Evaluation of AMSA in Previously Treated Patients With Acute Leukemia: Results of Therapy in 109 Adults

By Sewa S. Legha, Michael J. Keating, Kenneth B. McCredie, Gerald P. Bodey, and Emil J. Freireich

AMSA was evaluated in the treatment of 109 adults with previously treated acute leukemia. Of the 102 evaluable patients, 82 had AML, 17 ALL, and 3 CML in blastic phase. A number of different dose schedules of AMSA were explored, and we conclude that the optimum dose of AMSA for remission induction in acute leukemia is 120 mg/sq m/day for 5 days. Complete remissions were observed in 23 (28%) patients with AML and in 1 patient with ALL. Patients who achieved complete remission were maintained on AMSA using a dose of 30–40 mg/sq m/day for 5 days repeated at 4-wk intervals. The median duration of complete remission was 12 wk (3–59 wk), and the respondents survived significantly longer than the failures (27 wk versus 8 wk, p = 0.002). The side effects associated with AMSA therapy included mild nausea and vomiting, stomatitis, diarrhea, phlebitis, alopecia, and myelosuppression-related infections. Our results indicate that AMSA is a useful new antileukemic agent for the treatment of relapsed acute leukemia and appears to have activity comparable to that of the currently available drugs, such as cytarabine and the anthracycline antibiotics.

More, we found that the lowest dose at which AMSA induced complete remissions in acute leukemia was 90 mg/sq m/day for 5 days. Since the publication of our previous report, we have explored additional dose schedules of AMSA with the aim of defining the best therapeutic dose schedule. In this article, we describe our entire experience with AMSA in a large group of patients with acute leukemia who had relapsed or failed to respond following conventional chemotherapy.

MATERIALS AND METHODS

Patients

This study was initiated in April 1978 and was closed to further patient entry in December 1980. A total of 109 patients were registered during this period of time, including 62 patients reported previously. The general characteristics of these patients are summarized in Table I. There were 86 patients with AML, 20 with ALL, and 3 patients with the blastic phase of chronic myeloid leukemia. Eight-five patients were less than 50 yr of age, 24 were older than 50 yr. Three-fourths of the patients were ambulatory and their AMSA therapy was initiated as outpatients. The remainder of the patients were in the hospital, generally because they were febrile and were receiving antibiotics. All patients had received prior chemotherapy with conventional agents, including cytarabine and one of the anthracycline antibiotics, and had either failed to achieve a remission (14 patients) or had previously achieved a remission and had relapsed before AMSA treatment was initiated. The median number of prior treatment regimens was 2 (range 1–4), and 33 patients had received 3 or more prior treatment regimens. Patients were required to have a minimum of 30% blasts in the bone marrow and to have evidence of bone marrow failure before they were eligible for AMSA protocol. No patient was excluded because of poor performance status. All patients were required to sign an informed consent form approved by our institutional review board.

Dose Schedules of AMSA

The drug was obtained from the Investigational Drug Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, Md. The starting dose level of AMSA was 50 mg/sq m/day on 3 consecutive days. The dose was subsequently increased by 25%–50% dose increments to 120 mg/sq m/day. Because the myelosuppression with the 3-day courses was transient, the dose schedule of AMSA was then increased in a stepwise manner to 75–90 mg/sq m.

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daily for 5, 7, and 10-day courses. Since the myelosuppressive
toxicity and gastrointestinal toxicity were excessive with the 10-day
courses, it was finally elected to increase the daily dose to 120
mg/sq m, and the course of treatment limited to a 5-day period. This
dose was believed to be optimum and was utilized for a total of 32
patients in order to determine adequately the response rate commen-
surate with a phase II evaluation.

The total daily dose of AMSA was mixed in 500 ml 5% dextrose
and water (AMSA is not compatible with saline-containing solu-
tions) and infused over 60–90 min. Patients were monitored with
pretreatment measurements of serum electrolytes, renal and hepatic
function, and daily blood counts including hemoglobin, white blood
cell count, differential count, along with platelet counts. A bone
marrow aspirate and biopsy were obtained on day 10 or 11 following
initiation of AMSA therapy and were subsequently repeated at
3-4-day intervals in order to determine whether the patient’s
leukemic infiltrate was increasing or decreasing as a result of
treatment. If there was no reduction of leukemic infiltrate 2 wk after
the first course, a second course of treatment was started. In patients
who showed reduction of bone marrow leukemic infiltrate (percent
blasts x percent cellularity) to less than 10%, further administration
of AMSA was withheld until either remission was obtained or there
was evidence of increasing leukemic infiltrate. A minimum of two
courses of treatment was attempted before a patient was considered
to have failed AMSA therapy. Patients receiving AMSA therapy as
outpatients were evaluated in the clinic at least on a once weekly
basis. Patients who developed fever or infection were hospitalized
and treated with broad spectrum antibiotics. Supportive care with
blood transfusions, platelets, or granulocyte transfusions was pro-
vided when indicated.

Patients who showed a significant degree of response to treatment
were maintained on AMSA. An attempt was initially made to give
consolidation courses of AMSA in a dose range of 60–75 mg/
sq m/day for 5 days, but because of significant associated morbidity,
most patients were switched to maintenance therapy after achieving
complete remission. The maintenance dose of AMSA varied
between 30 and 40 mg/sq m/day for 5 days, repeated at 4-wk
intervals.

Response Criteria
A patient was considered to be in complete remission when bone
marrow examination showed recovery of normal hematopoiesis with
less than 5% blast forms and peripheral blood showed recovery of
granulocyte count to at least 1000 cells/cu mm and platelet count in
excess of 100,000 cu mm. Patients showing a reduction in bone
marrow blasts to 6%–25% accompanied by a similar recovery of
peripheral blood counts were classified as partial responders.
Patients who showed significant improvement in the peripheral
hematologic parameters short of meeting the criteria for complete or
partial response and showing significant reduction in bone marrow
blasts but not to less than 25%, were classified as having hematologic
improvement. Patients who either failed to clear peripheral blasts or
after having cleared the peripheral blasts failed to show any evidence
of recovery of normal elements were classified as failures of therapy.

The duration of remission was measured from the time the
remission was first documented to the time of first documentation of
relapse. A relapse was defined as reappearance of 6% or greater
number of blasts in the bone marrow. Survival was measured from
the first day of AMSA therapy to the time of death. Patients who
relapsed after achieving remission with AMSA or failed to achieve a
remission were subsequently treated with investigational chemother-
apy or bone marrow transplantation.

RESULTS

Of the 109 patients in this study, 7 were not assess-
able for response to therapy. Among them there were 5
who died early—within 2 wk of initiating AMSA
therapy. Therapy was interrupted after 2 days of
treatment in one patient because of the question of his
eligibility for this treatment, and one patient was lost
to follow-up after finishing his 5-day course of treat-
ment. Among the 102 patients evaluable for response,
AMSA failed to reduce the number of blasts in the
peripheral blood of 14 patients, who were clearly
refractory to this therapy. The remaining 88 patients
experienced varying degrees of antileukemic effect,
although 25 patients had no significant reduction in
the bone marrow leukemic infiltrate. Sixty-three
patients (61%) achieved bone marrow hypoplasia and
24 patients from this group achieved a complete remis-

sion. The overall complete remission rate was 24% for
the total group. Among the 82 evaluable patients with
acute myeloblastic leukemia, 23 (28%) achieved a
complete remission. Among the 17 evaluable patients
with acute lymphoblastic leukemia, only one (6%)
achieved a complete remission. Patients with CML-
blastic phase failed to respond to AMSA.

Acute Myeloblastic Leukemia

Among the 86 patients with AML, there were 3
early deaths, and 1 patient was lost to follow-up,
leaving 82 evaluable for response. The dose levels of
AMSA received by these patients and the correspon-
ding response rates are shown in Table 2. Overall, a total
of 23 patients (28%) achieved a complete remission.
One patient achieved a partial remission and 5 patients
had hematologic improvement. Total AMSA dose less
than 450 mg/sq m was considered less than optimum
for remission induction. However, one patient achieved
a complete remission with a regimen of 120 mg/
sq m/day × 3. Two of five patients who received 90

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Table 1. Patient Characteristics

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<td>Median age (range)</td>
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mg/sq m/day × 5 achieved complete remission. However, both patients required two courses to achieve complete remission. Subsequently, we used a dosage regimen of 90 mg/sq m/day × 7 days, which was clearly effective, but 3 of 15 patients had prolonged hypoplasia of the bone marrow. Consequently, the dose was reduced to 75 mg/sq m/day × 7 days, which was better tolerated. Because the dose level of 90 mg/sq m/day × 5 days was active and had no significant toxicity, AMSA dose was escalated to 120 mg/sq m/day × 5 days. Nine of 29 AML patients (31%) treated with this dose of AMSA achieved complete remission. Since approximately 60% of the patients experienced significant stomatitis on enterocolitis at this dose, further dose escalations of AMSA were not felt justified.

Characteristics of Responding Patients

The median time to achievement of complete remission was 38 days (range 25–112). Ten of 23 complete remissions occurred after 6 wk, 8 because they required 2 or more courses of AMSA treatment and 2 because of prolonged hypoplasia of 60 and 70 days following the first course of treatment. Sixteen patients achieved complete remission following the first course of AMSA, 5 required 2 courses, and 2 required 3 courses. All patients requiring more than one course of AMSA to achieve remission had shown significant reduction in their bone marrow leukemic infiltrate following the first course of AMSA. The effect of pretreatment patient characteristics on the probability of complete remission is shown in Table 3. The most significant factor affecting the response rate was the number of induction treatment regimens prior to AMSA treatment. AMSA induced complete remission in 14 of 58 patients (24%) who had either failed primary induction (13 patients) or attempts at induction with cytarabine and one of the anthracycline antibiotics, indicating lack of cross-resistance between these drugs and AMSA. Three of 13 patients who had never achieved remission with the currently available antileukemic agents achieved complete remission when treated with AMSA. The highest response rate was observed in patients who received AMSA for their first relapse from a previous remission induced with cytarabine and anthracyclines.

Patients who achieved complete remission with AMSA were maintained on the drug as single agent therapy. Initial attempts at consolidation therapy with AMSA at 75 mg/sq m/day for 5 days resulted in severe myelosuppression, generally leading to sepsis and hospitalization with each course of treatment. Accordingly, the maintenance dose of AMSA was reduced to 30–40 mg/sq m/day for 5 days, which was well tolerated by a majority of patients. The lowest absolute granulocyte count with the latter dose ranged between 100 and 500/cu mm and platelet counts ranged from 20,000 to 50,000/cu mm at the time of maximum myelosuppression. The duration of myelosuppression was generally short and in most patients courses could be repeated at 28-day intervals.

The median duration of complete remission induced by AMSA was 12 wk, with a range of 3–59 wk (Fig. 1). In 6 patients, the remission duration was 4 wk or less: 3 never received any AMSA maintenance, 2 because of organ dysfunction, and the third because he received a bone marrow transplant while in remission and subsequently died from complications related to that proce-
dure. The remissions lasted 6 mo or longer in 5 patients, 2 of whom stayed in remission for 12 and 14 mo. In addition to the 23 patients who achieved complete remission, 6 patients with myeloblastic leukemia experienced some degree of hematologic improvement, one of them qualifying for a partial remission. The patient achieving partial remission had a complete recovery of peripheral blood elements but continued to have abnormal percentage of blasts in the bone marrow and received treatment for a period of 12 mo. The duration of hematologic improvement was short, ranging from 6 wk to 6 mo.

Acute Lymphoblastic Leukemia

A total of 20 patients with lymphoblastic leukemia received AMSA. Their median age was 26 yr with a range of 16–68 yr. Three patients were excluded from analysis, 2 because of early death within the first 2 wk of treatment, and one because the patient received only 2 injections when his therapy was interrupted. Of the remaining patients, 6 received AMSA doses of less than 90 mg/sq m/day × 5 days, which was considered inadequate for remission induction. Among the remaining 11 patients who received adequate doses of AMSA, 4 had antecedent history of lymphoma subsequently transformed into leukemic phase. Only 7 patients had typical ALL for evaluation of response to AMSA therapy. Among these patients one achieved a complete remission at a dose level of 75 mg/sq m/day × 7 days. Two patients showed hematologic improvement and received AMSA therapy for 3 mo and 8 mo. The patient who achieved a complete remission had T-cell variant of ALL and required 2 courses of therapy before achieving a complete remission, which lasted for 6 wk.

Survival

Of the 107 patients on whom the follow-up is available, 66 patients survived induction therapy with AMSA and subsequently received additional treatment for progressive leukemia. Forty-one patients, including 5 early deaths, died during induction therapy with AMSA. The length of survival related to AMSA response is shown in Fig. 2. The median length of survival for patients who achieved complete remission was 27 wk, with a range of 12–66 wk. The median duration of survival of 70 patients who failed to respond to AMSA was 8 wk. The difference in survival of responders and failures was highly significant ($p = 0.002$). The median survival of 8 patients who experienced hematologic improvement was 48 wk, with a range of 6–104+ wk.

Toxicity Associated With AMSA Therapy

The spectrum of side effects observed during AMSA therapy is shown in Table 4. Among the 109 patients assessable for AMSA toxicity, 22 (20%) experienced none of the side effects listed in Table 4. The incidence of side effects other than myelosuppression was quite low.

Myelosuppressive toxicity. AMSA therapy re-
sulted in intense myelosuppression that was clearly dose related. In the AMSA dose range that was therapeutically active (450 mg/sq m to 630 mg/sq m), most patients had no circulating granulocytes and required platelet support for periods of 3–4 wk following therapy. In the small group of patients treated with doses in excess of 750 mg/sq m, the duration of myelosuppression was approximately 6 wk. Ten patients experienced hypoplasia of the bone marrow lasting longer than 6 wk, resulting in death of 5 patients. Five patients recovered after they experienced bone marrow hypoplasia lasting 50–70 days. Patients invariably required hospitalization by day 10–12 after initiation of therapy for myelosuppression-related fever and infections, and approximately half of the patients had serious infections with gram-negative bacteria or fungi.

Gastrointestinal toxicity. Nausea and vomiting of a mild degree were experienced by approximately one-third of the patients receiving AMSA. Stomatitis was the most frequent and significant toxicity associated with AMSA therapy, and its incidence was clearly dose related. It was not observed at dose levels below 90 mg/sq m/day × 5 days, its incidence was approximately 60% at the maximum tolerated dose of 120 mg/sq m/day × 5 days, and it was observed in 80% of the patients receiving higher dose levels. Mucosal toxicity in some patients manifested as pharyngitis, laryngitis, esophagitis, or enterocolitis. It was generally mild, but approximately 10% of the patients developed severe ulceration. A small proportion of patients developed diarrhea, especially with the higher doses.

Phlebitis. The actual incidence of phlebitis could not be estimated because many patients received AMSA through the indwelling central venous catheter. Patients who received AMSA through the peripheral veins frequently experienced pain along the course of the vein during infusion. In some patients there was reddening of the skin overlying the course of the vein, sometimes with considerable perivenous inflammation, but no extravasation necrosis occurred. The venous irritation was minimized by diluting the total AMSA dose in a minimum of 500 ml of i.v. fluid.

Hyperbilirubinemia. An elevation of serum bilirubin level following administration of AMSA was observed in 30% of the patients. The median peak bilirubin elevation was 4 mg/dl, with a range of 1.5–21 mg/dl. The median time to peak elevation of bilirubin was 12 days, with a range of 2–41 days. There was no significant elevation of the liver enzymes accompanying the elevation of serum bilirubin, indicating hepatocellular damage was not the cause of hyperbilirubinemia. In a few instances where examination of liver was possible at autopsy, no significant pathologic changes except a mild degree of fatty change was observed. Hyperbilirubinemia was generally reversible, and the bilirubin level returned to normal as the patient recovered from myelosuppression and infectious complications accompanying it. Since hyperbilirubinemia is observed in a similar frequency during induction with other treatment regimens, we doubt the role of AMSA in its etiology.

Alopecia. Because of treatment of the patients with anthracyclines in the past, the incidence of alopecia cannot be estimated accurately; however, it was definitely observed in four patients, who lost 50%–75% of their scalp hair during AMSA therapy. However, there were other patients who experienced no hair loss while receiving AMSA.

Arrhythmias and seizures possibly related to AMSA. We have previously reported neurologic and cardiac rhythm disturbances in patients receiving AMSA therapy. A total of seven instances of such disturbances were recorded in the total patient population. Three patients experienced grand mal seizures while receiving AMSA, and all three recovered completely. One patient had an underlying neurologic disorder, but the two others had no known neurologic abnormality that could have resulted in the seizure disorder. Three patients were documented to have ventricular fibrillation during the infusion of AMSA or soon after completing the infusion. All three were severely hypokalemic and had additional metabolic disturbances that could have predisposed them to this cardiac arrhythmia. One of these patients died on the same day, the second patient died within a week because of complications related to cardiac arrest; one patient was successfully resuscitated. Another patient had transient respiratory arrest soon after completing AMSA infusion, but was also receiving intravenous promethazine when this episode occurred. Three patients experienced supraventricular arrhythmias, which occurred during the course of their therapy but not while receiving AMSA. Whether any of these neurologic or cardiac abnormalities were actually caused by AMSA is uncertain. No such disturbances
were recorded in patients who were in good metabolic balance and free of predisposing factors for cardiac or neurologic complications.

**DISCUSSION**

The results of this trial reveal that AMSA is an active antileukemic agent, with an overall response rate of 28% in patients with acute myeloblastic leukemia. The response rate in lymphoblastic leukemia is somewhat lower; however, the number of patients in our trial is too small to derive firm conclusions. The response rate to AMSA was approximately 30% among the different dose schedules that used a total AMSA dose of 450–630 mg/sq m over a period of 5–7 days. Based on the evaluation of a number of different dose schedules of AMSA, we believe that the optimum dose is 120 mg/sq m/day for 5 days. We observed 9 complete remissions in 29 patients (31%) treated with this dosage regimen. Since the toxicity of AMSA is clearly dose related and becomes prohibitive at dose levels of 750 mg/sq m and higher, there is really no advantage to using dose levels higher than 120 mg/sq m × 5 days.

Antileukemic activity of AMSA has also been reported by a number of other investigators. In a phase II trial in a total of 46 patients with refractory acute leukemia, they reported complete remission in 6 of 42 evaluable patients, all remissions occurring among patients treated with 200 mg/sq m/day × 5 days. Of 6 patients achieving complete remission, 3 had lymphoblastic leukemia and 3 had myeloblastic leukemia. None of the patients entered at doses of 75–150 mg/sq m/day × 5 responded. The most significant toxicity was stomatitis, which occurred in 85% of the patients and was of intolerable severity in 25% of the patients. Using a similar dose schedule, Lawrence and associates reported complete remissions with AMSA at doses of 840–1000 mg/sq m divided over 5 days and emphasized the severe stomatitis observed with these doses. More recently, Van Echo and associates conducted a phase II trial of AMSA and reported a response rate of approximately 20% using AMSA in a total dose of 600 mg/sq m given over 10 days. They also indicated that doses greater than 600 mg/sq m resulted in prolonged aplasia and severe mucositis. Based on results of these trials it is clear that AMSA has reproducible antileukemic activity in patients with previously treated and refractory acute leukemia, especially the myeloblastic variety.

Antileukemic agents utilized for initial remission induction include cytarabine, thioguanine, and anthracycline antibiotics such as daunomycin and adriamycin. The achievement of remissions with AMSA in patients refractory to these agents indicates that there is no clinical cross-resistance between these agents and AMSA. Moreover, AMSA was capable of inducing complete remission in patients who never achieved any remission with the standard agents, further supporting its potent antileukemic activity. Based on the reproducible activity of AMSA in previously treated patients, it should be the treatment of choice for second-line treatment of relapsed acute leukemia. Although 5-azacytidine is currently used for this indication, poor remission induction ability of that drug coupled with its severe toxicity makes AMSA a better treatment choice.

Although the treatment regimens currently used for remission induction in acute leukemia induce remissions in 60%–75% of the patients, 80% experience relapse with 2 or 3 yr. The development of new antileukemic agents for treatment of relapsed patients as well as for consolidation of remission achieved with the standard regimens is of paramount importance. The discovery of AMSA as a new antileukemic agent has the potential of making a significant impact on both of these situations. Based on its substantial activity as well as lack of significant toxicity, AMSA has now been incorporated into induction regimens for previously untreated patients. The main thrust of two currently ongoing studies using AMSA combinations in induction regimens is to determine whether AMSA can substitute effectively for the anthracyclines (adriamycin or daunomycin) because of the cardiac toxicity associated with these drugs. In our institution we are using AMSA in combination with cytarabine, vincristine, and prednisone (AMSA-OAP) for induction therapy and for consolidation therapy for poor prognosis patients who achieve complete remission with our standard induction regimen of adriamycin, cytarabine, vincristine, and prednisone. Preliminary results of these trials indicate that the remission rates with AMSA and cytarabine-containing regimens are comparable to those seen with anthracycline and cytarabine combinations. Since AMSA is free from any serious toxicity associated with its short-term usage, it has the potential of becoming an important component of standard remission induction regimens for adults with acute leukemia.

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