CONCISE REPORT

Initial Experience With AMSA as Single Agent Treatment Against Malignant Lymphoproliferative Disorders

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Thirty previously treated adults with lymphoma received AMSA as single agent therapy. All patients had previously received adriamycin-containing chemotherapy regimens and either failed to respond initially or responded but subsequently relapsed. The dose used was 40 mg/sq m i.v. daily \(\times 3\). For patients with compromised marrow reserve or elevated bilirubin, a 25% reduction was used. Ten of 30 patients achieved an objective response (3 CR, 3 PR, and 4 \(<\)PR). Of the 3 patients achieving a complete remission, 2 with histiocytic lymphoma remain in remission and are currently off treatment at 14+ and 18+ mo. The response rate to AMSA was found to correlate with the type of response to frontline therapy and also with the number of previous relapses. Complete remissions on AMSA were only seen in patients who had achieved a CR on frontline treatment and who were treated on their first relapse. AMSA is an active drug against malignant lymphoma and deserves further investigation.

DESPITE the recent advances in combination chemotherapy for the treatment of advanced malignant lymphomas, a significant fraction of patients (ranging from 30% to 50%) still fail to achieve a complete remission (CR). Furthermore, a proportion of those patients achieving complete remission will relapse and eventually succumb to progressive disease. Consequently, it is important to investigate new drugs to determine their activity in patients with either resistant or recurrent lymphoma.

During the phase I study of AMSA (4'-9-acridinylamino-methanesulfon-M-anisidine) in our institution, hints of activity were found against several tumors, including leukemia. This prompted us to initiate a phase II study of this drug in malignant lymphomas. This report constitutes a preliminary analysis of our experience with the first 30 patients treated at our institution.

MATERIALS AND METHODS

Patients over 15 yr old with malignant lymphoma who had received prior chemotherapy with at least one (frequently two or more) combination chemotherapy regimens and who were no longer responding were eligible for this study. All patients had received adriamycin as part of their previous therapy. A consent form was obtained prior to initiating therapy, according to institutional guidelines.

The dose and schedule selected for this study was based on our initial experience with AMSA in solid tumors during the phase I study. Patients with adequate marrow reserve and adequate tolerance to previous chemotherapy were treated with 40 mg/sq m AMSA daily \(\times 3\). Courses were repeated every 21 days, depending on recovery from myelosuppressive toxicity of the previous course. Patients with compromised marrow reserve and those with elevated bilirubin levels were treated with 30 mg/sq m AMSA daily \(\times 3\). The dose was not modified for patients with involvement of the bone marrow by lymphoma.

Histopathologic review of outside material was obtained on every patient. The material was reviewed by a member of our Department of Pathology. The Rappaport classification was used to determine the histologic subtype of the malignant lymphoma.

Complete remission (CR) was defined as total disappearance of disease as judged by restaging procedures performed after therapy. Restaging included the repetition of tests that were abnormal before institution of treatment, such as physical examination, CT scan, chest x-ray, bone marrow biopsies, etc. Partial remission (PR) was defined as reduction of 50% or more of the sum of products of 2 diameters of all tumor masses. Response less than PR was defined as any objective evidence of reduction of tumor size less than 50%.

We elected to consider as failures any patients who died of progressive disease before completing one course of treatment. Traditionally, these patients have been classified as inevaluable. However, if the patient expired of other causes unrelated to progressive disease before completing one course of treatment, they were judged as inevaluable. Three patients were in this category of inevaluable and have thus been excluded from this analysis.

RESULTS

Response

Thirty evaluable patients, ranging in age from 17 to 72 yr (median 52), have been treated. Table 1 illustrates the responses seen according to histologic subtype. Ten of 30 patients achieved an objective response. The duration of these responses in months are as follows: CR 8,14+,18+; PR 1,3,5; \(<\)PR 2,2+,8,8+.

Since the majority of responses were seen in the histiocytic and poorly differentiated lymphocytic lymphomas, an attempt was made to correlate the response to AMSA in these two subtypes with the kind of response to the frontline combination chemotherapy regimen. Table 2 illustrates this correlation. Complete remissions on AMSA were seen only in patients who achieved a CR on frontline chemotherapy regimens.
The overall response rate was also higher in patients who achieved a CR on frontline chemotherapy.

Table 2 shows the relation between the number of prior relapses experienced and the subsequent response to AMSA. Complete responses were only seen in patients who were treated upon their first relapse. The overall response rate was found to be inversely related to the number of previous relapses experienced.

Toxicity

The myelosuppressive toxicity of this regimen is shown in Table 3. Myelosuppression was the most frequent side effect observed. Both leukopenia and thrombocytopenia were seen frequently, but in most instances it was considered acceptable. The duration of myelosuppression was usually brief, thus resulting in documented infections in only two instances. In addition, there were three instances of neutropenia and fever of unknown origin that resolved with intravenous antibiotics.

The frequency of alopecia was difficult to assess since most patients had recently received other chemotherapy drugs. Gastrointestinal toxicity was infrequent, and most patients tolerated the drug with minimal nausea and vomiting. No instances of cardiac toxicity or neurotoxicity were observed.

**DISCUSSION**

AMSA is a new cytotoxic drug that belongs to the acridine group of compounds, which have been shown to bind preferentially to DNA. It inhibits DNA synthesis by intercalation with the DNA molecule.

Based on its activity against various experimental animal tumors, AMSA was selected for clinical studies.

The overall response rate of 30% (10/30) obtained with AMSA in this study when all histologic subtypes are included is quite encouraging in view of the fact that a sizable proportion of patients in this study had developed progressive disease after two or more prior combination chemotherapy regimens. If only those patients with histiocytic lymphoma and poorly differentiated lymphocytic lymphoma who received the drug upon their first relapse are included, the overall response rate is 4/7 (57%) and the complete response rate is 3/7 (43%). These results suggest that the use of AMSA earlier in the course of recurrent disease might be desirable, since ultimately it is the achievement of a second CR that might result in long-term salvage.

In general, second line trials against malignant lymphomas of aggressive histologic type have frequently met with limited success. The remissions obtained have been usually of short duration and thus have not resulted in long-term benefits for the patients. It is for this reason that the duration of response obtained in this study with AMSA is particularly encouraging. Of the 3 patients who achieved CR, 2 are still responding to treatment at 14+ and 18+ mo. Treatment has already been discontinued in both of these patients. The remaining patient who achieved CR relapsed after 8 mo. Both patients who remain in continuous CR were originally diagnosed as histiocytic lymphoma, and this diagnosis was again confirmed histologically at the time of relapse.

The toxicity of AMSA is mostly limited to myelosuppression. In general, the drug was well tolerated and its toxicity was quite predictable and usually of brief duration. Our experience with AMSA, as well as that of Ahmann, identifies this drug as active against lymphomas, and if further testing confirms this, its incorporation into frontline or second line combination chemotherapy regimens might be desirable. In order to more accurately assess the degree of activity of single agent AMSA against the various individual histologic subtypes of lymphoma, further experience in a larger number of patients will be required.
REFERENCES


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