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Phase I and II Study of AMSA in Childhood Tumours

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Summary. *Twenty-nine children with tumours that had failed to respond to conventional therapy have been treated with AMSA. There were 16 patients with haematological malignancies in whom treatment was initiated at 25 mg/m² for 3 days, increasing to 150 mg/m² for 5 days. There were one complete and four partial remissions in these patients, all of whom had received at least 500 mg AMSA/m². Thirteen children with solid tumours were treated. They received single doses of 120 mg/m² initially, increasing to 100 mg/m² for 5 days. No complete or partial responses occurred, but some antitumour activity was noted in neuroblastoma and retinoblastoma. Dose-related severe bone marrow toxicity occurred, but gastrointestinal and other toxicity was mild. An additional patient with T cell lymphoma, who received AMSA prior to a successful autologous bone marrow transplant, is described.*

AMSA is an active drug in childhood leukaemia. Further studies at the maximum tolerated dose are needed to assess enough patients with any single solid tumour type. In particular, the response of neuroblastoma warrants further study. Investigation of the use of AMSA either prior to bone marrow transplantation in leukaemia or in association with autologous marrow transplant in neuroblastoma and other solid tumours may be of value.

Introduction

4-(9-acridinylamino)Methanesulfon-*m*-anisidide (AMSA) is a synthetic acridine derivative active in a wide range of murine tumours. It has been shown to inhibit DNA synthesis [6] and appears to be effective on both proliferating and non-proliferating cells [11]. Phase I and early phase II studies have indicated some activity against solid tumours and leukaemias even in heavily pretreated patients [1–3, 6, 7, 9]. Myelosuppression, in particular leukopenia, occurs when it is used and this has been the dose-limiting toxic effect. Nausea, vomiting, and mucositis are reported but gastrointestinal effects appear to be mild except at high doses, when mucositis becomes significant. Mild elevation of liver enzymes, cardiac dysrythmias, and grand mal seizures have been reported. There has been relatively little information on the use of AMSA in children [8, 10], and it is important to assess its potential in these patients. This phase I and II study was undertaken to ascertain the response to AMSA of childhood tumours that had not responded to conventional therapy, and to evaluate the children's tolerance to AMSA and its toxicity.

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Patients and Methods

Children with tumours that had failed to respond to standard therapy were considered eligible for treatment provided that their disease was measurable and parental consent was obtained. Only children with primary central nervous system disease were excluded, because AMSA does not penetrate the spinal fluid adequately [14].

Twenty-nine children have been treated in the study. There were 13 boys and 16 girls, with an age range from 3 to 16 years and a median age of 9 years. There were 16 patients with haematological malignancies and 13 with solid tumours, and these are detailed in Table 1.

The AMSA was administered dissolved in 300 ml 5% dextrose and infused IV over 2 h. Once experience had been gained with a particular dose and toxicity was felt to be acceptable the next patients received a higher dose. Patients who had tolerated, but not responded to, a particular dose were re-treated at a higher dose. Courses were repeated every 21 days, depending on the recovery of the bone marrow. In children with haematological malignancies treatment was initiated at a dose of 25 mg/m² for 3 consecutive days. This was steadily increased to 150 mg/m² for 5 days to reach the maximum tolerated dose. The early patients with solid tumours received single doses of AMSA beginning at 130 mg/m² and rising to 180 mg/m². More recently, patients have received consecutive daily doses increasing to 100 mg/m² for 5 consecutive days. The courses and doses are shown in Table 2.

Patients with haematological malignancies were considered to have a complete response if they had a normocellular bone marrow with representation of all cell lines in normal numbers and less than 5% blasts. The peripheral blood was required to have a haemoglobin level > 10 g/dl, neutrophils $> 1.0 \times 10^9$/l and platelets $> 100 \times 10^9$/l. A partial remission

Table 1. Diagnoses of patients treated

Acute lymphatic leukaemia	10
Acute myeloid leukaemia	3
Lymphoma with marrow involvement	2
Malignant histiocytosis	1
Neuroblastoma	4
Osteogenic sarcoma	3
Ewing's sarcoma	2
Round cell tumour of bone	2
Retinoblastoma	1
Sacrococcygeal teratoma	1

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Table 2. Courses and doses of AMSA given

	Doses (mg/m^2)	No. of courses
Haematological malignancies	25 × 3	2
	50 × 3	2
	100 × 3	3
	150 × 3	2
	100 × 5	8
	120 × 5	4
	150 × 5	5
Solid tumours	120 × 1	6
	150 × 1	2
	180 × 1	3
	150 × 3	1
	75 × 5	10
	100 × 5	9

Table 3. Responses in haematological malignancies

Patient		Diagnosis	Therapy (mg/m^2)	Response
Boy	11 years	AML	100 × 5 100 × 5	Complete
Boy	14 years	AML	150 × 3 150 × 5 150 × 5	Partial
Girl	16 years	ALL	150 × 5	Partial
Girl	4 years	ALL	100 × 5 100 × 5	Partial
Boy	16 years	Lymphoma	100 × 3 100 × 2	Partial

was defined as a clearance of peripheral blood blasts and at least 50% reduction in the percentage of bone marrow blasts, with a decrease in cellularity if the initial marrow was hypercellular. In children with solid tumours, complete response was considered to be the disappearance of all measurable disease, and partial response required greater than 50% reduction in the product of the two largest perpendicular diameters in the most clearly measurable lesion with no progression in any other lesion. These responses were to be maintained for a minimum of 3 weeks.

Results

Of the 16 patients with haematological malignancies, one experienced complete response and four a partial response. The complete response occurred in an 11-year-old boy with acute myeloid leukaemia. He had been treated initially according to the current Medical Research Council Acute Myeloid Leukaemia trial, and remained in remission for 20 months. After relapse he failed to respond to vincristine, daunorubicin, and rubidomycin. He was then treated with two courses of AMSA at 100 mg/m^2 for 5 days, and entered a remission which has continued for 8 months, with no further treatment.

The partial responses occurred in another patient with relapsed acute myeloid leukaemia, two children with relapsed acute lymphatic leukaemia, and one boy with a primary bone lymphoma that had relapsed in the bone marrow. These patients each received a minimum total dose of 500 mg/m^2 and the treatment scheme of the individual patients is shown in Table 3.

Of the 13 patients with solid tumours, there were no responses that fulfilled the designated criteria. However, of the four children with neuroblastoma two showed significant change in their condition. One 6-year-old girl had progressive disease involving the marrow, lymph nodes, and bones in spite of treatment with cyclophosphamide, vincristine, VM26, melphalan, and *cis*-platinum. She received two courses of AMSA at 100 mg/m^2 initially, and was then maintained on AMSA 75 mg/m^2 75 mg/m^2 × 5 approximately every month for a year. During this time she felt well and her disease remained stable. A 3-year-old girl with widely disseminated disease after cyclophosphamide, vincristine, and adriamycin had a marked improvement in wellbeing, with loss of all pain, gain in appetite, and a 25%–50% decrease in all tumour sites. This response occurred after one course of AMSA at 100 mg/m^2 for 5 days, but only lasted for 3 weeks. One child with disseminated retinoblastoma who was treated early in the study with only single doses of AMSA every 3 weeks had stable disease during the 8 weeks of therapy.

The dose-limiting toxic effect of AMSA is marked myelosuppression. This occurred in all patients between 1 and 2 weeks after the AMSA was given. In view of the wide range of diagnoses in this group of patients, the variety and intensity of their previous therapy and the fact that 20 of the 29 had bone marrow involvement by tumour, a precise comparison of the levels of myelosuppression between patients is not meaningful. However, the degree of suppression was greater with increasing doses of AMSA and at doses of 100 mg/m^2 used for 3 or more days profound marrow toxicity was universal. The white cell count, and in particular the leukocytes, fell below $100 \times 10^9/mm^3$ and platelets below $100 \times 10^9/mm^3$. A fall of 1–3 g in haemoglobin was common. Most children needed antibiotic support and platelet transfusion but the anaemia recovered spontaneously in those children whose marrow was not invaded by tumour. Infective episodes were frequent during the nadir. In the majority of these no organism was found, but gram-negative septicaemia associated with perianal abscess occurred in three patients, staphylococcal sepsis was proven in one patient, and one patient died with systemic candidiasis. Marrow recovery occurred between 3 and 4 weeks in 25 of the 29 patients. Of those who failed to recover, three died from progressive marrow infiltration by tumour and one was the patient with systemic candidiasis, who died with a hypoplastic bone marrow 1 month after AMSA.

Gastrointestinal symptoms were mild or entirely absent in most patients. Nausea and occasional vomiting occurred in seven children, diarrhoea in three, and mucositis in four. In three patients the mucositis was marked and in one this progressed to osteomyelitis of the palate and subsequent necrosis. One child developed pain at the site of the secondary deposits of her retinoblastoma during the administration of AMSA, but this was easily controlled. One patient, the boy with myeloid leukaemia who achieved a complete response, developed a peripheral neuritis of the Guillain-Barré type 2 months after taking AMSA. He had marked weakness and incoordination of the limbs, which was accompanied by a mild facial palsy and absent reflexes. His cerebrospinal fluid had a raised protein level of 1.1 g/l. He has since been recovering gradually. No definite cause for the neuritis has been found

and the possibility of a reaction to AMSA should be considered. Marked feelings of malaise and depression were experienced by five patients during treatment, and in some cases for several days afterwards. No cardiac effects were noted.

AMSA has been used in a way previously undescribed in the literature in one patient. A 13-year-old boy, not included in the previous results, with a T cell lymphoma, presented with nodal and mediastinal involvement but a normal bone marrow. Initially he was treated with the United Kingdom Children's Cancer Study Group protocol for non-Hodgkin's lymphoma. After a remission of 1 year he relapsed whilst receiving treatment, locally in the neck and mediastinal lymph nodes, but continued to have a normal bone marrow, which was harvested at this time. He received local radiotherapy and further chemotherapy until he relapsed 6 months later with his bone marrow 98% replaced by blasts. At this time he was treated with AMSA 200 mg/m^2 for 5 days, followed 3 days later by an autograft of his previously harvested bone marrow. He did not receive total body irradiation at any time. He recovered well from this procedure and remained in complete remission, with no other treatment, for 2½ months before a further bone marrow relapse occurred.

Discussion

With one complete and four partial responses out of 16 heavily pretreated patients, this study suggests that AMSA is an active drug in both lymphatic and myeloid leukaemias in childhood. This is in accord with studies of adult leukaemia [1–3, 6, 7, 9]. In previous phase I and II trials treating haematological malignancies AMSA has been used in divided doses. Courses have ranged from 3 to 10 days, with recommended daily doses varying from 75 to 200 mg/m^2 [6]. Toxicity, in particular bone marrow suppression and stomatitis, appears to be insignificant up to doses of 100 mg/m^2, but below this dose antileukaemic effects are very small and no complete responses are reported. Adults with leukaemia treated at Memorial Sloan-Kettering Hospital have tolerated doses of 200 mg/m^2 [2] for 5 days, but the highest dose used so far in children has been 150 mg/m^2 × 5 at St Jude Hospital [8]. This was the maximum tolerated dose in the present study, but doses between 100 and 150 mg/m^2 may be necessary in patients with poor marrow reserve.

With solid tumours, although a range of dose levels has been used in other phase I trials, these have been much lower than in leukaemia. Courses at many institutions have consisted of single doses of 70–120 mg/m^2, repeated 3 weekly [6]. Four children at Sloan-Kettering [10] received 70 mg/m^2 on consecutive days and at St Jude [8] consecutive daily doses were used, but toxicity was found to be higher in children with solid tumours than in those with leukaemia, and the maximum dose achieved was 50 mg/m^2 for 5 days. In this study, increasing levels of single doses were used initially, but the total dose seemed disproportionately low compared with those reached in the leukaemia patients, particularly considering that many of the solid tumour patients also had bone marrow involvement. Latterly, consecutive daily treatment was used for these patients up to a dose of 100 mg/m^2 for 5 days. Although the toxicity was markedly increased compared with that observed following the single doses it did not appear, in our patients, to differ from that occurring in the children with leukaemias. Although no complete or partial responses occurred in the patients with solid tumours this may be because insufficient patients have been treated at high doses.

Disseminated neuroblastoma is a particularly disappointing tumour to treat. The four children in this study had extensive disease, which had proved resistant to intensive treatment with a wide range of chemotherapeutic agents. It is encouraging that in spite of this two of them showed some response to AMSA, and this is in accord with recent in vitro evidence [5]. The sensitivity of cultured human neuroblastoma to a range of antitumour drugs was assessed. AMSA with VM26 and adriamycin, was in the most effective group, and showed more activity than vincristine, VP16, *cis*-platinum, and melphalan. This evidence suggests it is important to continue to study the effect of AMSA in patients with neuroblastoma.

The successful use of AMSA in the patient with relapsed T cell disease prior to an autologous bone marrow transplant suggests two further potential uses for AMSA, which warrant further assessment. It may prove valuable, as in this boy, as a drug to use prior to therapeutic bone marrow transplant, either autologous or from matched donors in leukaemic patients. It is also possible that because of its severe marrow toxicity the full therapeutic potential of AMSA has not been achieved. Combining its use with an autologous bone marrow rescue technique would make it possible to increase the doses used. Gastrointestinal toxicity has been mild and should not preclude this. This form of therapy may be valuable in neuroblastoma and other solid tumours.

In conclusion, AMSA is an active drug in childhood leukaemia. Further studies at the maximum tolerated dose are needed to assess enough patients with any single solid tumour type. In particular, neuroblastoma warrants further study. Investigation of the use of AMSA either prior to bone marrow transplantation in leukaemia or in association with autologous marrow transplant in neuroblastoma and other solid tumours may be of value.

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