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to produce ataxia in mice (5). Unfortunately, autopsy was not permitted, which would have allowed brain examination, but there was no evidence of metastasis on computerized tomography scan 1 month prior to death. Perhaps these findings were also related to previous prolonged high serum levels of bleomycin.

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AMSA Therapy for Children With Lymphoblastic Malignancy

AMSA is an acriflavine derivative that inhibits DNA synthesis. Preliminary studies have suggested that AMSA is an active drug in patients with acute myelogenous leukemia (1-3) and acute lymphoblastic leukemia (ALL) (1-4). This report describes the response and toxic reactions observed in children with refractory ALL or lymphoblastic lymphoma who were treated with AMSA.

METHODS

Nine children 5-15 years of age with ALL or lymphoblastic lymphoma refractory to all standard chemotherapy, including doxorubicin, were entered in this study. Seven children had E-rosette-negative (E-) ALL; two had E-rosette-positive (E+) T-cell disorders (ALL and lymphoblastic lymphoma). AMSA was diluted in 5% dextrose in water and administered by iv infusion over 1-4 hours (median infusion time of 2 hours in five patients) daily for 5 days. In eight of the nine patients the total dose administered over the 5-day course was 450-675 mg/m² (median dose of 500 mg/m² administered to four patients). One patient with severe pre-existing liver disease received a cumulative dose of 175 mg/m² over 3 days. Prior to therapy, all patients with ALL had a bone marrow examination demonstrating leukemic relapse; the child with lymphoblastic lymphoma had a malignant pleural effusion and a large subcutaneous tumor. Studies to determine the toxicity of AMSA included serial determinations of blood cell counts along with measurement of serum bilirubin, SGOT, and creatinine.

RESULTS

Two of the nine children (22%) demonstrated a complete clinical resolution of disease after AMSA treatment. A 15-year-old boy with E- ALL, who had persistent blast cells in the peripheral blood and bone marrow despite the administration of doxorubicin 2 weeks previously, attained a complete remission after AMSA therapy. The duration of un­maintained complete remission was 4 months. This patient had severe chronic hepatitis and responded to a relatively low dose of AMSA (175 mg/m² over 3 days). However, increased toxic reactions, particularly nausea and vomiting, plus a transient increase in serum bilirubin from 1.2 to 3.3 mg/dl, were also noted. An 8-year-old boy with T-cell lymphoblastic lymphoma, who had developed progressive increase in a large subcutaneous tumor and malignant pleural effusion while on a combination chemotherapy regimen that included doxorubicin, demonstrated complete resolution of the disease and the malignant pleural effusion. The effusion, however, began to reaccumulate 2 weeks later but temporarily resolved after additional treatment with AMSA. Five other children, although they did not achieve a complete response, showed some evidence of antitumor activity demonstrated by improvement in bone pain, disappearance of blast cells from the peripheral blood, and/or development of marrow hypoplasia. In all, seven of nine children (78%) had some evidence of antitumor activity from AMSA.

Toxic effects of AMSA in this dose schedule included moderate to severe stomatitis (three of nine patients), pain at the infusion site (five of nine), transient headaches (one of nine), nausea and vomiting (two of nine), and mild abnormalities in liver function when it had been normal prior to treatment (two of eight). Two children had increased hair loss after AMSA.
The myelosuppressive effects of this dose schedule of AMSA were difficult to quantitate in our patients who had granulocytopenia and thrombocytopenia secondary to leukemic relapse. All children, however, demonstrated a further decrease in wbc and platelet counts after AMSA therapy. In the child with lymphoblastic lymphoma who had normal pretreatment marrow reserve, a total wbc count nadir of 300/mm³ and a platelet count nadir of 1000/mm³ occurred 15 days after the start of AMSA therapy. The granulocyte and platelet counts, however, returned to normal by Day 24 of AMSA therapy.

DISCUSSION

Two of the nine children with advanced lymphoblastic malignancy achieved a complete remission after AMSA therapy. One of the complete responders had an E; lymphoblastic lymphoma. All of the children treated with AMSA were refractory to anthracycline therapy. This indicates that these classes of compounds are not completely cross-resistant in children with lymphoid malignancy.

The therapeutic effectiveness of AMSA in patients with acute leukemia may be very dose-dependent. Arlin et al (3) noted an improved response rate of leukemic patients receiving AMSA in doses of 1000 mg/m² compared to those receiving 500 mg/m², both given over 5 days. The administration of AMSA at this dose range, however, produces marked myelosuppression (4,5), and stomatitis becomes a major problem when AMSA is infused at doses of 125–150 mg/m²/day over 5 days (4). All of our patients treated with AMSA who exhibited a response to treatment developed marked bone marrow hypoplasia, including the child with pre-existing liver disease who achieved a complete remission at a relatively low dose (175 mg/m² over 3 days). Since AMSA is metabolized in the liver, the response of this patient to a lower dose of AMSA may reflect altered pharmacologic clearance of the drug.

We conclude that the administration of AMSA in doses > 450 mg/m² over 5 days is associated with definite antitumor activity in children with lymphoblastic malignancy. The marked degree of marrow hypoplasia induced by this dose schedule of AMSA, however, may limit the ultimate ability to combine AMSA with other effective but very myelosuppressive agents.

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Allergic Reaction Following Administration of AMSA

We read with interest the report of Welt and his colleagues (1) describing the occurrence of an acute skin reaction following administration of AMSA. Due to the apparent rarity of this reaction, we report a similar case in an adult male treated for recurrent acute myelogenous leukemia (AML).

CASE REPORT

A 30-year-old Samoan male presented in January 1978 with recurrent fever, myalgias, gum bleeding, and a wbc count of 60,000/mm³. A diagnosis of AML was confirmed by bone marrow biopsy. Following a course of doxorubicin and cytarabine, the patient entered into a complete remission documented by bone marrow aspiration.

The patient remained well until February 1981 when recurrent AML was diagnosed, based on peripheral blood smear and bone marrow findings. A complete remission was obtained after retreatment with cytarabine and doxorubicin combination chemotherapy.

In September 1981 the patient re-presented with recurrent AML. At that time, treatment was initiated with 240 mg of AMSA in 500 ml of 5% dextrose in water at a rate of 1 mg/minute. Following the start of his infusion, the patient noted burning at the site of his iv line and was observed to have