

Improved Outcome in Adult B-Cell Acute Lymphoblastic Leukemia

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A total of 68 adult patients with B-cell acute lymphoblastic leukemia (B-ALL) were treated in three consecutive adult multicenter ALL studies. The diagnosis of B-ALL was confirmed by L3 morphology and/or by surface immunoglobulin (SIg) expression with >25% blast cell infiltration in the bone marrow (BM). They were characterized by male predominance (78%) and a median age of 34 years (15 to 65y) with only 9% adolescents (15 to 20y), but 28% elderly patients (50 to 65y). The patients received either a conventional (N = 9) ALL treatment regimen (ALL study 01/81) or protocols adapted from childhood B-ALL with six short, intensive 5-day cycles, alternately A and B. In study B-NHL83 (N = 24) cycle A consisted of fractionated doses of cyclophosphamide 200 mg/m² for 5 days, intermediate-dose methotrexate (IdM) 500 mg/m² (24 hours), in addition to cytarabine (AraC), teniposide (VM26) and prednisone. Cycle B was similar except that AraC and VM26 were replaced by doxorubicin. Major changes in study B-NHL86 (N = 35) were replacement of cyclophosphamide by ifosfamide 800 mg/m² for 5 days, an increase of IdM to high-dose, 1,500 mg/m² (HdM) and the addition of vincristine. A cytoreductive pretreatment with cyclophosphamide 200 mg/m², and prednisone 60 mg/m², each for 5 days was recommended in study B-NHL83 for patients with high white blood cell (WBC) count (>2,500/m²) or large tumor burden and was obligatory for all patients in study B-NHL86. Central nervous system (CNS) prophylaxis/treatment consisted of intrathecal methotrexate (MTX)

therapy, later extended to the triple combination of MTX, AraC, and dexamethasone, and a CNS irradiation (24 Gy) after the second cycle. Compared with the ALL 01/81 study where all the patients died, results obtained with the pediatric protocols B-NHL83 and B-NHL86 were greatly improved. The complete remission (CR) rates increased from 44% to 63% and 74%, the probability of leukemia free survival (LFS) from 0% to 50% and 71% (P = .04), and the overall survival rates from 0% to 49% and 51% (P = .001). Toxicity, mostly hematotoxicity and mucositis, was severe but manageable. In both studies B-NHL83 and B-NHL86, almost all relapses occurred within 1 year. The time to relapse was different for BM, 92 days, and for isolated CNS and combined BM and CNS relapses, 190 days (P = .08). The overall CNS relapses changed from 50% to 57% and 17%, most probably attributable to the high-dose MTX and the triple intrathecal therapy. LFS in studies B-NHL83 and B-NHL86 was significantly influenced by the initial WBC count < or >50,000/ μ L, LFS 71% versus 29% (P = .003) and hemoglobin value > or <8 g/dL, LFS 67% versus 27% (P = .02). Initial CNS involvement had no adverse impact on the outcome. Elderly B-ALL patients (>50 years) also benefited from this treatment with a CR rate of 56% and a LFS of 56%. It is concluded that this short intensive therapy with six cycles is effective in adult B-ALL. HdM and fractionated higher doses of cyclophosphamide or ifosfamide seem the two major components of treatment. © 1996 by The American Society of Hematology.

MATURE B-CELL ACUTE lymphoblastic leukemia (B-ALL) is a rare ALL subtype comprising only 2% to 4% of adults with ALL. The leukemic cells are characterized by L3 morphology according to the French-American-British (FAB) classification,¹ with rare exceptions,²⁻⁵ by expression of monoclonal surface immunoglobulin (SIg) and by specific nonrandom chromosomal translocations, t(8;14)(q24;q32), t(2;8)(p12;q24), and t(8;22)(q24;q11). B-ALL had formerly a poor prognosis in children, as well as in adults.^{6,7} When adult patients with mature B-ALL were treated with conventional ALL regimens in the last decade (1981 to 1992), reports of nine studies⁸⁻¹⁶ on small numbers of two to nine patients gave low complete remission (CR) rates of 0% to 67%, (weighted mean 35%) and poor leukemia free survival (LFS) rates of 0% to 33%. This is supported by our earlier results obtained with a conventional ALL regimen described in this report.

The current treatment strategies for mature B-ALL were pioneered in pediatric studies. Murphy et al¹⁷ introduced fractionated high doses of cyclophosphamide (HdC) and high-dose methotrexate (HdM), which had been shown to be successful in the treatment of Burkitt's lymphoma.¹⁸⁻²⁰ These drugs were applied in addition to vincristine, doxorubicin, and AraC. The French Pediatric Oncology Society (SFOP) used, in addition to HdC and HdM, vincristine, prednisone, doxorubicin, and AraC.²¹ The German Study Group for childhood ALL, BFM (Berlin-Frankfurt-Münster), initiated a B-ALL protocol for children using six cycles of HdM,

fractionated doses of cyclophosphamide or ifosfamide, in addition to AraC, VM26, doxorubicin, and steroids.^{22,23} For central nervous system (CNS) prophylaxis and treatment of

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Submitted July 14, 1995; accepted September 5, 1995.

Supported by the Bundesministerium für Forschung und Technologie, Federal Republic of Germany, Contract No. 01ZP88045 and by Deutsche Krebshilfe, Federal Republic of Germany, Contract No. M84/92Ho1.

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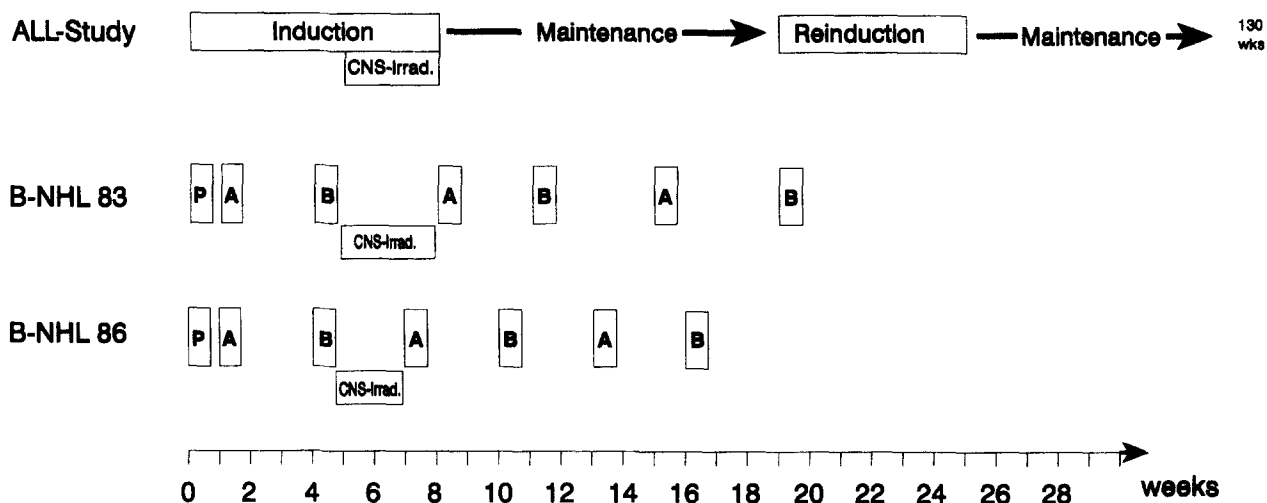


Fig 1. Overall schedules of treatment in the three protocols applied to adult patients with B-ALL. Total duration of therapy in the ALL 01/81 protocol, 130 weeks; in B-NHL83, 19 weeks; in B-NHL86, 17 weeks.

CNS involvement, HdM was supplemented by intrathecal therapy with MTX, later by the triple combination of MTX, AraC, and steroids, with or without CNS irradiation.^{22,23} With these protocols specifically designed for B-ALL, the outcome in children improved substantially to CR rates of 89% to 92%,²³⁻²⁵ and the LFS rose to 50% to 87%.^{21,23,24,26}

These successful pediatric approaches have been transferred to adults with B-ALL. The SFOP and the BFM protocols were used in single center or small multicenter studies^{16,27-30} with a total of 47 patients. The CR rates, as well as LFS, were superior compared with historical controls. This report presents the experience of the German multicenter study group for treatment of adult ALL (GMALL). In three consecutive studies, adult B-ALL patients aged 15 to 65 years have been treated since 1981, either with the conventional ALL protocol 01/81^{31,32} or with two successive modified pediatric protocols B-ALL83 or B-ALL86²³ accounting for 68 patients, the largest number of adult patients with B-ALL so far reported.

PATIENTS AND METHODS

Eligibility for Study

Patients were eligible if they were 15 to 65 years old, previously untreated or without intensive chemotherapy (see Table 3), if their Karnofsky performance status was $\geq 50\%$, if they had blast cells with the typical L3 morphology and/or expression of surface immunoglobulin, and if their ALL was not a secondary neoplasm. The diagnosis of B-ALL also required at least 25% bone marrow (BM) infiltration, according to the Murphy classification.³³ The first nine patients were treated with the conventional ALL protocol 01/81. From 1983 onwards, the modified pediatric protocols B-ALL83 or B-ALL86 were applied in two prospective studies; these were termed B-NHL83 and B-NHL86 protocols because they were also applied in the treatment of high-grade lymphoblastic non-Hodgkin's lymphoma (NHL).

Diagnosis

Morphology and cytochemistry. BM and peripheral blood (PB) smears were stained with a modified Wright staining technique and

the FAB L3 morphology had to be confirmed in the reference center for central morphology and cytochemistry (Gaßmann, Löffler, Kiel). Cytochemical examination of BM and blood smears included the following reactions according to standard procedures for acute leukemia patients: myeloperoxidase, periodic acid Schiff reaction (PAS), α -naphthyl acetate esterase (ANAE), acid phosphatase (AcP), and dipeptidylaminopeptidase IV (DAP IV). Blast cells with L3 morphology were positive for PAS in 70%, AcP in 20%, ANAE in 15%, terminal deoxynucleotidyl transferase (TdT) in 20% and negative for DAP IV.³⁴

Immunophenotyping. The morphological diagnosis on BM or PB samples was confirmed by immunological phenotyping for all participating hospitals in one reference center (Ludwig, Thiel, Berlin). Leukemic blast cells were analyzed for cytoplasmic immunoglobulin μ heavy chain (cyIgM), SIg, and TdT, as well as T- and B-lineage-associated antigen expression as previously described.^{35,36} The leukemia was classified as B-ALL when more than 20% of blast cells expressed SIg in combination with the B-lineage-associated antigens CD19, CD20, and CD24.

Chromosome analysis. Cytogenetic analysis was included in the central diagnostic program only in the last study B-NHL86 and was performed in 19 of the 35 study patients; for 10 patients in one of the three reference laboratories (Fonatsch, Lübeck; Heinze, Ulm; Hossfeld, Hamburg) and for nine in their own institutions.

Clinical investigations. Clinical investigations consisted of physical examination and PB and BM analyses. Lumbar puncture for cerebrospinal fluid (CSF) analysis was done at diagnosis irrespective of whether neurological symptoms were present. Routine laboratory analyses included lactate dehydrogenase (LDH) levels (normal range in the participating institutions 80 to 240 U/L). Furthermore, ultrasonography of the abdomen, x-ray of the chest, computer tomography of chest and abdomen, and echocardiography were performed.

Treatment Schedules

The treatment schedules are shown in Figs 1 and 2.

ALL study 01/81. This was an ALL protocol designed for all adult ALL patients without specification for ALL subtypes. The 8-week induction therapy consisted of vincristine, prednisone, daunorubicin, L-asparaginase (weeks 1 to 4) and cyclophosphamide, AraC, 6-mercaptopurine (6-MP), intrathecal MTX (10 mg/m²), and prophylactic

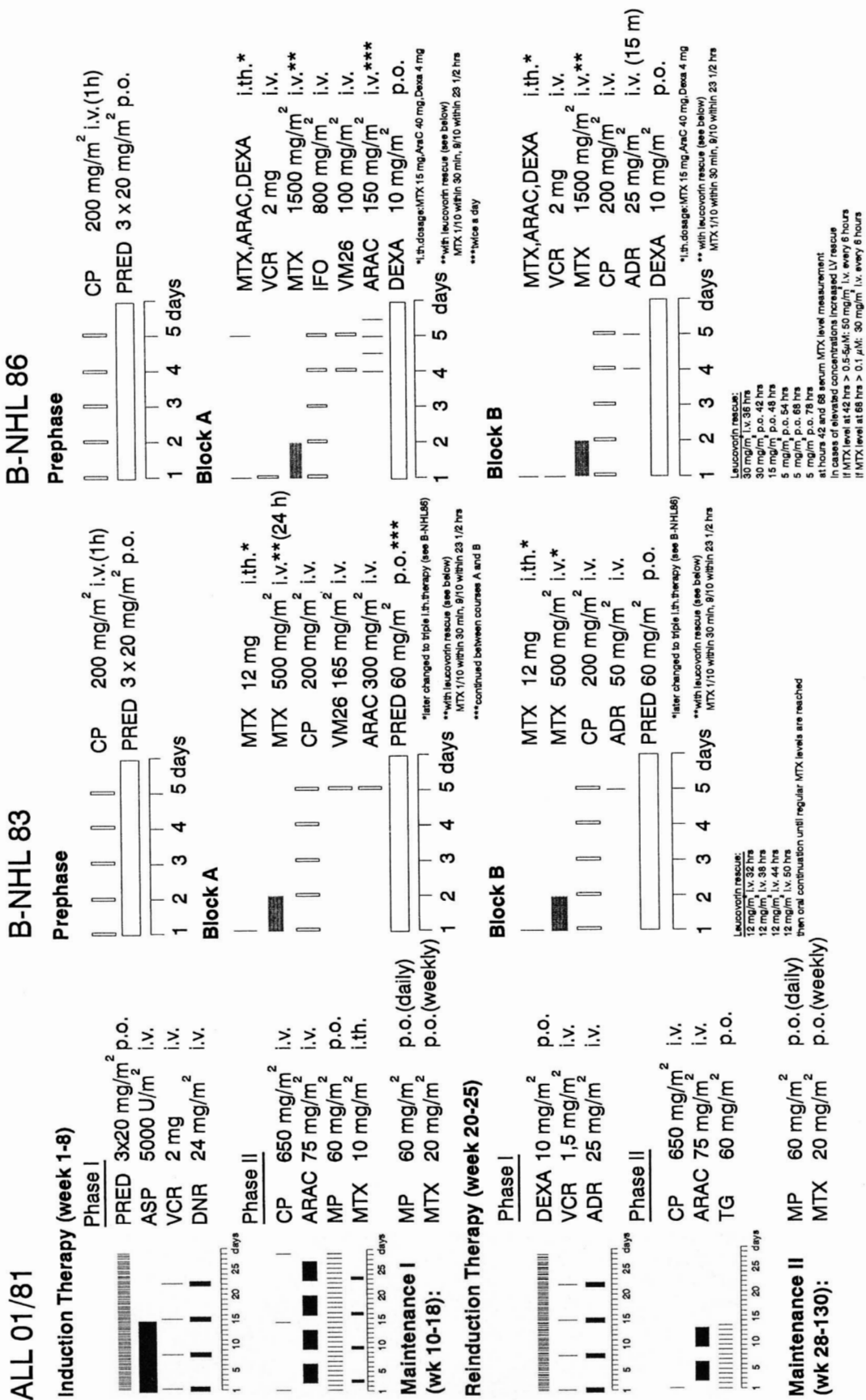


Fig. 2. Detailed therapy plans in the three protocols ALL 01/81, B-NHL83, and B-NHL86.

lactic cranial irradiation with 24 Gy (weeks 5 to 8). A similar reinduction therapy followed at 3 months. The maintenance therapy with 6-MP and MTX was scheduled for 2 years accounting for a total treatment period of 2½ years. Patients with a high WBC count, >25,000/μL and/or a large tumor cell mass received a cytoreductive prephase therapy with vincristine (1.5 mg/m², day 1) and prednisone (60 mg/m², days 1 to 7) before induction was started (for WBC >100,000/μL, reduced doses of 0.75 mg/m² and 30 mg/m², respectively). Dosages and time schedules are given in Fig 2 and are described in detail elsewhere.³¹

Pretreatment in Studies B-NHL83 and B-NHL86

To avoid tumor lysis syndrome and to correct possible metabolic disturbances, a cytoreductive phase of prednisone, 60 mg/m² orally combined with cyclophosphamide, 200 mg/m² intravenously (IV) each for 5 days was recommended for patients in the B-NHL83 study with high WBC (>25,000/μL) and/or large tumor mass. As this pretreatment was apparently of benefit in this study, it was made obligatory for all patients in study B-NHL86.

Study B-NHL 83

This B-NHL protocol consisted of six 5-day cycles, alternately A and B (Fig 2). Cycle A was composed of intermediate dose MTX (IdM), 500 mg/m², on day 1; one-tenth was given as a loading dose over 30 minutes and nine-tenths was administered in the form of a 23½-hour continuous IV infusion. In addition, fractionated cyclophosphamide was given for 5 days with VM26 and AraC IV on day 5. In cycle B, doxorubicin was applied instead of VM26 on day 5 and AraC was omitted. Oral prednisone, 60 mg/m², was given during and between the first two cycles.

In study B-NHL83, leukovorin rescue (Fig 2) started 32 hours after the beginning of IdM infusion with 12 mg/m² IV followed by similar doses at 38, 44, and 50 hours, then further oral doses at 6-hour intervals until the serum MTX level was <0.05 μmol/L.

Study B-NHL 86

This study also used six alternate 5-day cycles, A and B (Fig 2). Compared with B-NHL83, the following modifications were made. IdM was increased to high-dose MTX (HdM), 1,500 mg/m². The schedule of HdM administration was similar to that of IdM in study B-NHL83 with a different leukovorin rescue (see below). Ifosfamide, 800 mg/m², replaced cyclophosphamide. Further changes were the addition of vincristine on day 1 of each cycle, A and B, the replacement of prednisone by dexamethasone on days 1 to 5 of each cycle and the dose reduction of VM26 to 100 mg/m² and of AraC to 150 mg/m². The dose of doxorubicin was reduced to 25 mg/m² and given on days 4 and 5 instead of day 5 only. Because longer-lasting hematotoxicity and mucositis was observed particularly in older patients in study B-NHL83, the IdM dose of 500 mg/m² remained unchanged for patients between 50 and 65 years. In study B-NHL86, the doses of leukovorin and the total duration of leukovorin rescue were increased because of the higher dose of MTX, and a closer monitoring of MTX serum levels was incorporated (Fig 2).

The leukovorin rescue started with 30 mg/m² IV 36 hours after the beginning of HdM infusion. Thereafter oral doses of 30 mg/m², 15 mg/m², and three doses of 5 mg/m² were given at 42, 48, 54, 68, and 78 hours for regular decrease of serum MTX levels. For an irregular serum MTX level of >0.5 to 5 μmol/L at 42 hours, the patients received IV doses of 50 mg/m² every 6 hours up to 60 hours. If the serum MTX level at 68 hours was >0.01 μmol/L, IV leukovorin was continued every 6 hours at 30 mg/m² for a further four doses.

CNS Prophylaxis and Treatment

In study B-NHL83, patients with CR after the first two chemotherapy cycles (A and B) received a prophylactic cranial irradiation with

24 Gy. Patients with CNS involvement received 30 Gy together with a spinal irradiation. During the course of B-NHL83, for all ALL patients in the GMALL study group including those with B-ALL, the radiation dose for CNS-positive patients was reduced from 30 Gy to 24 Gy to reduce toxicity. The reason was that in the study ALL 01/81, patients with initial CNS involvement had no inferior outcome compared with those without CNS involvement.³² Furthermore, a substantial number of patients (all high-risk) were candidates for bone marrow transplantation (BMT) in first CR where the conditioning regimen included total body irradiation. Thus, in study B-NHL86, prophylactic CNS irradiation, as well as irradiation for CNS-positive patients, was 24 Gy, in the latter extended to the spinal column.

Intrathecal therapy to prevent CNS relapse in study B-NHL83 was started with MTX (15 mg) only. Also the intrathecal therapy was altered for all ALL patients including the B-ALL patients in the study group from MTX alone to a triple intrathecal therapy with MTX (15 mg), AraC (40 mg), dexamethasone (4 mg). Thus in study B-NHL83, some patients received MTX only and some the triple intrathecal therapy, and in study B-NHL86, all patients received the triple intrathecal therapy.

In studies B-NHL83 and B-NHL86 clinical centers were free to irradiate other sites of bulky disease or persistent organ infiltrations if considered necessary (see Table 3).

Evaluation

Complete remission was defined as disappearance of all L3 lymphoblasts from BM (<5%), PB, cerebrospinal fluid or any other sites, the latter confirmed by imaging procedures. Remission status was evaluated after the 8-week induction therapy in study ALL 01/81 and after each of the first two cycles of studies B-NHL83 and B-NHL86. Nonresponders were defined as patients with partial remission, failure, progression, or CR after more than 2 cycles. Early death was any death during the first 8 weeks in study ALL 01/81 and in the first two cycles in studies B-NHL83 and B-NHL86. Death in CR was defined as any death after achievement of CR within further treatment courses or thereafter.

Statistical Analysis

The statistical analysis was performed by the Biometric Centre for Therapy Studies (D. Messerer, Munich) and N. Gökbuegt (Frankfurt). The influence of entrance parameters on the achievement of CR was evaluated by the χ^2 -test. Median values were compared by the Wilcoxon-Mann Whitney test. The probabilities for overall survival and LFS were computed by the method of Kaplan and Meier.³⁷ The overall survival was calculated from the beginning of therapy to the date of last review or death in all evaluable patients; LFS was determined from the date of CR to the date of last review or date of BMT in censored patients and to the date of death in CR or relapse in events. The univariate comparison between survival curves was performed by the log-rank test.³⁸

The date of analysis was March 1995. The maximum follow-up for study ALL 01/81 was 1½ years (562 days), when the last patient died. The follow-up for study B-NHL83 was 321 days (lost to follow-up by return to home country) to 3,092 days. For study B-NHL86, the follow-up was 383 days to 1,763 days.

RESULTS

Patient Accrual

In study ALL 01/81, nine evaluable patients were recruited between October 1978 and June 1983. Between July 1983 and June 1989, 24 evaluable patients entered the protocol B-NHL83 and from July 1989 to January 1993, 35 evaluable patients entered the B-NHL86 protocol. Of the total 76 adult

Table 1. Patient Characteristics in Adult B-ALL

Patient Characteristics	ALL-Study 01/81 N = 9 (%)	B-NHL 83 N = 24 (%)	B-NHL 86 N = 35 (%)	Total N = 68 (%)
Sex				
Male	7 (78)	19 (79)	27 (77)	53 (78)
Female	2 (22)	5 (21)	8 (23)	15 (22)
Age				
Median (range)	34 (16-64)	33 (15-58)	36 (18-65)	34 (15-65)
15-20	1 (11)	3 (12)	2 (6)	6 (9)
20-50	5 (56)	16 (67)	22 (63)	43 (63)
50-65	3 (33)	5 (21)	11 (31)	19 (28)
Bleeding	6 (67)	7 (29)	11 (31)	24 (35)
Infections	2 (22)	10 (42)	11 (31)	23 (34)
Peripheral lymph nodes	7 (78)	14 (58)	22 (63)	43 (63)
Hepatomegaly	6 (67)	13 (54)	20 (57)	39 (57)
Splenomegaly	4 (44)	6 (25)	22 (63)	32 (47)
CNS involvement	0	2 (8)	6 (17)	8 (12)
Other organ involvement	2 (22)	7 (29)	14 (40)	23 (34)
WBC				
Median (range)	36,900 (16-88,600)	10,500 (990-105,000)	16,130 (4,7-318,500)	12,300 (0.9-318,500)
<10,000/ μ L	0	12 (50)	10 (29)	22 (32)
10-50,000/ μ L	7 (78)	8 (33)	18 (51)	33 (48)
>50,000/ μ L	2 (22)	4 (17)	7 (20)	13 (19)
Granulocytes				
<500/ μ L	0	2 (8)	0	2 (3)
500-1,500/ μ L	1 (11)	3 (12)	2 (6)	6 (9)
>1,500/ μ L	8 (89)	19 (79)	33 (94)	60 (88)
Platelets				
<25,000/ μ L	7 (78)	7 (29)	10 (29)	24 (35)
25-200,000/ μ L	2 (22)	10 (42)	22 (63)	34 (50)
>200,000/ μ L	0	7 (29)	3 (9)	10 (15)
Hb				
<8 g/dL	3 (33)	5 (21)	5 (14)	13 (19)
>8 g/dL	6 (67)	19 (79)	30 (86)	55 (81)
LDH				
<500 U/L	—	5 (28)	1 (3)	6 (12)
>500 U/L	—	13 (72)	32 (97)	45 (88)

Period of study, patient accrual, and clinical parameters of evaluable patients at entry for the three studies. The distribution of leukemia cell infiltration in organs other than BM and the incidence of clinical manifestations in patients at entry to the three studies are listed.

B-ALL patients from 24 different centers enrolled in the three consecutive studies, 68 patients are evaluable. Reasons for exclusion were: L3 cell infiltration of BM <25% (3), incomplete documentation (3), poor physical condition with a Karnofsky performance status of 20% (1), and B-ALL as second neoplasm (1).

Diagnosis

Of the 68 evaluable patients, the diagnosis of B-ALL was confirmed in 37 patients by L3 morphology of the blast cells and additional immunological diagnosis by the presence of SIg and other B-cell markers. In 13 patients, the diagnosis was confirmed by L3 morphology only and in 11 patients by demonstration of SIg only. In six further patients, there were discrepancies between morphological and immunological diagnosis. Five patients positive for SIg showed an L1 or L2 morphology. One patient showed an L3 morphology and had the typical translocation t(8;14), but the immunological diagnosis was AML. In one patient, the immunological and morphological investigation was not evaluable and thus the diagnosis was based on the demonstration of the cyto-

netic translocation t(8;14) alone. All of these 68 patients were treated according to one of the three protocols. Three patients with FAB L3 morphology had a different immunophenotype, two common ALL and one pre-B-ALL, and were thus not treated according to the B-NHL protocols.

In a total of 19 patients in study B-NHL86, cytogenetic analysis was available. In one patient the diagnosis was based on the demonstration of t(8;14) alone, as mentioned above. Seven other patients showed B-ALL/NHL-associated translocations; t(8;14) in six patients and t(8;22) in one patient. Of the remaining 11 patients, one had t(2;8) plus t(14;18); t(11;14) or t(1;13) or t(4;14) were present in one case each. In one patient, an abnormal clone with del(9), as well as a clone with normal diploid cells, was observed. One patient showed an aberrant karyotype with complex chromosome abnormalities. Five patients had only normal diploid metaphases, which may have been due to the analysis of PB cells instead of BM cells. Of the above patients, two with aberrations not typical for a B-ALL, the t(11;14) and t(4;14) were included in the B-ALL protocol based on L3 morphology or SIg because the cytogenetic result was obtained after initiation of treatment.

Table 2. Overall Results in Adult B-ALL

	ALL 01/81	B-NHL 83	B-NHL 86
Study period	1981 to 1983	7/83 to 6/89	7/89 to 12/93
Patients enrolled	9	27	40
Patients evaluable	9	24	35
CR	4 (44%)	15 (63%)	26 (74%)
Non/late responder	4 (44%)	7 (29%)	6 (17%)
Early death	1 (11%)	2 (8%)	3 (9%)
Death in CCR	2 (50%)*	0	2 (7%)*
Relapse	2 (50%)	7 (47%)	6 (23%)
Probability of LFS	0	50%	71%
Probability of survival	0	49%	51%
Follow-up† (range)	562 d‡	321§-3,092 d	383-1,763 d

Outcome of therapy in the three protocols used to treat adult B-ALL patients.

* Death in CR: in each group 1 patient after BMT.

† Censored observations for survival.

‡ Last death.

§ Lost to follow-up.

There was good agreement between the survival probability for the patients where B-ALL was confirmed by morphology only with 0.58 and for the largest patient group in whom the diagnosis was confirmed by morphology and immunology, with a probability of survival of 0.65. However, the survival for patients diagnosed by immunology ($N = 11$) alone was inferior (0.30). This is mainly due to the five patients with a diagnostic discrepancy, B-ALL being confirmed by immunology, but with L1 or L2 morphology, who had very a poor survival probability of 0.20. The two patients who were included on the basis of morphology or immunology, but who had translocations not typical for B-ALL, t(11;14) and t(4;14), had a poor outcome; both were treatment failures and died at days 75 and 285. The patient with the del(9) aberration relapsed at day 159 and died.

Entrance Parameters

All patients had, according to the entry criteria, an infiltration of the BM with blast cells of 25% or more. A blast cell infiltration of >90% was seen in 34 patients (60%), an infiltration between 50% and 90% in 14 (24%), and between 26% and 50% in nine patients (16%). In all three studies, there was a predominance of male patients, with 77% to 79% (Table 1). Also the median age was similar in all studies with 34, 33, and 36 years. A total of only six patients (9%) were adolescents between 15 and 20 years old; 28% were in the older age group between 50 and 65 years. Sex distribution among the different age groups was similar. There was also no difference in the three studies with regard to the rate of infection at diagnosis.

A marked increase of WBC count above 50,000/ μL was seen in 19% of patients at diagnosis in the three studies, and 32% had a normal WBC. Only a minority (3%) of the patients had a granulocyte count below 500/ μL , and the majority (88%) had a granulocyte count above 1,500/ μL . This contrasts with the infection rate found in 34%. Platelet counts were decreased below 25,000/ μL in 35% of the patients, which corresponded to the bleeding rate of 35%. Only a few

patients (19%) presented with an anemia (Hb <8 g/dL). LDH was increased >240 U/L in all except two patients; in 88%, it was above 500 U/L.

A total of 12% of the patients had a CNS involvement at diagnosis. This was confirmed by demonstration of L3 or SIg positive blast cells in the cerebrospinal fluid or by CT scan of the brain and by clinical symptoms. The extent of peripheral lymph node enlargement, hepatomegaly, splenomegaly, and other organ involvement was similar in all studies (Table 1). In 34% of the patients, other organs were involved; pleura/lung (5), mediastinal tumor (3), stomach (6), gut (3), abdominal masses (2), kidney (1), ascites (1), skeleton (4), thyroid (2), skin (1), epidural masses (1), parotid (1), and orbital cavity (1). All of these patients had a BM infiltration of >25% blast cells.

Therapy Application and Treatment Results

The results of treatment are summarized in Table 2. Of the nine patients in study ALL 01/81, only four (44%) achieved CR in contrast to 63% and 74% in studies B-NHL83 and B-NHL86. CR was documented in studies B-NHL83 and 86 after one course in 54% and 63%, respectively and the remainder after two courses (Table 3). The three patients in study B-NHL83 and the one patient in B-

Table 3. Therapy Realization in B-ALL Studies B-NHL83 and B-NHL86

	B-NHL 83	B-NHL 86
Evaluable	N = 24	N = 35
Prephase treatment		
None	6 (25%)	2 (6%)
Cyclo/Pred	12 (50%)	28 (80%)
Other	6 (25%)	5 (14%)
VCR + PRED	3	3
VCR + PRED + DNR	2	1
VCR + PRED + CYCLO + DOXO (CHOP)	1	1
Applicability of treatment cycles A/B		
6 cycles	10 (42%)	20 (57%)
4/5 cycles	2 (8%)	3 (9%)
2/3 cycles	8 (33%)	9 (26%)
1 cycle	4 (17%)	3 (9%)
Reasons for not completing 6 cycles		
Failure/progression	6	7
Early death/death in CR	2	4
BMT	2	2
Withdrawal/protocol violation	4	2
Irradiation of CNS and other sites		
CNS 24 Gy CR patients	11 (73%)	18 (69%)
No CNS irradiation	4 (27%)	8 (31%)
Irradiation of other sites	0	5 (19%)
Abdomen	0	3 (11%)
Orbita	0	1 (4%)
Thoracic spine	0	1 (4%)
Time for achievement of CR		
After 1 cycle	13 (72%)	22 (81%)
After 2 cycles	2 (11%)	4 (15%)
More than 2 cycles	3 (18%)	1 (4%)

Therapy realization in the short, intensive protocols B-NHL83 and B-NHL86 used for B-ALL patients. Details of therapy actually received and reasons for incomplete application of therapy cycles are given.

Table 4. Results of BMT in Adult B-ALL Studies

Age/Sex	Study	Therapy Cycles	Status Before BMT	Type of BMT	Survival after BMT (days)	Cause of Death
25M	ALL 01/81	Induction + reinduction	CR	allo	68	Death in CR (CMV pneumonia)
24M	B-NHL 83	2	CR	allo	2,568*	—
28M	B-NHL 83	6	CR	auto	2,519*	—
26M	B-NHL 86	2	PR	allo	56	Death with persisting blast cells after BMT
26F	B-NHL 86	2	CR	allo	877*	—
27M	B-NHL 86	2	CR	allo	153	Death in CR (fungal pneumonia)

Status and outcome of six patients who received BMT.

* Last follow-up for patients in CCR.

NHL86 who needed more than 2 cycles to achieve CR were not included in the CR rate. There was a higher nonresponder rate of 44% in study ALL 01/81 compared with 29% and 17% in studies B-NHL83 and B-NHL86.

The early death rates within the first 8 weeks in study ALL 01/81 and within the first two treatment cycles in studies B-NHL83 and B-NHL86 were 11% (N = 1), 8% (N = 2), and 9% (N = 3). The patient with early death in ALL 01/81, a 41-year old woman, died on day 26 from pneumonia. In study B-NHL83, the early death patients were a 52-year old man who died from bleeding after 25 days, and a 46-year old man who died of severe necrotizing generalized mucositis (after one cycle, day 20). In study B-NHL86, a 30-year old man died of central dysregulation with toxic brain oedema, most probably HdM-induced (after two cycles, day 38), a 42-year old man died of a pulmonary embolism with double-sided leg vein thrombosis (at day 35), and a 27-year-old woman died of septicemia with *Pseudomonas* and fungal infection (after one cycle, day 53).

Pretreatment

Of the 59 patients in studies B-NHL83 and B-NHL86, a total of 40 (68%) patients had a prephase treatment with cyclophosphamide and prednisone. Of these patients, seven had additional medication; one patient had daunorubicin, and six patients had vincristine. In study B-NHL83, where the pretreatment was recommended, 12 patients (50%) received it and in study B-NHL86, where the treatment was obligatory, 28 patients (80%) were pretreated (Table 3). Concomitantly, the fraction of patients without pretreatment decreased from 25% in B-NHL83 to 6% in B-NHL86. Other pretreatments were applied in 25% of B-NHL83 patients versus 14% in B-NHL86 (Table 3). The exceptions were six patients with vincristine and prednisone, three patients with vincristine, prednisone, and daunorubicin, and two patients with vincristine, prednisone, doxorubicin, and cyclophosphamide (CHOP) (see Table 3). The probability of survival for the 12 patients in B-NHL83 who received the recommended cytoreductive treatment with prednisone and cyclophosphamide was 0.66 compared with 0.31 (not significant) for the 12 patients who received none or another pretreatment. The difference in outcome, the improved clinical status of the pretreated patients and the fact that tumor lysis syndrome could be avoided were the reasons that it was given on an obligatory basis in B-NHL86. The survival of all 40 patients with cyclophosphamide and prednisone pretreatment in studies B-NHL83 and B-NHL86 was 0.56 compared

with 0.36 for 19 patients without or with other pretreatment ($P = .09$). In neither study was a patient lost during this treatment period.

Treatment/Cycles

The six proposed treatment cycles could be given in 42% (B-NHL83) and 57% (B-NHL86) of patients (Table 3). The median time for completion of six cycles in B-NHL83 was 165 days and in B-NHL86, was 138 days. Reasons for not completing six cycles (Table 3) in the 14 patients of study B-NHL83 and in the 15 of B-NHL86 were failure or progression in six and seven patients, respectively, early death in two and four (one in CR) patients, withdrawal or protocol violation in four and two, and BMT in two and two patients. The median duration of treatment for all patients in studies B-NHL83 and B-NHL86 was 139 and 130 days, and for the CR patients, 160 and 131 days.

CNS Prophylaxis and Treatment

A prophylactic cranial irradiation with 24 Gy (Table 3) was given in the B-NHL studies 83 and 86 after two cycles (one A and one B) in 73% and 69% of the CR patients, respectively. Extension to 30 Gy was only applied in one patient with CNS involvement who achieved CR later than two cycles of therapy. Reasons for not applying CNS irradiation were protocol violation in two and five, withdrawal in 0 and one, and BMT in two and two patients.

Irradiation of Other Sites

For abdominal involvement, 24 Gy was given to three patients with stomach or gut infiltration; for orbital infiltration, one patient received 24 Gy; for epidural masses, one patient was given 24 Gy to the thoracic spine.

BMT

Within these three studies, six patients with a median age of 26 years (24 to 28) had a BMT; five were allogeneic and one autologous (Table 4). Five patients were transplanted in first CR and one in partial remission. Two patients died of transplant-related mortality, one on day 68 from CMV pneumonia and one on day 153 from fungal pneumonia. The patient transplanted in partial remission died with persisting leukemic blast cells on day 56. Three patients are alive in CR at 877, 2,519, and 2,568 days.

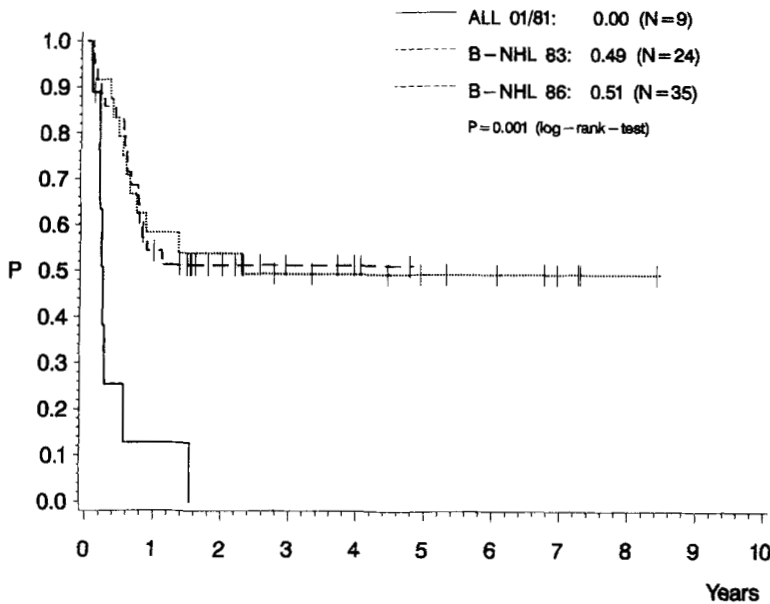


Fig 3. Probability of overall survival in the adult B-ALL studies ALL 01/81, B-NHL83, and B-NHL86.

Survival

Among the nine patients of the ALL study, there were no survivors and the last patient died at 1½ years (Fig 3). The probabilities for overall survival in the B-NHL studies 83 and 86 are similar with 49% and 51% at 8 and 4 years. The last death in B-NHL83 occurred after 2 years, a 50-year old man after his third relapse, and in B-NHL86 after 1 year, a 60-year old woman who never achieved CR.

LFS

The median LFS for the 15 CR patients in study B-NHL83 is not yet reached and the probability of LFS is 0.50 at 8 years (Fig 4). For the 26 CR patients in study B-NHL86, the median of LFS is also not yet reached and the probability of LFS at 4 years is 0.71.

Relapse Time and Localization

In study ALL 01/81, one relapse occurred in the BM and one in the CNS. In the B-NHL83 study, all relapses occurred within 12½ months and in B-NHL86 within the first 7 months. There have been no further relapses during the following 6½ years in B-NHL83 and 3½ years in B-NHL86. The primary sites of relapse changed in the studies (Table 5). The BM was the primary site in 43% of B-NHL83 patients and this increased to 83% in B-NHL86. The rate of isolated CNS or combined BM and CNS relapses decreased from 57% to 17%, respectively. The median time to BM relapse was 92 days and to CNS and combined BM and CNS relapse was 190 days. Of the two patients with initial CNS involvement in study B-NHL83, neither had a relapse, and in the study B-NHL86, two of three CR patients re-

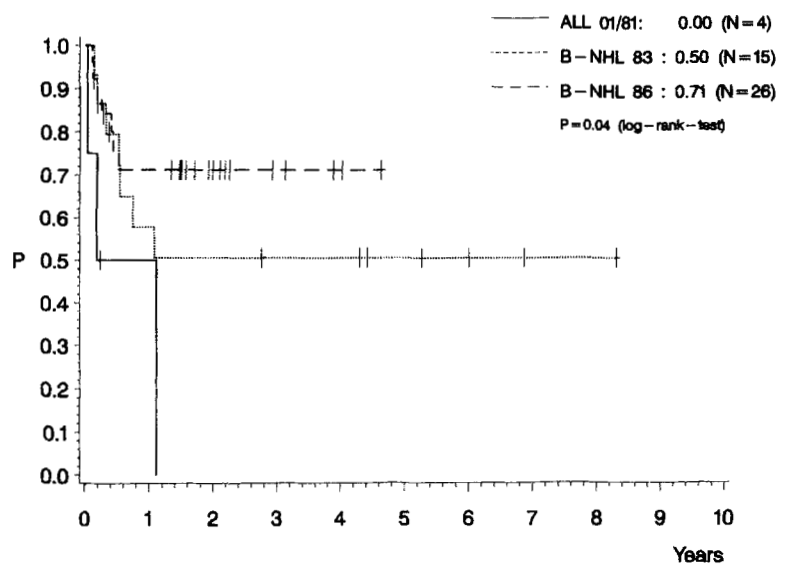


Fig 4. Probability of LFS in the adult B-ALL studies ALL 01/81, B-NHL83, and B-NHL86.

Table 5. Relapse Localization in B-ALL

Localization	ALL-Therapy N = 2	B-NHL 83 N = 7	B-NHL 86 N = 6
BM	1 (50%)	3 (43%)	5 (83%)
CNS	1 (50%)	3 (43%)	0
CNS + BM		1 (14%)	1* (17%)

Differences in distribution of relapse site in the therapy studies ALL 01/81, B-NHL83, and B-NHL86.

* CNS, BM, and skin.

lapsed, one in the BM and one simultaneously in BM, CNS, and skin.

Prognostic Factors

Analyzing patients in studies B-NHL83 and B-NHL86 together, there was a tendency for higher complete remission rates for several entrance parameters (Table 6), eg, for male versus female sex (74% v 54%), for age <50 v >50 years (74% v 56%), and for patients without infection (76% v 67%). However, the only factor significant for achievement of CR was the involvement of other organs (Table 6) being 79% without versus 57% with ($P = .03$). The influence of entrance parameters on LFS was investigated by univariate analysis (Table 6). There was a significant influence of the initial WBC count (Fig 5) on the probability of LFS. Patients with WBC <50,000/ μ L had a LFS of 0.71 versus 0.29 for those with WBC >50,000/ μ L ($P = .003$). A significant difference was also found between the LFS for patients with initial Hb <8 g/dL, 0.27 versus 0.67 LFS for those with Hb >8 g/dL ($P = .02$). When the LFS was correlated to the pretreatment, those 40 (29 CR) patients who received cyclophosphamide and prednisone had a LFS of 0.77 and those 19 (12 CR) patients without or with other pretreatment, a LFS of 0.33 ($P = .009$). Neither age above 50 years (Fig 6) nor initial LDH >500 U/L (Fig 7) had a significant adverse effect on LFS. Infection or bleeding at diagnosis, CNS involvement (Fig 8), and other organ involvement had no influence on LFS.

Toxicity

Major toxicity in both studies B-NHL83 and B-NHL86 was hematotoxicity, with WHO grade 3 to 4 toxicity for granulocyte count in 39% and 81%, respectively, for platelet count in 50% and 35%, and for hemoglobin level in 33% and 42%. Hematotoxicity was substantially more pronounced in B-ALL patients of both studies above 50 years, with WHO grade 3 or 4 toxicity for granulocytes in 96% of patients compared with 71% below 50 years, for platelets in 83% versus 47%, and for hemoglobin level in 65% versus 28%. The hematotoxicity even increased from cycle to cycle in elderly patients. Mucositis WHO grade 1 to 4 was observed in 50% of therapy cycles in B-NHL83 and in 53% in B-NHL86, but was more pronounced in study B-NHL86, with WHO grade 3 to 4 mucositis in 20% compared with none in B-NHL83. Although the frequency of overall gastrointestinal toxicity including mucositis, stomatitis, and diarrhoea was not different in B-ALL patients below or above 50 years, the impression was that it lasted longer in the older patients,

Table 6. Correlation of Outcome to Entrance Parameters

	B-NHL83 + B-NHL86			
	CR Rate % (evaluable patients)	P	Probability of LFS (CR patients)	P
Patient characteristics				
Sex				
Male	74% (46)	.16	0.62 (34)	.85
Female	54% (13)		0.69 (7)	
Age				
<50 yrs	74% (43)	.18	0.65 (32)	.42
>50 yrs	56% (16)		0.56 (9)	
Bleeding				
No	73% (41)	.35	0.66 (30)	.50
Yes	61% (18)		0.57 (11)	
Infection				
No	74% (38)	.35	0.56 (28)	.16
Yes	62% (21)		0.81 (13)	
Clinical parameters				
Peripheral lymph nodes				
No	78% (23)	.24	0.60 (18)	.89
Yes	64% (36)		0.65 (23)	
Hepatomegaly				
No	73% (26)	.59	0.57 (19)	.69
Yes	67% (33)		0.67 (22)	
Splenomegaly				
No	68% (31)	.76	0.69 (21)	.37
Yes	71% (28)		0.58 (20)	
CNS involvement*				
No	69% (49)	.70	0.61 (34)	.90
Yes	63% (8)		0.60 (5)	
Other organ involvement				
No	79% (38)	.03	0.58 (30)	.19
Yes	57% (21)		0.78 (11)	
Laboratory findings				
WBC				
<50,000/ μ L	71% (48)	.64	0.71 (34)	.003
>50,000/ μ L	64% (11)		0.29 (7)	
Granulocytes				
>1,500/ μ L	69% (52)	.90	0.64 (36)	.84
<1,500/ μ L	71% (7)		0.53 (5)	
Platelets				
>25,000/ μ L	69% (42)	.91	0.68 (29)	.28
<25,000/ μ L	71% (17)		0.49 (12)	
Hb				
>8 g/dL	73% (49)	.14	0.67 (36)	.02
<8 g/dL	50% (10)		0.27 (5)	
BM replacement				
<50%	78% (9)	.51	0.86 (7)	.49
>50%	67% (48)		0.63 (32)	
LDH‡				
<500 U/L	83% (6)	.41	0.40 (5)	.14
>500 U/L	67% (45)		0.67 (30)	

Correlation of outcome to entrance parameters, B-NHL83 and B-NHL86.

* Missing data in two patients.

‡ BM replacement in two patients >25% but exact number not known.

‡ Missing data in eight patients.

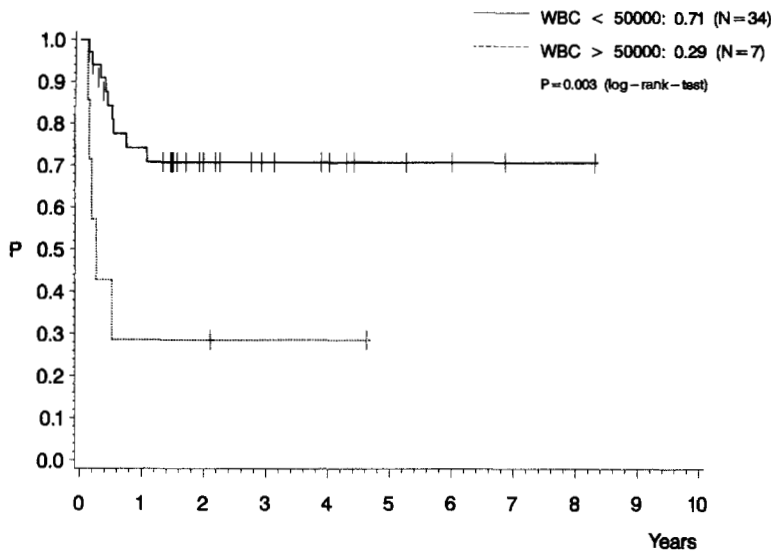


Fig 5. Probability of LFS for patients in studies B-NHL83 and B-NHL86 with initial WBC <50,000/ μ L compared with those with WBC >50,000/ μ L.

although this statement is limited because the duration of mucositis was not documented. Other toxicities recorded were elevated transaminase in 13%, severe infections in 9%, and pain, WHO grade 3 to 4, in 9%.

In study ALL 01/81, the cause of death in CR in a 25-year old man was CMV pneumonia after BMT at day 208 and in a 61-year old man, pneumonia at day 67. In study B-NHL86, deaths in CR occurred in a 65-year old man from bleeding with subdural hematoma (after three cycles, day 95) and in a 27-year old man from fungal pneumonia after allogeneic BMT (day 153).

DISCUSSION

When adult B-ALL patients were treated from 1981 onwards according to a conventional ALL protocol with induction, reinduction, and maintenance, the outcome was fatal and all nine patients who entered the study died within 19

months. Thus, in 1983, it was decided to use a strategy designed for childhood B-ALL. Therapeutic innovations in the successful American,^{17,24} French,²¹ and German^{22,23} pediatric B-ALL protocols were firstly, higher doses and fractionation of cyclophosphamide, the best single agent for therapy of Burkitt's lymphoma,¹⁸ to expose the rapidly dividing B-cells to active alkylating metabolites of cyclophosphamide over a longer period.¹⁷ The second change was the introduction of high-doses of methotrexate at different levels, 1 g/m²,¹⁷ 3 or 8 g/m²,²¹ 0.5 or 5 g/m²,²³ which is also cytotoxic in the B-ALL blast cells exhibiting a high proliferation rate.³⁹ In some studies, high-dose AraC was also included.^{24,25} Whereas it is convincing that fractionated HdC and HdM had the major impact, the value of high-dose AraC and of the other single components, such as anthracyclines, steroids, vincristine, VM26, or etoposide, is difficult to assess.

The patients in these three studies had the typical clinical characteristics of B-ALL with male predominance and high

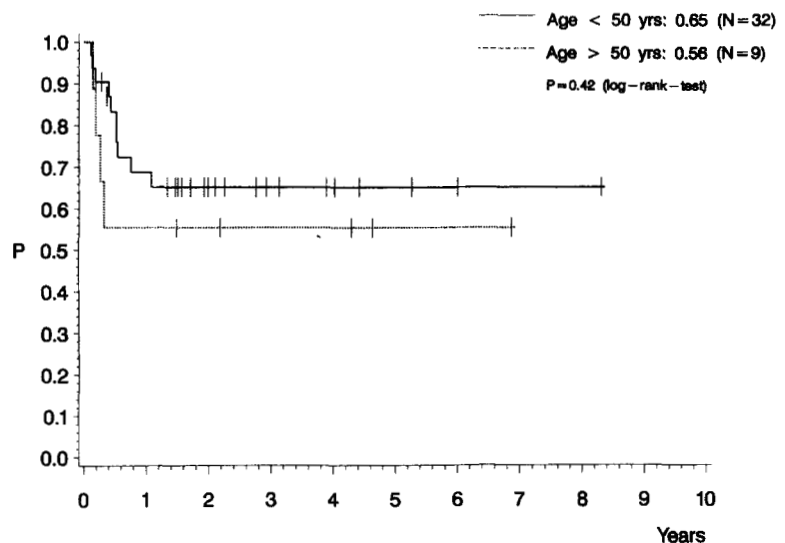


Fig 6. Probability of LFS for patients in studies B-NHL83 and B-NHL86 aged <50 years compared with patients over 50 years.

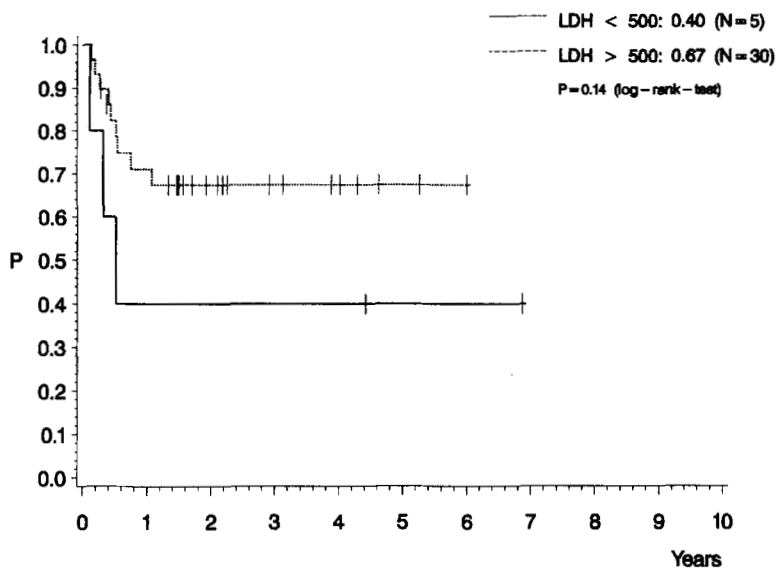


Fig 7. Probability of LFS for patients in studies B-NHL83 and B-NHL86 with initial LDH <500 U/L compared with those with LDH >500 U/L.

incidence of other organ involvement, similar to that observed in Burkitt's lymphoma. However, the incidence of abdominal masses in B-NHL83 and B-NHL86 (4% and 6%) was lower than that observed in childhood B-ALL studies (range, 31% to 54%).^{17,22-25} Also the CNS involvement of 12% was lower than that observed in earlier adult B-ALL reports, 63%,²⁷ 38%,⁴⁰ 30%,¹⁶ and 20%.¹³ The incidence varied between our studies from 0% to 8% and 17% and a similar variation in the incidence was also seen in the BFM pediatric B-ALL studies.²³ There is no explanation for the lower overall incidence of CNS disease or for the changing incidence observed. Three B-ALL patients had a large mediastinal mass, and the diagnosis of a mediastinal large B-cell lymphoma with sclerosis⁴¹⁻⁴³ characterized by a lack of BM involvement might have been considered, but was excluded because our three patients had 40%, 95%, and 70% blast cell infiltration in the BM.

The diagnosis of B-ALL in this set of patients is not quite uniform. The patients with diagnosis based on L3 morphol-

ogy alone had a very similar outcome to the patient group diagnosed by L3 morphology, as well as by SIg and other B-cell markers, with survival probabilities of 0.58 and 0.65, respectively. However, three other patients with L3 morphology had a different immunophenotype, two c-ALL and one pre-B-ALL and were, therefore, not treated according to the B-NHL protocols. It could well be that the patient group where diagnosis was confirmed by L3 morphology only includes patients with immunophenotypes other than B-ALL. Similar rare cases with FAB L3 morphology, but an immunophenotype of B-precursor or even T-lineage ALL, have already been reported.^{44,45} By contrast, in our series, five patients who were positive for SIg showed an L1 or L2 morphology. As discussed for similar cases by Sullivan,⁴⁶ in these patients the immunophenotyping took precedence over the morphological features, and they were treated according to the B-NHL protocols. However, their outcome was very poor, and four of the patients died, one after BMT. Also, the two patients where diagnosis of B-ALL was based on

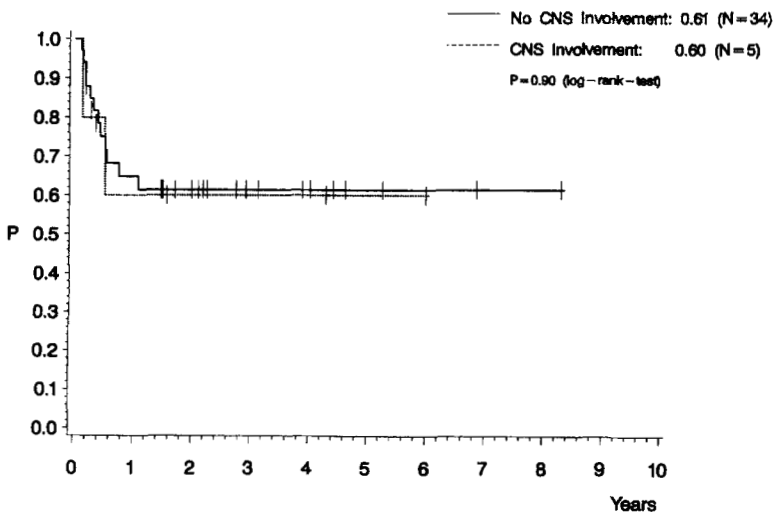


Fig 8. Probability of LFS for patients in studies B-NHL83 and B-NHL86 with initial CNS involvement compared with those without.

morphology and immunology, but who had atypical cytogenetic aberrations, had a fatal outcome with therapy failure and death. Thus, it remains open whether such patients with discrepancy in diagnosis should be treated according to such a B-NHL protocol or with a conventional ALL chemotherapy schedule, but in any case they seem to be candidates for immediate BMT. Certainly the exclusion of these patients with discrepant diagnoses from our series would have improved the results.

The complete remission rate could be substantially improved to 63% and 74% compared with the 44% achieved in the conventional 8-week induction period. These CR rates are similar to those observed in other smaller adult B-ALL series,^{16,27-30} which range from 60% to 100% with a weighted mean of 77%. The majority of CR patients obtained their CR after only one cycle, with an increasing tendency from 13 of 18 patients (72%) in B-NHL83 to 22 of 27 patients (81%) in B-NHL86. Also, the LFS showed an improvement with an increase of probability from 50% to 71% from study B-NHL83 to B-NHL86. This might be attributable to a variety of treatment changes, most probably to the increase of HdM from 0.5 g/m² to 1.5 g/m² and the higher dose of fractionated ifosfamide (800 mg/m² compared with 200 mg/m² cyclophosphamide). However, this did not lead to a correspondingly better survival. There are several possible, but not definite, reasons for this. There was a somewhat higher proportion of older patients in B-NHL86. Also, of the patient group with discrepant diagnosis and poor outcome, two were in B-NHL83 compared with six in B-NHL86. Furthermore, two of three BMT patients in B-NHL86 died versus none of two BMT patients in B-NHL83. Despite the therapy intensification, the time for completion of six cycles was not prolonged in the B-NHL86 study with a median of 138 days compared with 165 days in B-NHL83.

Of clinical relevance is the application of the 5-day cytotoxic prephase therapy with cyclophosphamide and prednisone in studies B-NHL83 and B-NHL86. The reason why the patients with the cyclophosphamide and prednisone pretreatment had a superior LFS, also partly reflected in a tendency for better overall survival of 0.56 for the 40 patients compared with 0.36 without or with other pretreatment, is not quite clear. That the clinical condition of most patients already improved considerably during these 5 days and that a tumor lysis syndrome could be avoided might be reasons. Also the omission of a pretreatment or a pretreatment with vincristine and prednisone instead of cyclophosphamide and prednisone may reflect postponement of the start of B-ALL therapy because of delayed diagnosis. That by earlier diagnosis of B-ALL and stricter application a high percentage of patients can receive this pretreatment is shown in study B-NHL86, where 80% of all patients received the pretreatment phase.

In both studies B-NHL83 and B-NHL86, the six treatment cycles could be applied in a fair proportion, 42% and 57%, of the patients. The main reason that the full treatment could not be applied was failure or progression of disease. Some patients, in B-NHL83 17% and in B-NHL86 14%, responded immediately after the start of treatment with HdM, but progressed thereafter. Of the 4 patients who achieved CR later than the first two cycles 2 died, 1 was rescued with salvage

chemotherapy (COPBLAM), and 1 was rescued with an autologous BMT. Thus, the aim is to achieve CR or a good PR even after the second cycle followed by immediate BMT.

In our B-ALL studies, the proportion of patients aged >50 to 65 years (28%) was higher than in other reported B-ALL series.^{16,27,30,40} These encouraging results for elderly B-ALL patients contrasts with other B-lineage ALL subtypes (early pre-B-ALL, common ALL) where increasing age is associated with a constantly decreasing CR rate, and there is a very low cure rate in older patients.^{7,47-49} The impact of an elevated versus normal LDH, found of significance in childhood B-ALL,²⁶ cannot be assessed in this series of patients because only two B-ALL patients had a normal level of <250 U/L. At the cut-off level of 500 U/L, there was a difference in LFS (0.67 v 0.40) which, however, did not reach significance.

The outcome for patients with CNS involvement in the studies B-NHL83 and B-NHL86 with a CR rate of 62% and LFS rate of 60% was not adversely influenced, in contrast to one¹⁶ and in agreement with two other recent reports.^{27,40} The rate of isolated and combined CNS relapses in the three studies was 50%, 57%, and 17%. Because in all three studies the CR patients received a prophylactic cranial irradiation, the lower CNS relapse rate in study B-NHL86 has to be attributed to the increased dose of HdM and the stricter triple intrathecal therapy.

The cranial irradiation given after the second cycle (B1) usually caused a delay in treatment by exacerbating the mucositis and neutropenia, particularly in older patients above 50 years. Therefore, in the new B-ALL protocol 05/93, cranial irradiation is omitted to avoid treatment delay and aggravation of mucositis and pancytopenia. In this ongoing study, it will be evaluated whether a higher dose of HdM, 3 g/m² instead of 1.5 g/m², together with the triple intrathecal chemotherapy can substitute for the omission of the prophylactic cranial irradiation.

After the poor chemotherapy results for B-ALL patients in the study ALL 01/81, the participating centers in the B-NHL83 and 86 studies were free to enter patients in first CR for BMT. The immediate improvement of the results after the adoption of the pediatric treatment schedules might be the reason why only a small number of patients were referred for BMT. Thus, BMT did not influence substantially the results in this series of adult B-ALL patients. Also, in a recent study with acute lymphoblastic lymphomas including B-ALL patients, BMT was found to be not recommendable for adult B-ALL patients in first CR.⁴⁰ Based on the results of the studies B-NHL83 and B-NHL96, with LFS of 0.50 at 8 years and 0.71 at 4 years, the strategy in the ongoing trial is that only patients who do not achieve CR within two cycles should undergo BMT.

Major toxicity was hematological with decrease in granulocytes, hemoglobin, and platelets. However, this was not so pronounced as in the conventional ALL protocol.³¹ The reasons might be the short duration of treatment and that most of the B-ALL patients had sufficient initial levels of Hb and platelets; in particular, almost all of them had normal granulocytes at diagnosis. The other noteworthy side effect of treatment was mucositis, more marked after the second cycle when the patients received the cranial irradiation. He-

matotoxicity was more pronounced in the elderly B-ALL patients 50 to 65 years old, and this was the main reason that in B-NHL86 the HdM remained unchanged at 500 mg/m² for these patients. The early death rate in these studies was 9%, which is similar to other adult B-ALL series using intensified regimens, varying from 8% to 40%. The major reason for early death was infection. Whether an improved recovery of neutrophils using granulocyte colony-stimulating factor (G-CSF) after the treatment cycles can reduce the mucositis and infection rate is currently under evaluation in a prospective randomized study.

Although the CR rates and LFS in this, as well as in other adult B-ALL studies, have improved by application of successful pediatric protocols, the outcome is still inferior compared with childhood B-ALL. Among differences in the disease biology, not yet clearly identified in B-ALL, differences in the metabolism of chemotherapeutic agents may contribute, eg, the processing of the antimetabolite methotrexate. In vitro the increased formation of long chain MTX polyglutamates correlates with better prognosis in pediatric B-lineage leukemias and B-lineage blast cells. In adults, ALL cells accumulate significantly lower levels of MTX polyglutamates.^{48,50,51} Although blast cells from B-ALL patients were not tested in either of these studies in vitro, such a difference in the MTX metabolism could contribute to the shorter remission duration, particularly in a situation where HdM is a major treatment component.

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