Efficacy of Daunorubicin in the Therapy of Adult Acute Lymphocytic Leukemia: A Prospective Randomized Trial by Cancer and Leukemia Group B


The efficacy of the addition of intensive therapy with daunorubicin (45 mg/m² IV on days 1, 2, 3) to an otherwise identical induction program consisting of vincristine, prednisone, and L-asparaginase was assessed in 177 previously untreated adults (≥20 years of age) with acute lymphocytic leukemia (ALL). In the prospectively randomized phase of the investigation, 46 patients received daunorubicin in induction, whereas 53 did not. The two groups were otherwise comparable for pretreatment variables. A complete response was observed in 38/46 patients (83%) treated with daunorubicin, compared to 26/53 (47%) induced with vincristine, prednisone, and L-asparaginase alone (P = .003). The high response rate attributable to the use of the anthracycline was confirmed by the nonrandomized treatment of 78 subsequent patients, in whom a complete response rate of 76% was attained. A common program for central nervous system therapy and for maintenance therapy was employed in 103 patients achieving complete response. Maintenance consisted of cycles of 6-mercaptopurine (6-MP) and methotrexate with periodic reinforcement with vincristine and prednisone. Maintenance therapy proved to be minimally toxic. The average duration of complete response was 15 months and was not affected by the induction program employed. Approximately 25% of responders are projected to remain in continuing complete response for 36 months. The failure of the daunorubicin-containing programs to produce a higher percentage of long-term survivors, despite the higher complete response rates achieved, was thought to be due to the use of a maintenance program that was weak in intensity and dependent on reinforcement with vincristine and prednisone. These data clearly establish the increased effectiveness of vincristine, prednisone, L-asparaginase, and daunorubicin, as compared to this combination without daunorubicin, in the induction of complete response in adults with ALL. The results support the concept of an intensive, rather than a conservative, chemotherapeutic approach as the most appropriate strategy for the treatment of adult ALL.

Progress in the effective therapy of acute lymphocytic leukemia (ALL) in adults has been considerably slower than in the childhood disease. More than 90% of children regularly attain complete remission with induction programs consisting of vincristine, prednisone, and L-asparaginase.1,2 When similar programs are employed in adults, only half of patients respond completely.3-5 Moreover, whereas almost half of children with ALL achieve long-term unmaintained remission, a continuous pattern of relapse is commonly observed in the older population. Long-term survival is attained by only 15%-20% of adult patients in complete response.3,10 In both children and adults, survival is markedly affected by the attainment of complete response, and the potential for cure exists only after complete response.

In Cancer and Leukemia Group B (CALGB) Study 7113, induction therapy, consisting of 3 weekly injections of vincristine and prednisone followed by L-asparaginase, was studied in 149 patients with ALL who were 20 or more years of age.3 A complete remission rate of 58% was observed. Twenty of 33 patients (61%) who failed these initial attempts at induction achieved complete response when daunorubicin, at 45 mg/m² IV/wk, was administered for 3 weeks subsequent to the initial therapy. Thus, although the use of daunorubicin was reserved for patients who were refractory to vincristine, prednisone, and L-asparaginase, the complete response rate in this less favorable group was significantly augmented by the addition of anthracycline to the induction program.

The present study, conducted in previously...
untreated adult patients with ALL, was designed to test whether the addition of intensive therapy with daunorubicin early in induction (45 mg/m² IV on days 1, 2, 3) to standard induction therapy with vincristine, prednisone, and subsequent L-asparaginase would improve the complete remission rate, the duration of complete response, and the frequency of long-term survival.

The study began as a prospective, randomized clinical trial. Patients were randomized to receive induction therapy with vincristine, prednisone, and L-asparaginase, with or without the addition of daunorubicin. Randomization was terminated when the induction rate attained with daunorubicin proved to be significantly superior to that observed without daunorubicin. Subsequently, all patients were treated with the induction program containing the anthracycline. The effects of immunotherapy with the methanol extraction residue of (MER) bacille Calmette-Guérin (BCG) on the duration of complete response was also assessed. All patients received a single program for central nervous system (CNS) prophylaxis and a single chemotherapeutic maintenance program, consisting of courses of 6-mercaptopurine (6-MP) and methotrexate with periodic reinforcement with vincristine and prednisone.

MATERIALS AND METHODS*

Patients with ALL at least 20 years of age were entered on study beginning in August 1976 at participating CALGB institutions. Prospective randomization to induction therapy was performed by the sealed envelope technique. Treatment assignments were balanced within and across institutions by the Latin square design. The identities of the induction programs remained unknown to the investigators until all entries to the randomized portion of the study were completed.

Patients were continued on protocol until relapse and followed for survival thereafter. The development of central nervous system leukemia was considered as evidence of relapse, but patients were followed on study until marrow relapse. All patient entries were concluded in September 1980. These data are updated to June 1982.

Treatment

Induction Phase

In the initial phase of this study patients were prospectively randomized to one of two programs.

Group 1. Patients received vincristine, 2 mg IV, on days 1, 8, and 15 and prednisone, 40 mg/m²/day PO, days 1–22. The dose of prednisone was then reduced between days 22 and 29. L-Asparaginase, 500 IU/kg/day for 10 days IV, was begun on day 22. The median time of observation from patient entry was 47 months.

Group 2. Patients in this group were randomized to receive the same drugs as group 1 patients, plus daunorubicin, 45 mg/m² IV, on days 1, 2, and 3. These patients were observed for a median time of 50 months from entry on study.

Following the evaluation of 99 patients, it became apparent that addition of daunorubicin to the induction program resulted in a significantly superior complete response rate compared to induction with vincristine, prednisone, and L-asparaginase alone. Consequently, randomization to induction therapy was discontinued (October 1978), and all subsequent patients were treated with vincristine, prednisone, daunorubicin, and L-asparaginase.

Group 3. Patients in this group were subsequently entered on study nonrandomly. The median observation time from patient entry was 29 months.

Response to induction was assessed by bone marrow examination on day 33 according to CALGB criteria. Patients achieving an M1 marrow were continued on study.

One hundred ninety-three adults with ALL were registered. One hundred seventy-seven (92%) were evaluable for response to induction. The study cohort consisted of 53 evaluable patients (of 56) who were not treated with daunorubicin and 46 of 52 patients who were.

Following discontinuation of randomization to vincristine and prednisone therapy, 78 of 85 patients treated with vincristine, prednisone, and daunorubicin in a nonrandomized fashion were appropriate for analysis.

The three ineligible patients treated without daunorubicin were considered on review to have acute myeloid leukemia. Among the 137 patients assigned to receive daunorubicin, 3 were ineligible owing to incorrect diagnosis, 4 were major protocol violations, and 1 died prior to any therapy. Three patients were improperly randomized, and in two patients, inadequate records were provided.

Central Nervous System Therapy

Prior to induction therapy, all patients had a lumbar puncture, and the spinal fluid was assessed for the presence of CNS leukemia. Cellular morphology was usually examined in cytocentrifuged specimens. In those patients in whom central nervous system leukemia could be documented prior to day 36, weekly intrathecal instillation of methotrexate was employed until the central nervous system phase of therapy was reached.

Beginning on day 36, all patients achieving complete response were treated with external beam irradiation to the whole brain and the spinal cord above the second cervical vertebra. The total midline dose employed was 24 Gy, with a daily increment of 2 Gy midline. The duration of therapy did not exceed 16 days. Central nervous system radiotherapy was monitored by the quality assurance program for radiation therapy of CALGB. In addition, methotrexate (12–15 mg) was instilled intrathecally each week for 6 weeks starting on day 36.

Maintenance Chemotherapy

Maintenance therapy in patients achieving complete remission consisted of 6-MP, 200 mg/m²/day PO, administered for 5 days concurrently with methotrexate, 7.5 mg/m²/day PO. Nine days without therapy then elapsed before the next treatment course. Following three such courses, 2 weeks of consolidation therapy with vincristine, 2 mg IV on days 1 and 8, and prednisone, 40 mg/m² PO/day for 14 days, were given. Drug doses were modified for toxicity. Bone marrow examination was generally performed bimonthly during maintenance. Maintenance was continued until relapse or was terminated after a minimum of 36 months.

Immunotherapy

Thirty-five of the first 78 patients achieving complete response following induction therapy were randomized by induction program...
to immunotherapy with MER. Up to 200 μg of MER was inoculated intradermally into five sites each month, beginning on the first day of maintenance. Immunotherapy was planned for 2 years. Forty-three patients were concurrently randomized not to receive MER. By February 1980, it was concluded that immunotherapy with MER was toxic and produced no advantage with regard to duration of complete response and whether or not daunorubicin had been employed during induction. Accordingly, immunotherapy was discontinued.

Statistical Analysis
Remission duration and overall survival were calculated using the product-limit technique. Differences in patterns of recurrence and death were determined using Breslow's modification of the Kruskal-Wallis test. Differences among treatments in distribution of patient and disease features were examined using the chi-square test for contingency tables. Multivariate regression analyses, using Cox's linear logistic model, were performed to identify features prognostic of response.

RESULTS

Induction Phase
The clinical characteristics of the 177 evaluable patients are given in Table 1 for the three patient groups.

Table 1. Comparability of Induction Treatment Groups by Initial Patient and Disease Characteristics

<table>
<thead>
<tr>
<th>Feature</th>
<th>Group 1 (N = 52)</th>
<th>Group 2 (N = 46)</th>
<th>Group 3 (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent male</td>
<td>58</td>
<td>67</td>
<td>64</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (years)</td>
<td>40.9</td>
<td>36.5</td>
<td>38.6</td>
</tr>
<tr>
<td>Median</td>
<td>36.5</td>
<td>29.8</td>
<td>34.7</td>
</tr>
<tr>
<td>Mean percent blasts in marrow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of patients with ≥90%</td>
<td>84</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>Mean percent circulating blasts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of patients with ≥76%</td>
<td>48</td>
<td>57</td>
<td>50</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent with ≥4 cm</td>
<td>38</td>
<td>39</td>
<td>21</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent with ≥4 cm</td>
<td>31</td>
<td>33</td>
<td>21</td>
</tr>
<tr>
<td>Percent with any nodal involvement</td>
<td>56</td>
<td>56</td>
<td>39</td>
</tr>
<tr>
<td>Percent with mediastinal mass</td>
<td>19</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9.3</td>
<td>9.8</td>
<td>9.7</td>
</tr>
<tr>
<td>Percent &lt;7.0</td>
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<td>16</td>
</tr>
<tr>
<td>Percent ≥12.0</td>
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<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Platelet count (/μL)</td>
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<td></td>
</tr>
<tr>
<td>Mean</td>
<td>90,900</td>
<td>79,200</td>
<td>73,600</td>
</tr>
<tr>
<td>Median</td>
<td>54,600</td>
<td>56,900</td>
<td>48,500</td>
</tr>
<tr>
<td>Percent &lt;25,000</td>
<td>25</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Percent ≥150,000</td>
<td>13</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>WBC (/μL)</td>
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<td></td>
<td></td>
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<td>42,100</td>
</tr>
<tr>
<td>Median</td>
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<td>19,000</td>
<td>17,100</td>
</tr>
<tr>
<td>Percent &lt;5,000</td>
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<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Percent ≥30,000</td>
<td>77</td>
<td>63</td>
<td>67</td>
</tr>
<tr>
<td>Percent ≥100,000</td>
<td>13</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>No. with CNS disease during induction</td>
<td>3</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Pretreatment Characteristics
The distribution of pretreatment features among the three groups was similar, with no significant differences (Table 1). Eighteen of 177 evaluable patients (10%) were found to have CNS leukemia at presentation or during induction. Immunodiagnostic studies of the malignant lymphocytes obtained either from peripheral blood or bone marrow were available in 38% of group 1 patients, 22% of group 2 patients, and 60% of group 3 patients. This distribution results from the increased availability of these immunologic techniques at the participating institutions as the study proceeded. The surface characteristics of the lymphocytes indicated that the leukemia was neither distinctly B or T cell in 85%, 82%, and 79%, in groups 1, 2, and 3, respectively, and was of T cell in origin in 15%, 9%, and 15%, respectively, in patients in whom such studies were available.

Ten patients were reported to have a mediastinal mass in group 1 as compared to four and eight patients in groups 2 and 3 (group 1 v group 2, P = .25). The Philadelphia chromosome was present in 1/15 and 7/41 patients in whom cytogenetics were evaluable and who were treated, respectively, without and with anthracycline.

Induction Response Rate
Fifty-six, 52, and 85 patients were entered as group 1, 2, and 3, respectively. Twenty-five of 53 evaluable patients (47%) randomized to receive vincristine, prednisone, and L-asparaginase achieved a complete response compared to 38/46 evaluable patients (83%) randomized to receive vincristine, prednisone, L-asparaginase, and daunorubicin. This highly significant difference (P = .003) in the frequency of complete response among randomized entries was responsible for the termination of randomization to induction therapy. Subsequently, 59/78 evaluable patients (76%) treated with vincristine, prednisone, L-asparaginase, and daunorubicin achieved complete response. The overall complete response frequency was thus 78% (97/124) in patients receiving the anthracycline in induction. The response results obtained with daunorubicin did not differ from the randomized to nonrandomized phase of the study (group 2 v group 3) (P = .36). Improvement in the frequency of complete response with daunorubicin was seen in all age groups.

Where lymphocyte marker data are available, only 5/17 (29%) of group 1 patients, whose malignant lymphocytes were non-T, non-B, achieved complete response compared to 37/45 (82%) of such patients to whom daunorubicin was administered. All 11 patients whose disease was identified as T cell in origin
responded completely; 3 patients were treated without and 8 were treated with daunorubicin. Four of 11 patients with known T cell disease had CNS leukemia.

An M1 marrow was not achieved in the presence of central nervous system leukemia in any of the three patients in group 1. Four of five group 2 and six of ten group 3 patients presenting with CNS leukemia remitted completely.

Toxicity During Induction

There were 20 deaths during induction. The deaths were related primarily to sepsis in eight patients and to hemorrhage in three patients who received only vincristine and prednisone. Of the three group 2 patients who died during induction, one died of sepsis, one of hemorrhage, and one of an unrelated preexisting disease. Of the six deaths that occurred in the nonrandomized group of patients, four were due to sepsis, one due to uncontrollable central nervous system leukemia, and one consequent to a rapid tumor lysis syndrome.

Severe (<1,000/μL), or life-threatening (<500/μL) granulocytopenia was twice as common when anthracycline was used (87% vs 40%) (P = .001). Severe thrombocytopenia (<50,000/μL) and life-threatening thrombocytopenia (<20,000/μL) was more common in group 2 and 3 patients (76%) than in group 1 (36%) (P = .04). These effects, however, did not result in a significant increase in severe, life-threatening, or fatal hemorrhage (10% vs 12%) or infection (30% vs 40%) in groups 1 vs 2 plus 3. Nausea and vomiting were more frequent in the anthracycline-treated patient. About 20% of patients in both groups developed abnormalities of hepatic function during induction that were attributed to L-asparaginase. Anaphylaxis to L-asparaginase was not observed.

Prognostic Factors in Induction

Owing to the large differences in response observed in the patients randomized to study, highly significant differences emerged when weighted by the individual pretreatment features. Using a multivariate approach, the most significant prognostic variable for response was treatment program (P = .001) and then age (< or ≥40) (P = .017). None of the other pretreatment characteristics listed in Table 1, when tested in various combinations, added significantly to the multivariate response model. A linear decrease in response was observed in patients treated without daunorubicin as a function of increasing age (P = .01), which was not observed in either of the two anthracycline-treated groups. Differences in response favoring anthracycline treatment were noted in patients under 40 (86% vs 63%; P = .09) and over 40 (78% vs 35%; P = .02). The consistent advantage for treatment with daunorubicin resulted in a highly significant difference when calculated on an age-adjusted basis (83% vs 54%; P = .002).

Maintenance Therapy

Of the 122 patients achieving M1 marrow, 103 (84%) were evaluable for the maintenance phase of the study. Twenty-two of 25 complete responders were derived from group 1, 30 of 38 from group 2, and 51 of 59 from group 3. The status of these patients and the reasons for excluding patients from maintenance phase evaluation are summarized in Table 2.

Drug Dosing During Maintenance

During the first year of maintenance therapy, 73%, 75%, and 76% of the stipulated dose of methotrexate was received by patients in group 1, group 2, and group 3, respectively. Dosing with 6-MP averaged 81%, 78%, and 79% in these groups, respectively. Over 90% of the total planned dose of vincristine was administered during the first year of therapy in each study cohort. Twenty-six percent, 36%, and 35% of group 1, 2, and 3 patients, respectively, averaged greater than 90% of medication doses during the first year of maintenance, with only 21%, 16%, and 15% of each group averaging less than 50%. When the number of cycles of maintenance therapy given during the first year was analyzed (six maximum), the results obtained were again simi-

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Total</th>
<th>Continuing</th>
<th>Marrow</th>
<th>CNS</th>
<th>CNS and</th>
<th>Extramedullary</th>
<th>Died in</th>
<th>Lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>22</td>
<td>5</td>
<td>13</td>
<td>0</td>
<td>2</td>
<td>1*</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Group 2</td>
<td>30 (2)</td>
<td>5 (1)</td>
<td>19</td>
<td>2 (1)</td>
<td>2</td>
<td>2*</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Group 3</td>
<td>51 (6)</td>
<td>21 (2)</td>
<td>20 (1)</td>
<td>3 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate patients in each grouping with central nervous system disease in induction. The reasons for excluding patients from maintenance phase evaluation were one protocol violation and patient refusal in two cases among the group 1 patients. In groups 2 and 3, there were four patient refusals, two hematologic relapses during the CNS phase of therapy, two patients with uncontrollable CNS disease, two patients with sustained infection acquired during induction, two protocol violations, and one death that was unrelated to the disease or its therapy. One patient could not tolerate 6-MP due to nausea and vomiting. Two complete responders were removed from study to pilot the early intensification with cytosine arabinoside and daunorubicin, which is now employed in CALGB 8011.

*Simultaneous with marrow relapse.
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lar: 4.5, 4.6, and 3.8 cycles were administered to groups 1, 2, and 3, respectively. There was no significant difference in the amount of these drugs administered during the second year of maintenance therapy as compared to the first year.

Drug Toxicity During Maintenance

Severe or life-threatening granulocytopenia and/or thrombocytopenia was highest during the first maintenance cycle. The first course of this cycle was coincident with the CNS phase of therapy. Thirty percent of group 1 patients experienced severe toxicity, and 5% experienced life-threatening hematologic toxicity. In group 2 plus 3 patients, 19% had severe or life-threatening toxicity (group 1 vs. group 2 plus 3, P = .17). Thereafter, hematologic toxicity was considered to be no worse than severe and was observed in less than 5% of the entire patient group at risk. Severe mucositis and hepatic dysfunction were similarly most common in the first maintenance cycle and were present in 28% of patients and diminished thereafter.

Duration of Response

The complete response duration for each induction therapy employed is given for the randomized and nonrandomized patient groups in Fig 1. Whereas the median duration of complete response was somewhat longer in the group treated without daunorubicin (18.3 months vs. 12.7 months, P = .58), each treatment leads to approximately 25% of patients in complete response at 3 years. Five patients in group 1 and five patients in group 2 remain at risk for relapse. In group 3, with 21 patients still in complete response, the median duration of response was 17.7 months. The relapse pattern in group 3 appeared to be similar to that observed in groups 1 and 2.

The median duration of response was unaffected by age or induction program in either of the two randomized treatment groups. No significant relationship could be established between the duration of complete response and the percent of total dose of methotrexate or 6-MP administered, or the severity of resultant hematologic toxicity encountered.

Ten of the 18 patients with CNS leukemia demonstrable during induction achieved a complete remission (Table 2). Daunorubicin was employed in induction in all (4/5 group 2, 6/10 group 3). Of these ten patients, two refused postinduction therapy and three remain in complete response. Seven complete responders without CNS disease at presentation relapsed with CNS disease. Three of these patients were known to have T-cell-derived disease.

Patients in Continuing Complete Response

Five group 1 patients and five group 2 patients remain in complete response for more than 36 months of observation. The longest duration of active continuing response is 69 months in group 1 and 61 months in group 2. Twenty-one group 3 patients remain in complete response. The longest duration of continuing response in this group is 41 months, due to the later initiation of this phase of the study.

Survival

Survival by induction therapy is shown in Fig 2. The median survivorship of all evaluable patients was 16.3 months; 15.4 months for group 1 and 20.2 months for group 2. The median survival in group 3 patients was 16.5 months. The most significant factor affecting survival was the frequency of complete response. The median survival of nonresponders was 5 months in group 1 and 2 months in group 2. For all complete responders, median survivorship was 29.5 months for group 1, 23.2 months for group 2, and 20.8 months for group 3 (Fig 3). The effects of the higher induction frequency achieved with daunorubicin in patients greater than 40 years of age is also reflected in survival. For those patients treated without daunorubicin, a significant difference in survival was seen in patients who were less than 40 (19 months) compared to those over 40 (6 months) (P = .002). Median survivals of 22 months and 15 months (P = .16) were attained in patients treated with daunorubicin who were below and above age 40, respectively. When considered by decade, age at presentation had no effect.

REGIMEN CNSR FAIL TOTAL MEDIAN

RAN (DNR) 7 15 22 18.3
RAN DNR 7 23 30 12.7
NON RAND DNR 25 26 51 17.7

Fig 1. Duration of complete response as a function of induction therapy. Group 1 was randomized to induction with vincristine, prednisone, asparaginase; group 2 to induction therapy with the same program plus daunorubicin. Group 3 was subsequently nonrandomly treated with vincristine, prednisone, asparaginase, and daunorubicin. The median observation time for all group 1, 2, and 3 patients was 47 months, 50 months, and 29 months respectively. One patient in group 3, who died in complete response of causes unrelated to ALL or its therapy, has been represented as a failure.
on the duration of complete response. Thus, the marked correlation displayed between survivorship and age at presentation for the combined patient groups was mainly a function of the initial complete response rate.

**DISCUSSION**

It is not surprising that the investigation of the less common adult ALL should have been patterned after the successful and more rapidly concluded pediatric studies. Yet, induction programs consisting of vincristine, prednisone, and L-asparaginase, which are effective in inducing complete responses in 90% of children, are little more than half as effective when employed in adults.\(^1\)\(^-\)\(^5\) Moreover, the median duration of complete response and the percent of patients remaining in continuous complete response for 3–4 years of maintenance therapy are markedly lower in adults than in children.\(^1\)\(^-\)\(^5\)\(^,\)\(^15\) The outcome remains less satisfactory in adults when more aggressive pediatric programs are translated to adults.\(^3\)\(^,\)\(^5\)\(^,\)\(^15\)\(^,\)\(^16\) Thus, patients age appears to be a powerful prognostic factor for both response rate and response duration. Indeed, even within the “pediatric” population, the frequency of complete response attained in early adolescence is less than that observed in patients beginning treatment between ages 7 and 10.\(^2\)\(^,\)\(^17\)\(^,\)\(^18\) Among adults, response frequency diminishes with increasing age.\(^4\)

The attenuated cytoreductive effect of vincristine and prednisone in adult ALL appears to be improved by the addition of the anthracycline antibiotics, daunorubicin and doxorubicin. In generally uncontrolled studies, an augmentation of complete response from approximately 50% to 75% was observed whether the anthracycline is added to the induction program concurrently or sequentially to vincristine and prednisone (± L-asparaginase).\(^3\)\(^,\)\(^5\)\(^,\)\(^7\)\(^,\)\(^15\)\(^,\)\(^16\)\(^,\)\(^19\)\(^-\)\(^26\)

The current prospective, randomized clinical trial clearly establishes the increased effectiveness in adult ALL of induction therapy consisting of vincristine, prednisone, L-asparaginase, and daunorubicin, compared to an otherwise identical program that omits daunorubicin. The randomized groups appeared to be comparable for pretreatment characteristics and other prognostic factors. Thirty-eight of 46 (83%) patients were successfully induced with the daunorubicin program, compared to 25 of 53 (47%) of patients treated without daunorubicin \((P = .003)\). Continued study of the daunorubicin program indicated that 76% of 78 subsequently evaluated patients achieved complete response. The response observed was thus similar to that obtained with daunorubicin during the randomized phase of the investigation \((P = .36)\). Although severe granulocytopenia and thrombocytopenia were more frequent when daunorubicin was employed, patient deaths during induction, which were mainly septic, were no more frequent. Furthermore, persistent toxicities resulting from the use of the anthracycline did not impair the entry of eligible patients into the maintenance phase of the study. It was hoped that the increased cell kill produced by the supplementation of the induction program with daunorubicin might result in an increased duration of complete response. This effect was not seen.

The maintenance program employed in the current study consisted of courses of 6-MP and methotrexate and was heavily dependent on repetitive reinforcement with vincristine and prednisone. Toxicity during maintenance was minimal. Clearly, the continued leukemic cytoreduction during maintenance that is required for successful and potentially “curative” treatment of ALL did not occur in the vast majority of patients. Given the minimal drug toxicity encountered during maintenance, maximally tolerable doses were not used.\(^2\)\(^7\)\(^-\)\(^29\)\(^,\)\(^30\) The coupling of an improved frequency of complete response with a failure to improve complete response duration observed in the current study
appears to derive from a number of factors. Included would be the capture response of a cohort of "bad risk" patients, consequent to the augmentation of induction response by daunorubicin. These patients would be putatively resistant to vincristine/prednisone/L-asparaginase. This latter group would be poorly responsive to the minimally toxic and perhaps inadequately aggressive maintenance program, which was heavily reliant on vincristine and prednisone reinforcement. Unfortunately, it appears that too few patients will be at risk at 3+ years of maintenance to evaluate the relative effectiveness of daunorubicin supplementation in producing long-term survivors with sufficient statistical confidence.

Much recent comment has been directed to the effect of pretreatment prognostic variables.\(^{4,5,18,31-34}\) The complete response frequency obtained in the daunorubicin-treated patients was sufficiently high that the influence of almost all prognostic variables, including age, was obliterated. At presentation, the incidence of central nervous system disease was 10%. With adequate prophylaxis "de novo," central nervous system disease was, as in childhood ALL, an uncommon primary site of relapse.\(^8\) Solitary extranodal sites of primary relapse were also uncommon, perhaps because of the relatively early marrow relapse. Eight of 56 patients (14%) tested proved to be Philadelphia chromosome positive; 3 were evaluable for a short-lived complete response.\(^{15}\)

A number of promising leads to increasing the curative potential of therapy of adult ALL are available. We have demonstrated the salutary effect of daunorubicin added to induction therapy in a prospective randomized trial. Furthermore, the high frequency of complete response obtained was confirmed in a subsequent nonrandomized segment of the study. The low incidence of primary central nervous system relapse reflects the efficacy of the program of central nervous system prophylaxis employed.

The relapse rate of 75% of complete responders indicates the failure of the maintenance program to eliminate these residual leukemic cells remaining after induction chemotherapy. More intensive consolidation and maintenance programs have been piloted.\(^{36,37}\) These programs result in about an 80% complete response rate and a median duration of complete response in excess of 2 years. In one study with a median follow-up of 5.5 years, 59% of patients remain in complete response at 45 months.\(^{36,37}\)

Thus, it would appear that given the chemotherapeutic agents currently available, both a high intensity of induction therapy and of subsequent therapy are necessary for better control of adult ALL. A program using a full second induction with cytosine arabinoside and daunorubicin is currently being evaluated by CALGB.

Despite the relative scarcity of adults with ALL, progress is being made in the development of potentiually curative treatment programs. The current study is the largest prospective therapeutic trial yet reported in adults. Hopefully, the conclusions derived will be incorporated into the new generation of investigations, which will improve the results of the therapy of what has, to-date, been an all too unyielding disorder.

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