

# High Cure Rate With a Moderately Intensive Treatment Regimen in Non-High-Risk Childhood Acute Lymphoblastic Leukemia: Results of Protocol ALL VI From the Dutch Childhood Leukemia Study Group

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**Purpose:** Here we report the results of a nationwide cooperative study in the Netherlands on acute lymphoblastic leukemia (ALL) in children. The aim of the study was to improve the cure rate and to minimize side effects in a group of non-high-risk ALL patients, especially with regard to the CNS. A second aim was to study potential prognostic factors.

**Methods:** Children (age 0 to 15 years) with non-high-risk ALL (WBC count  $< 50 \times 10^9/L$ , no mediastinal mass, no B-cell phenotype, and no CNS involvement) were treated with a uniform protocol, ALL VI. The treatment protocol used 6-week induction regimen with three drugs (vincristine, dexamethasone, and asparaginase), three weekly doses of intravenous (IV) medium high-dose methotrexate ( $2 \text{ g/m}^2$ ), and 2-year maintenance therapy that consisted of alternating 5-week periods of methotrexate and mercaptopurine and 2-week periods of vincristine and dexamethasone. In the first year of maintenance, triple intrathecal therapy was administered every 7 weeks.

**Results:** From December 1, 1984 until July 1, 1988,

291 children with ALL were diagnosed; 206 were categorized as non-high-risk (71%), and 190 were treated according to protocol ALL VI. At 8 years, the event-free survival (EFS) rate was 81% (SE = 3%) and survival rate 85% (SE = 2.9%); the median follow-up time was 7.3 years (range, 36 to 117 months). The CNS relapse rate was 1.1% (two of 184 patients who achieved a complete remission [CR]). The only factor found to be of negative prognostic importance in terms of EFS ( $P = .05$ ) was a positive acid phosphatase reaction.

**Conclusion:** For children with non-high-risk ALL, the combination of IV medium high-dose methotrexate ( $2 \text{ g/m}^2$  times three), triple intrathecal therapy in the first year of maintenance treatment, and the use of dexamethasone for induction and pulses during maintenance treatment has proved to be highly effective, especially in the prevention of CNS relapse. A high cure rate was achieved without the use of anthracyclines, alkylating agents, and cranial irradiation.

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IN 1984, the Dutch Childhood Leukemia Study Group (DCLSG) started a population-based study in the Netherlands for children with non-high-risk acute lymphoblastic leukemia (ALL) based on the classic St Jude protocols. This study, ALL VI, closely resembled the preceding DCLSG ALL V study.<sup>1</sup> However, the results of the ALL V protocol had proved disappointing in terms of event-free survival (EFS;  $54.7\% \pm 4.5\%$  for group A and  $62.5\% \pm 4.5\%$  for group B at 5 years) and especially the number of CNS relapses, which had been high (18%). Moreover, at the time protocol ALL VI was drafted, it had become apparent that cranial irradiation had unwanted late side effects.<sup>2,3</sup> Therefore, a combination of three alternative methods for presymptomatic CNS treatment was used in ALL VI. The first was the use of intravenous medium high-dose methotrexate ( $2 \text{ g/m}^2$  in 24 hours for three courses) with citrovorum factor rescue after 36 hours.<sup>4,5</sup> The second was the prolonged administration of triple intrathecal therapy during the first year of maintenance.<sup>6,7</sup> The third was the use of dexamethasone in induction and in pulses during maintenance instead of the standard corticosteroid prednisone. This change was based on the experience of Cancer and Leukemia Group B (CALGB),<sup>8</sup> which demonstrated in a randomized study significantly less CNS relapses if dexamethasone was substituted for prednisone in a supposedly equivalent dos-

age. In protocol ALL VI, cranial irradiation was omitted. All patients were treated uniformly and there was no randomization, as it was projected that with current results an answer to a two-arm study would not be obtained within a reasonable time span, considering the patient numbers in the Netherlands (the annual accrual rate is approximately 65 new cases with non-high-risk ALL).

Thus, the primary goal of this study was to improve the cure rate without cranial irradiation. A second goal was to study potential prognostic factors with the aim to restrict the non-high-risk group in future treatment protocols to patients without risk-increasing characteristics. Preliminary results were published in 1990.<sup>9</sup> The results of this protocol for a group of patients that comprises 71% of all newly diagnosed patients with ALL in the Netherlands during the study period are now reported after a median follow-up time of 7.3 years (range, 36 to

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117 months) (one patient was lost for follow-up evaluation 36 months after study entry).

METHODS

Patients

This nationwide, multicenter study was limited to newly diagnosed non-high-risk patients, defined previously in the DCLSG protocol ALL V<sup>1</sup> as follows: age 0 to 15 years, initial WBC count less than  $50 \times 10^9/L$ , and absence of a mediastinal mass and/or cerebromeningeal leukemia at diagnosis, defined as the absence of blasts (cytomorphologically) in a CSF specimen collected at diagnosis, to be confirmed by the DCLSG laboratory. Also, patients with B-ALL, morphologic (French-American-British [FAB] type L3) or immunophenotypic (serum immunoglobulin M positivity), were excluded from the study, as well as patients pretreated with corticosteroids and/or cytostatic drugs shortly before the diagnosis of ALL. Informed consent was obtained according to institutional guidelines before treatment was started.

Diagnosis

The diagnosis of ALL was made by cytomorphologic and cytochemical examination of blood and bone marrow smears at the local institution, followed by confirmation and classification according to the FAB criteria by the DCLSG laboratory.<sup>10,11</sup> For a diagnosis of ALL,  $\geq 25\%$  blasts in the bone marrow was mandatory. Acid phosphatase positivity was determined as previously described.<sup>12</sup>

Immunophenotyping was performed by the Central Laboratory of the Red Cross Blood Transfusion Service for patients diagnosed between December 1984 and December 1986<sup>13</sup> and by the DCLSG laboratory for patients diagnosed after 1986.<sup>14</sup> The relative DNA content per cell was calculated as the DNA index<sup>15</sup> by the Department of Experimental Therapy of the Netherlands Cancer Institute, Amsterdam.

Handmirror cells (HMC) were defined and counted at the DCLSG laboratory.<sup>16</sup>

Karyotyping of leukemic cells was performed in cytogenetic laboratories in the university hospitals.<sup>17</sup>

The absence of CNS involvement was assessed in a sample of

CSF drawn at diagnosis, sent to the DCLSG laboratory and mixed 1:1 with transport medium,<sup>18</sup> and checked for leukemic cells by cytomorphology.<sup>19</sup>

Treatment

The treatment scheme of the ALL VI study is outlined in Fig 1. Remission induction consisted of vincristine (2 mg/m<sup>2</sup>/wk by intravenous [IV] push times six; maximum, 2.5 mg/dose), dexamethasone (6 mg/m<sup>2</sup> daily divided into three doses for 4 weeks, then tapered off to 0 mg in 10 days), and asparaginase (200 U/kg/d IV for 14 days during weeks 5 and 6). On days 15 and 29, methotrexate and prednisolone were administered intrathecally in equal doses (doses according to age: < 1 year, 6 mg; 1 year, 8 mg; 2 years, 10 mg;  $\geq 3$  years, 12 mg).

After complete remission [CR] was achieved, three weekly courses of IV methotrexate (2,000 mg/m<sup>2</sup>: 400 mg/m<sup>2</sup> IV push and 1,600 mg/m<sup>2</sup> IV in 24 hours) were administered with intrathecal methotrexate and prednisolone 1 hour before each methotrexate push injection (dose according to age given in Remission Induction section), followed by citrovorum factor rescue and starting at 36 hours after the start of each methotrexate infusion (dose adapted to age: < 2 years,  $5 \times 5$  mg; 2 to 5 years,  $5 \times 10$  mg;  $\geq 6$  years,  $5 \times 15$  mg; orally at 6-hour intervals)

Maintenance treatment consisted of mercaptopurine (50 mg/m<sup>2</sup>/d orally) and methotrexate (30 mg/m<sup>2</sup>/wk orally or IV) for 5 weeks, alternated with vincristine and dexamethasone (doses as for induction treatment) for 2 weeks.

During the first year of maintenance treatment, intrathecal triple therapy was administered as follows: methotrexate and prednisolone (doses as described earlier) and cytarabine (dose according to age: < 1 year, 15 mg; 1 year, 20 mg; 2 years, 25 mg;  $\geq 3$  years, 30 mg) every 7 weeks on the same day as the first dose of vincristine. The total duration of treatment was 116 weeks.

During maintenance treatment, *Pneumocystis carinii* prophylaxis was recommended. (trimethoprim-sulphamethoxazole [TMP/SMZ], 75 to 100 mg TMP/m<sup>2</sup>/d in one or two doses).

Evaluation Criteria

CR was defined as less than 5% blasts in the bone marrow and (recovery of) normal hematopoiesis, absence of blasts in the periph-

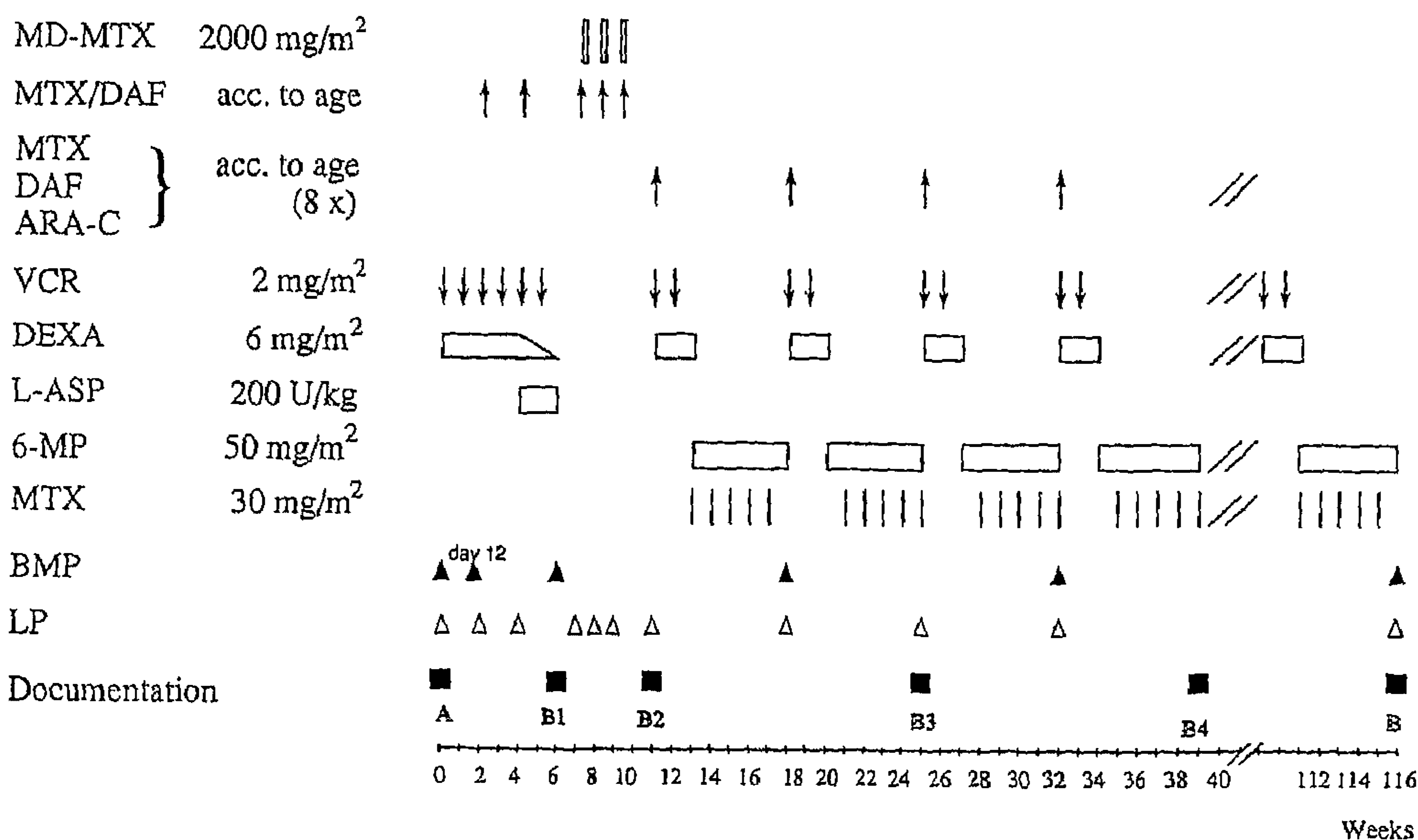


Fig 1. Treatment scheme of protocol ALL VI. MD-MTX, medium high-dose methotrexate; DAF, prednisolone; VCR, vincristine; DEXA, dexamethasone; L-ASP, asparaginase; 6-MP, mercaptopurine; MTX, methotrexate; ARA-C, cytarabine; BMP, bone marrow puncture; LP, lumbar puncture.

eral blood, and no evidence of disease at any other site. Relapse was defined as  $\geq 20\%$  blast cells in the bone marrow and/or blast cells in the peripheral blood, and/or CNS involvement, and/or leukemic infiltrates elsewhere.

CNS relapse was defined as the presence of blasts (cytomorphologically) in two successive CSF specimens, collected at least 24 hours apart without major blood contamination, confirmed by the DCLSG laboratory in the second specimen.

Results of treatment were evaluated by bone marrow examinations on days 12 and 42, and subsequently every 12 to 14 weeks during and up to 3 years after chemotherapy. All slides had to be sent to and examined at the DCLSG laboratory. Every 3 months, registration forms with data on dosage, toxicity, and results of treatment for each patient were sent to the DCLSG Operations Office. For comparison of treatment results achieved by the German Berlin-Frankfurt-Münster (BFM) Group, the BFM risk factor<sup>20</sup> for each patient was calculated.

### Statistical Methods

Event-free survival (EFS) was defined as the time from diagnosis to induction failure (no remission at day 42), relapse, death in remission, or the occurrence of a second tumor. Patients who did not enter remission by day 42 were included in the analysis and considered as treatment failures on day 0. The duration of survival was calculated from diagnosis to time of death; the time to latest follow-up evaluation was considered a censored observation. All analyses were based on data for all patients who entered the study; no patients have been excluded for whatever reason (treatment refusal, toxicity, etc).

Survival curves were calculated according to the Kaplan-Meier method<sup>21,22</sup> and standard errors using Greenwood's formula.<sup>23</sup> The statistical significance of differences in life-table curves was determined by the two-sided log-rank procedure,<sup>23</sup> and for ordered variables by the log-rank test for linear trend.<sup>23</sup> To summarize the prognostic importance of a variable for EFS analysis, the following information is given: the total number of patients in each category, the total number of observed events (O) and the estimate of the relative risk of having an event (E) per time unit computed via the O/E ratio.<sup>23</sup>

## RESULTS

### Patients

From December 1, 1984 to July 1, 1988, 291 consecutive children with ALL were diagnosed; 206 (70.8%) of them fulfilled DCLSG criteria for non-high-risk ALL. One hundred ninety children (65.3%) were entered onto the ALL VI study. Sixteen patients did not enter the study by mistake (one patient) or because of institutional choice (15 patients). One hundred fifty-two children were treated in one of the centers and 38 in a general hospital.

The characteristics of the 190 patients are listed in Table 1. The majority of patients was between 1 and 9 years old (87.9%), had a WBC count less than  $10 \times 10^9/L$  at diagnosis (70.0%), had FAB L1 morphology (75.3%) and common ALL (73.6%), and was treated in a center (80.0%).

Of 16 patients who did not enter the ALL VI study, 11 were 1 to 9 years old (69%), eight had a WBC count less than  $10 \times 10^9/L$  at diagnosis (50%), 11 had FAB L1

morphology (69%), 10 had common ALL (63%), and they were all treated in a center.

### Treatment Results

Treatment results are updated as of April 1, 1995. The median follow-up time was 7.3 years (range, 36 to 117 months). The overall results of treatment are listed in Table 2; EFS and survival are shown in Fig 2. The EFS estimation at 6 years is 82% (SE = 2.8%); the estimated proportion of patients still alive at 6 years after diagnosis is 87% (SE = 2.4%). The corresponding estimates at 8 years are 81% (SE = 3%) and 85% (SE = 2.9%), respectively. The outcome of the 16 patients not included in the ALL VI study was slightly worse than of those included in the study, but the difference did not reach statistical significance.

### Induction Treatment

Of 190 patients who entered the ALL VI study, 184 (96.8%) achieved a CR. One patient died of septicemia before treatment. Three children died during induction treatment: a boy with Down's syndrome died of septicemia, another boy died of accidental intrathecal administration of vincristine, and a third boy died of veno-occlusive disease and tumorlysis syndrome after the first injection of vincristine. Two children failed to achieve remission and died.

### Maintenance and Consolidation Treatment

After the induction period, four children died in first remission: two of septicemia during maintenance treatment, one during medium high-dose methotrexate treatment unexpectedly overnight at home (no autopsy was performed), and one of fungal cerebral abscesses, also during maintenance treatment.

Treatment modifications occurred in four patients. In one patient, medium high-dose methotrexate application was delayed for 2 months because of severe liver function disturbances. In two patients, maintenance treatment was terminated after 1 year because of severe liver toxicity in one and recurrent severe infections in the other. In one patient, maintenance treatment was interrupted for 2 months because of complicated appendicitis.

Twenty-five of 184 patients who achieved CR relapsed: 22 (12%) had an isolated bone marrow relapse and three (1.6%) an extramedullary relapse (two CNS [1.1%] and one testis [0.5%]) (Table 2). Nine children relapsed during treatment (eight bone marrow and one CNS) and 16 children relapsed after cessation of therapy (14 bone marrow, one CNS, and one testis). No combined bone marrow/CNS relapses occurred.

The prognosis after relapse was poor; the median sur-

Table 1. Patient Characteristics

Variable	No. of Patients	%
Age, years		
< 1	1	0.5
1	9	4.7
2-5	115	60.5
6-9	43	22.6
10-15	22	11.6
Sex		
Male	98	51.5
Female	92	48.5
WBC count ( $\times 10^9/L$ )		
< 10	133	70.0
10-24	43	22.6
25-49	14	7.4
Platelet count ( $\times 10^9/L$ )		
< 20	36	19.0
20-99	94	49.7
$\geq 100$	59	31.2
Unknown	1	—
FAB morphology		
L-1	143	75.7
L-2	46	24.3
Unknown	1	—
Acid phosphatase reaction		
Strong	14	8.4
Weak	18	10.8
Negative	134	80.7
Unknown	24	—
Immunophenotype		
c-ALL	130	81.3
Pre-B ALL	25	15.6
AUL	5	3.1
Unknown	30	—
Institution		
Center	152	80.0
General hospital	38	20.0
BFM risk factor		
< 0.8	103	57.0
0.8-1.19	63	34.8
$\geq 1.2$	15	8.2
Unknown	9	—
Cytogenetics		
Diploid	40	33.3
Hypodiploid	7	5.8
Pseudodiploid	15	12.5
Hyperdiploid (46-50)	18	15.0
Hyperdiploid ( $> 50$ )	32	26.7
Other	8	6.7
Unknown	70	—
Cytogenetics structure abnormality		
6q-	8	6.7
t(8;14)	1	0.8
Other	40	33.6
None	70	58.8
Unknown	71	—
DNA index		
< 1.16	85	68.0
$\geq 1.16$	40	32.0
Unknown	65	—
HMC (%)		
< 5	58	47.5
5-9	24	19.7
$\geq 10$	40	32.7
Unknown	68	—
% BM blasts at day 12		
< 5	75	51.7
5-19	38	26.2
$\geq 20$	32	22.1
Unknown	39	—

Abbreviations: AUL, acute undifferentiated leukemia; BM, bone marrow.

Table 2. Results of Treatment (April 1, 1995) in the ALL VI Study

Period of accrual	12/84-7/88
Total no. of patients	190
Deaths before treatment	1
Deaths during induction	3
No response	2
CR rate	
No.	184
%	96.8
Relapse	25
Site	
BM	22
CNS	2
Testis	1
Second tumor	1*
Deaths in first CR	4
Alive in first CR	155
Follow-up duration	
Range, months	36-117
Median, years	7.3

\*Second tumor after CNS relapse.

vival time is 25 months. Of 25 patients who relapsed, 15 (60%) died. The median estimates of survival postrelapse were significantly shorter for patients who relapsed on therapy ( $n = 9$ ) than for those who relapsed off therapy ( $n = 16$ ) (5 and 36 months, respectively;  $P = .008$ ). One child died of a secondary malignancy (acute nonlymphocytic leukemia) after relapse.

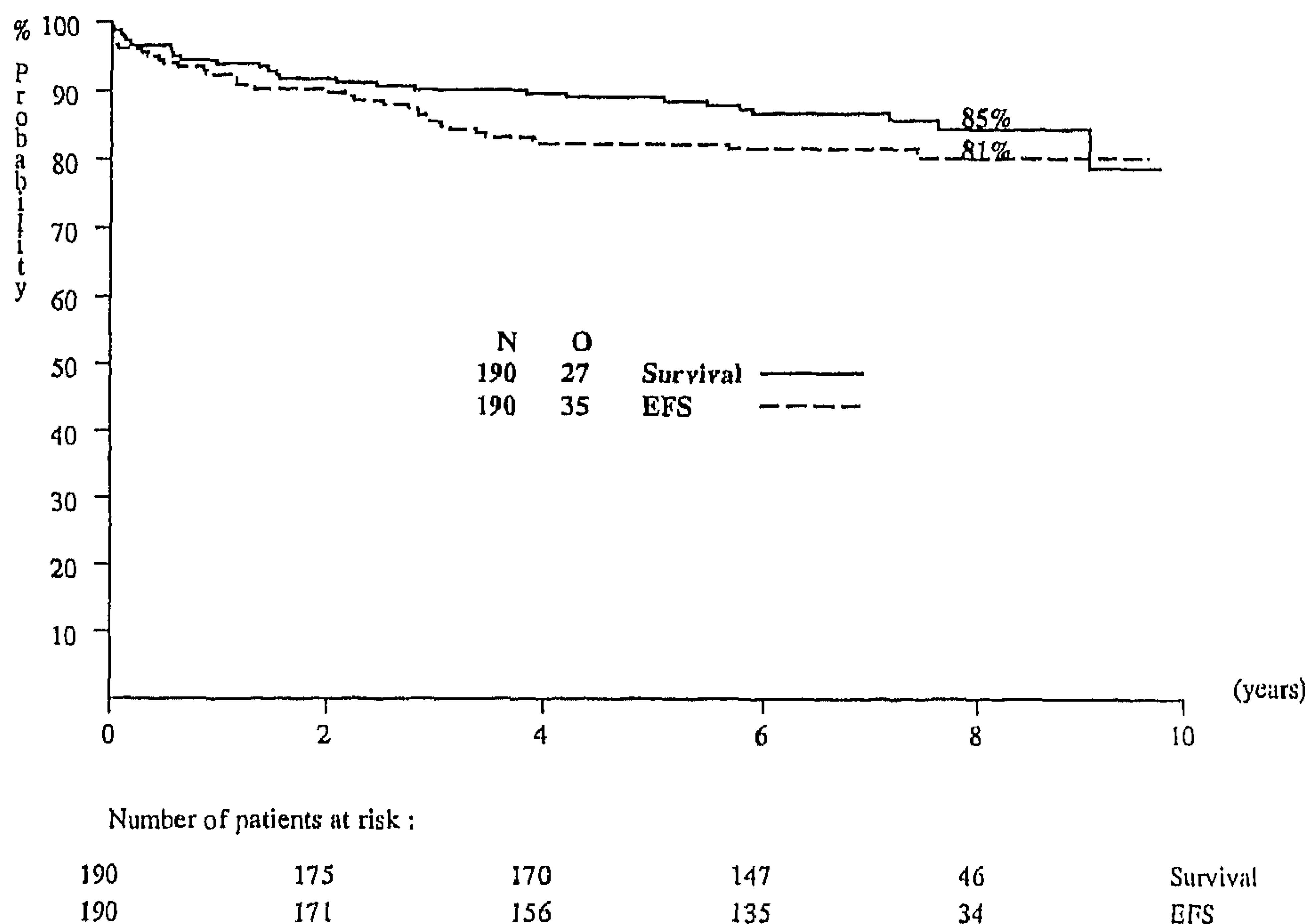
Treatment was well tolerated and in general could be given on an outpatient basis. However, in the dexamethasone periods, obesity, sleep disorders, and character disturbances were more pronounced than in the previous study using prednisone.

### Prognostic Factors

When the ALL VI study started, it was planned to evaluate a considerable number of prognostic factors, as follows: immunophenotype, DNA ploidy, karyotype, bone marrow at day 12, and HMC percentage. However, because of the limited number of patients ( $N = 190$ ), and especially the paucity of events (35 in total), the chance to detect a given prognostic factor is low. This is particularly true if a variable has many nonordered categories (ie, cytogenetics). On the other hand, dividing patients according to too many variables, one may obtain, just by chance, a significant result at the conventional alpha level of .05.

To choose a limited number of factors to analyze, the previous study of the DCLSG, ALL V, in which the same eligibility criteria were used, was analyzed.<sup>1</sup> Indeed, in this study, in which 240 patients were entered and 101 events reported, three factors appeared to be associated with a worse prognosis by univariate analyses: strong/weak acid phosphatase reaction ( $P = .0001$ ), high WBC count ( $P = .0002$ ), and low platelet count ( $P = .01$ ). For

Fig 2. Kaplan-Meier curve of EFS and survival.



this reason, we have particularly looked at these factors to see if they were still of prognostic importance in the present study, as well as at the DNA index<sup>24,25</sup> and early bone marrow response to induction treatment.<sup>26,27</sup>

Table 3 shows that the acid phosphatase reaction was still of weak prognostic importance in this study ( $P = .05$ ): the stronger the reaction, the worse the prognosis. Those with a strong positive reaction, representing 14 of 166 [8.4%] patients in the population, had a 2.8-fold

increased risk of failure compared with those with a negative reaction (134 of 166 [80.7%]). Where in ALL V the initial WBC count was linearly correlated with a worse prognosis, this was not the case in ALL VI ( $P = .38$ ): patients with a WBC count of 10 to  $24 \times 10^9/L$  seem to have a worse prognosis (relative risk, 1.93) than those with a low WBC count ( $< 10 \times 10^9/L$ ), but patients with the highest values (WBC count 25 to  $49 \times 10^9/L$ ), have a similar prognosis (relative risk, 0.90) as those with a low WBC count. The initial platelet count seems to be correlated with prognosis, although it does not reach statistical significance. Like in the ALL V study, patients with a normal platelet count at diagnosis have an approximately 50% reduction in the risk of having an event compared with those with a very low ( $< 20 \times 10^9/L$ ) or low ( $20$  to  $99 \times 10^9/L$ ) platelet count. Conversely, one may say that patients with a diminished platelet count have a twofold increased risk of having an event. Patients with a high DNA index ( $\geq 1.16$ ), who represent 32% of the patients entered onto the study, have a relative risk of 0.46 compared with those with a low DNA index ( $< 1.16$ ). Due to the low number of events (21 in total), one may not conclude that the true relative risk is statistically different from 1 ( $P = .14$ ).

Finally, day-12 bone marrow findings ( $< v \geq 5\%$  blast cells) were of no prognostic significance. However, an important group of patients (39 of 184 [21%]) either had a hypoplastic bone marrow or bone marrow puncture was not performed. Among available patients, 52% (75 of

Table 3. Prognostic Factors Analysis for EFS

	No. of Patients	No. of Events	Relative Risk	$P^*$
<b>Acid phosphatase reaction</b>				
Negative	134	20	1.00	.05
Weak	18	3	1.16	
Strong	14	5	2.83	
<b>WBC count (<math>\times 10^9/L</math>)</b>				
$< 10$	133	21	1.00	.40
10-24	43	12	1.87	
25-49	14	2	0.87	
<b>Platelet count (<math>\times 10^9/L</math>)</b>				
$< 20$	36	8	1.00	.16
20-99	94	19	0.91	
$\geq 100$	59	7	0.50	
<b>DNA index</b>				
$< 1.16$	85	17	1.00	.16
$\geq 1.16$	40	4	0.47	

\*Log-rank test for linear trend.

145) were good responders (< 5% blasts at day 12), whereas the remaining patients responded poorly. The outcome of these two groups, in terms of disease-free survival, was similar in this series (relative risk, 1.04).

### DISCUSSION

The results of protocol ALL VI for children with non-high-risk ALL are encouraging, with a projected long-term cure rate of 80%. The EFS rate at 6 years is 82%. In particular, the number of CNS relapses ( $n = 2$ ) and other extramedullary relapses (testes,  $n = 1$ ) was low. The most important cause for treatment failure was isolated bone marrow relapse. Nine (5%) of 190 patients experienced treatment-related toxicity (four very early).

The ALL VI study was preceded by the ALL V study (1979 to 1982) with identical criteria for patient eligibility.<sup>1</sup> In both studies, vincristine and asparaginase were given during induction, but in the ALL V study, prednisone (40 mg/m<sup>2</sup>/d orally) was given instead of dexamethasone (6 mg/m<sup>2</sup>/d orally). CNS prophylaxis in the ALL V study consisted of cranial irradiation (dose according to age: < 1 year, 15 Gy; 1 to 2 years, 20 Gy;  $\geq 2$  years, 25 Gy) with five courses of intrathecal administration of methotrexate and prednisolone (12.5 mg/m<sup>2</sup>/dose; maximum, 15 mg/dose), compared with intrathecal methotrexate and prednisolone on day 15 and 29 of induction treatment, three courses of IV medium high-dose methotrexate after CR, and continuation of intrathecal triple therapy during the first year of maintenance in the ALL VI study. Furthermore, patients in ALL V were randomized to receive rubidomycin (four weekly doses, 25 mg/m<sup>2</sup>) during induction treatment (group B [ $n = 118$ ]) or not to receive this fourth drug (group A [ $n = 122$ ]). In the ALL V study, the EFS rate at 10 years for group A was 49% (SE = 4.5%) and for group B 56% (SE = 4.5%) ( $P = .07$ ). In both groups, the number of CNS relapses (19 in group A and 12 in group B) was as high as the number of bone marrow relapses (20 in group A and 13 in group B). There were six combined relapses (bone marrow plus CNS) in group A and four in group B.

The combination of IV medium high-dose methotrexate (three times), prolonged intrathecal therapy, and substitution of prednisone by dexamethasone has proved to be highly effective in preventing CNS relapse and thus improving overall treatment results in non-high-risk ALL patients. The efficacy of IV methotrexate in the CNS depends on the duration of exposure above a specific threshold of the drug in plasma (> 24 hours,  $> 1 \times 10^{-6}$  mol/L), the plasma concentration (CSF-to-plasma ratio, 2% for methotrexate), and concurrent intrathecal methotrexate at the start of the infusion.<sup>28-32</sup> Intermediate-, medium-, and high-dose 24-hour IV infusions of methotrexate with citrovorum factor rescue

have been applied in many studies in the last decade to increase treatment efficacy and, serving as a substitute for cranial irradiation, to decrease toxicity.<sup>4,5,33</sup>

In St Jude Total Therapy Study X, high-dose methotrexate (15 courses at 1,000 mg/m<sup>2</sup>) was compared with cranial irradiation.<sup>34</sup> CR durations at 4 years were significantly longer in the methotrexate group (67% v 56%), with a lower rate of isolated bone marrow and testicular relapses compared with the irradiated group, but no difference in the occurrence of CNS relapse was observed. In a nonrandomized study, the Pediatric Oncology Group (POG) investigated the effectiveness of early intensification with a combination of high-dose IV methotrexate and mercaptopurine to take advantage of the synergy of these drugs and with the objective to decrease CNS relapses.<sup>35,36</sup> At 7 years, only one CNS relapse had occurred in 59 lower-risk patients; the EFS of this group had a plateau at 82.4%  $\pm$  7.5%. In the higher-risk group ( $n = 83$ ), nine patients suffered a CNS relapse. The EFS rate at 4 years of this higher-risk group was 57.4%  $\pm$  9.1%. The incidence of CNS relapse in both groups together was 11%, which is slightly higher than the 5% to 9% observed in previous POG studies. In the current DCLSG protocol ALL 8, a prospective randomized study is being performed to determine the effectiveness of the addition of conventional oral mercaptopurine versus IV high-dose mercaptopurine to high-dose methotrexate infusions as early intensification in medium-risk ALL patients.

Intrathecal methotrexate therapy during induction, consolidation, and maintenance treatment, which was associated with intensive systemic therapy in study CCG 105, provided a CNS relapse-free survival rate at 7 years of 91% for 507 intermediate-risk ALL patients.<sup>37</sup>

Triple intrathecal chemotherapy (methotrexate, cytarabine, and hydrocortisone), extended throughout the intensification and maintenance periods plus upfront intrathecal methotrexate for patients with B-progenitor ALL has proved to be even more effective in prevention of CNS relapse. In the POG ALinC 13 study, the estimation of freedom from isolated CNS relapse in 381 good-risk non-B-, non-T-ALL patients, which consists of 58% of all ALL patients, was 97.2% ( $\pm$  1.3%) at 5 years.<sup>38</sup> The higher effectivity of dexamethasone compared with prednisone is probably based on a combination of factors: dexamethasone has a longer duration of biologic action, less protein binding capacity leading to increased plasma free drug availability to lymphoblasts, and better penetration to CSF and a longer CSF half-life than prednisone.<sup>39</sup> In vitro drug-sensitivity testing has shown that dexamethasone appears to be sevenfold more potent than prednisone.<sup>40</sup> The results of the ALL VI study confirm the data

reported by Jones et al,<sup>8</sup> who found a considerable reduction of CNS relapses in a randomized trial of dexamethasone versus prednisone.

One of the aims of this study was to identify prognostic factors. However, with 190 patients and 35 events, leading to an estimated EFS rate of 80% at 7 to 8 years, it was difficult to reach this goal; with increasingly effective therapy, prognostic factors tend to lose their significance.

It must be kept in mind that non-high-risk status according to the criteria applied in ALL VI still leaves 29% of all children with ALL out of the study. Given the unequal criteria and composition of non-high-risk, standard-risk, and low-risk groups in other protocols, one might ask what the results are of all children with ALL (0 to 15 years) diagnosed in the accrual period of the ALL VI study. In the Netherlands at that time, high-risk patients were treated according to institutional protocols, some of which were based on the German BFM treatment strategy. The estimated EFS rate at 6 years for the total 291 children newly diagnosed with ALL in this period in the Netherlands was 72% (SE = 3%).

These overall data compare well with the overall results of other groups, including the BFM (69%)<sup>28</sup> and the Dana-Farber Cancer Institute (DFCI; 70%).<sup>41,42</sup> They are in the same range as the outcome data for recently treated children with B-precursor ALL in the combined POG and Childrens Cancer Group studies, in which the 4-year EFS

rate for 3,113 B-lineage patients age 1 to 9 years with a WBC count less than  $50 \times 10^9/L$  was 80.3%.<sup>43</sup>

In the St Jude Study XI, the 5-year EFS rate for lower-risk ALL patients, defined as age 1 to 9 years and WBC count less than  $50 \times 10^9/L$ , was 85% (SE = 3%).<sup>44</sup> However, in this study, two thirds of lower-risk patients received intensive therapy.<sup>45</sup> Thus, despite comparable results, the DCLSG ALL VI protocol may be preferable for this category of patients.

A major advantage of ALL VI treatment is that good results were achieved without the use of anthracyclines, alkylating agents, and cranial irradiation, which decreased the risk of late cardiac failure, second malignancies, and disturbances of cognitive functions. However, a longer follow-up duration and special studies are necessary to evaluate any late sequelae.

#### APPENDIX Board Members 1984

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