A Randomized Clinical Trial of Daunorubicin and a Combination of Prednisone, Vincristine, 6-Mercaptopurine, and Methotrexate in Adult Acute Nonlymphocytic Leukemia

Peter H. Wiernik and Arthur A. Serpick

SUMMARY

Twenty-two adult patients with acute nonlymphocytic leukemia received daunorubicin, and 21 received a combination of prednisone, vincristine, 6-mercaptopurine, and methotrexate in a randomized study. The single agent was superior to the combination in inducing complete remission (50 versus 28%). In addition, patients who completely responded to daunorubicin did so in a median of 19 days, whereas the median time to complete response with the combination of prednisone, vincristine, 6-mercaptopurine, and methotrexate was 64 days. Deaths during therapy were fewer with daunorubicin than with the combination of prednisone, vincristine, 6-mercaptopurine, and methotrexate (36%, as compared to 52%). Daunorubicin is a highly effective drug in the treatment of adults with acute nonlymphocytic leukemia.

INTRODUCTION

In recent years, several new classes of chemotherapeutic agents have proven efficacious in ANLL. (The term "acute nonlymphocytic leukemia" is used here to include acute myelocytic leukemia and its variants acute myelomonocytic and acute monocytic leukemia.) Since survival in this disease correlates well with the achievement of complete remission (12), it is necessary to determine which of the currently available therapies has the potential for inducing a complete remission in the greatest number of cases. A retrospective analysis of our sequential experience with a combination of agents designated POMP and with daunorubicin suggested that both therapies were equally active and that, when optimum schedules were used, remission rates with each approached 50% (Ref. 9; P. H. Wiernik and A. A. Serpick, unpublished observations). The present prospective randomized study was undertaken to establish whether (a) one therapeutic regimen resulted in complete remission in a significantly greater percentage of cases, (b) the interval from the onset of therapy to complete remission was significantly shorter with one scheme, so that patients were at risk from their disease and its therapy for shorter periods of time, and (c) the duration of unmaintained remission was different for the 2 regimens.

MATERIALS AND METHODS

Forty-three consecutive previously untreated and unselected adults with ANLL were assigned to daunorubicin or POMP therapy by the random card method. Daunorubicin was given at a dose of 60 mg/sq m BSA rapidly i.v. daily for 3 consecutive days. The bone marrow was examined 5 days after the last dose of daunorubicin. If the marrow was hypocellular without blasts, no therapy was given, and the marrow was reexamined 3 days later. If the marrow was hypercellular with blasts, another 3-day daunorubicin course was given. If the marrow was hypocellular with blasts and there was no evidence of significant antileukemic effect in the peripheral blood, another 3-day daunorubicin course was also given. However, if the marrow was hypocellular with blasts and the peripheral blood showed definite improvement, such as a rising platelet count and/or absence of leukemic cells, therapy was withheld, and the marrow was examined in 3 days. If the patient did not achieve complete remission after 3 courses of daunorubicin, he was considered an induction failure and crossed over to the POMP induction regimen. A course of POMP therapy is depicted in Table 1. The combination of drugs was repeated at approximately 10-day intervals until complete remission was achieved or a maximum of 5 unsuccessful courses had been administered. The same judgments of the status of the marrow and peripheral blood described above dictated whether another course would be given and, if so, when. Induction failures were treated with the daunorubicin scheme. No consolidation or intensification therapy was given after either regimen, and remissions were unmaintained. Blood and platelet transfusions were used liberally, and vigorous empiric or specific antibiotic therapy was given as indicated. Gastrointestinal tract sterilization was not attempted, and special patient isolation techniques were not used. A complete remission was diagnosed according to our previously published criteria (12). After complete remission was diagnosed, patients...
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Table 1
One course of the combination chemotherapy schedule used in this study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>p.o.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>500 mg/sq m</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>5 mg/sq m</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vincristine</td>
<td>2 mg/sq m</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

were followed monthly with physical examinations, peripheral blood counts, and bone marrow aspirations until relapse occurred.

RESULTS

Some characteristics of the patient population under study are given in Table 2. There were more females than males in the study, and 3 times as many females as males were entered into the daunorubicin induction group. We have shown previously, however, that sex has no prognostic significance in ANLL (12). The median age of the POMP group is slightly greater than the daunorubicin group, but the difference is not significant. The median ages of both the daunorubicin and POMP groups are significantly greater than that of our original POMP series, however (9). Approximately 24% of patients in both treatment groups of the present study were over 60 years of age. In most cases, therapy was begun within 2 weeks of diagnosis. Data on the response to therapy are given in Table 3. Fifty % of the patients treated with daunorubicin alone achieved a complete remission, as did 28% of the patients treated with POMP. The responders in both groups had a median age comparable to that of the entire population under study. Only 3 of the 10 patients over 60 years of age obtained a complete remission, all 3 with daunorubicin. The diagnosis to therapy time interval was not shorter for the responders than for the nonresponders. Of considerable interest is the time necessary to induce complete remission. Patients remitting with daunorubicin did so in a median of 19 days and were free from the morbidity and potential mortality associated with leukemia and granulocytopenia considerably earlier than patients treated with the combination induction program. The median time to complete response to POMP was greater than 3 times the median time to complete response to daunorubicin.

The mortality during induction therapy was significant in both groups. In most cases, it was impossible to determine whether the disease or its therapy was the factor most responsible for death. Table 4 summarizes the pertinent data related to mortality. Thirty-six % of the patients treated with daunorubicin and 52% of the patients treated with POMP died during induction therapy. In both treatment groups the patients who died had a median age greater than the responding patients and greater than the median age for all patients in the study. Infection was a significant factor in the death of 16 of the 19 patients who died during induction therapy. In the daunorubicin group, 7 patients died of overwhelming infection, as did 9 patients in the POMP group. One patient in each group died without hemorrhage, infection, or other obvious complication, and 1 patient in the POMP group died of a myocardial infarction documented at postmortem examination during the 3rd POMP course. He had shown only a slight antileukemic response to therapy at the time of his death.

Some data on hematological toxicity are given in Table 5. Granulocytopenia in the daunorubicin group was more profound. Granulocytopenia in the daunorubicin group was equally severe in patients dying during induction and patients remitting. Patients receiving the combination induction program...
therapy who achieved complete remission had, as a group, less granulocytopenia than those dying.

All patients who received daunorubicin experienced total or near total capital alopecia, usually after the 2nd course of therapy. Twelve of the 22 daunorubicin-treated patients experienced nausea and 10 vomited several hours after drug administration. Stomatitis occurred in 9 patients. Temperature elevation averaging 2.5°F above pretreatment level occurred in 14 patients several hours after 1 or more daunorubicin injections. The fever resolved spontaneously, usually within 4 h of the initial rise, and was unexplained except for its temporal relationship to daunorubicin administration. No patients had evidence of daunorubicin cardiotoxicity. Paravenous administration of daunorubicin in 2 patients resulted in sclerosis of cutaneous and s.c. tissues that led to permanent woody induration of the affected area.

Four patients receiving POMP had moderately severe stomatitis and 1 had corticoid-induced psychosis necessitating reduction of the steroid dosage. Nausea related to drug administration occurred in 5 patients treated with POMP, but only 2 vomited.

Remission duration was comparable in both groups (Table 6). The median duration of remission was 9 weeks in the daunorubicin group and 8 weeks in the POMP group. The ranges for remission duration were wide, however. Two patients in the combination therapy group had complete remissions lasting 1 year, and 1 patient in the daunorubicin group remained in remission for 11.5 months. The median survival of the remitting patients in both therapy groups were comparable: 1 year for patients treated with daunorubicin and 11 months for combination therapy patients. The survival of these patients is comparable to those in whom remissions have been maintained, according to our previous experience. Survival, therefore, was probably not impaired by withholding maintenance therapy. On relapse, remission was reinduced with the same or opposite regimen with equal frequency (41%). Those patients who failed the primary induction therapy failed to achieve complete remission on cross-over to the other regimen. Three patients who were treated initially with daunorubicin survived 3 courses without achieving remission. One died 3.5 months later during therapy with POMP. The remaining 2 patients lived an additional 6 and 24 months, respectively, but did not achieve remission with POMP or a myriad of other antileukemic agents. Four patients who received POMP for initial therapy who did not achieve remission were crossed over to daunorubicin. Three died at 2, 3, and 4 months during their therapy, and 1 lived 12 months without ever achieving remission. The importance of achieving a maximal response on the first drug encounter is obvious.

Table 7 shows that the median survival for the responders is greater than that of the therapeutic failures. Therefore, the achievement of complete remission was a factor of significant prognostic import, a point which we have made previously in a larger group of patients (12).

**DISCUSSION**

Previous results with POMP therapy in adult patients with ANLL have been reported by Henderson and Serpick (9). That study resulted in a complete remission rate of 26%. The results in the present study compare favorably with those of the earlier study.

Boiron et al. (4) have reported results with daunorubicin comparable to those in the present study. The French investigators obtained a 54% complete remission rate in 64 patients with ANLL, 48 of whom were adults. Of the 36 adult patients who had not received prior therapy, 55% achieved complete remission in a mean treatment time of 31 days with a range of 15 to 62 days. Of the total group of 35 remitting patients, 26 relapsed after a mean remission duration of 155 days, 4 died in remission, and 5 were still in remission at the time of their report for 12 to 24 months. The patients in that study were treated with daunorubicin, 60 to 80 mg/sq m BSA daily, for a variable number of days, usually 3 to 5.

In a report by Baudo et al. (2), 1 of 3 adults with ANLL who had completed daunorubicin therapy (20 to 30 mg/sq m BSA daily for 5 days) achieved complete remission. That patient had been treated unsuccessfully prior to daunorubicin therapy with methyl-GAG.
Burgess, et al. (6) gave daunorubicin to 25 adults with acute leukemia and produced a complete remission in 36%. There were 10 adult AML patients who had no prior therapy, and 30% of these patients achieved complete remission. Most patients also received prednisone, and 9 were also treated with vincristine. Because therapy was not standardized, it is difficult to interpret their report.

Bernard et al. (3) remark on having reviewed data on 1299 patients with acute leukemia who were treated in this country and theirs with daunorubicin. They conclude that daunorubicin induces a higher complete remission rate in AML than any other drug. Complete data are not given, however. These authors noted that daunorubicin cardiac toxicity is dose related. Five of 13 patients who received a total cumulative dose of >30 mg/kg had some manifestation of cardiac toxicity, while only 2 of 1010 patients treated with <30 mg/kg had such findings. None of the patients in the present study received more than 25 mg/kg total dose of daunorubicin.

The European Organization for Research on the Treatment of Cancer (EORTC) studied 71 patients with ANLL who were treated with daunorubicin (10). Only 25% achieved a complete remission, and 40% obtained a complete or good partial remission. It is not clear from their report how many of the patients were adults.

In this country, only Bornstein et al. (5) have reported on daunorubicin therapy, 1 mg/kg daily for 5 days, in adults with ANLL. Only 8 patients in the study had received no prior therapy, and 2 (25%) of these obtained a complete remission. Two patients with chronic myelogenous leukemia in blast crisis were included in the study, and it is not possible to determine from the report whether or not they are included in the group of 8 previously untreated patients. Evaluation of the study is further complicated by the fact that all patients received daily prednisone in addition to daunorubicin.

In the present study, daunorubicin 60 mg/sq m BSA was administered daily for 3 days. The results are superior to most other clinical trials of daunorubicin. No direct comparison with other studies is entirely valid, however, since this drug schedule has not been reported by other investigators. Schedule of administration may be of paramount importance with this drug. The results in the present study are superior to those reported by Greene et al. (7) from this laboratory, with the use of daunorubicin in a different dosage and schedule (180 mg/sq m for 1 day). It is hoped that a predictive test based on the measurement of daunorubicin reductase in leukemic cells (1) might allow selection of patients who are likely to respond to daunorubicin and therefore improve upon the clinical results with this drug.

Although combinations of effective agents usually produce results superior to those for single agent therapy in acute leukemia (8), the results of this study suggest that the single agent daunorubicin is superior to an extensively studied combination of effective agents, POMP, in adult ANLL. The median age of the daunorubicin group was 5 years less than the POMP group, and the daunorubicin group included more female patients. We do not believe, on the basis of our prior (12) and subsequent experience (P. H. Wiernik and A. A. Serpick, unpublished observations), that these minor discrepancies between the 2 groups are significant. It is true, however, that the 2 induction regimens used in this study were not equally marrow suppressive. Granulocytopenia with the POMP regimen was not as severe as with daunorubicin, and this implies that higher doses of the components of the POMP regimen might be more marrow suppressive and, perhaps, result in greater therapeutic response. When a higher-dose POMP regimen was used elsewhere for adult patients with ANLL, only a 20% complete response rate was obtained in a small group of patients (11). Therefore, one may suspect that the low response rate to the POMP regimen is a manifestation of the intrinsic activity of the drugs in the combination themselves rather than a problem with dosage.

REFERENCES

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