Intermittent Combination Chemotherapy With Adriamycin for Childhood Acute Lymphoblastic Leukemia: Clinical Results

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One hundred thirty-seven children with previously untreated acute lymphoblastic leukemia were entered into a new program that included intermittent combination chemotherapy featuring Adriamycin. Remission induction was initially randomized to vincristine and prednisone with or without an anthracycline. All children received asparaginase consolidation and central nervous system prophylaxis with cranial irradiation and intrathecal methotrexate. There were no primary failures of CNS prophylaxis.

Complications were primarily infectious. Clinical evidence of cardiotoxicity and leukoencephalopathy were not observed. The time to enter complete remission and the presence of an anterior mediastinal mass at diagnosis were found to be statistically significant adverse prognostic factors, whereas presenting age and white blood count were not. With a median follow-up of 26 mo, and using life plot analysis, 65% of the children have remained in continuous complete remission.

Many factors within the past 15 yr have contributed to a marked improvement in the prognosis of childhood acute lymphoblastic leukemia (ALL): an increasing number of effective chemotherapeutic agents, combination chemotherapy, modified dose schedules, intensive treatment during remission, central nervous system (CNS) prophylaxis, and vigorous supportive care. In some recent studies 50% of children with ALL have remained disease-free for at least 5 yr.

During the past 4 yr we have developed a treatment program derived from a series of sequential studies. These included evaluation of the addition of a third agent to vincristine and prednisone (VP) induction therapy, confirmation of the efficacy of CNS prophylaxis, and demonstration of the effectiveness of a cyclic intensive intermittent combination chemotherapy program involving Adriamycin (Adria, Wilmington, Del.) during remission. On the basis of these clinical investigations we have evolved a treatment program for children with ALL, the results of which are presented here.

MATERIALS AND METHODS

The diagnosis of ALL was established by two or more experienced morphologists. Patients with lymphoma were included if the bone marrow contained more than 25%, lymphoblasts at the time of diagnosis. The criteria for complete remission included: peripheral blood without leucopenia.
Fig. 1. Protocol design, schematic. v, vincristine: induction 1.5 mg/sq m; thereafter 2.0 mg/sq m intravenously (maximum 2.0 mg). PRED, prednisone: induction 40 mg/sq m/day; thereafter 120 mg/sq m/day x 5 days, orally. A, Adriamycin: 30 mg/sq m intravenously. 6-MP, 6-mercaptopurine: 225 mg/sq m/day x 5 days, orally. ASP, asparaginase: 56,000 IU/sq m/dose for patients <6 yrs old; 28,000 IU/sq m/dose for patients ≥6 yrs old, intravenously. MTX, methotrexate: 7.5 mg/sq m/day x 5 days; intravenously day 1, intramuscularly days 2–5; 12 mg/sq m intrathecally (maximum 12 mg). Cranial rads: 2400 rads/13 fx/17 days.

blasts, granulocytes more than 500/cu mm and platelets more than 75,000/cu mm, and a normocellular bone marrow with fewer than 5% lymphoblasts. Relapse was defined as follows: (1) more than 50% lymphoblasts in a single bone marrow aspirate, or (2) progressive repopulation of lymphoblasts in excess of 5%, culminating in more than 25% in two or more bone marrow samples separated by 1 wk or more, or (3) more than 25% lymphoblasts in the bone marrow and 2% or more circulating lymphoblasts, or (4) leukemic cell infiltration in extramedullary organs (biopsy proven), or (5) lymphoblasts in the cerebrospinal fluid (CSF).

Statistics
Survival was analyzed by the life-table method of Berkson and Gage and by χ² analysis.

Treatment Program
The treatment regimen is diagrammed in Fig. 1. Remission induction therapy consisted of VP. The first 56 patients were randomized to receive VP only, VP-daunorubicin, or VP-Adriamycin. The percentage of complete remissions of the patients who received the anthracyclines did not differ from that of the whole population. Patients who failed to enter complete remission by day 22 received “consolidation” chemotherapy through the completion of asparaginase and then one additional course of the four-drug combination (Adriamycin, 6-mercaptopurine, and VP).

Early consolidation was accomplished with a total of five doses of asparaginase administered every other day. CNS prophylaxis consisted of whole-brain irradiation using a linear accelerator to 2400 rad/13 fractions/17 days and five doses of intrathecal methotrexate (i.t. MTX) given within the same time span. Thereafter i.t. MTX was administered every 18 wk. Oral 6-mercaptopurine was withheld during CNS prophylaxis.

Treatment in remission involved 5-day courses of combination therapy (Adriamycin and vincristine on day 1, 6-mercaptopurine and prednisone on days 1–5) given every 3 wk. After completion of a total cumulative Adriamycin dosage of 450 mg/sq m body surface area, Adriamycin was replaced by parenteral MTX for the duration of treatment. Dose adjustments of all chemotherapeutic agents were designed to permit administration of maximally tolerated doses of myelosuppressive agents. Therapy was electively discontinued after 30 mo continuous complete remission.

Renal and hepatic function were monitored with every third course of chemotherapy. Bone marrow aspirations were performed every 9 wk and lumbar punctures every 18 wk for diagnostic and therapeutic reasons. Potential Adriamycin cardiotoxicity was assessed every 3 mo during and following Adriamycin therapy by simultaneous recordings of EKG phonocardiograms and echocardiograms.
One hundred thirty-seven consecutive children 20 yr old and younger presenting to the Sidney Farber Cancer Institute and the Children’s Hospital Medical Center with previously untreated ALL were entered into the study between October 1973 and June 1977. The presenting clinical characteristics of these patients are listed in Table 1.

Three patients presented with CNS symptoms. One had hemiparesis; however, cytocentrifuge of the CSF was negative for lymphoblasts, and the hemiparesis was presumed to be the result of CNS hemorrhage. Another child presented with a right facial nerve weakness that completely resolved after treatment with radiation therapy. Her CSF contained no lymphoblasts at the time of the cranial nerve involvement. The third child presented with headaches and diplopia, and the CSF contained many lymphoblasts.

Three additional patients presented with moderate papilledema and severe anemia. Following red cell transfusion and initiation of chemotherapy the papilledema cleared. These children subsequently had normal CSF cytology.

In patients without clinical evidence of CNS disease we routinely deferred lumbar puncture for at least 3 wk after diagnosis because of the risk of introducing lymphoblasts into the CSF during that procedure.

Three patients were found to have CSF lymphoblasts on day 22: two were asymptomatic, and one had developed ptosis during the induction period. In all three patients CSF lymphoblasts cleared with i.t. MTX, and they received 2850 rads rather than routine (2400 rads) CNS prophylaxis.

RESULTS

The results are summarized in Table 2 and Fig. 2. Of the 137 patients, 1 died of congestive heart failure during induction, and 7 failed to enter complete remission by day 60 and were considered induction failures. Thus 129 patients entered complete remission (94%). Of these, 6 were withdrawn or lost to follow-up,
3 died in remission [at 6 wk of interstitial pneumonitis, at 18 mo of presumed viral pneumonitis and myocarditis, and at 16 mo (a child with Down syndrome who experienced CNS hemorrhage, in the absence of thrombocytopenia, for unexplained reasons)], and 24 relapsed.

As indicated in Table 3, presence of anterior mediastinal mass (AMM), elevated white blood cell count (WBC), T-cell disease, and lymphomalike presentation with bone marrow involvement did not statistically significantly influence the percentage of induction of complete remission. Acute undifferentiated leukemia (AUL) and age were important factors in determining remission induction. Ten patients had AUL characterized morphologically by an increased cytoplasmic to nuclear ratio, more distinct nucleoli as compared to lymphoblasts, absence of cytoplasmic granules, and characterized histochmically by negative staining with periodic acid-Schiff and peroxidase. Four of the ten patients with AUL failed to enter complete remission (p < 0.001). Children less than 2 or more than 9 yr old had a significantly higher rate of in-

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Induction Failures} & \textbf{No. of Induction Failures/Total Entries} & \\
\hline
Total & 7/137 (5\%) & \\
Early death & 1/137 (1\%) & \\
AUL & 4/10 (40\%) p < 0.001 & \\
AMM & 0/13 (0\%) & \\
WBC $\geq$ 25,000/cu mm & 2/38 (5\%) p NS & \\
< 25,000 & 5/99 (5\%) & \\
Age (yr) & \\
2-9 & 1/91 (1\%) p = 0.005 & \\
<2, >9 & 6/46 (13\%) & \\
<2 & 2/8 (25\%) & \\
>9 & 4/38 (11\%) p = 0.01 & \\
T-cell disease & 1/9 (11\%) p NS & \\
Non-T-cell disease* & 4/76 (5\%) p NS & \\
Lymphoma with positive marrow & 0/4 (0\%) p NS & \\
\hline
\end{tabular}
\caption{Induction Failures}
\end{table}

AUL, acute undifferentiated leukemia; AMM, anterior mediastinal mass; WBC, white blood cell count; NS, not significant.

* Markers not obtained in 52 patients.
Table 4. Relapses

<table>
<thead>
<tr>
<th></th>
<th>No. of Relapses/Complete Remission</th>
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<tbody>
<tr>
<td>Total</td>
<td>24/129 (19%)</td>
</tr>
<tr>
<td>Induction</td>
<td></td>
</tr>
<tr>
<td>≤ 30 days</td>
<td>16/107 (15%) p = 0.01</td>
</tr>
<tr>
<td>&gt; 30-60 days</td>
<td>8/22 (36%)</td>
</tr>
<tr>
<td>T-cell</td>
<td></td>
</tr>
<tr>
<td>I-cell</td>
<td>5/8 (63%) p &lt; 0.001</td>
</tr>
<tr>
<td>Non-I-cell</td>
<td>5/72 (7%)</td>
</tr>
<tr>
<td>AMM positive</td>
<td></td>
</tr>
<tr>
<td>WBC ≥ 25,000/cu mm</td>
<td>6/36 (17%) p NS</td>
</tr>
<tr>
<td>&lt; 25,000/cu mm</td>
<td>18/93 (19%)</td>
</tr>
<tr>
<td>Age 2-9 yr</td>
<td></td>
</tr>
<tr>
<td>&lt; 2, &gt; 9 yr</td>
<td>15/90 (17%)</td>
</tr>
<tr>
<td>AUL</td>
<td></td>
</tr>
<tr>
<td>Lymphoma with marrow involvement</td>
<td>4/4 (100%) p &lt; 0.001</td>
</tr>
</tbody>
</table>

21/24 in bone marrow (BM) only; 1/24 BM + CNS + testes; 1/24 CNS and testes; 1/24 BM + CNS; 1/24 CNS only. NS, not significant.

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Relapses

Table 4 shows that age and WBC did not influence the rate of relapse, whereas the following factors were important: time required for entrance into complete remission; presence of an AMM; AUL; T-cell disease; and lymphoma-like disease presenting with bone marrow involvement. Of the 129 patients who achieved complete remission, those who did so in 30 days or less did significantly better than those who required 31–60 days (p = 0.01).

The bone marrow was the primary relapse site in 21 of the 24 patients. One patient relapsed in bone marrow, testes, and CNS; one in testes and CNS; and one in CNS only. This last relapse occurred in the patient with ptosis and CSF lymphoblasts present before institution of CNS prophylaxis. All extramedullary relapses occurred in patients with T-cell disease established by immunologic criteria. Included in the relapse group were all four patients who had originally presented with presumed lymphoma and bone marrow involvement. Of the four, three also had AMM, and one had T-cell disease. As shown in Fig. 2, 96 children remained in complete remission from 1 to 45 mo (median 26). Thirty-five patients had therapy discontinued after 30 mo in continuous remission and were followed for a median of 7 mo off therapy (maximum 15 mo). Two relapsed, both in the bone marrow 9 mo after stopping drugs.

Complications

The complications of therapy are enumerated in Table 5. These included neurotoxicity induced by vincristine, anaphylaxis caused by Escherichia coli asparaginase, oral mucositis associated with Adriamycin or MTX, and symptoms ascribed to prednisone (hypertension in three patients and withdrawal arthralgia, myalgia, vomiting, or headache in five).

Seldom was toxicity severe enough to cause more than temporary cessation of therapy or reduction of drug dosage. Four children had allergic responses to E. coli asparaginase, but they subsequently tolerated Erwinia asparaginase. Al-
Table 5. Complications of Treatment

<table>
<thead>
<tr>
<th>Chemotherapy related</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug toxicity</td>
<td></td>
</tr>
<tr>
<td>Vincristine (neurotoxicity)</td>
<td>28 (20%)</td>
</tr>
<tr>
<td>Asparaginase (anaphylaxis)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Adriamycin/methotrexate (stomatitis)</td>
<td>23 (17%)</td>
</tr>
<tr>
<td>Prednisone (hypertension; withdrawal)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Otitis media</td>
<td>52 (38%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>42 (31%)</td>
</tr>
<tr>
<td>Fever of undetermined origin</td>
<td>36 (26%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>CNS prophylaxis related</td>
<td></td>
</tr>
<tr>
<td>Post-CNS prophylaxis syndrome</td>
<td>28 (20%)</td>
</tr>
<tr>
<td>Arachnoiditis</td>
<td>11 (8%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

though 23 patients had at least one episode of severe mucositis, only 3 had marked recurrences necessitating prolonged dose reductions. Of the three patients who developed hypertension on 120 mg/sq m prednisone, all were able to tolerate subsequent courses at 40 mg/sq m. Steroid-withdrawal complications were successfully managed by gradually decreasing prednisone dosage for 72 hr instead of abruptly discontinuing the drug after a 5-day course.

Infections were frequent, usually minor, and often associated with granulocytopenia. Most common were upper respiratory infections. Fifty-two children had 101 episodes of otitis media, and 42 children had 52 episodes of pneumonia. The attack rate for pneumonia was 1.7 episodes/mo at risk. Half of the pneumonias occurred in the first 6 mo of treatment, and half of those in months 2 and 3. Of those patients with pneumonia, eight had interstitial pneumonitis; five were biopsied, and two were found to have *Pneumocystis carinii*. Three patients died in complete remission, two of whom had interstitial pneumonitis. Fifteen patients had sinusitis, radiologically documented, usually mild, always associated with hypogammaglobulinemia, and recurrent in eight patients.

Fever of undetermined origin were commonly encountered, most frequently during periods of granulocytopenia. In a randomly chosen 12-mo period (Sept. 1975–Aug. 1976) during which time 108 patients were undergoing treatment, a total of 16 patients were hospitalized on 22 occasions for periods of 2–24 days (median duration 6 days). School-age children attended their classes approximately 80% of the time.

The incidence of infectious complications, and, in particular, fevers of undetermined origin, was increased during and in the month following CNS prophylaxis; 80 patients experienced 205 episodes of infection, 63 (31%), of which occurred within the first 3 mo of therapy. Of 52 episodes of pneumonia, 17 (33%), occurred within the first 3 mo of therapy.

A CNS syndrome consisting of somnolence, anorexia, lethargy, headache, and vomiting after CNS prophylaxis occurred in 28 children. Arachnoiditis, characterized by back and lower extremity pain, headache, and low-grade fever, was initially more common in older, larger patients. After July 1974, the maxi-
mum dose of i.t. MTX was changed to 12 mg. This adjustment, more nearly approximating the ratio of spinal fluid volume to body surface area, markedly decreased the incidence of arachnoiditis.

Seizures of undetermined etiology occurred in three patients in association with CNS prophylaxis. After completion of prophylaxis, additional i.t. drugs were not administered to those patients. They remained well without further seizures or other neurologic sequelae.

DISCUSSION

The above regimen provided effective treatment for childhood ALL. Of the seven remission induction failures, four had AUL (two of these were under 2 yr of age), two were over 18 yr of age, and one 12-yr-old failed for no apparent reason. The induction death occurred in an adolescent whose family’s religious beliefs prevented early medical intervention.

During consolidation, asparaginase doses were adjusted for age as a result of previous studies suggesting a relative intolerance to asparaginase in older children.5 On this protocol neither hyperglycemia, pancreatitis, nor hepatic dysfunction were observed.

CNS relapse (meningeal leukemia) occurred in three patients, two of whom had concurrent relapse at other sites. All three of the CNS relapses occurred in patients with T-cell leukemia. We believe that technical factors relating to dose of irradiation and size of the field, as well as carefully controlled and reproducible daily administrations of irradiation, were responsible for this favorable experience. One might also attribute these results to the superiority of the systemic chemotherapy or to the efficacy of maintenance i.t. MTX. Although data on any of these explanations could not be evaluated, updated information from our previous protocol showed no primary CNS relapses in the 32 patients entering complete remission, and no primary CNS relapse in 15 patients following cessation of all therapy.

Five patients received 2850 rads instead of the usual 2400 rads—the three patients with CNS lymphoblasts on day 22, the patient presenting with CNS hemorrhage, and the patient who presented with diplopia and CSF lymphoblasts. Rationale for the boost was based upon prior observations showing that subclinical disease could often be controlled with lower doses of irradiation compared to doses necessary to control overt disease. Therefore in view of the fact that subclinical disease had been effectively controlled by doses of 2400 rads and that there appeared to be a rather steep dose-response curve at lower doses the boost was indicated to attain an equivalent rate of local control.

This study involved brain irradiation followed by systemic MTX treatment during remission. The recently described leukoencephalopathy and neuropsychiatric abnormalities with high intravenous doses of MTX were not observed. The difference may be related to the dose of MTX or to the prolonged time (approximately 1 yr) between irradiation and the institution of systemic MTX.

The theoretical advantage of cyclical pulse combination chemotherapy has been previously reported and its clinical efficacy demonstrated. The efficacy of the Adriamycin combination in this regimen was demonstrated by the fact...
that over 90% of the patients were in continuous complete remission at 15 mo (corresponding to the time of cessation of Adriamycin).

In this study we employed intermittent courses of intensive chemotherapy. Maximum safe doses were used in accordance with strict protocol guidelines. Presumably because of the intermittent nature of the treatment, which allowed for interval recovery from immunsuppression, opportunistic infections, which occur more commonly with continuous (daily) treatment, were infrequent. Granulocyte nadirs usually occurred 12-14 days following Adriamycin and 14-21 days after MTX. Significant thrombocytopenia was not encountered in this regimen. There were three deaths during complete remission. In contrast to the experience of others, there were only two documented episodes of Pneumocystis carinii pneumonitis, both successfully treated.

In our previous experience using Adriamycin in combination for the treatment of ALL we encountered congestive heart failure at cumulative Adriamycin doses of 490-540 mg/sq m in 5 of 32 patients, presumably on the basis of cardiomyopathy. In the current treatment program no patient received more than 450 mg/sq m Adriamycin, and concurrent or delayed cardiotoxicity was not diagnosed either by clinical standards or by integrated phonoelectro- and echocardiography.

In this study, chemotherapy was discontinued for all patients who were in continuous complete remission for 30 mo. As of August 1977 there were 35 such patients who had been followed for as long as 15 mo since cessation of treatment. Only two had relapsed. In our previous pilot protocol only one relapse occurred among 15 patients followed 20-29 mo after cessation of treatment. Others have reported relapse rates of 15% in children followed for up to 2 yr after cessation of therapy. The majority of these relapses occurred in the first 12 mo.

It is becoming increasingly clear that ALL is a heterogeneous group of diseases. This thesis suggests that treatment failure in a group of patients may relate to various prognostic factors and that treatment programs highly effective for some categories may be much less effective in others. The most discreetly separable distinct subpopulation is the T-cell group. Failure rates for these patients (Table 4) were significantly greater than for non-T-cell patients. Other factors, such as an AMM, elevated WBC, older age, and lymphomalike presentation, are covariables with T-cell disease. The interrelationship of prognostic variables (and covariables) will be definitively presented elsewhere.

In summary, we have demonstrated the efficacy of a treatment program that utilizes Adriamycin and intensive intermittent chemotherapy in childhood ALL. We suggest that future ALL regimens modify treatments based on the prognostic significance of heterogeneous subpopulations, such as AUL, T-cell disease, late entry into remission, and lymphomalike presentation with bone marrow involvement.

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ADRIAMYCIN AND CHILDHOOD ALL

REFERENCES

Intermittent combination chemotherapy with adriamycin for childhood acute lymphoblastic leukemia: clinical results

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