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Chemotherapy for bone marrow relapse of childhood acute lymphoblastic leukemia*

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Summary. Results of the BMF study group trials ALL-REZ 83 and 85 for relapsed acute lymphoblastic leukemia (ALL) are presented. For children with late marrow relapse, remission rates of about 90% were seen in both studies. In children treated for early marrow relapse, the remission rate in study ALL-REZ 85 was superior (86% vs 62%). The probability of event-free survival for all patients and for those with early marrow relapse was also statistically significant ($P < 0.05$). Children with T-cell ALL had an extremely unfavourable prognosis in both studies.

Introduction

Oxazaphosphorines have not been widely used for the treatment of childhood acute lymphoblastic leukemia (ALL), although they are known to be effective, especially in T-cell ALL and perhaps even more in B-cell ALL and non-Hodgkin's lymphoma. Cyclophosphamide has been included in treatment schedules of the BFM study group since 1970 [9], and the results have been unexpectedly good, even in children with T-cell ALL. Therefore, it seemed to be useful to include an oxazaphosphorine derivative in a protocol for relapsed ALL. As all children who relapsed after BFM treatment had received cyclophosphamide, ifosfamide was introduced in the treatment schedule for relapse, combined with other drugs known to be effective in ALL. The results of two BFM study group trials in relapsed ALL are be presented.

Patients and treatment

Since June 1983, 170 children and adolescents with bone marrow relapse of non-B-cell ALL or non-Hodgkin's lymphoma have been enrolled in two studies. Almost all patients had previously received treatment according to one of the BFM first-line protocols. Distribution of patients within the two subsequent studies (ALL-REZ 83 and 85) and patient characteristics are shown in Table 1. Age and sex as well as the median duration of the first remission were comparable in both studies. By definition, early relapses were those that occurred during therapy or up to 6 months after the discontinuation of first-line treatment, late relapses were those taking place thereafter. Bone marrow relapse could be either isolated in the presence of at least 25% blast cells in the marrow or combined with extramedullary sites. In the latter condition, bone marrow infiltration with leukemic cells had to exceed 5% and the extramedullary relapse, usually in the CNS or testicular tissue, had to be proven cytologically or histologically.

Table 1. Characteristics of patients with marrow relapse

	Study 83	Study 85
Patients (n)	58	112
Girls	41%	36%
Median age at relapse	9.6 years	7.4 years
Median duration, 1st CR	2.4 years	2.2 years
Early relapse	48%	53%
Bone marrow transplant	19%	13%

Treatment consisted of eight courses of intensive short-term polychemotherapy (Fig. 1) in patients with early marrow relapse, preceded by different induction courses in both experiments: E in study 83 (Fig. 2) and F in study 85 (Fig. 3). The only difference between the R-blocks (Figs. 4 and 5) in both studies was the regimen used for the administration of methotrexate (MTX). In study 83, all patients uniformly received MTX at a dose of 500 mg/m^2 in a 24-h infusion, followed by two doses of 15 mg/m^2 leukovorin each at 48 and 54 h after the start of MTX infusion. In study 85, patients were randomised to receive MTX in all treatment courses at a dose of 12 g/m^2 given during a 4-h infusion period, with 12 doses of leukovorin starting at 24 h after MTX (limb H) or at a dose of 1 g/m^2 (limb M) given over 36 h with the same leukovorin regimen as used in study 83.

After a total of eight R-blocks, treatment was continued with daily oral 6-thioguanine and biweekly i.v. MTX, both drugs given at a dose of 50 mg/m^2 each for 2 years. Children with CNS relapse were to be irradiated a second time at doses that were dependent on age and the preceding dose of radiotherapy; they also received prolonged triple intrathecal chemotherapy with MTX, cytarabine and prednisolone for 2 years after the diagnosis of relapse.

Bone marrow transplantation (BMT) was a constituent of treatment for children with a compatible donor. BMT was to be done soon after the second remission had been achieved, usually after two or three courses of chemotherapy. If no place for BMT was available, treatment was to be

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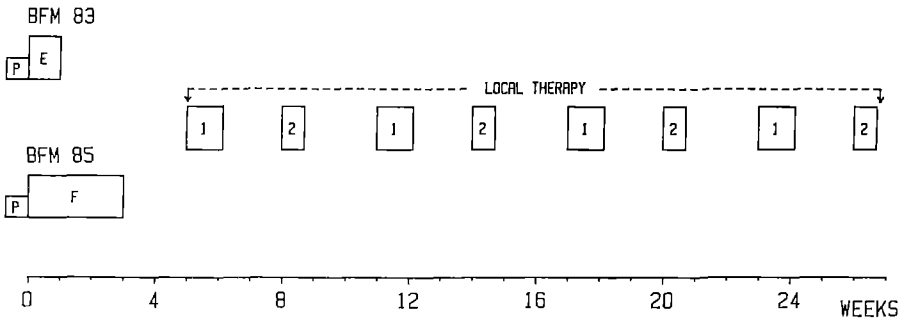

Fig. 1. Treatment design of two relapse studies for patients with bone marrow relapse. Induction protocol E in study ALL-REZ BFM 83 was replaced by protocol F in the subsequent study ALL-REZ BFM 85. Since 1985 patients have been initially randomised to receive MTX at a high or intermediate dose (BFM 85: randomization HDMTX vs IDMTX for all therapy elements)

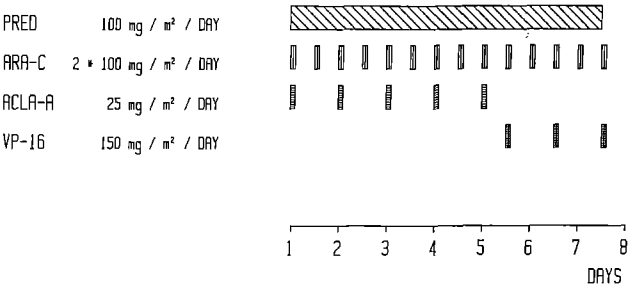

Fig. 2. Induction protocol E for children with early medullary relapse in study ALL-REZ BFM 83

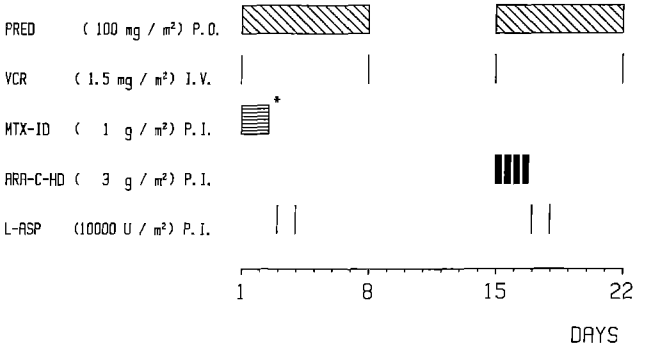

Fig. 3. Induction protocol F with intermediate-dose MTX (version F-M) as used for children with early medullary relapse in study ALL-REZ BFM 85. * Randomized vs HD-MTX (12 g/m^2) in version F–H

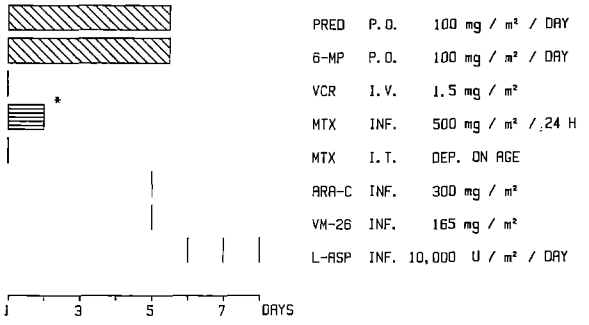

Fig. 4. The same combination polychemotherapy block R1 was given in studies ALL-REZ BFM 83 and 85, the only exception being different MTX doses. * BMF 85, randomization: HD-MTX Inf. (12 g/m^2/4 h), ID-MTX Inf. (1 g/m^2/36 h)

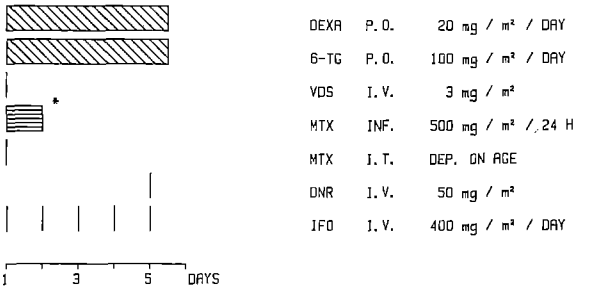

Fig. 5. Polychemotherapy block R2 in study ALL-REZ BFM 83 and 85 alternates with block R1. Only the MTX dose varied in both studies. * BMF 85 see legend to Fig. 4

continued according to the protocol until transplantation became possible.

As can be seen in Table 1, in studies 83 and 85 19% and 13% respectively, of the patients with bone marrow relapse underwent BMT. This report refers only to children who remained on chemotherapy; therefore, patients who underwent transplants were completely ruled out from analysis. Life-table curves were constructed according to the Kaplan-Meier method. Cox regression was used to detect prognostic factors within a multivariate model.

Results

As shown in Table 2, remission rates were comparable for children with late marrow relapses, about 90% in both studies. However, despite aggressive induction therapy for early relapsed patients, the remission rate (62%) was disappointingly poor in study 83 due to either non-response (6/26 patients) or toxic deaths (4/26 patients), whereas in study 85 second remissions were obtained in 86% of patients and there was only 1 toxic death.

Even more interesting is the impact of treatment on the probability of maintaining second complete remissions (2nd CR). As outlined in Fig. 6, the life-table curves of children with isolated and combined bone marrow relapse are superimposed. Therefore, it is justifiable to include patients with extramedullary relapse concurrent with bone marrow relapse. Figure 7 shows the probability of event-free survival for patients in both studies, the observed difference being statistically significant at $P < 0.05$. For patients with early marrow relapse, there is also a significant difference in the estimated length of the 2nd CR (Fig. 8),

Table 2. Remission rates in patients with marrow relapse (transplanted patients excluded)

	Totals	Early death	Non-resporders	2nd CR achieved
Early relapse:				
Study 83	26	4	6	16 (62%)
Study 85	51	1	6	44 (86%)
Late relapse:				
Study 83	21	0	2	19 (90%)
Study 85	46	2	2	42 (91%)

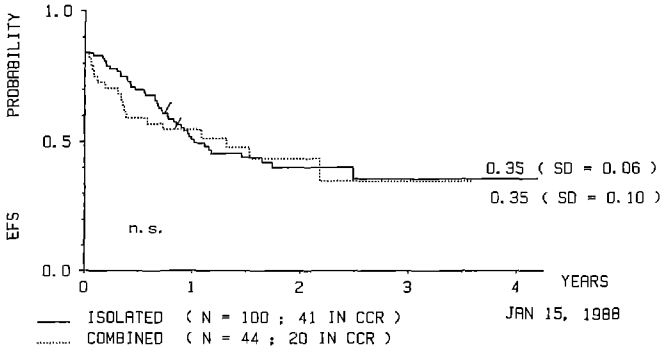

Fig. 6. Comparison of the probabilities of event-free survival (*EFS*) between children with isolated and combined bone marrow relapse in studies ALL-REZ BFM 83 and 85 (*diagonal slash* indicates last follow-up). *n.s.*, not significant

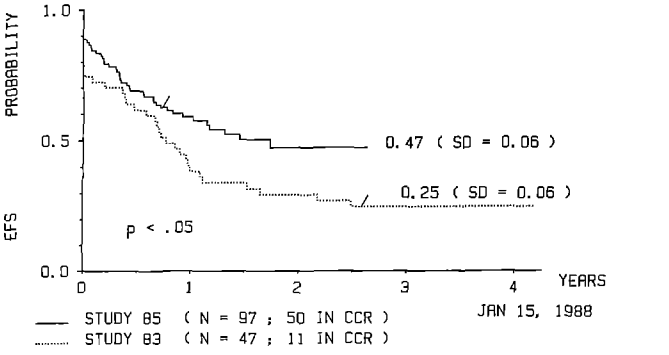

Fig. 7. Probability of event-free survival (*EFS*) in patients with marrow relapse in study ALL-REZ BFM 83 vs study ALL-REZ BFM 85, from the start of treatment

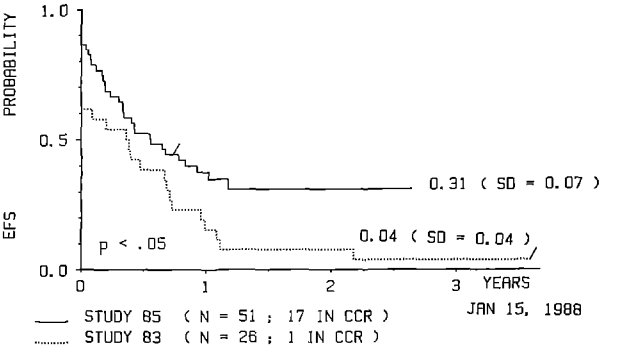

Fig. 8. Probability of event-free survival (*EFS*) in patients with early marrow relapse in study ALL-REZ BFM 83 vs study 85; the studies used different treatments for remission induction

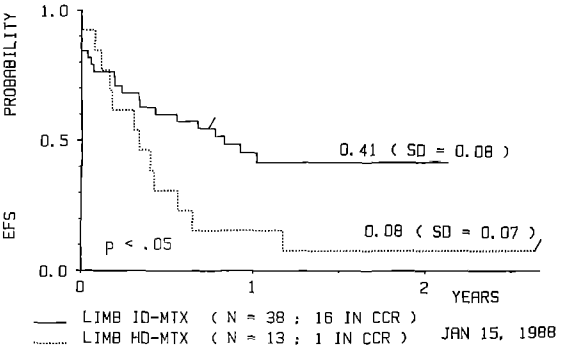

Fig. 9. Comparison of event-free survival (*EFS*) between treatment limbs M and H of study ALL-REZ BFM 85 in children with early marrow relapse

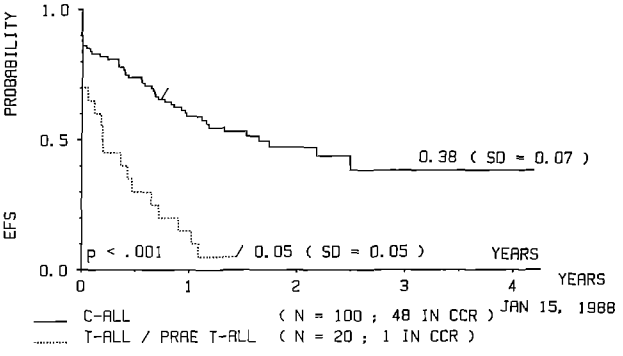

Fig. 10. ALL-REZ BFM 83 and 85 chemotherapy; BM relapse: influence of immunology. Probability of event-free survival (*EFS*) in patients with T-cell ALL and common ALL

which is due only to limb M of study 85 (Fig. 9). Comparing Figs. 8 and 9, it can easily be seen that the results of study 83 and limb H of study 85 are equally poor. Therefore, limb H was prematurely closed to patient entry, which explains the unequal number of patients in these limbs.

One subgroup of patients with an extremely unfavourable prognosis are children with T-cell ALL. These patients exhibit not only a much lower remission rate but also markedly shorter durations of 2nd CR (Fig. 10) than non-T-cell ALL patients. The difference observed between these patient groups is highly statistically significant. Of course, there is an overlap between T-cell leukemia and early relapse because most of the T-cell patients suffer early relapses. Using multivariate analysis, however, we found that in addition to the time of relapse, T-immunology is an independent prognostic factor. Interestingly, treatment with moderate-dose MTX in study 85 did not influence the prognosis in this patient group.

Discussion

The results of study ALL-REZ BFM 83 show that children with bone marrow relapse of ALL have 25% probability of event-free survival (including remission induction failures) at 4 years, which will probably be improved in study ALL-

REZ BFM 85. Taking into consideration that almost all of these patients were intensively pretreated according to BFM protocols, these results are surprisingly good. When looking at the life-table curves, there is already the suggestion of a plateau starting at 2.5 years, with all children from study 83 who remained in 2nd CR being beyond that time span and off treatment. Compared with other treatment results for relapsed ALL, these figures are similar to those obtained with bone marrow transplantation [3, 5, 11]. In almost all relapse studies using chemotherapy, the results are clearly inferior [1, 2, 4, 6–8, 10].

As new drugs were not used in the relapse protocol, the reason for these results must be the newly designed combination, suggesting that altered drug doses compared with initial treatment or drug interactions may play an important role in not only the treatment of relapse but treatment in general. This is best shown by the strikingly different results obtained in study 85 with the two different MTX regimens. Only one drug out of a complex setting of polychemotherapy, given in a different dose and time schedule and requiring different regimens for detoxification with leukovorin, produces completely different results. However, this is not true for the subset of children with T-cell leukemias. Obviously, the combination of drugs used in this protocol is less effective in T-cell disease. Thus, it is not only a question of the intensity of treatment but also of specificity, which implies that subsets of ALL are biologically heterogeneous diseases and must accordingly be treated with different regimens.

As mentioned above, an astonishing finding was the superior outcome for children with T-cell ALL who had been treated with BFM first-line protocols since 1970. One major difference between BFM and other regimens was the quite high dose of cyclophosphamide given during consolidation. Of course, the good results obtained in T-cell disease cannot conclusively be related to cyclophosphamide; on the other hand, this possibility cannot be ruled out. In the relapse studies, the ifosfamide dose was very moderate. Hence, in view of the poor outcome for patients with relapsed T-cell disease, it seems reasonable that oxazaphosphorines be more extensively used in this subset of patients. A pilot study using high-dose ifosfamide that has just begun is aimed towards the improvement of remission rates as well as the duration of 2nd CR in children with very early relapse and all children with T-cell disease.

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