Cancer Chemother Pharmacol (1981) 6: 137–140

Cancer Chemotherapy and Pharmacology



# A Phase I and II Study of m-AMSA in Acute Leukaemia

M. L. Slevin[1], M. S. Shannon[2], H. G. Prentice[2], A. J. Goldman[1], and T. A. Lister[1]

[1] Imperial Cancer Research Fund Department of Medical Oncology, St Bartholomew's Hospital, London EC1A 7BE

[2] Academic Department of Haematology, Royal Free Hospital, Pond Street, London N W 3, Great Britain

***Summary.*** *Thirty-two patients with relapsed or resistant acute leukaemia were treated with m-AMSA at doses ranging from 50–150 mg/m² daily for 5 days.*

*Complete remission was achieved in three of 18 patients with acute myeloblastic leukaemia, two of nine patients with acute lymphoblastic leukaemia, and none of five patients with blastic crisis of chronic myeloid leukaemia. The complete remissions all occurred at doses of 100 mg/m² per day or above.*

*Haematological toxicity occurred in all patients and was dose-related. Nausea and vomiting were mild and easily controlled. Alopecia was uncommon at the lower doses but occurred in all patients receiving the higher doses. Stomatitis was noted in only 8% of courses at 50 mg/m² but was seen in 50% of courses at 150 mg/m². Mild and transient elevations of liver enzymes were common.*

*m-AMSA is an active drug in acute leukaemia, with acceptable toxicity. Its place in combination chemotherapy is now being explored.*

## Introduction

m-AMSA [4′-(9-acridinylamino)-methanesulfon-m-anisidide] is one of a group of acridine derivatives synthesized by Cain et al. in Auckland, New Zealand [2]. It has been shown to intercalate DNA and is cytotoxic for several animal tumours, including L1210 leukaemia [2]. Phase I studies in patients with solid tumours and acute leukaemia have demonstrated dose-related haematological toxicity, mild gastrointestinal toxicity, and local phlebitis. Alopecia was uncommon at the doses used for solid tumours, but occurred with the higher doses used in acute leukaemia. Mild elevation of liver enzymes, cardiac dysrythmias, and neurotoxicity, including grand mal fits, have occasionally been reported [3]. This phase I/II study was undertaken to assess the activity of m-AMSA in patients with relapsed and refractory acute leukaemia, and as initial therapy in the myeloid blastic crisis of chronic myeloid leukaemia.

*Reprint requests should be addressed to* T. A. Lister

## Patients and Methods

*Patients.* a) Eighteen adults with acute myeloblastic leukaemia (AML) who had failed to respond to combination chemotherapy comprising adriamycin, cytosine arabinoside, and 6-thioguanine or had relapsed after such therapy, were entered into the study.

b) Nine patients (five adults and four children) with acute lymphoblastic leukaemia (ALL) who had relapsed and were resistant to therapy including vincristine, prednisolone, adriamycin, L-asparaginase, and cyclophosphamide or had received maximal doses of adriamycin, were treated with m-AMSA. None of these patients had evidence of central nervous system leukaemia.

c) Five previously untreated adults with the myeloid blast crisis of chronic myeloid leukaemia (CML blast crisis) were entered into the study.

Patient characteristics are shown in Table 1.

## Methods

m-AMSA was administered in 500 ml 5% dextrose water as an IV infusion over 1–2 h, daily for 5 days. This was repeated approximately every 21 days, depending on the fitness of the

**Table 1.** Patient characteristics

| Diagnosis | Sex | | Age | | |
|---|---|---|---|---|---|
| | M | F | Mean | Median | Range |
| AML | 7 | 11 | 43 | 43 | 17–69 |
| ALL | 8 | 1 | 16 | 13 | 2.5–47 |
| CML blast crisis | 2 | 3 | 42 | 43 | 23–52 |

0344-5704/81/0006/0137/$ 01.00

patient and the recovery of the bone marrow. Once experience had been gained with a particular dose, and toxicity was felt to be acceptable, the next group of patients received a higher dose of m-AMSA, administered according to the same schedule. Patients who had not responded to m-AMSA and who were still generally fit were re-treated at a higher dose. Sixteen patients received 50 mg/m$^2$, five patients 75 mg/m$^2$, 11 patients 100 mg/m$^2$, and 12 patients 150 mg/m$^2$.

## Supportive Care

*Infection*

*Prophylaxis.* All patients received prophylactic gastrointestinal tract decontamination with Framycetin, Nystatin, and Colistin.

*Treatment.* Fever over 38° C or other evidence of infection was an indication for IV antibiotics and granulocyte transfusions where appropriate and available.

*Haemorrhage.* Platelet transfusions were given when the platelet count was less than $20 \times 10^9$/l or if clinically indicated, regardless of the platelet count.

*Assessment of Response*

*Complete remission* required the patient to be in normal health with haemoglobin > 10 g/dl, neutrophils > $1.0 \times 10^9$/l and platelets > $100 \times 10^9$/l. The bone marrow was required to be normocellular, with representation of all cell lines in normal numbers with less than 5% blasts.

*Partial remission* was defined as a clearance of the peripheral blood blasts and a 50% reduction in the percentage of bone marrow blasts, together with a decrease in cellularity if the initial bone marrow was hypercellular.

## Results

Complete remission was achieved in three of eighteen patients with AML, two of nine patients with ALL, and none of five patients with CML blast crisis. In addition, partial remission was noted in six of 18 patients with AML, four of nine patients with ALL, and two of five patients with CML blast crisis. Included in the group of partial remitters are two patients with ALL who became aplastic with no evidence of leukaemia, and who failed to regenerate normal bone marrow before bone marrow transplant at 32 days in one case, and death due to septicaemia at 40 days in other. The details of response to treatment are shown in Table 2.

The complete remissions all occurred with the 100 or 150 mg/m$^2$ dose of m-AMSA; four of five complete remitters received 150 mg/m$^2$, and one of five complete remitters received 100 mg/m$^2$. (One child with ALL, who achieved complete remission with m-AMSA at a dose of 150 mg/m$^2$, only received 3 days' therapy; all other patients received the planned 5 days' therapy.) Partial remissions, however, were seen at lower doses. Of 12 partial remissions, four occurred at 50 mg/m$^2$, two at 75 mg/m$^2$, two at 100 mg/m$^2$, and four at 150 mg/m$^2$ (Table 2). Two patients with AML remain in complete remission at 6 months and 3 months (receiving no therapy), and one relapsed at 3 months. The two complete remitters with ALL relapsed after 3 months and 1 months.

**Table 2.** Response to m-AMSA

| Diagnosis | m-AMSA mg/m$^2$ | No. of patients[a] | No. of courses | Response | |
|---|---|---|---|---|---|
| | | | | PR | CR |
| AML | 50 | 7 | 12 | 1 | 0 |
| | 75 | 4 | 4 | 1 | 0 |
| | 100 | 8 | 9 | 2 | 1 |
| | 150 | 8 | 8 | 2 | 2 |
| ALL | 50 | 4 | 6 | 1 | 0 |
| | 75 | 1 | 1 | 1 | 0 |
| | 100 | 2 | 3 | 0 | 0 |
| | 150[b] | 4 | 7 | 2 | 2[b] |
| CML blast crisis | 50 | 5 | 8 | 2 | 0 |
| | 75 | 0 | 0 | 0 | 0 |
| | 100 | 1 | 1 | 0 | 0 |
| | 150 | 0 | 0 | 0 | 0 |

[a] Twelve patients who did not respond to the initial dose of m-AMSA had dose escalations and are therefore included twice in this table

[b] Includes one child with ALL who had only 3 days' therapy

*Toxicity*

Details of the toxicity encountered at each dose of m-AMSA are shown in Table 3. Haematological toxicity occurred in all patients and was dose-related. The duration of neutropenia and thrombocytopenia was assessable only in the patients who achieved complete remission, as in the non-responding patients it was impossible to distinguish drug-related bone marrow toxicity from that associated with progressive leukaemic infiltration of the bone marrow. The duration of neutropenia and thrombocytopenia in the complete remitters is shown in Table 4.

Nausea occurred in 32% and vomiting in 18% of courses, and were generally mild and easily controlled. Stomatitis was noted in only 8% of courses at 50 mg/m$^2$, but was seen in 50% of courses at 150 mg/m$^2$. In those patients without alopecia from prior chemotherapy, this sign was seen in only one patient receiving 50 mg/m$^2$, but occurred in all patients receiving 150 mg/m$^2$. Mild and transient elevations of the liver enzymes were common.

**Table 3.** Number of courses of treatment during which toxicity was experienced

| m-AMSA mg/m$^2$ | No. of patients | No. of courses | Nausea | Vomiting | Stomatitis | Alopecia | Hepatic toxicity | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Bilirubin (> 17 mmol/l) | Alk. Phos. (> 100 IU/l) | SGOT (> 40 IU/l) |
| 50 | 16 | 26 | 5 | 3 | 2 | 3 | 4 | 1 | 2 |
| 75 | 5 | 5 | 2 | 1 | 1 | 1 | 0 | 1 | 3 |
| 100 | 11 | 12 | 5 | 2 | 3 | 4 | 3 | 1 | 1 |
| 150[a] | 12 | 16 | 7 | 5 | 8 | 8 | 6 | 2 | 4 |

SGOT = serum glutamic oxalocetic transaminase; Alk. Phos., alkaline phosphatase
[a] Includes one child with ALL who had only 3 days' therapy

**Table 4.** Duration of cytopenia (days) in complete remitters

| Name | Diagnosis | m-AMSA mg/m$^2$ | Neutrophils | | | Platelets | |
|---|---|---|---|---|---|---|---|
| | | | < 100 | < 500 | < 1,000 | < 50,000 | < 100,000 |
| SC | AML | 150 | 14 | 22 | 22 | 13 | 15 |
| PD | AML | 150 | 15 | 21 | 32 | 23 | 36 |
| MW | AML | 100 | 2 | 9 | 12 | 8 | 11 |
| LE | ALL | 150 | 12 | 13 | 15 | 6 | 18 |
| PJ | ALL | 150[a] | 20 | 20 | 33 | 10 | 15 |

[a] Received m-AMSA for only 3 days

No evidence of renal failure, as determined by urea and creatinine estimations, was noted. Neurotoxicity was not encountered.

One patient died with clinical and post-mortem evidence of cardiac failure, after receiving one course of m-AMSA. She was a 51-year-old female who had achieved complete remission of AML following combination chemotherapy, including adriamycin 450 mg/m$^2$. She was admitted in relapse, having had no therapy for 4 months, and was treated with m-AMSA 150 mg/m$^2$ for 5 days. At the time of admission she was not dyspnoeic and had no signs of cardiac failure either clinically or on chest X-ray. During the nadir (day 11) she developed a right lower lobe pneumonia, which was treated with broad-spectrum antibiotics. The temperature did not settle, and a few days later the patient became hypotensive with signs of cardiac failure and pulmonary oedema. At post mortem a large, dilated, pale heart was seen. Histological examination showed no evidence of leukaemic infiltration and no haemorrhage. There was no cytoplasmic vacuolation on light microscopy. However, multiple microscopic focal areas of recent muscle necrosis were seen on staining with Haematoxylin and Eosin (H and E), Martius Scarlet Blue (MSB), and Lie stains [5]. There was no inflammatory infiltrate and no fibrosis. The coronary arteries were patent.

## Discussion

This study confirms that m-AMSA is an active drug in AML and ALL, and the results are comparable to those of previously reported studies [1, 4]. Arlin et al. [1] report complete remission in six of 36 evaluable patients, and Legha et al. [4] obtained complete remission in 12 of 44 evaluable patients. The data of Arlin et al. [1] also show a dose response to m-AMSA, with no complete remissions occurring below a dose of 200 mg/m$^2$ per day for 5 days.

The toxicity reported here is also similar to that previously reported. Mucositis was dose-related, but was only severe enough to necessitate the discontinuation of oral intake in two children. This is in contrast to the patients reported by Arlin et al. [1], who received 200 mg/m$^2$ per day for 5 days: 85% had mucositis and oral intake was not possible in 25% of the patients. The patient who died of unexplained cardiac failure is of concern, but no conclusion as to the relationship with m-AMSA can be drawn. Although there was no cytoplasmic vacuolation on light microscopy, this does not exclude the possibility that the prior adriamycin exposure contributed to the cardiac failure. The lack of inflammatory infiltrate suggests that the focal areas of recent muscle necrosis were not caused by a myocarditis. Nonetheless, the

cytotoxic therapy could have prevented an inflammatory response.

As the majority of leukaemias in this study had not been demonstrated to be resistant to adriamycin and cytosine arabinoside, no conclusion can be drawn from these data about cross resistance to m-AMSA. However, eight of 12 complete remitters with m-AMSA reported by Legha et al. [4] had been demonstrated to be resistant to cytosine arabinoside and anthracycline. This suggests that m-AMSA may have a role in the preparation of patients with relapsed acute leukaemia for bone marrow transplantation.

Further studies are now in progress to assess the activity of m-AMSA in combination with cytosine arabinoside in patients with relapsed and resistant acute leukaemia.

*Acknowledgements.* We are pleased to acknowledge the assistance of Dr. John Amess in the Department of Haematology, Dr. A. G. Hausfeld in the Department of Histo-pathology, St. Bartholomew's Hospital. We also thank Mrs. J. Barton, who helped prepare the manuscript of this paper.

## References

1. Arlin ZA, Sklaroff RB, Gee TS, Kempin SJ, Howard J, Clarkson BD, Young CW (1980) Phase I and II trial of 4′-(9-acridinylamino)-methanesulfon-m-anisidide) in patients with acute leukaemia. Cancer Res 40: 3304
2. Cain BF, Atwell GJ (1974) The experimental antitumour properties of 3 congeners of acridylmethanesulphonanilide (AMSA) series. Eur J Cancer 10: 539
3. Issel BF (1980) Amsacrine (AMSA). Cancer Treat Rev 7: 73
4. Legha S, Keating M, Bodey G, McCredie K, Freireich E (1980) Phase II trial of 4′-(9-acridinylamino)-methosulfon-m-anisidide in adults with acute leukaemia. Proc Am Assoc Cancer Res/ASCO 21: 442
5. Lie JT, Holley KE, Kampa WR, Titus JL (1971) New histochemical method for morphologic diagnosis of early stages of myocardial ischaemia. Mayo Clin Proc 46: 319

Received February 9/Accepted March 18, 1981