Failure of Late Intensification Therapy to Improve a Poor Result in Childhood Lymphoblastic Leukemia


ABSTRACT

This clinical study, begun in 1975, tested the efficacy of early and delayed intensification treatments in children with acute lymphoblastic leukemia. Regardless of presenting features, all patients received 4 weeks of conventional induction therapy with daily prednisone and weekly vincristine and daunorubicin. One-third were randomized to receive, in addition, two doses of asparaginase during induction therapy, while another one-third received four doses of both asparaginase and cytarabine after remission induction. Preventive central nervous system therapy uniformly included 2400 rads cranial irradiation and five doses of intrathecal methotrexate. Remissions were maintained with daily p.o. mercaptopurine and weekly i.v. methotrexate. Of the 277 assessable patients, 254 (92%) entered complete remission, and 102 (37%) remain clinically free of leukemia for 4.6 to 8.0 years (median, 6.3 years). The three treatment groups showed no significant differences in either remission induction rate or outcome, even when the analysis was based on risk assignment. A “late intensification” phase of therapy, added to the maintenance protocol for 65 patients who had been in continuous complete remission for 14 to 30 months, failed to extend remission duration, as judged from statistical comparison with matched controls (p = 0.84). When tested as a time-dependent covariate in the Cox proportional-hazards model, delayed intensification again showed no important effect on duration of complete remission. We conclude that limited early or aggressive late intensification of therapy, as described here, does not improve outcome in childhood acute lymphoblastic leukemia.

INTRODUCTION

The treatment of childhood ALL continues to evolve because optimal therapy has not yet been devised. One approach to improve results has been to intensify remission induction therapy, based on the idea that greater fractional kill of leukemic cells early in treatment will forestall or prevent the emergence of drug-resistant clones (11, 31). Because of clinical data in support of this hypothesis (21, 29), Total Therapy Study IX (1) was designed early in treatment will forestall or prevent the emergence of drug-resistant clones. Because of clinical data in support of this hypothesis (21, 29), Total Therapy Study IX (1) was designed to test 2 major treatment modifications: (a) addition of a fourth drug to an otherwise conventional induction regimen; and (b) inclusion of a consolidation phase of therapy (then considered intensive) immediately after 3-drug remission induction.

In 1980, the results of Study IX were projected to be no better, and possibly worse, than those of previous trials (2–4). Prompted by evidence suggesting that LIT will extend remissions (5, 6), the decision was made to include such a phase for all patients who remained on therapy. We report here the end results for all 3 modifications.

MATERIALS AND METHODS

Previously untreated patients <20 years old, including those with undifferentiated ALL, were admitted to the study from December 1975 to May 1979, contingent on informed written consent. To ensure that patients with unfavorable prognostic features would be evenly distributed among the 3 treatment arms, those with an initial leukocyte count >100 × 10⁹/liter, CNS disease, a mediastinal mass, or sheep erythrocyte rosette-forming blasts were randomized separately.

Cerebrospinal fluid and bone marrow aspirates were examined routinely every 3 months during treatment or at any time relapse was suspected. These intervals were gradually extended after elective cessation of therapy. Since July 1982, routine follow-up procedures have been performed for 2 years after completion of therapy instead of the usual 5 years. All boys had testicular biopsies before treatment was discontinued.

Our criteria for diagnosis of ALL and definitions of remission and relapse are reported elsewhere (30). Briefly, complete remission duration is defined as the interval between substantiation of remission and clinical evidence of relapse. CNS leukemia is diagnosed when leukemic cells are found in a Wright-stained centrifugate of cerebrospinal fluid. Testicular leukemia is proven by biopsy.

Therapy. All patients received 4 weeks of remission induction therapy consisting of daily prednisone and weekly vincristine and daunorubicin (Table 1). Those in Group 2 also were given 2 doses of asparaginase on Days 3 and 9, while those in Group 3 had an intensive phase of asparaginase and cytarabine twice weekly for 4 doses, added immediately after remission induction. Patients not entering complete remission by Day 28 had their induction chemotherapy extended for 2 additional weeks. Asparaginase i.v. (10,000 IU/sq m) and cytarabine i.v. (300 mg/sq m) were added on Days 28 and 35, and prednisone and vincristine were continued for 2 more weeks. Induction therapy was considered to have failed if leukemic cells persisted in the bone marrow at Day 42, and those patients were dropped from the study (but counted as failures).

Preventive CNS therapy, as detailed in Ref. 16, was begun as soon as complete remission was induced (Groups 1 and 2) or immediately after the intensive phase (Group 3). Patients with CNS leukemia at diagnosis were given weekly intrathecal methotrexate followed by craniospinal irradiation (2400 rads for ages 1 to 2 years and 3000 rads if >2 years).

Upon completion of CNS prophylaxis, all patients received the same maintenance therapy, 6-mercaptopurine (50 mg/sq m/day) plus i.v. methotrexate (20 mg/sq m/week). Dosages were adjusted to maximal tolerance based on leukocyte counts of 2 to 3.5 × 10⁹/liter with absolute granulocyte and lymphocyte counts >0.5 × 10⁹/liter. All therapy was discontinued after 30 months of continuous complete remission.

When it became apparent, in August 1980, that treatment results would probably not show improvement over previous studies (2–4), therapy was intensified for the 65 patients who remained in remission longer than 12 months. In Group 1, patients received 4 weeks of conventional induction therapy as described above, followed by an intensive phase of therapy, as described here, immediately after achievement of complete remission. Patients in Groups 2 and 3 received 2 doses of asparaginase on Days 3 and 9 and 4 doses of cytarabine twice weekly for 4 doses, added immediately after remission induction. Patients not entering complete remission by Day 28 had their induction chemotherapy extended for 2 additional weeks. Asparaginase i.v. (10,000 IU/sq m) and cytarabine i.v. (300 mg/sq m) were added on Days 28 and 35, and prednisone and vincristine were continued for 2 more weeks. Induction therapy was considered to have failed if leukemic cells persisted in the bone marrow at Day 42, and those patients were dropped from the study (but counted as failures).

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Table 1
Outline of therapy for Study IX

Remission induction (4 wk)

Group 1
Prednisone 40 mg/sq m/day p.o. for 28 days
Vincristine 1.5 mg/sq m/wk i.v. (maximum dose/injection, 2.0 mg) on Days 1, 8, 15, and 22
Daunorubicin 25 mg/sq m/wk i.v. on Days 2, 8, 15, and 22

Group 2
As in Group 1, but add:
Asparaginase 10,000 IU/sq m on Days 3 and 9

Group 3
As in Group 1, but after remission induction:
Asparaginase 10,000 IU/sq m i.v. twice/wk for 4 doses
Cytarabine 300 mg/sq m i.v. twice/wk for 4 doses

Preventive CNS therapy
Cranial irradiation 2400 rad in 18 days (2000 rad for ages 1 to 2 yr)
Methotrexate 12 mg/sq m intrathecally 5 times (maximum dose, 15 mg) given with irradiation

Continuation chemotherapy (30 mo)
6-Mercaptopurine 50 mg/sq m/day p.o.
Methotrexate 20 mg/sq m/wk i.v.

while receiving maintenance chemotherapy. LIT, as outlined in Table 2, was continued for 5 weeks beyond the planned 30 months of maintenance therapy. When LIT began, patients had been in remission from 14 to 30 months; hence, the number of pulses given to each patient was a function of time remaining in the planned 30-month continuation phase.

Statistical Analysis. The $\chi^2$ test for contingency tables was used to compare differences in the distribution of clinical features or remission induction rates among discrete groups of patients. The Kaplan-Meier procedure (19) was used to estimate the proportion of patients in complete remission as a function of time to failure. For patients not responding to induction therapy, time to failure was considered to be zero; for all others, it was defined as the time from complete remission to relapse at any site. Distributions of remission lengths were compared by the log-rank test. Kaplan-Meier analyses were also done after stratification of patients by prognostic group, using criteria of both the Children's Cancer Study Group (23) and this institution. By St. Jude criteria, a "high-risk" patient is one with a leukocyte count >100 $\times 10^9$/liter, a positive sheep erythrocyte rosette test, CNS involvement, or a mediastinal mass.

Remission durations for the 65 patients who received LIT were compared with those for 65 controls also treated in Study IX, by use of a rank test for censored matched pairs (32). The 2 groups had been carefully matched in terms of leukocyte count, age at diagnosis, and duration of complete remission at the time LIT was begun. The Cox proportional-hazards model (8) was used to assess the effect of each potential prognostic variable on complete remission duration, while simultaneously adjusting for the influence of other covariates. Since patients received LIT at different times in their treatment course, it was entered as a time-dependent covariate. Other variables included leuko-
cyte count, age, sheep erythrocyte rosette formation, race, mediastinal mass, platelet count, sex, and hemoglobin level.

RESULTS

Patient Accrual and Presenting Features. Two hundred ninety consecutive patients were enrolled in the study. The cutoff date for statistical analysis was December 13, 1983, with a median follow-up of 76 months. Of those entered, 13 were considered to be ineligible or not assessable for response to induction therapy. The reasons included inaccurate diagnosis (5 patients), B-cell ALL (6 patients), and early death before treatment and randomization (2 patients).

The presenting features of the 3 groups were similar (Table 3). Altogether, there were 146 boys (53%) and 23 black patients (8%). The median age in the study was 5 years (range, 2 to 19 years, 11 months); 51 patients (18%) were 2 years old or less, and 73 (26%) were older than 10 years. Leukocyte counts ranged from 1 to 860 x 10⁹/liter (median, 13 x 10⁹/liter). Twenty-four patients (9%) had a mediastinal mass, and 12 (4%) had CNS leukemia at diagnosis. Bone marrow blasts were positive for sheep erythrocyte-rosette formation in 33 (13%) of 260 patients tested.

Treatment Outcome. Complete remission was induced in 254 (92%) of the 277 assessable patients (Table 4). Induction rates for the 3 treatment groups were essentially the same, whether analyzed for Day 28 or 42 of therapy. Because Groups 1 and 3 received identical therapy for the first 4 weeks, their responses were combined and compared with those of Group 2; again, there was no difference in remission rates at Day 28 (160 of 189 versus 79 of 88; p = 0.25). Similar results were obtained when patients were placed in different risk groups before analysis (data not shown). The clinical and biological features of the 38 patients who had failed induction by Day 28 were compared with those of 239 children who achieved a complete remission (Table 5). Those who failed had significantly higher leukocyte counts, were older, and were more likely to be black and to have CNS disease or mediastinal mass. Of the 21 patients who failed initial induction therapy by Day 42, 15 subsequently attained a complete remission on alternative treatment, but only 2 remain in continuous complete remission.

Overall, 102 (37%) of the 277 patients remain in initial complete remission; 117 (42%) are in initial hematological remission; and 149 (54%) survive. There was no difference in outcome (proportion of patients in initial complete remission) among the 3 treatment groups (Chart 1), even when times to failure were analyzed by category of risk assignment (data not shown).

Sixty-five patients, in continuous complete remission for 14 to 30 months, were eligible to receive LIT (Table 2). Forty-nine (75%) remain in continuous complete remission, off all therapy, for 4.6 to 6.3 years; 5 relapsed during therapy (3 marrow and 2 testicular); 10 had marrow (7) or CNS (3) relapses after completion of treatment; and one died in remission of disseminated varicella. Remission durations for the LIT group showed no significant differences from results for 65 age- and leukocyte count-matched controls (Chart 2). Moreover, analysis of LIT as a time-dependent covariate in the Cox proportional-hazards model disclosed no important effect on length of complete remission. After adjustment for all other potential prognostic factors, only leukocyte count and age retained significance (p < 0.001; data not shown).

Extramedullary Relapses. Solitary extramedullary relapses ended initial complete remissions in 37 children. Twenty-three relapses occurred in the CNS, 20 while the patients were still on therapy. Only one of the 16 patients <2 yr of age at diagnosis had a CNS relapse after receiving preventive therapy that included 2000 rads cranial irradiation. Seven of the 23 children with CNS relapse have been off therapy in complete remission for 25+ to 55+ months (median, 30 months). Although only 4 of 12 children with CNS disease at diagnosis remain in continuous complete remission, none has had CNS relapse as the first disease-related event following therapeutic craniospinal irradiation.

There were 14 testicular relapses, including 7 in patients who

<table>
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<tr>
<th>Table 4</th>
<th>Clinical course of 277 patients</th>
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<tr>
<td></td>
<td>No. of patients</td>
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<tr>
<td>---------</td>
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</tr>
<tr>
<td>Group 1</td>
<td>94</td>
</tr>
<tr>
<td>Group 2</td>
<td>88</td>
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<td>Group 3</td>
<td>95</td>
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<td>Total</td>
<td>277</td>
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<th>Table 5</th>
<th>Clinical and biological features of patients who achieved remission at day 28 versus those who failed</th>
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<tr>
<td>Feature at diagnosis</td>
<td>Leukocyte count x 10⁹/liter</td>
</tr>
<tr>
<td>Patients</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Attaining remission</td>
<td>114</td>
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<td>Failing induction</td>
<td>8</td>
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| p       | <0.0001 | 0.04 | 0.007 | 0.002 | 0.01 |
were found to have subclinical testicular leukemia by elective biopsy at the end of continuation chemotherapy (70 boys underwent this procedure). All 4 patients with overt testicular disease during continuation chemotherapy developed subsequent hematological or CNS relapses. Of the 7 patients with occult disease at the end of continuation chemotherapy, 5 have been off therapy for 9 to 43 months in complete remission, one died of widespread Epstein-Barr viral infection while in remission, and one developed a hematological relapse 9 months later. Three children had testicular leukemia following cessation of therapy for 16, 28, and 41 months, respectively. Bilateral testicular irradiation and additional systemic chemotherapy were administered, and all 3 patients are in hematological remission. One has been off therapy a second time for 10 months. Sixteen children relapsed simultaneously in the CNS and marrow, and 4 in the testis and marrow. Only 3 of these patients are still in second remission (2 are off therapy for 11 and 46 months).

Complications. Two patients in Group 2 died of bacterial infections during induction therapy. Of the 88 in Group 2 who received concomitant asparaginase and prednisone during initial remission induction therapy, 11 (12.5%) developed nonketotic hyperglycemia, as reported previously (26). Hyperglycemia did not occur in Groups 1 or 3. Of the 183 patients who received asparaginase initially, 19 had anaphylactoid reactions to Erwinia coli asparaginase, half of whom developed respiratory distress or hypotension. They subsequently received Erwinia asparaginase without adverse reactions.

Continuation chemotherapy was well tolerated. One-third of the patients had substantially elevated liver enzyme levels during chemotherapy, but in each instance the levels returned to normal after cessation of treatment. Two patients, who are now off therapy, have portal hypertension manifested by splenomegaly and thrombocytopenia. Two other patients have chronic active hepatitis. Pneumocystis carinii pneumonia developed in 8 patients who were in initial complete remission but were not given prophylactic trimethoprim-sulfamethoxazole (Bactrim) for various reasons. Most patients in the study did receive Bactrim prophylaxis, resulting in a lower incidence of P. carinii pneumonia than encountered in the preceding trial (4). Two patients died from infection while in initial complete remission (one, disseminated cytomegalovirus infection and one, viral pneumonia).

Late intensification treatment (95% of courses delivered) was adequately tolerated. Leukopenia was a transient problem in some patients after cyclophosphamide treatment but did not result in life-threatening toxicity. Most patients developed marrow hypoplasia after the last month of treatment, but the complication resolved within 2 to 3 weeks. Four patients had allergic reactions to asparaginase given i.m., but in all instances the effects were milder than observed when the drug was administered i.v. during remission induction. A single patient experienced hemorrhagic pancreatitis after receiving asparaginase and subsequently recovered. Varicella infection occurred in 2 children and was fatal in one.

Second cancers were diagnosed in 3 patients. A 7-year-old boy, off therapy for 31 months, had a basal cell carcinoma on his forehead within the irradiated area. Hodgkin's disease involving the spleen and left cervical, left supraclavicular, splenic hilar, and celiac lymph nodes was diagnosed in a 5-year-old boy after 25 months of continuation chemotherapy. He was treated with 2000-rad mantle and inverted-Y radiotherapy and 14 months of additional chemotherapy. The boy responded well and has been off all therapy for 2 years. A 6-year-old boy with Down's syndrome developed acute nonlymphoblastic leukemia 22 months after the completion of therapy for ALL and died of persistent disease 9 months later.

DISCUSSION

In Total Therapy Study IX, limited early intensification of therapy did not yield a therapeutic gain for any risk category of patients. Similarly, Komp et al. (20) found that 4-drug induction with cyclophosphamide, prednisone, vincristine, and asparaginase not only failed to improve remission rates, but also contributed significantly to an increased early death rate from infection. In a Children's Cancer Study Group clinical trial for patients with unfavorable prognostic features, the addition of cyclophosphamide to prednisone, vincristine, and asparaginase did not improve remission frequency but did increase the severity of myelotoxicity. 

In Total Therapy Study IX, 2 of the 11 patients with testicular leukemia were found to have occult leukemia by treatment. The documentation of occult leukemia in children with leukemia is important for several reasons. First, it may represent an occult site for infection and serves as a rationale for the use of prophylactic antibiotic therapy. Second, the presence of occult leukemia may provide an opportunity for early detection and possibly for treatment before the development of overt leukemia.

In a study of 100 children with ALL, the incidence of occult leukemia was found to be 42% (21). The significance of occult leukemia is not clear, but it may be related to the presence of occult leukemia in the bone marrow, which is known to be a reservoir for occult leukemia. The presence of occult leukemia in the bone marrow may also be related to the presence of occult leukemia in the peripheral blood, which is known to be a reservoir for occult leukemia. The presence of occult leukemia in the bone marrow may also be related to the presence of occult leukemia in the peripheral blood, which is known to be a reservoir for occult leukemia.
losuppression (22). More recently, early consolidation therapy with cyclophosphamide and Adriamycin failed to improve the outcome for children who had received prednisone, vincristine, and asparaginase for remission induction (7).

Factors responsible for the unfavorable outcome of Study IX could not be identified with certainty. Although the induction regimen included either 3 or 4 agents, dosages of daunorubicin and asparaginase were low by comparison with other studies (17, 18, 22, 24, 28) and well below maximal tolerance. Moreover, the value of adding daunorubicin to prednisone and vincristine for induction therapy has not been clearly established. While Jacquillat et al. (17) have reported a higher remission rate for patients treated with this 3-drug combination, a trial conducted by the Cancer and Leukemia Group B (15) failed to show therapeutic benefit from addition of daunorubicin. The failure of our early consolidation phase may be related to improper choice of drugs, suboptimal scheduling, or inadequate dosages, as suggested also by Camitta et al. (7) for their trial of intensified chemotherapy including cyclophosphamide and doxorubicin. Indeed, this phase of therapy was well-tolerated and was not associated with any appreciable degree of myelosuppression. Jones et al. (18), by contrast, have reported significantly extended remissions in patients given sufficient dosages of asparaginase after remission induction with vincristine and a corticosteroid.

Preventive CNS therapy included 5 doses of intrathecal methotrexate; no other drugs were used. This contrasts with other studies (22, 23) that used 6-mercaptopurine in this phase. Methotrexate was given i.v. during continuation chemotherapy; hence, variations in methotrexate absorption should not have been a factor in treatment outcome (9). However, recent findings at this center indicate that outcome is significantly influenced by methotrexate clearance rates, even when the drug is administered by the i.v. route (12). 6-Mercaptopurine was given p.o. at a lower dosage than used by other groups (22, 23) and has been shown to have variable bioavailability when administered by this route (33). Thus, while therapeutically effective absorption of methotrexate appears assured, some patients might have received an inadequate dosage of 6-mercaptopurine. Although no single component of therapy can be causally related to these suboptimal results, the high number of early relapses (5 within the first week after CNS prophylaxis) implicates inadequate reduction of the initial leukemia cell burden and delay of systemic therapy as prime factors. Moreover, the relatively high frequency of CNS leukemia in this study may be related to the lack of early intrathecal therapy or subsequent suboptimal remission maintenance (25).

The concept of late intensification therapy was developed by Bodey et al. (5), who reasoned that the introduction of alternative drugs at a time when the leukemic cell number is minimal might eradicate resistant cells and lead to cure. After studying 62 adults with ALL or acute nonlymphoblastic leukemia, they suggested that LIT plus Bacillus Calmette-Guérin immunotherapy results in prolonged disease-free survival. By contrast, we found no evidence to support a therapeutic advantage from addition of this phase.

In theory, anticancer drugs could cure if dosages were increased sufficiently and drug combinations alternated rapidly enough to increase the fractional kill of malignant cells before development of drug resistance (14, 31). Past failures to demonstrate the efficacy of intensified chemotherapy in ALL have not diminished the appeal of this concept. To the contrary, many leukemia therapists now acknowledge the importance of aggressive early therapy. Frei and Sallan (13) have demonstrated the prognostic significance of initial cytoreduction rate by correlating greater early kill of leukemic cells with extended remissions. More recently, aggressive early therapy incorporating teniposide (VM-26) and cytarabine in an otherwise standard 3-drug regimen has produced encouraging results at this center (10). The most exciting experience with early, very aggressive therapy has been reported by Riehm et al. (27) in the Berlin-Frankfurt-Münster (BFM) studies conducted in West Germany.

We conclude that mere addition of drugs to standard regimens will not improve treatment outcome in children with ALL. Inclusion of a late intensification phase does not appear to compensate for inadequate early therapy.

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