CONCISE REPORT

Primary Therapy of Acute Promyelocytic Leukemia: Results of Amsacrine- and Daunorubicin-Based Therapy

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Remission rates for patients with acute promyelocytic leukemia (APL) have improved with the use of anthracyclines and proper management of disseminated intravascular coagulopathy. In a prospective randomized trial of chemotherapy in patients with acute nonlymphoblastic leukemia, there were 16 patients with APL. All 7 of the patients receiving the daunorubicin-containing regimen and 5 of 9 receiving the daunorubicin-containing regimen achieved a remission. All patients, except 2 of the 3 who underwent bone marrow transplantation, remain alive and in remission from 1+ to 25+ mo. Amsacrine is an effective replacement for daunorubicin in the treatment of APL, and its use does not compromise the favorable remission duration characteristic of APL.

The introduction of daunorubicin for the treatment of leukemia and the emergence of a greater understanding of the pathogenesis of disseminated intravascular coagulation (DIC) and its therapy have led to improved remission rates for patients with acute promyelocytic leukemia (APL). Until recently, it has been suggested that patients with APL are uniquely sensitive to the anthracyclines and that their use in APL was mandatory. We have previously seen patients with APL who had relapsed from primary therapy of their leukemia and subsequently responded to amsacrine in combination. Therefore, in spite of the prior favorable results with the anthracyclines, these patients have been included in a randomized trial comparing amsacrine in combination with daunorubicin in the primary therapy of acute leukemia. This report will review our results with the APL patients treated in this program.

MATERIALS AND METHODS

Patient Entry

Between April 1981 and December 1982, 109 adults with previously untreated acute nonlymphoblastic leukemia (ANLL) were seen at Memorial Hospital. Of these, there were 16 patients with APL. The age ranged from 20 to 71 yr (median 31). None of these leukemias occurred after treatment of another neoplasm. The criteria for the diagnosis of APL were as described previously. All patients either had DIC on presentation (12 patients) or developed the syndrome after initiation of chemotherapy (4 patients). Cytogenetic evaluation of bone marrow was performed in 15 patients. Ten patients had the classic translocation, t(15q;17q), 4 did not yield metaphases, and 1 patient had a normal karyotype.

Treatment of DIC

All patients received appropriate therapy for DIC, as described previously. This included initiation of heparin by continuous infusion at 7.5–15 U/kg/hr, replacement of coagulation factors as fresh-frozen plasma, and of platelets either once or twice daily. The dose of heparin was titrated according to the level of serum fibrinogen. With decreasing values, the dose was elevated, and with increasing values, the heparin was decreased. In virtually all cases, the heparin was stopped with completion of the 5 days of chemotherapy.

Chemotherapy

On presentation, all patients received cytarabine, 25 mg/sq m i.v. bolus, on day 1, followed by 160–200 mg/sq m by infusion daily for 5 days and 6-thioguanine, 100 mg/sq m, every 12 hr for 10 doses. They were also randomized to receive either amsacrine, 190–225 mg/sq m daily for 3 days (AAT), or daunorubicin, 50–60 mg/sq m daily for 3 days (DAT). The first 7 patients were treated at the higher doses of all drugs, whereas the last 9 patients were treated at the lower dose levels. Following successful induction of remission, the patients received 1 or 2 courses of "consolidation" with the same chemotherapy, except that amsacrine and daunorubicin were given for only 2 days and the cytarabine and thioguanine for only 4 days. Following the consolidation phase, patients were further randomized to maintenance or no maintenance chemotherapy. Younger patients with HLA-compatible siblings were offered bone marrow transplantation.

RESULTS

Of the 16 patients treated, 7 received amsacrine in combination and 9 received daunorubicin in combination. Of the 7 patients who received amsacrine, 7 achieved a complete remission (CR); 5 of the 7 remissions were accomplished with one course of therapy, while 2 additional patients required a second course of AAT. The median time to CR, as measured by a normal bone marrow and WBC >1.0 × 10^9/liter and platelet count >100 × 10^9/liter, was 24 days (range 17–54) and 24 days (range 18–58), respectively. The patients receiving chemotherapy after induction of remission remain in remission at 6, 9, 25, and 30 mo. Two of the 3 patients who underwent bone marrow transplantation died while still in remission at 4 and 5 mo posttransplant, respectively. The third patient is in remission at 8 mo.
Of the 9 patients receiving daunorubicin, one died of an intracerebral hemorrhage on day 6, and 3 patients achieved remission after one course of therapy. The time to CR in these patients, as measured by a normal bone marrow and WBC > 1.0 x 10^9/liter, was 25, 26, and 34 days, and as measured by platelet count > 100 x 10^9/liter, was 19, 26, and 27 days. Two additional patients had persistent leukemia after the first course and subsequently received treatment with the amsacrine arm. Both of these patients have achieved a complete remission. The time to CR in these patients was 39 and 49 days for WBC > 1.0 x 10^9/liter, and 36 and 53 days for a platelet count > 100 x 10^9/liter. All of the patients receiving chemotherapy after induction of remission remain in remission at 9, 10, 13, and 19 mo. The one patient who underwent bone marrow transplantation remains in CR at 31 mo. In this small series, maintenance chemotherapy did not appear to be important. The 6 patients receiving maintenance chemotherapy and the 2 patients who did not all remain in remission.

**DISCUSSION**

Since the landmark paper of Bernard, daunorubicin or its analogs have been an integral part of induction therapy for patients with acute promyelocytic leukemia. With regimens that include an anthracycline, remission rates from 60% to 80% have been reported. In all cases where the remission rates were satisfactory, appropriate treatment of DIC was a common feature. These patients generally had a better overall survival than that of the patients with the other subtypes of ANLL. Our own experience at this institution, comparing protocols either containing anthracyclines or not, shows a significant difference favoring patients with APL treated with anthracycline. In spite of this, the majority of patients with APL still die of their disease. We have successfully treated patients with APL with amsacrine after they had relapsed from primary therapy. Therefore, patients with APL were considered as appropriate candidates for a randomized trial comparing amsacrine in combination with daunorubicin in combination. The preliminary results in this small trial suggest that, as with other more common varieties of ANLL, there is no difference in CR rate for the patients with APL receiving the amsacrine-based regimen or those receiving the daunorubicin-based regimen, as long as careful attention is paid to the treatment of DIC. It also suggests that the favorable outcome for patients with APL is more a reflection of disease-responsive-ness than of the use of anthracyclines.

**REFERENCES**

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