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Treatment of acute leukaemia with *m*-AMSA in combination with cytosine arabinoside

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Summary. A series of 46 patients with acute leukaemia were treated with amsacrine (*m*-AMSA) and cytosine arabinoside (ara-C). Complete remission (CR) was achieved in 15 of 38 (40%) patients with acute myelogenous leukaemia (AML) and 4 of 8 (50%) patients with acute lymphoblastic leukaemia (ALL). The CR rate was significantly higher ($P<0.05$) for the younger, previously treated patients with AML (9/16) than for the older previously untreated ones (6/22), because of higher treatment mortality in the latter group.

Myelosuppression was prolonged and profound. Major nonhaematological toxicity affected the gastrointestinal tract (nausea, vomiting, mucositis, bleeding and ileus associated with severe diarrhoea). Many patients also developed reversible hepatic dysfunction and two elderly patients died of cardiac arrhythmia.

Further trials of this combination are justified in patients with relapsed or resistant leukaemia, but for older patients dose reduction is recommended.

Introduction

Amsacrine (*m*-AMSA), an acridine orange derivative which possesses DNA-intercalating properties similar to those of the anthracyclines, has been shown in phase I–II studies to be active in both acute myelogenous leukaemia (AML) and acute lymphoblastic leukaemia (ALL), and remission rates of 20%–35% have been reported [3, 8, 16, 21]. Preliminary results of the use of *m*-AMSA in combination regimens for poor-risk patients with acute leukaemia have also been encouraging [2, 17, 18, 27]. The experience at St Bartholomew's Hospital (SBH) and the Royal Free Hospital (RFH) of the use of *m*-AMSA in combination with cytosine arabinoside (ara-C) for the treatment of poor-risk patients with acute leukaemia is reported below.

Patients and methods

Patients

Forty-six patients form the basis of this study (Table 1). All twenty-two patients with AML who had received no prior therapy were more than 60 years old (range 60–72 years). Sixteen patients with AML and eight with ALL had received prior therapy. Four patients with AML had disease resistant to primary conventional therapy that included adriamycin. One patient with recurrent AML was treated at each of the three relapses with *m*-AMSA and ara-C.

Pretreatment abnormalities in elderly patients with AML. Multisystem abnormalities prior to treatment were noted more frequently in patients over 60 years of age, irrespective of diagnosis or previous treatment. Electrocardiographic or chest X-ray abnormalities and hypoalbuminaemia were significantly more frequent in the elderly previously untreated patients with AML (Table 2). The frequency of abnormal hepatic or renal function was significantly greater ($P=<0.05$) in patients who died early during induction therapy (less than 21 days from the initiation of treatment) than in those who achieved remission. In two patients, liver function improved following treatment.

Treatment

It was intended that each patient should receive a minimum of two cycles. Patients in whom complete remission, or a substantial reduction in leukaemia was achieved, were given up to three cycles if toxicity was acceptable.

m-AMSA 100 mg/m^2 (a dose determined by the phase I experience published previously [21]), diluted in 500 ml 5% dextrose solution was infused over 1 h via a central venous catheter, daily for 5 days. Ara-C was administered at a dose of 100 mg/m^2 per day by continuous IV infusion for 7 days. Drug doses were reduced by 25% in three elderly patients with marrow fibrosis, disseminated intravascular coagulation and previous exposure to chemotherapy (for ovarian cancer), respectively. *m*-AMSA was discontinued after 4 days in a patient who developed palpitations and ventricular ectopics.

Assessment of response. Complete response (CR) was defined as described previously [21] and required the patient to be in normal health with haemoglobin greater than 10 g/dl, neutrophil count greater than 1.0×10^9/l and platelet count of more than 100×10^9/l. The bone marrow at remission was required to be normocellular and contain less than 5% blast cells (with no lymphoblasts in the case of ALL). Lesser responses were considered as failures.

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Table 1. Patient characteristics

Diagnosis	AML		ALL[b]
	Previously untreated	Previously treated	
Number of patients	22 (4)[a]	16 (1)[a]	8
Disease status			
Relapsed disease		12	8
Refractory disease		4	0
Age (years)			
Mean	65	42	17
Median	64.0	44.0	12
Range	60–72	11–75	4–31
Male: female	12:10	12:4	7:1

[a] Figures in parentheses indicate numbers of patients with refractory anaemia with excess blasts or a diagnosis of hypoplastic AML

[b] All patients had recurrent disease following initial therapy

Table 2. Pretreatment abnormal parameters

Feature	Previously untreated AML		Previously treated AML+ALL	
	No.	%	No.	%
Total number	22	100	24	100
Renal impairment[a]	8	37	1	4
Hepatic dysfunction[b]	6	28	5	21
Albumin (<33 g/l)	4	18	0	0
Abnormal ECG	7	33	0	0
Abnormal chest X-ray	3	15	0	0

[a] Elevated urea or creatinine

[b] Elevated SGOT, bilirubin or alkaline phosphatase

Table 3. Response to therapy

Diagnosis	Disease status	No. of patients	CR	Fail	Early death
AML	Previously untreated	22	6	4	12
	Recurrent	12	6	3	3
	Refractory[a]	4	3	0	1
	Total	38	15	7	16
ALL	Recurrent	8	4[b]	2[c]	2

[a] Disease resistant to first-line therapy

[b] Three of four treated at first relapse; fourth patient was in fourth relapse of ALL

[c] Both patients in fourth relapse

Results

Efficacy

1. Acute myelogenous leukaemia. Complete remission was achieved in 15 of 38 patients (40%). The Ch rate was 6/22 (27%) in the previously untreated older patients, compared with 9/16 (56%) in the younger previously treated patients. Table 3 shows that the frequency of resistant leukaemia was comparable in the two groups, but early death (death occurring within 21 days of starting therapy) accounted for the lower CR rate in the older patients. Of the 10 who were evaluable for response in the latter group, 6 achieved CR. Remission was achieved with one cycle in 12 of 15 patients. Some subjects, 3 older patients and 4 previously treated patients in whom response was observed after one cycle of therapy, subsequently received up to three further cycles of either m-AMSA or alternative therapy. Two patients (aged 18 and 27 years) underwent allogeneic bone marrow transplantation; one died of cytomegalovirus pneumonitis without evidence of leukaemia, while the other relapsed after 3 months and died.

The median duration of remission in the previously untreated group was 16 months. All but one of the patients relapsed within 3 years (range 3–36 months), in three cases after more than 2 years of remission. Durable remission (longer than 6 months) was not achieved in any patient with subsequent salvage therapy, but a 61-year-old woman was successfully re-treated twice with the same regimen, having received a total dose of 2 g/m^2 *m*-AMSA. Median survival was 20 months (range 1–50 months) in those achieving remission, but the median overall survival was less than 1 month owing to death during induction in twelve of twenty-two patients.

The median remission duration in the previously treated group was only 7½ months (2–28 months). All patients relapsed and died, the median survival being 13 months (range 2–30 months).

2. Acute lymphoblastic leukaemia. Complete remission was achieved in four of eight patients with one cycle of therapy. Three patients subsequently received consolidation treatment with *m*-AMSA and ara-C. Two patients were lost to follow-up abroad, and remission in the other two lasted 4 and 9 months. Both died rapidly following relapse.

Toxicity

Nausea and vomiting were frequent, but controllable by antiemetics. The majority of patients developed mucositis and diarrhoea, but severe mucositis developed in only 6 patients and diarrhoea in 11 patients.

Gastrointestinal bleeding related to thrombocytopenia occurred in two elderly patients. Nine patients (7 untreated, 2 previously treated; total 22%) developed a syndrome of severe gastrointestinal dysfunction manifested by abdominal distension and severe watery diarrhoea associated with the presence of fluid levels on a plain abdominal X-ray. The frequency of this complication did not correlate obviously with the severity of oral mucositis. Five of the seven elderly patients with this syndrome died. Clostridium difficile was isolated in two of the seven patients.

Most patients developed some degree of hepatic dysfunction manifest mainly as hyperbilirubinaemia (Table 4), but this was reversible, except in patients with multisystem failure, in whom jaundice was often present during the terminal phase. Renal impairment was also mild and reversible except in the terminally ill.

Two of the previously untreated patients suffered cardiac arrest within 12 h of the first dose of *m*-AMSA: one

Table 4. Non haematological toxicity

Feature	Previously untreated AML	Previously treated AML/ALL
No.	19[a] (100%)	24 (100%)
Nausea/vomiting	18 (95)	18 (75)
Diarrhoea	18 (95)	11 (46)
Mucositis	14 (74)	14 (58)
Ileus	7 (37)	2 (8)
GI bleed	2 (11)	0
Hepatic dysfunction	15 (79)	19 (79)
Renal dysfunction	8 (42)	0
Cardiac dysfunction	3 (11)	0

[a] Three patients who died within 3 days of starting therapy were excluded

man aged 72 years had an abnormal pretreatment electrocardiograph (left axis deviation and lateral ischaemia), but normal serum potassium. The other patient was an obese 61-year-old woman with long-standing hypertension, who was normokalaemic during the 3 days before treatment but had mild hypokalaemia on the day of treatment. She developed ventricular fibrillation and died 3 days later without recovering consciousness.

The mean adriamycin dose was 200 mg/m^2 for ALL and 312 mg/m^2 for patients with AML treated previously with anthracyclines. With the exception of one patient, who developed palpitations and ventricular extopics which resolved on stopping *m*-AMSA, cardiac dysfunction was not observed in the previously treated group.

Myelotoxicity was comparable in the assessable patients to that seen following *m*-AMSA alone [21]. The mean duration of neutropenia (less than 1.0×10^9/l) was 30 days. The mean duration of thrombocytopenia (less than 100×10^9/l) was 32 days in patients with AML. Bone marrow recovery was much more rapid in the younger patients with ALL.

Discussion

The combination of *m*-AMSA and ara-C had antileukaemic activity in the majority of evaluable patients.

The remission rate in the previously treated patients was higher than than that achieved in the phase I study [21], but that study did not include patients in first relapse. Approximately one-third of patients with resistant or relapsed AML treated with *m*-AMSA in combination with other drugs [2, 6, 16, 18, 27] have achieved CR. The study of Hines et al. [13] was exceptional in that the use of *m*-AMSA (75 mg/m^2 on days 7, 8, and 9) following high-dose ara-C (3G/m^2, q 12 h × 12) resulted in a CR in 70% of patients with relapsed or refractory AML. However, all patients were under 65 years of age (mean 41 years). Similarly, 10 of 14 patients with AML (age less than 55 years) achieved CR with *m*-AMSA and moderate-dose ara-C [26]. Keating et al. [15] found that *m*-AMSA in combination with vincristine, ara-C and prednisolone (*m*-AMSA-OAP) produced a higher remission rate than expected in poor-prognosis, previously untreated patients with AML.

The overall response rate to *m*-AMSA alone in patients with ALL has been approximately 20% [2, 3, 8, 16]. Although the combination of *m*-AMSA and ara-C induced remission in this study in four of eight patients with recurrent ALL, three of four were treated in first relapse, and it is likely that all three would have responded to alternative therapy.

Toxicity was acceptable in the previously treated younger patients, but was excessive in those over 60 years of age. Whether the deaths of elderly patients were a consequence of poor tolerance of hypoplasia or related to multisystem pretreatment dysfunction, or a combination of these factors is open to question. Death before the expected onset of severe hypoplasia suggests that the pre-existing abnormalities were an important contributory factor. The majority of studies [2–5, 17, 24, 28] but not all [10, 11, 19] have reported advanced age to be an adverse prognostic factor. The duration of cytopenia was similar in both previously treated and untreated patients, but was longer in patients with AML than ALL. Liver dysfunction was reversible in the assessable patients, although several patients developed severe jaundice terminally. Irreversible hepatic toxicity attributable to *m*-AMSA is uncommon [1]. The marked gastrointestinal dysfunction manifest as ileus and severe diarrhoea has also been noted in patients treated with other intensive chemotherapy regimens at SBH and cannot be entirely attributed to the use of *m*-AMSA [22].

Two of the patients died of cardiac dysarrhythmia after the first dose of *m*-AMSA. Cardiac toxicity has been reported sporadically [2, 9, 12, 25], but the overall incidence in 3200 patients reviewed by Grillo Lopez et al. [12] was noted to be 2.3%, and death occurred in only 0.2%. Most patients developing arrhythmias following administration of *m*-AMSA have had hypokalaemia at the time [2, 9, 12, 23]. One of the patients reported above was normokalaemic at the time of treatment. Steinherz et al. [23] found that *m*-AMSA induced changes detectable by echocardiography in 18 of 27 patients who had previously received anthracyclines. The frequency of abnormalities was related to both the total anthracycline dose and the rate of administration of *m*-AMSA. In the present study, only patients not previously treated with adriamycin developed clinical or electrocardiographic evidence of cardiac dysfunction. The availability of simple tests like the radionuclide scan may allow more critical assessment of toxicity during therapy [20].

In summary, the combination of *m*-AMSA and ara-C in the manner used in this study induced remission in a substantial proportion of patients with relapsed or refactory acute leukaemia, but this regimen proved excessively toxic in elderly patients. Achievement of remission allowed suitable patients to proceed to bone marrow transplantation. Randomised trials are in progress to determine whether *m*-AMSA in combination with other drugs is superior to conventional regimens for the therapy of poor-prognosis patients [7]. The high response rate in evaluable elderly previously untreated patients suggests that it may be appropriate to investigate as with other regimens [14] the efficacy of reduced doses of *m*-AMSA and ara-C in patients with a high probability of life-threatening complications.

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