CONCISE REPORT

Treatment of Refractory Adult Lymphoblastic Leukemia (ALL) With 4′(9-Acridinylamino) Methanesulfon-M-Anisidine (AMSA)

By Zalmen A. Arlin, Michael P. Fanucchi, Timothy S. Gee, Sanford J. Kempin, Roland Martelmann, Charles W. Young, and Bayard D. Clarkson

Twenty-four adults with ALL were treated with AMSA alone or in combination. Twenty-two were treated at time of relapse and two patients after failing primary induction therapy. All had been treated with anthracyclines prior to receiving AMSA. Of the 22 patients with ALL in relapse, 4 achieved a complete remission. Two of these patients have relapsed while receiving maintenance chemotherapy; one died 1 mo after achieving remission due to the occurrence of cholecystitis in the setting of pancytopenia and one patient underwent bone marrow transplantation and is in remission at 8 mo after the second remission. Both patients who failed primary induction therapy remain in remission at 11 and 36 mo, respectively. The use of AMSA should be considered for patients with ALL who fail primary induction as well as those whose leukemia becomes resistant to conventional agents.

ACUTE LYMPHOBLASTIC LEUKEMIA is an example of a curable neoplasm. Children with this disease can expect a cure rate approaching 50%, and recent studies indicate that a similar outcome is also possible in adults. Although these results are more favorable than what has been achieved in the majority of malignancies, approximately half of these patients still relapse. Thus, either new approaches or new drugs are required in order to improve the survival of those patients whose disease cannot be cured by conventional means. AMSA is an acridine derivative that has undergone extensive trials in patients with acute leukemia. Most of the studies have been accomplished in adults with acute nonlymphoblastic leukemia, and these indicate that approximately 15%–30% of patients with acute nonlymphoblastic leukemia in relapse will achieve a remission. The main toxicity of the drug includes a high incidence of phlebitis when it is administered through a peripheral vein and commonly patients complain of nausea, vomiting, stomatitis, and approximately 25%–33% of patients experience hepatic dysfunction. In rare instances, fatal cardiac arrhythmias have been seen in patients with severe electrolyte abnormalities who received the drug. To date, these have not been encountered in patients whose serum electrolytes have been normal.

The drug can safely be administered in combination with cytosine arabinoside and thioguanine, and a remission rate in ANLL approaching 35% of patients can be anticipated. The pattern of toxicity seen in combining the drug is very similar to when it is given as a single agent. The purpose of this article is to outline our experience in acute lymphoblastic leukemia using AMSA both as a single agent and in combination.

MATERIALS AND METHODS

Twenty-four adults were treated. The median age of the patients was 30 yr, with a range of 16–58 yr. There were 14 males and 10 females. According to the FAB classification, 22 patients had L1 morphology and 2 had L2. All but 2 patients had previously achieved a remission and had subsequently relapsed while receiving maintenance chemotherapy. The median duration of prior therapy in the “relapse” group was 12 mo, with a range of 5–87 mo. The two patients who had failed induction therapy only had received therapy for 1–2 mo before receiving AMSA. All patients had previously received an anthracycline prior to beginning this trial.

AMSA was administered as a 30–60-min infusion after dilution in 250 ml 5% dextrose in water. Most infusions were administered through a subclavian central i.v. line. The 11 patients receiving AMSA as a single agent received a dose of 150–200 mg/sq m/day for 5 days. Thirteen patients received AMSA at 120 mg/sq m/day for 5 days to a maximum dose of 185 mg/sq m/day for 4 days, in combination with cytosine arabinoside 25 mg/sq m i.v. followed by 200 mg/sq m by continuous infusion daily for 5 days and 6-thioguanine 100 mg/sq m every 12 hr for a total of 10 doses (AAT). Once the patients achieved remission, they were maintained with other agents.

RESULTS

The response to treatment is shown in Table 1. Of the 11 patients who received AMSA alone, 3 achieved a complete remission, 1 was an early death, and 7 failed as demonstrated by persistent blasts in the bone marrow. Of the 13 patients who received AMSA in combination, 3 achieved a complete remission, 2 were early deaths, and 8 were failures.

Four of the six responders had relapsed previously.
while receiving conventional maintenance chemotherapy. Two of these patients have relapsed again after 1 and 5 mo of maintenance chemotherapy, respectively; 1 died 1 mo after achieving remission due to the occurrence of cholecystitis in the setting of pancytopenia; and 1 patient underwent bone marrow transplantation immediately after successful induction with AAT and is currently still in remission at 8 mo after achieving her second remission. Both patients who failed primary induction therapy with combinations of vincristine, prednisone, and adriamycin and who have subsequently achieved remission with AMSA alone or in combination followed by sequential maintenance chemotherapy are still in remission. The first patient has been in continuous remission for 36 mo and is currently off all therapy. The second patient has been in continuous complete remission now for 11 mo and remains on maintenance chemotherapy.

Toxicity

The toxicity encountered was as described previously.11 In the responders, the duration of pancytopenia lasted a median of 30 days, and as seen in Table 2, nausea, vomiting, stomatitis, and hepatic dysfunction were common. No patient experienced either cardiac arrhythmia or congestive heart failure.

DISCUSSION

The introduction of a new active agent for the treatment of a disease, like ALL, which already has effective therapy, requires that the drug must be either less toxic than what has been used or that it offers an improved chance of survival for patients whom conventional therapy fails to cure. Since the remission induction rate for ALL is now 85%-97%1,3 and since manageable toxicity is encountered, it is unlikely that any new agent will supplant the drugs currently used for induction therapy. However, since a large percentage of both adults and children still relapse after continuation of conventional treatment, the development of newer active agents remains important. Depending on the protocol, it has been possible to identify prognostic factors that indicate a likelihood of ultimate relapse, and it is for these patients that new agents may offer the greatest benefit. Precedence for adding new drugs for patients with “poor prognosis” ALL has already been established. With the addition of the VM-26 and cytosine arabinoside, an improved remission duration has been achieved for children with ALL.13 AMSA, at the recommended dose of 600–700 mg per course has important activity against ANLL as well as ALL in relapse.14–16 Our two patients who failed primary induction therapy and had subsequent long-term remissions suggest that AMSA may have an important role in the management of patients with relatively resistant disease. Since the toxicity encountered was manageable, the administration of AMSA to high-risk patients may be a reasonable alternative to further intensification of conventional therapy.17 At the present time, patients who have a high expectation of cure with conventional agents should not receive AMSA, however, patients at high risk of relapse should have AMSA incorporated into their treatment program. It is possible that this approach will increase the curability of patients with “poor prognosis” ALL.

REFERENCES

5. Legha SS, Keating MJ, Zander AR, McCredie KB, Bodey

Table 1. Results of AMSA Trials in ALL

<table>
<thead>
<tr>
<th>I. AMSA alone</th>
<th>II. AMSA and AraC and TG</th>
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<tr>
<td>Patients entered</td>
<td>11</td>
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<tr>
<td>Complete remissions</td>
<td>3</td>
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<tr>
<td>Early deaths</td>
<td>1</td>
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<tr>
<td>Failures</td>
<td>7</td>
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Table 2. Toxicity

<table>
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<th>Complete remissions</th>
<th>Early deaths</th>
<th>Failures</th>
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<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>19/24 79%</td>
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<td>Stomatitis</td>
<td>18/24 75%</td>
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<td>Hepatic dysfunction</td>
<td>4/24 17%</td>
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<tr>
<td>Cardiac arrhythmia</td>
<td>None</td>
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<tr>
<td>Clinical congestive heart failure</td>
<td>None</td>
<td></td>
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<tr>
<td>Duration of pancytopenia in six</td>
<td>Median 30 days,</td>
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<td></td>
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<tr>
<td>patients who achieved CR</td>
<td>range 21–40</td>
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