR | 11 | 10 |

*One patient received both XRT and chemotherapy.

*Table* 2. m-*AMSA hematologic toxicity*

| Dose level | Previous treatment* | No. of patients | WBC $\leq$3000/mm$^3$ | Platelets 10$^5$/mm$^3$ |
|---|---|---|---|---|
| 60 mg/m$^2$ | Yes | 4 | 4 | 3 |
| | No | 5 | 1 | 0 |
| 90 mg/m$^2$ | Yes | 4 | 2 | 1 |
| | No | 6 | 1 | 0 |
| 120 mg/m$^2$ | Yes | 2 | 2 | 1 |
| | No | 2 | 1 | 0 |
| Total | | 23 | 11 | 5 |

*Chemotherapy ± radiation.

Sufficient data to determine granulocyte nadirs was available in 16/23 patients. The values for the three dose levels were as follows: 60 mg/m$^2$ (7 patients)—WBC 2300, day 11; 90 mg/m$^2$ (6 patients)—WBC 2250, day 13; 120 mg/m$^2$ (3 patients)—WBC 2700, day 10.

Non-hematologic toxicity included: nausea and vomiting (6/23) and alopecia (1/23). Nausea and vomiting were mild to moderate in 4/5 instances. Liver function abnormalities occurred in 2 patients and consisted of transient elevations of liver enzymes (SGOT, LDH) or bilirubin.

## CONCLUSIONS

Twenty-three patients with advanced gallbladder and cholangiocarcinoma were treated with *m*-AMSA. Two partial responses (9%, 95% confidence interval 2.8–33.6%) and moderate hematologic toxicity were seen. It appears that *m*-AMSA administered intravenously by this schedule produces occasional tumor regression in this patient population. The overall activity appears to be quite similar to that reported in patients with hepatomas [8, 9, 10], with less than 20% of treated patients responding objectively.

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