# Second Cessation of Therapy in Childhood Lymphocytic Leukemia

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**In an attempt to achieve better estimates of prognosis in children with recurrent acute lymphocytic leukemia, we studied the clinical courses of 17 patients who had relapsed in the bone marrow after elective cessation of therapy and had been treated again with systemic combination chemotherapy without meningeal prophylaxis. Sixteen patients attained second complete remission and were followed for 3–5 yr. Each child relapsed during continuation chemotherapy: 8 in the bone marrow, 6 in the central nervous system, 1 in the testes, and 1 in both the marrow and central nervous system. In 4 of the 7 patients with isolated extramedullary relapse, a new remission was induced, and after 30–44 mo of continuous second bone marrow remission, all therapy was again stopped. Two children remain in remission, off treatment, for 6+ and 27+ mo. Three patient variables (length of first complete remission, time from cessation of therapy to relapse, and number of initial sites of relapse) were of value in predicting the length of second hematologic remission. The results of this study indicate that children who relapse after cessation of therapy should be treated as intensively as newly diagnosed patients, because new prolonged remissions may be achieved. A second course of preventive treatment to the central nervous system is recommended.**

IN 1974 Aur et al.[1] reported the results of cessation of therapy in 132 children with acute lymphocytic leukemia (ALL) who had remained in first complete marrow remission for 2–3 yr. Treatment was discontinued electively because there was no evidence that more prolonged therapy would be beneficial and the risk of unwarranted toxicity appeared high. Seventeen of these children subsequently developed bone marrow relapses while off therapy and were admitted to a treatment program for leukemia recurring after elective cessation of therapy. This is an unusual circumstance; so there is little information available on clinical course and prognosis in these patients, and guidelines for stopping therapy a second time are poorly defined. In an earlier publication[2] we presented the therapeutic responses of this group, with emphasis on the frequency of remission reinduction and the sites and frequency of relapse. Our purpose here is to report subsequent results, notably that treatment was stopped for a second time in 4 patients who had remained in hematologic remission for at least 30 mo, and to relate selected patient features and treatment variables to the length of second remission.

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## MATERIALS AND METHODS

### *Definitions*

Diagnostic criteria, definitions of remission and relapse, and ratings of leukemic activity in bone marrow are the same as those used in the earlier publications.[2,3] The duration of second hematologic remission extends from the day remission is reinduced until evidence of marrow relapse is found. Survival on study is the time from admission to this protocol until death.

### *Patients*

From September 1973 to August 1975, 17 children who developed hematologic relapse after cessation of therapy entered this study of secondary treatment with the written consent of their parents. These patients had been treated in Total Therapy Study VI, VII, or VIII,[4-6] and their clinical characteristics on admission to this study were summarized earlier.[2]

The effectiveness and toxicity of continued treatment were determined by periodic physical and laboratory examinations. Complete blood counts were obtained weekly during therapy, and liver and kidney function tests, bone marrow aspirations, and cerebrospinal fluid (CSF) examinations were done every 12 wk. After cessation of therapy, bone marrow and CSF were examined every 4–6 wk during the first 6 mo and then every 3 mo for 2–3 yr.

### *Therapy*

Details of the basic plan of chemotherapy have been presented.[2] Briefly, treatment for all patients included an induction phase with prednisone, vincristine, and adriamycin; patients who attained an M-1 marrow were randomized to receive or not receive an intensive phase with asparaginase and cytosine arabinoside for 2 wk. Continuation chemotherapy consisted of weekly oral methotrexate and daily mercaptopurine. Since all patients had received preventive central nervous system (CNS) treatment early in their first remission, a second course was not initially included in the reinduction protocol. Meningeal relapses were treated with intrathecal injections of methotrexate weekly × 4 and monthly thereafter. Testicular relapses were treated with radiation therapy to the involved gonad (2400 rads).

Based on results from studies of newly diagnosed patients,[1,3] therapy was stopped for a second time in children who remained in second marrow remission for at least 30 mo. Open bilateral testicular biopsies were routinely performed to document complete remissions.

Chemoprophylaxis with trimethoprim sulfamethoxazole (Bactrim)[7] was routinely administered to each patient in the study.

### *Analysis of Data*

A logrank test[8] was used in comparisons to identify patient features with statistically significant prognostic value. With only 16 assessable patients in the study, it is unlikely that any small differences were detected.

## RESULTS

Sixteen patients attained second complete marrow remission; 1 child failed to respond to reinduction therapy and was removed from the study. After 3–5 yr of follow-up observation, the median duration of remission was 10 mo (range 3–58+ mo); however, each patient relapsed while receiving continuation therapy: 8 in the bone marrow, 6 in the CNS, 1 in the testes, and 1 in both marrow and CNS (Table 1). Of 9 patients relapsing in the bone marrow, only 1 (patient 16) remains alive. He had had a prolonged second complete remission of 30 mo and was scheduled to be taken off therapy when a marrow examination disclosed leukemic infiltration. He has now attained a third complete remission and has survived 6.5 yr since the initial diagnosis. Of the 6 patients with meningeal relapse, 3 subsequently developed marrow relapse and died.

Four children (patients 2, 5, 6, and 12) were successfully treated for their

**Table 1. Clinical Courses of Patients Treated for Relapse Following Cessation of Therapy**

| Pt. No. | Race, Sex, Age (yr) | Time to Relapse After First Cessation of Therapy (mo) | Length of Second CR (mo) | Sites of Relapse* | Length of Second HR (mo) | Survival on Study (mo), Outcome |
|---|---|---|---|---|---|---|
| 1 | WG, 8 | 7 | 5 | H | 5 | 19, died |
| 2 | WG, 5 | 8 | 8 | CNS | 58+ | 59+, off therapy for 27+ mo |
| 3 | WG, 16 | 4 | 7 | H | 7 | 13, died |
| 4 | WB, 6 | 7 | 6 | CNS→H | 7 | 22, died |
| 5 | WB, 9 | 32 | 8 | CNS | 35 | 51+, off therapy for 3 mo→relapse (H) |
| 6 | BB, 7 | 13 | 30 | T | 45 | 51+, off therapy for 1 mo→relapse (H) |
| 7 | WB, 12 | 2 | 8 | H | 8 | 16, died |
| 8 | WB, 6 | 6 | 7 | H+CNS | 7 | 18, died |
| 9 | WB, 5 | 3 | 4 | H | 4 | 18, died |
| 10 | WG, 6 | 8 | Induction failure—removed from study | | | |
| 11 | WG, 6 | 3 | 5 | CNS→H | 12 | 24, died |
| 12 | WB, 5 | 9 | 25 | CNS | 46+ | 47+, off therapy for 6+ mo |
| 13 | WB, 15 | 32 | 22 | H | 22 | 31, died |
| 14 | BG, 14 | 6 | 6 | CNS→H | 15 | 33, died |
| 15 | WB, 7 | 6 | 5 | H | 5 | 13, died |
| 16 | WB, 7 | 11 | 30 | H | 30 | 37+, in 3rd remission |
| 17 | WB, 16 | 2 | 3 | H | 3 | 10, died |
| Median | | 7 | 7 | | 10 | 23 |

Abbreviations: CR, complete remission; HR, hematologic remission; H, hematologic; CNS, central nervous system; T, testicular.

*The plus sign indicates combined relapse, and the arrow indicates sequential relapse.

extramedullary leukemia, and after second hematologic remission of 30+, 30+, 38+, and 44+ mo, therapy was stopped for a second time. In two instances treatment was extended beyond 30 mo to ensure at least 1 yr of complete remission after extramedullary relapse. Before second cessation of therapy, each of these 4 children received a course of craniospinal irradiation (2200 rads to cranium and 2200 rads to spine), because 3 had developed active CNS leukemia during second marrow remission. In the 3 boys, open testicular biopsies disclosed no evidence of residual leukemia. Patients 5 and 6 rapidly developed new marrow relapses at 1 and 3 mo after therapy was discontinued, but both have now attained third remission. By contrast, the remaining 2 children are still in second unmaintained remission for 6+ and 27+ mo.

With the exception of one case each of mild varicella and viral hepatitis, no major complications were observed. Second courses of CNS irradiation, administered to 4 children, were well tolerated, but a longer follow-up will be needed to evaluate any delayed toxicity.

Analysis of the relationships between selected patient variables and the duration of second hematologic remission yielded several significant results (Table 2). An initial complete remission duration of less than 3 yr, relapse occurring within 6 mo of cessation of therapy, and the presence of hematologic plus extramedullary sites of relapse on admission to the study all proved to be unfavorable prognostic indicators. The 9 patients with one or more of these features had median

**Table 2. Influence of Selected Variables on Length of Second Hematologic Remission**

| Feature | No. of Patients | Median Months of HR | *p* Value* |
|---|---|---|---|
| Features at diagnosis† | | | |
| Sex | | | |
| Male | 11 | 8 | 0.62 |
| Female | 5 | 12 | |
| Age | | | |
| <4 yr | 9 | 10 | 0.20 |
| >4 yr | 7 | 8 | |
| Leukocyte count | | | |
| $<10^3$/cu mm | 7 | 7 | 0.20 |
| $>10^3$/cu mm | 9 | 12 | |
| Response to initial therapy | | | |
| Length of first CR | | | |
| <3 yr | 8 | 6 | <0.01 |
| >3 yr | 8 | 30 | |
| Time off therapy | | | |
| <6 mo | 5 | 7 | 0.03 |
| >6 mo | 11 | 22 | |
| Sites of relapse | | | |
| Hematologic only | 12 | 22 | 0.04 |
| Hematologic and other | 4 | 6 | |
| Features at relapse | | | |
| Age | | | |
| <7 yr | 9 | 9 | 0.25 |
| >7 yr | 7 | 7 | |
| Leukocyte count | | | |
| $<4 \times 10^3$/cu mm | 6 | 8 | 0.57 |
| $\geq 4 \times 10^3$/cu mm | 10 | 7 | |
| Bone marrow blasts | | | |
| <50% | 7 | 10 | 0.47 |
| ≥50% | 9 | 7 | |
| Treatment variables | | | |
| Intensive phase | | | |
| Yes | 8 | 15 | 0.25 |
| No | 7 | 7 | |

Abbreviations: CR, complete remission; HR, hematologic remission.

*Determined by logrank test.[8]

†There was no patient with mediastinal mass or CNS leukemia.

hematologic remission of 7 mo (range 3–17 mo), as compared with 35 mo (range 15–58 mo) for the 7 patients with no unfavorable characteristics ($p < 0.01$). An intensive phase of therapy, age at diagnosis, sex, and initial leukocyte count had no demonstrable value as prognostic features. Similarly, of three features examined at relapse (age, leukocyte count, and proportion of marrow replacement by lymphoblasts), none was significantly related to the length of second marrow remission.

## DISCUSSION

Bone marrow relapse in children with ALL remains a poor prognostic sign. Despite the great likelihood of reinducing remission, 9 of the 17 patients reported here developed bone marrow recurrences with 3–30 mo after attaining second

remission, and all but 1 of the 9 have died. It should be stressed, however, that therapeutic responses are better in children who develop bone marrow relapse after elective cessation of therapy than in those who relapse during therapy.[2] In a recent study of patients who developed marrow relapses while receiving combination chemotherapy, second remissions lasted only a few months.[9] In fact, prolonged subsequent remissions following bone marrow relapse during therapy have not been observed at this institution; so elective cessation of therapy has not been possible. For patients who relapse after cessation of therapy but do not develop second marrow relapse during retreatment, the prognosis appears more favorable. In this study we were able to stop treatment for a second time in 4 such patients.

The importance of clinical and laboratory findings in predicting the outcome of childhood leukemia is well established. When initially diagnosed with ALL, none of our patients had features that today are considered "high risk."[10] However, their ages and leukocyte counts ranged widely enough, both at diagnosis and at relapse, to permit an estimate of prognostic value. Neither factor had a significant bearing on the length of second hematologic remission. The only treatment variable in the study, an intensive phase of chemotherapy given early in remission to one-half of the patients, was likewise unrelated to duration of remission. Factors that did correlate with the duration of second remission were length of first complete remission, time off therapy (unmaintained remission), and the number of initial sites of relapse. Although it has not been possible to predict relapse after cessation of therapy in individual patients,[11] these results may be of value in identifying prospectively those children who are likely to attain prolonged second remission once they do relapse.

The lengths of second marrow remission in this study varied widely, from 3 mo to 58+ mo (median 10 mo), despite uniform application of a standardized treatment. This may have resulted from differences in the growth potential of subpopulations of neoplastic cells not eradicated by initial treatment. For instance, the significant correlation between long first and second remissions (Table 2) could be taken to indicate a slower growth rate of leukemic cells in these patients than in those with brief remissions. Alternatively, this variable therapeutic responsiveness could signify a difference in the biologic nature of the relapses. Serial cytogenetic studies have indicated only minor changes in the karyotype of leukemic cell populations examined before and after relapse. These findings were taken to support the contention that relapse "signifies the re-emergence of the original malignant clone from a dormant or suppressed state."[12] If so, treatment of recurrent leukemia with previously used agents would be expected to produce only temporary remissions in the best of circumstances. This proposal explains very well the course of patients who in the present study relapsed soon after retreatment following brief unmaintained remissions. For the remaining patients, whose first and second remissions were relatively prolonged, one could speculate that chemotherapy had completely eradicated the original leukemic cell population, and after treatment was stopped, a new clone of leukemic cells had emerged due to the persistence of a leukemogenic factor. Since these resurgent cells may not have been exposed to chemotherapy, they might be more sensitive to drug action, resulting in an improved therapeutic response. The emergence of different clones of leukemic cells in previously treated patients is supported by several recent reports demonstrating malignant transformation of engrafted normal marrow cells in patients with leukemia,[13] the presence

of distinct lymphocytic and monocytic leukemic cell populations in the same patient,[14] and "second leukemias" (myeloblastic type) in patients with ALL who were in extended remission.[15]

The frequency of meningeal leukemia as the first site of relapse was as high in these patients as in children in initial remission who in earlier studies did not receive CNS prophylaxis.[16] We attribute this to the failure to give preventive CNS treatment immediately after marrow relapse. Although originally excluded from the reinduction plan because each child had previously received CNS prophylaxis, this phase of therapy has now been added to our current protocol study of patients who relapse off therapy, and its effectiveness is being evaluated. It is well recognized that foci of leukemic cells may be found in extramedullary sites during complete hematologic remission,[17] and disease activity may return because of the growth of drug-resistant cells in these tissues. In fact, lymphoblasts in the spinal fluid of some patients in this study had acquired resistance to methotrexate,[2] necessitating the use of other antineoplastic drugs for effective intrathecal therapy. The decision to administer a second course of CNS irradiation to children eligible to have their therapy stopped again was based on earlier findings that patients not receiving preventive CNS irradiation before termination of therapy were at highest risk to relapse during unmaintained remissions.[1,11] It was reasoned that such preventive therapy would be especially beneficial to patients who had developed meningeal leukemia during second remission, as intrathecal chemotherapy may not have completely eradicated the disease.

The incidence of testicular involvement should also be emphasized. Of 11 boys admitted to the study, 4 presented with combined marrow and testicular involvement; another patient developed gonadal infiltration while in prolonged second marrow remission. In the Total Therapy program at this center, 145 boys have been removed from treatment after prolonged first remissions. Of the 39 who subsequently relapsed, 16 (0.41%) had testicular leukemia with or without a concomitant marrow relapse. A study by British investigators has demonstrated that in a series of 60 patients with ALL the highest frequency of testicular relapse occurred within 1 yr after treatment was stopped.[18] Because the frequency of testicular involvement, as the first site of relapse, is high in children who relapse off therapy, open testicular biopsies were performed in all boys before therapy was stopped again.

Guidelines for stopping therapy a second time in children with ALL are not well defined. When this protocol was designed, 30 mo of complete hematologic remission (or, at least, 12 additional mo of hematologic remission after an extramedullary relapse) was chosen as the time to stop all treatment. This criterion was based on results obtained with patients who had not experienced bone marrow relapse.[1] Whether longer periods of chemotherapy would substantially increase the duration of second remission is difficult to determine, owing partly to the limited experience with second cessation of treatment[11,19] and partly to a lack of understanding of the nature of relapse. If hematologic relapses are related mainly to the emergence of drug-resistant leukemia, as most believe,[20] it is unlikely that remission can be prolonged by merely extending the second continuation phase of treatment, especially if one or more of the antileukemic agents had been used in the original course of therapy. Rather than extend the duration of therapy in such cases, the use of additional phases of treatment with alternative agents should be considered.

We conclude that children with ALL who relapse after cessation of therapy

should be treated as intensively as newly diagnosed patients and that particular emphasis should be placed on early detection and prevention of extramedullary disease.

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