Outcome Following Late Marrow Relapse in Childhood Acute Lymphoblastic Leukemia

By Judith Chessells, Alison Leiper, and David Rogers

Thirty-four children with acute lymphoblastic leukemia, who developed bone marrow relapse after treatment was electively stopped, received reinduction, consolidation, continuing therapy, and intrathecal (IT) methotrexate (MTX). Sixteen children who relapsed within six months of stopping treatment had a median second-remission duration of 26 weeks; all next relapses occurred in the bone marrow. In 18 children who relapsed later, the median duration of second remission was in excess of two years, but after a minimum of four years' follow-up, 16 patients have so far relapsed again (six in the CNS). CNS relapse occurred as a next event in four of 17 children who received five IT MTX injections only and in two of 14 children who received additional regular IT MTX. Although children with late marrow relapses may achieve long second remissions, their long-term outlook is poor, and regular IT MTX does not afford adequate CNS prophylaxis. It remains to be seen whether more intensive chemotherapy, including high-dose chemoradiotherapy and bone marrow transplantation, will improve the prognosis in this group of patients.

CHILDREN WITH acute lymphoblastic leukemia (ALL) who have a bone marrow relapse after treatment is electively stopped tend to do better than those who relapse during therapy.[1-3] It has previously been shown that the length of hematologic remission after such a relapse is directly related to the length of time off treatment,[2,4] but there is little information about the long-term prognosis in this group of patients.

We report the results of long-term follow-up in a group of 34 consecutive patients who experienced bone marrow relapse after electively stopping treatment and have now been studied for a minimum of four years.

PATIENTS AND METHODS

The patients are 34 children who had a first bone marrow relapse after stopping treatment for ALL. The patients had been diagnosed between 1971 and 1976 and had originally received treatment according to protocols designed or being piloted for the Medical Research Council (MRC) Working Party on ALL in childhood.[5] The protocols involved induction with prednisolone, vincristine, and L-asparaginase (MRC-UK ALL II, III, and V); or with COAP (cyclophosphamide, vincristine, cytosine arabinoside (ara-C), and prednisolone); or prednisolone and vincristine followed by COAP plus vincristine, doxorubicin and L-asparaginase (MRC-UK ALL IV); and continuing chemotherapy with 6-mercaptopurine, methotrexate (MTX), and vincristine/prednisolone reinforcements.

All patients had received CNS prophylaxis with cranial irradiation (2,400 rad) and intrathecal (IT) MTX and/or spinal irradiation. All had received two or three years of maintenance (continuing) chemotherapy, the duration of maintenance being the subject of randomization in most instances.

The patients represent all those on follow-up study in our clinic who had had a bone marrow relapse off treatment as a first event between 1974 and 1979. No patient in this series had a previous extramedullary relapse, and no patient had a concurrent CNS relapse, but six boys in the series had concurrent testicular infiltration.

From mid-1977 onwards, all boys had wedge biopsies of both testicles before stopping treatment; the management of patients with positive biopsy specimens and/or isolated relapse has been described elsewhere.[6] The six boys had concurrent testicular infiltration before the introduction of routine biopsies. Biopsies were not repeated on any of the patients. All patients have now been studied for four to nine years after relapse.

Treatment After Relapse

All patients were reinduced with prednisolone and vincristine and 25 patients received consolidation therapy with cyclophosphamide, cytosine arabinoside, vincristine, and prednisolone (COAP); and doxorubicin, vincristine, and L-asparaginase as in the MRC-UK ALL IV induction therapy.[5] Nine patients received induction with vincristine, prednisolone, daunorubicin, and four weeks of L-asparaginase. One patient received bone marrow transplantation (BMT) in second remission from an HLA-compatible sibling donor. The rest received continuing (maintenance) chemotherapy with 6-mercaptopurine and MTX with vincristine and prednisolone reinforcements. Four patients received MTX intramuscularly and the rest orally. The six boys with testicular infilatration received radiotherapy to both testicles in a dose of 1,500 rad (two patients) and 2,400 rad (four patients).

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Table 1. Patients With Late Marrow Relapse: Clinical Features

Characteristics	Group I	Group II	Group III
Time off treatment	<6 mo	6 mo–1 yr	>1 yr
No. of patients	16	9	9
Initial WBC >20 × 10^9/L	9	1	...
No. of male patients	7	4	3
Concurrent testicular relapse	4	...	2
Previous negative testicular biopsy	2	1	2

All patients received IT MTX as further CNS prophylaxis. In patients relapsing between 1974 and 1977, this comprised a course of five IT MTX injections (12 mg/m^2, maximum of 12 mg) given during induction and consolidation. From 1978 onwards, because some children had developed CNS relapse,[2] all patients received additional regular IT MTX every four to six weeks during chemotherapy, and two children received a second course of cranial irradiation before stopping treatment a second time.

RESULTS

Response to Treatment

The clinical details of the 34 children are given in Table 1 in which patient data are divided into three groups according to the amount of time off treatment before relapse. The only child who received BMT was in group I. The response to treatment is illustrated in Table 2 in which it can be seen that three of the children in group I failed to achieve remission.

The median duration of second remission in patients in group I was only six months and only three patients remained in remission for more than one year. A second bone marrow relapse was the next event in all patients, including the patient treated by BMT who relapsed after two years. In patients relapsing more than six months off treatment, the median remissions were two to three years (Table 2); bone marrow relapse was the next event in nine of the 18 patients, a combined bone marrow and CNS relapse occurred in one, isolated CNS relapse in five, and a second neoplasm in one.

Table 2. Response to Treatment

Characteristics	Group I	Group II	Group III
Total No. of patients	16	9	9
No. of second complete remissions	13	9	9
Median duration (wk)	26	106	156
CNS relapse next event	0	3*	3
Bone marrow relapse next event	13	6*	4
No. still in second remission	0	0	2
Second neoplasm	0	1	0
No. surviving	1	2	5

*One patient combined CNS and marrow relapse.

The duration of second remission was equivalent whether the patient's induction comprised initial daunorubicin and L-asparaginase or the MRC-UK ALL IV protocol.

CNS Complications

Six of the 18 children, including the child with combined bone marrow and CNS relapse, in groups 2 and 3 had a CNS relapse as next event. This complication occurred in two of the 14 children receiving long-term IT MTX, in both cases after chemotherapy had again been stopped (one with accompanying marrow relapse). CNS relapse occurred in four of the remaining 17 children who received short-term IT MTX (one had elected to stop treatment). Three of the five children with isolated CNS relapse remain well in second CNS remission, having undergone a second course of craniospinal irradiation, and two of them have recently stopped treatment.

CT scans were performed in six asymptomatic children who had received regular IT MTX via lumbar puncture and scans were normal in all. One child in group III who had a bone marrow relapse three years after treatment received regular IT MTX via an intraventricular Ommaya reservoir (the only one in the series) and developed signs and computed tomography (CT) changes consistent with MTX leukoencephalopathy. One patient in group II developed a second neoplasm. Her original CNS prophylaxis had comprised cranial irradiation and IT MTX. Bone marrow relapse occurred ten months after elective cessation of therapy. A second remission was induced, and she remained on chemotherapy and was receiving regular IT MTX when, four years from diagnosis, she developed signs of spinal cord compression and was found on myelography to have an intramedullary tumor in the cervical region. A temporary remission was achieved with radiotherapy, but she died from tumor recurrence and was found at postmortem to have a cystic astrocytoma of the spinal cord.

Second Cessation of Therapy

Treatment was electively stopped a second time in seven children remaining in second remission. One child in group I, the only one in the series who received a BMT in second remission, had a combined marrow and testicular relapse two years after transplantation.

In the other six children, treatment was stopped after three to four years of chemotherapy. The only patient in this category in group II who had received regular IT MTX but declined further irradiation had a bone marrow and CNS relapse six months later. Five patients in group III stopped treatment: one developed a marrow relapse, two experienced CNS relapse (one despite regular IT MTX), and two remain in second remission. One of the two children in group III with CNS relapse as a second event has now been off treatment a third time for less than six months, and one boy in group II with isolated CNS relapse as a second event has also recently stopped treatment a second time.

Survival

The survival of all three groups of patients is illustrated in Fig 1. The median survival after first relapse ranges from one year in group I to greater than four years in group III, but as can be seen in the figure, only two patients have survived without subsequent relapse, and one of these has MTX-radiation encephalopathy.

There was no clear relationship between duration of initial remission and second remission in those patients relapsing more than a year after therapy (group III). Six patients had relapsed one year to 18 months off therapy; one is well and remains in second remission off treatment, and two remain in second marrow remission after treatment of CNS relapse. One patient relapsing between 18 months and two years after therapy has relapsed and died. Only two children presented after more than two years of unmaintained remission: one has subsequently relapsed again in the bone marrow and the other, the patient in this series with the longest first remission duration (six years from start of therapy and three years off therapy), survives with encephalopathy.

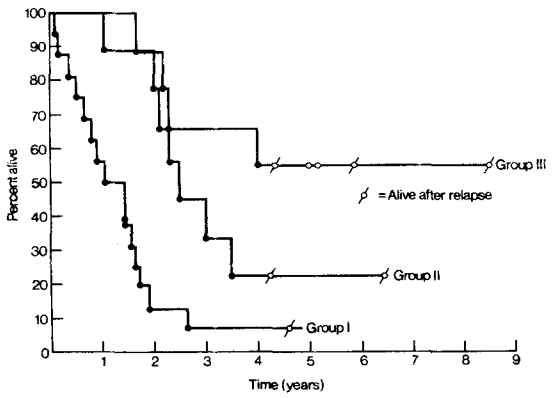

Fig 1. Survival rates from the time of first relapse for patients with early (group I), intermediate (group II), and late (group III) relapses.

DISCUSSION

These results confirm our previous observations that children who have a bone marrow relapse long after treatment has been electively stopped may achieve longer second remissions.[2]

The median remissions of patients relapsing more than six months after therapy compare favorably with those reported in other small series in which patients received intermittent combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP),[7] or cyclophosphamide, vincristine, cytosine arabinoside, and prednisolone (COAP).[8]

Nevertheless, longer follow-up of our patients has shown that only two of the 34 children remain off treatment in second remission, although an additional three children are well in second hematologic remission after CNS relapse. It is, perhaps, hardly surprising that the patients in group I all developed another bone marrow relapse since they presumably had residual undetected disease at the time of stopping therapy, and after reinduction, they received continuing chemotherapy with the same drugs as before. Even when alternative strategies are used, as recently reported by Rivera et al,[4] patients with early relapse off treatment did little better than those relapsing on therapy.

Although our patients in groups II and III had longer remissions, our results with two of 18 long-term survivors are inferior to those reported by the St Jude Children's Research Hospital group (Memphis), who reported eight of 16 such patients in prolonged second remission.[4] However, if our CNS reprophylaxis had been ade-

quate, at least three more patients would presumably have remained in second remission.

A high incidence of CNS relapse as a next event was reported in an early study from St Jude Childrens' Hospital.[3] These workers have now reported adequate CNS reprophylaxis with monthly IT MTX and ara-C.[4] The administration of regular IT MTX alone by the lumbar route did not prevent CNS relapse in our study, whereas the only patient in our series who received intraventricular MTX developed leukoencephalopathy despite the fact that six years had elapsed between the start of IT therapy and cranial irradiation. In this unrandomized study there was no evidence for superiority of either the MRC-UK ALL IV protocol or the induction with daunorubicin and L-asparaginase; both regimens are less intensive than our current protocol.[9]

The patients in this study with combined marrow and testicular relapse have done much worse than our patients with occult or overt testicular infiltration without bone marrow involvement,[6] presumably because they have more extensive disease. It is noteworthy that all presented before the introduction of routine testicular biopsy; it is possible that we are now more alert to the presence of clinical testicular infiltration. Disappointingly, it is apparent from the data in Table 2 and from our wider experience[6] that the introduction of routine testicular biopsy before stopping treatment has not prevented subsequent marrow relapse and there is, moreover, a substantial incidence of false-negative biopsies. The place for routine testicular biopsy in management of ALL remains unclear.

We conclude that children who relapse after treatment has been electively stopped may have long-term second remissions, but for the majority the outlook is poor, and regular IT MTX alone does not afford adequate prophylaxis against CNS relapse. We are now treating all children relapsing off therapy with intensive induction and consolidation, and we are comparing the outcome of those with an HLA-compatible donor to whom BMT is offered with the outcome of those receiving further intensive therapy and further cranial irradiation.[9] It remains to be seen whether these approaches will improve the outcome for children with ALL and late marrow relapse.

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