Amsacrine With High-Dose Cytarabine Is Highly Effective Therapy for Refractory and Relapsed Acute Lymphoblastic Leukemia in Adults


Thirty-six patients with relapsed acute lymphoblastic leukemia (ALL) and four with primary refractory ALL were treated with a regimen that included amsacrine, 200 mg/m², intravenously daily for three days with cytarabine, 3 gm/m², by infusion over three hours daily for five days. There were 27 remissions in the 36 relapsed patients and two in the four patients with primary refractory disease. Seventeen of the 23 patients with common ALL, four of the six with T-cell ALL, one of the three with B-cell ALL, and seven of eight whose cells were not characterized responded. Toxicity of this regimen was comparable to other reinduction regimens for ALL, but the side effects characteristic of high-dose cytarabine therapy were absent. Since these results compare favorably with conventional induction regimens, its use in the primary treatment of adults and children with high-risk ALL is proposed.

RESULTS

The clinical characteristics of the patients treated are noted in Table 1. The majority of the patients were in relapse, but a smaller group with primary refractory leukemia were also included. Of 36 relapsed patients, there were 23 in first relapse, 12 in second relapse, and one patient in fourth relapse. Fourteen received amsacrine/HiDAC as primary reinduction therapy and 22 patients after failing or relapsing from other therapy.

Results of treatment are shown in Table 2. Of the four evaluable patients with primary refractory disease, there were two responders. These occurred in one patient whose disease was refractory to vincristine and prednisone and in whom bone marrow metaphases showed the presence of trisomy 8 and in a second patient who had failed primary induction chemotherapy with vincristine, prednisone, and doxorubicin. There were 27 remissions in the 36 patients with relapsed ALL who were treated. Three patients died without evidence of leukemia on days 12, 34, and 44 from sepsis. These included a 63-year-old male with mental retardation who died with some recovery of normal bone marrow and no leukemia, a 61-year-old female, and a 66-year-old male whose marrow also showed no leukemia. Six died with persistent leukemia. This included a patient with T-cell ALL who had a tetraploid clone (M. Andreaeff, personal communication), four with CALLA+ ALL, and one patient with B-cell ALL. As seen in Table 2, the number and duration of prior remissions did not affect the remission rate, but the numbers treated were small. Of the 14 patients receiving the

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regimen as primary reinduction therapy, there were ten CRs; of the 22 receiving the regimen as secondary treatment for relapse, there were 17 remissions. Remission duration lasted from less than 1 to greater than 9 months, with a median of 4 months, and was especially short in the patients with B-cell ALL.

Table 3 shows the results of treatment according to the cell phenotype. Remissions were seen in the common ALL, T-cell ALL, as well as the B-cell ALLs. Patients whose cells could not be readily characterized and patients with null cell ALL also responded.

The side effects are shown in Table 4. Side effects characteristic of HiDAc including conjunctivitis, cutaneous, and CNS toxicity were absent. Hepatic dysfunction was common, as was diarrhea, but in most instances, hepatic dysfunction was reversible. The median time to CR was 28 days.

**DISCUSSION**

Recent reports have indicated that there has been a general improvement in the outlook for adults with ALL. Remission rates of 70% to 80% are now the norm, and of these about 40% are likely to attain long-term survival. These results are still inferior to those obtained in children, and in part this may be because of biologic differences between the disease in children and adults (eg, the relative incidence of the Philadelphia chromosome). However, even if these patients are excluded from analysis, substantial numbers will still relapse from their disease. For this reason, it is important to develop new drugs and new drug combinations that when incorporated into primary therapy may increase the overall cure rate. The experience reported here suggests that amsacrine and HiDAc may be such a combination. The treatment is especially effective in relapsed ALL and in occasional patients with primary refractory ALL. Remission is usually achieved within a month, but unmaintained remissions last a median of only 4 months. Thus, patients who achieve remission should receive further treatment, which could include either allogeneic or autologous bone marrow transplantation. The intensive therapy described by Rivera et al is an alternative. However, the latter is most effective in children under the age of 10 with a first remission lasting more than 18 months. It may not be applicable to adults with ALL in relapse.

The treatment is well tolerated, and side effects are generally reversible. The side effects characteristic of HiDAc are absent. This is consistent with our larger experience in patients with acute myelogenous leukemia and blastic chronic myelogenous leukemia who receive this combination. The toxicity profile compares favorably with alternate therapies.

These results show that the efficacy of the combination is at least comparable to the results achieved if patients were to
receive for their relapse the same therapy that had induced remission initially. To determine whether this therapy is superior, a randomized trial between this combination and primary therapy may be necessary.

The importance of this combination of HiDAC and amsacrine may be more in its possible incorporation into total therapy programs for previously untreated ALL than for its use in relapsed or refractory disease. Until recently vincristine and prednisone with either daunorubicin or t-asparaginase have induced the highest CR rates in ALL. The results of the amsacrine-HiDAC combination suggest that this may be an equally effective induction regimen and raise the possibility of a change in our approach to primary therapy. After traditional induction programs and the achieving of a remission, patients have generally received consolidation or intensification therapy, and this approach has led to the best long-term results. To minimize the risk to these patients, most programs have reduced the total dose of drug administered during consolidation from the ideal developed in relapsed disease. With the traditional approach, patients will be neutropenic during induction due to the presence of leukemia and again during the consolidation therapy due to the myelosuppressive chemotherapy. Administering amsacrine/HiDAC as primary induction therapy followed by consolidation with vincristine, prednisone, and asparaginase at a minimum will reduce the total duration of cytopenia. Furthermore, it will test the importance of delivering maximum doses of the effective agents and could result in a higher cure rate. A trial in untreated adults and in children with high-risk ALL will be required to determine whether this approach represents an advance.

REFERENCES


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