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Recurrent Childhood Lymphocytic Leukemia: Outcome of Marrow Relapses After Cessation of Therapy*

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A. Introduction

Leukemia therapists have long agreed that relapse – particularly in the bone marrow – signals the end of opportunities to obtain long-lasting remissions. This thinking can be traced to the emergence of drug-resistant lymphoblasts, the hallmark of leukemia in relapse, and to the lack of sufficient numbers of uniformly treated patients for analysis and comparison. It is becoming clear, however, that in patients with recurrent acute lymphocytic leukemia (ALL), treatment responses differ widely. Second hematologic remissions, for instance, are significantly longer in children who relapse after therapy is electively stopped than in those who relapse during therapy (Chessells and Cornbleet 1979; Ekert et al. 1979; Kearney et al. 1979; Rivera et al. 1976, 1978). Furthermore, in some patients, treatment can be stopped altogether for a second time with the possibility of continued disease-free survival (Rivera et al. 1979). The purpose of this article is to review the clinical course of 56 patients who were retreated for marrow relapses that developed after cessation of intensive initial treatment.

B. Patients Studies

From 1966 to 1978, 288 of 645 (0.44) children with ALL who were entered in Total-Therapy Studies I–VIII at St. Jude Children's Research Hospital (SJCRH) had all therapy stopped. The details of each study group have been presented in earlier publications (Aur et al. 1978; Simone et al. 1972). Treatment was discontinued after 2–3 years of complete remission; thereafter, the patients had marrow and cerebrospinal fluid examinations at intervals ranging from every 2 months during the 1st year to annually after the 5th year off therapy. Of these 288 patients, 72 (0.25) have relapsed. Fifty-six children developed marrow relapses during unmaintained remissions; in 43 only the marrow was involved, whereas in the remaining 13 the testes and central nervous system (CNS) were involved as well. Sixteen additional patients had isolated extramedullary relapses: 11 testicular and 5 CNS (Table 1). This review includes only the 56 patients who developed hematologic relapses with or without other sites of leukemic involvement.

Table 1. Results of stopping therapy in childhood ALL: SJCRH Studies I–VIII[a]

No. of patients entered			645
No. electively removed from treatment			288
No. still in remission (2–14 Yr)			216
No. relapsing			72
Sites of relapse in 72 patients			
1. Bone marrow		*2. Extramedullary*	
BM alone	43	CNS	5
BM+CNS	5	Testicular	11
BM+T	6		
BM+T+CNS	2		
	56		16

[a] As of 1 June 1980. BM, bone marrow; CNS, central nervous system; T, testicular

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C. Retreatment Without CNS Prophylaxis

From 1970 to 1973, when no uniform second treatment plan was available, 13 patients who relapsed off therapy were treated again with essentially the same therapy as used originally. CNS prophylaxis at the time of relapse was not used. Only 2 of these 13 patients are living free of disease; both are off therapy for a second time for 39+ and 51+ months and survive 11+ and 14+ years from diagnosis. An additional patient refused further treatment and has been lost to follow-up.

From 1973 to 1976, 17 children with leukemia in relapse were enrolled in the institution's first formal relapse protocol (see Table 2). Each received reinduction chemotherapy with prednisone, vincristine, and adriamycin (4 weeks), and all were randomized at the time of remission to receive or not to receive an intensive phase of chemotherapy with asparaginase and cytosine arabinoside (ara-C) (2 weeks). Continuation therapy consisted of mercaptopurine and methotrexate (MTX) (30 months). CNS prophylaxis was not used. Sixteen patients attained second remissions and were followed for 5–6 years; the median duration of marrow remission was 10 months (range 3–78+). Each child relapsed again: eight in the marrow, six in the CNS, one in the testes, and one in both marrow and CNS. Remission durations were not discernibly different between children who did or did not receive the intensive phase of chemotherapy. In four of the seven patients with new isolated extramedullary relapses, remissions were reinduced and, after 30–44 months of continuous second marrow remission, all therapy was stopped again. In three of these four patients, new marrow relapses developed within 1–7 months; one child remains in remission 48+ months after having treatment stopped for a second time.

The lengths of second remissions in this study varied widely, from 3 to 78+ months, despite uniform application of a standardized treatment. Analysis of the relationships between selected patient variables and the duration of second hematologic remission yielded several significant results. The features analyzed were sex, age, and leukocyte count at diagnosis and at relapse; length of first complete remission; time off therapy to relapse; proportion of blasts disclosed by marrow examination; and number of sites at the time of relapse off therapy. An initial complete remission duration of less than 3 years, a relapse occurring within 6 months of cessation of first therapy, and the presence of marrow plus extramedullary sites of relapse on admission to the study all proved to be unfavorable prognostic indicators.

D. Retreatment Including CNS Prophylaxis

The overall incidence of second marrow and/or extramedullary relapses in the preceding study – 16/16 patients – together with the moderate toxicity encountered during treat-

Table 2. Treatment Programs for recurrent ALL[a]

	First study (No. = 17)	Second study (No. = 23)
Reinduction phase (4 wk)	Pred 40 mg/m²/day p.o. × 28 VCR 1.5 mg/m²/wk IV × 4 Adria 40 mg/m² IV days 1 and 15	Same as first study
Intensive phase (2 wk)	ASP 10,000 IU/m²/wk IV × 2 ara-C 300 mg/m²/wk IV × 2	None
Continuation phase (30 mo)	MP 50 mg/m²/day p.o. MTX 40 mg/m²/wk p.o.	ara-C 300 mg/m²/wk IV MTX 40 mg/m²/wk p.o.
Late intensive phase (4 wk)	None	Same as reinduction
CNS prophylaxis	None	I.T. MTX 10 mg/m² + ara-C 50 mg/m² wkly × 4 during induction and every 6 wks during continuation therapy

[a] Pred, prednisone; VCR, vincristine; Adria, adriamycin; ASP, asparaginase; ara-C, cytosine arabinoside; MP, mercaptopurine; MTX, methotrexate; p.o., orally, IV, intravenously; I.T., intrathecally

ment indicated that additional therapy was needed. The proportion of patients having the meninges as a first site of relapse was unusually high, equalling the figure for patients with marrow relapses. This indicated that systemic relapses had nullified the effects of earlier successful CNS prophylaxis. We reasoned that under this circumstance a new prophylactic CNS treatment would be especially beneficial. This hypothesis was tested in a second study in which two major questions were asked. Will the periodic administration of intrathecal chemotherapy, given at the time of relapse and throughout second remission, significantly reduce the incidence of CNS leukemia? Will the administration of a *late* intensive phase of chemotherapy at the end of 30 months of continuation therapy prevent subsequent marrow relapses off therapy?

Briefly, treatment consisted of (1) the same reinduction therapy as in the first study but with the addition of four weekly injections of MTX plus ara-C, (2) 30 months of continuation therapy with ara-C and MTX and intrathecal injections of both agents every 6 weeks, and (3) a late intensive phase of therapy with the same three agents – prednisone, vincristine, adriamycin – successfully used for reinduction of remission (4 weeks) (see Table 2). Then, treatments were stopped a second time.

In these patients intrathecal chemotherapy replaced cranial irradiation because on admission to the study each child had received a course of irradiation to the brain at the time of initial diagnosis. Although the toxicity of a second course of cranial irradiation is not known at present, there is histopathologic evidence that CNS toxicity may be related to high doses of radiation (>2000 rads) (Price and Jamieson 1975). Therefore, rather than administer additional irradiation, we elected to study the effectiveness of intrathecal chemotherapy alone for the prevention of CNS leukemia.

All 23 patients studied in the second protocol attained complete remission and have now been followed for 20 months to 4 years. The median duration of hematologic remission was 14 months (3–50+). Although 14 patients have again relapsed in the marrow, none has developed a CNS relapse. This represents a significant improvement over the high frequency of CNS relapses in the preceding study ($P=0.02$ by the log rank test). Nine patients remain in continuous second complete remissions for 19 to 50+ months. In five patients, treatment was stopped again, and only one child has developed a subsequent relapse after a year of unmaintained remission. Vomiting, often severe, was the major form of toxicity and was attributed to intravenous as well as intrathecal administration of ara-C.

Periodic prophylaxis with intrathecal chemotherapy effectively prevented CNS leukemia but did not appreciably influence the median duration of marrow remission. In fact, children not receiving a second course of CNS prophylaxis had median remission time of 10 months vs. 14 months for patients in the later study. Combinations of ara-C and MTX for continuation treatment of second remissions were not therapeutically superior to combinations of mercaptopurine and MTX but did induce more pronounced gastrointestinal toxicity. The fact that more than one-half (0.60) of the patients in this group have relapsed again indicates a need for more effective methods of therapy aimed mainly at prevention of marrow relapses.

The final two patients to relapse off therapy were recently entered in a new treatment protocol and are now in remission for 6+ months each.

E. Long-Term Disease-Free Survival

Of the 56 patients reported here, 38 have died of leukemia, one was lost to follow-up, and 17, about one-third, survive (Table 3). Nine survivors are still receiving therapy, and eight are off therapy again. Among those being treated,

Table 3. Outcome of marrow relapses after elective cessation of therapy

No. of patients	56
No. dying of leukemia	38
No. lost to follow-up	1
Survivors in remission	17 (0.30)
Survivors	
In second remission	14
On therapy (6–23+ mo)	7
Off therapy (1–51+ mo)	7
In third remission	3
On therapy (7–18+ mo)	2
Off therapy (6+ mo)	1

seven are in second remission for 6 to 23+ months and two have been reinduced into new remissions after a second relapse off therapy. The durations of their third hematologic remissions are 7+ and 18+ months. Of the eight patients who had treatment stopped for a second time, one completed therapy only recently and six are in unmaintained second remissions for 12+ to 51+ months. Another child who also developed a second relapse off therapy attained a third remission and is now off treatment a third time for 6+ months.

Among the 17 survivors, 14 have had long-term leukemia-free remissions. Their median survival since diagnosis is 9 years (range 5–14 years), with a median of 33+ months (range 19+ to 76+ mo) of continuous complete remission since their last relapse.

F. Discussion

These results demonstrate that prolonged second remissions are attainable in about one-third of the patients who develop a marrow relapse after elective cessation of initial cure-oriented therapy. Most importantly, in a certain proportion of children therapy may be stopped altogether for a second time. Although it is still not possible to predict the likelihood of relapse in individual patients after cessation ot treatment (Simone et al. 1978), statistical analysis of patient variables at the time of relapse can provide a reliable estimate of prognosis. Patients whose first complete remission lasts longer than 3 years, whose first relapse occurs more than 6 months after cessation of therapy, and whose site of relapse is exclusively hematologic have a significantly better chance to attain a extended second remission.

Other large series of patients are not available for comparison. Instances of extended second remissions have been reported, but only in patients who relapsed after unmaintained remissions following short-term initial therapy, i.e., 3–13 months (Leventhal et al. 1975).

When first diagnosed with ALL, none of the children in these studies had clinical or biologic features that are today regarded as carrying a "high risk" for early treatment failure. The most plausible explanation for their variable therapeutic responsiveness is that subpopulations of leukemic cells not eradicated by initial treatment have different growth potentials, which would account for the wide range in duration of second remissions (3 to 78+ months). For the few patients who remain free of leukemia after completing a second course of therapy, one could speculate that there relapses stemmed from the emergence of a new (and hence more drug-sensitive) clone of leukemic cells. Evidence for the emergence of different clones of leukemic cells in previously treated patients is supported by several recent reports (Fisher et al. 1977; Merteksmann et al. 1978; Spector et al. 1979).

The treatment results presented here were obtained by administering a second program of thera y :omparable to that originally given to these children. The only notable exception was that CNS prophylaxis was not repeated in about one-half of the subjects, because at the onset of the study the need for such additional treatment was unknown. Repeating a treatment that has become ineffective would not be recommended today. It should be stressed, however, that even in this circumstance about onethird of our patients responded well to therapy, an outcome that compares favorably to results for initially treated childhood ALL. Ultimately, the prospects for obtaining larger proportions of long-term remissions following relapse will depend on the development of more effective chemotherapy, preferably with agents not used earlier, to suppress the emergence of drug-resistant disease. A new protocol study to test the value of cyclic combination chemotherapy for maintenance of second remissions is underway at this center.

We conclude that children with ALL who develop marrow relapses during unmaintained remissions should be retreated just as aggressively as *newly diagnosed* patients.

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