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Outcome of Children With High-Risk Acute Lymphoblastic Leukemia (HR-ALL): Nordic Results on an Intensive Regimen With Restricted Central Nervous System Irradiation

Ulla M. Saarinen-Pihkala, MD, PhD,[1]* G. Gustafsson,[2] N. Carlsen,[3] T. Flaegstad,[4] E. Forestier,[5] A. Glomstein,[6] J. Kristinsson,[7] M. Lanning,[8] H. Schroeder,[9] and L. Mellander[10] on behalf of the Nordic Society of Pediatric Hematology and Oncology (NOPHO)

Background. Improvement in outcome of childhood high-risk (HR) ALL was sought with a very intensive Nordic protocol leaving most patients without CNS-RT. ***Methods.*** A total of 426 consecutive children entered the NOPHO-92 HR-ALL program. HR criteria included WBC $\geq 50 \times 10^9$/L, CNS or testicular involvement, T-cell, lymphomatous features, t(9;22), t(4;11), or slow response. Of these, 152 children had very high risk (VHR) with special definitions. CNS consolidation was based on high-dose MTX (8 g/m^2) and ARA-C (12 g/m^2) alternating. VHR patients also received cranial RT. ***Results.*** The 9-year EFS was $61 \pm 3\%$, OS $74 \pm 2\%$, and EFS for T-ALL $62 \pm 4\%$. Cumulative incidence of isolated CNS relapse was $4.7 \pm 1\%$, and CNS relapse in total $9.9 \pm 2\%$. Poor prognostic factors were WBC $\geq 200 \times 10^9$/L and a very slow response. ***Conclusions.*** HR-ALL was successfully treated on the NOPHO-92 regimen, with a relatively low CNS relapse rate for non-irradiated children. WBC $\geq 200 \times 10^9$/L and very slow response emerged as strong poor prognostic factors. Pediatr Blood Cancer 2004;42:8–23. © 2003 Wiley-Liss, Inc.

Key words: ALL in children; CNS irradiation in ALL; CNS relapses in ALL; high-risk ALL; methotrexate; high-dose

INTRODUCTION

Intensive cytostatic therapy has improved the outcome of childhood acute lymphoblastic leukemia (ALL) dramatically since the early 1970s [1], the overall survival having increased from 25% up to 75% owing to intensification of therapy and treatment adapted to risk groups [2–16]. Specifically, in the Nordic countries the 5-year event-free survival (EFS) of childhood ALL has increased from 57% to 77% during the past two decades [5]. Twelve prominent childhood ALL study groups reported their results in the December 2000 issue of *Leukemia* [6–16]. The 5-year EFS values varied between 70% and 80% in most of the studies on children diagnosed with ALL during the 1990s.

Despite the excellent survival figures in general, improvement regarding high-risk ALL (HR-ALL) has been modest. In HR-ALL, the event-free survival has remained inferior with a 5-year EFS of about 50–70% [6–15], only occasional centers achieving higher EFS rates [16].

The elements of HR-ALL therapy have traditionally been intensive multi-agent induction and consolidation, plus one or more delayed intensifications. Cranial radiotherapy (RT) plays an important although declining role in the central nervous system (CNS) directed treatment. Also maintenance therapy has been intensive, and more or less modified LSA2-L2-type [17] rotational elements have frequently been used.

The Nordic HR-ALL protocol, started in 1992, has certain characteristic features. Cranial RT has been restricted to a small subpopulation (33% of children with HR-ALL,

[1]Hospital for Children and Adolescents, University of Helsinki, Helsinki, Finland

[2]Childrens Cancer Research Unit, Karolinska Institute, Stockholm, Sweden

[3]Odense University Hospital, Odense, Denmark

[4]Tromsö University Hospital, Tromsö, Norway

[5]Department of Pediatrics, University Hospital, Umeå, Sweden

[6]Rikshospitalet, University Childrens Hospital, Oslo, Norway

[7]Department of Pediatrics, University Hospital, Reykjavik, lceland

[8]Department of Pediatrics, Oulu University Hospital, Oulu, Finland

[9]Aarhus Municipal Hospital, Aarhus, Denmark

[10]Department of Pediatrics, University Hospital, Queen Silvia's Childrens Hospital, Gothenburg, Sweden

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*Correspondence to: Ulla M. Saarinen-Pihkala, Hospital for Children and Adolescents, University of Helsinki, Stenbäckinkatu 11, 00290 Helsinki, Finland. E-mail: ulla.pihkala@hus.fi

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10% of all ALL patients), while the CNS prophylaxis is taken care of by systemic high-dose (HD) therapy with methotrexate (MTX) and cytarabine (ARA-C) as well as with intrathecal (i.t.) medications. In the present report, we describe the outcome of children with HR-ALL using the Nordic HR-ALL protocol NOPHO-1992, which resulted in favorable EFS and overall survival (OS) rates and only modest frequency of CNS relapses.

Regarding the risk stratification of children with ALL, there is no definite international consensus. A presenting WBC of $>50 \times 10^9$/L and ages less than 1 year and above 10 years have been agreed upon by the NCI workshop [18]. Response to induction treatment has been used in different ways, as by response to 1-week course of steroids used by the BFM group [19], or by day 7 or day 14 bone marrow responses utilized by CCG [20]. In addition, immunophenotypic and cytogenetic features have been used to stratify patients. There is quite a good international consensus that certain unfavorable features carry an ultra-high risk of relapse, such as a very high initial WBC count, Philadelphia chromosome positivity t(9;22), near haploidy, or MLL gene rearrangements [21]. The overwhelmingly most important risk factor is, however, the therapy given. Therefore, some risk factors may lose importance when the therapy is becoming more intensive, while other factors may appear. Stratification according to risk factors and risk-oriented therapy form a dynamic process being constantly in evolution, and they need always to be analyzed together.

In the present report about the NOPHO-1992 HR-ALL protocol, we analyze risk factors within this HR category, in order to find out which patients did not do well on this particular HR protocol. The specific questions were—who would require cranial RT, and who might make candidates for allogeneic stem cell transplantation (SCT) in first remission (1 CR)?

PATIENTS AND METHODS

Patients

The data is population-based in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden); all consecutive children diagnosed with ALL (non-B-cell, age 1–15 years) during January 1992 through June 2000 numbered in total 1,456 patients. Of these 1,030 were categorized as non-HR, and 426 (29%) as high risk or very-high risk. Of these 426 ALL patients, 253 (59%) boys and 173 (41%) girls are included in this study. The clinical characteristics of the patients are presented in Table I. The NOPHO-92 HR-ALL protocol was approved by the

TABLE I. Children With High-Risk ALL (HR-ALL): Clinical Characteristics at Diagnosis

	HR < 5 (n = 196)	HR ≥ 5 (n = 78)	VHR (n = 152)	Total (n = 426)
	n (%)	n (%)	n (%)	n (%)
Sex				
Males	111 (57)	42 (54)	100 (66)	253 (59)
Females	85 (43)	36 (46)	52 (34)	173 (41)
Age (years)				
1–<5	196 (100)	—	—	196 (46)
5–<10	—	56 (72)	73 (48)	129 (30)
≥10	—	22 (28)	79 (52)	101 (24)
WBC $\times 10^9$/L				
<50	62 (32)	34 (44)	69 (45)	165 (39)
50–<100	77 (39)	23 (30)	23 (15)	123 (29)
100–<200	34 (17)	16 (21)	25 (16)	75 (18)
≥200	23 (12)	5 (6)	35 (23)	63 (15)
Phenotype				
T-cell	32 (16)	13 (17)	88 (58)	133 (31)
B-precursor	163 (83)	63 (81)	55 (36)	281 (66)
Unknown	1 (1)	2 (3)	9 (6)	12 (3)
Mediastinal mass				
Present	27 (14)	6 (8)	73 (48)	106 (25)
CNS involvement				
Present	14 (7)	0 (0)	17 (11)	31 (7)
Poor response, total[a]				
Day 15 M3	15	5	22	42 (10)
Day 29 M2/M3	11	6	13	30 (7)
Poor-risk translocations				
t(9;22)	6	8	11	25 (6)
MLL/11q23	4	0	3	7 (1)

[a]Poor response—as only HR criterion, n(%): for HR < 5 = 10 (7); for HR ≥ 5 = 7 (9); for VHR = 11 (7); for total = 28 (7).

local Ethics Committees, and informed consent was obtained from the subject's guardians.

Diagnostic Studies

The diagnosis of ALL was established at a Pediatric Oncology center and included bone marrow morphology from aspirate smears and biopsy samples. Flow cytometric immunophenotyping was performed with phycoerythrin and fluorescein isothiocyanate-conjugated monoclonal antibodies against an established panel of antigens (HLA-DR, CD2, CD3, CD7, CD19, CD20, CD13, CD33, CD34, and CD10). In evaluation of extra-medullary leukemia and organomegaly, the minimum requirements were examination of the cerebrospinal fluid (CSF), chest X-ray, and abdominal ultrasound.

Cytogenetic Investigations

Chromosome banding analyses on bone marrow and/or peripheral blood samples were performed using standard methods [22] in 15 cytogenetic laboratories in the five Nordic countries. The definition and description of clonal abnormalities have followed the recommendations of ISCN (1995). During the recent years, FISH, Southern blot, and reverse transcriptase PCR have been increasingly applied for verification or characterization of chromosomal abnormalities, as well as for the detection of MLL rearrangements (11q23-translocations), TEL/AML1 (t(12;21)(p13;q22)), and BCR/ABL (t(9;22)(q34;q11)).

High-Risk (HR) Criteria

Patients were allocated to the HR group according to one of the following criteria: (1) Presenting WBC of $\geq 50 \times 10^9$/L; (2) Testicular involvement or CNS involvement defined as ≥ 5 WBC/μl and the presence of blasts on a cytospin preparation; (3) T-cell ALL; (4) Lymphomatous features, with one clinical and one laboratory criterion present (clinical criteria: mediastinal mass; spleen enlargement to the umbilicus level; enlarged lymph nodes with ≥ 3 cm diameter. Laboratory criteria: WBC $> 50 \times 10^9$/L; Hb ≥ 100 g/L; T-cell ALL); (5) Poor-prognosis translocations t(9;22) or t(4;11); (6) Slow response to induction chemotherapy, defined as M3 status (>25% blasts) on day 15 bone marrow, or as a M2 status (5–25% blasts) or M3 status on day 29 bone marrow. M3 on day 29 was defined as very slow response.

For the HR-ALL patients, the following subcategories were established: HR < 5, HR ≥ 5, and VHR (>5 years; very high risk). All children below 5 years of age were treated on the HR protocol (HR < 5, n $= 196$). Children ≥ 5 years of age were treated either on the HR (HR ≥ 5, n $= 78$) or on the VHR protocol. The VHR group (n $= 152$; 10% of the whole ALL material) included only children ≥ 5 years of age at diagnosis, who had CNS-ALL, or lymphomatous features, or slow response, or T-cell ALL together with other HR features (e.g., WBC $\geq 50 \times 10^9$/L or lymphomatous features).

Treatment

The induction therapy consisted of prednisone 60 mg/m^2/day, vincristine weekly, doxorubicin 40 mg/m^2/day four times, intrathecal (i.t.) MTX four times, plus a 10-day course of L-asparaginase at 1,000 IU/kg/dose (Fig. 1). The second part of induction consisted of two courses of cyclophosphamide at 1,000 mg/m^2, low-dose ARA-C, and oral mercaptopurine (6-MP) (Fig. 1 and Table II).

The first CNS consolidation was given in the form of two infusions of high-dose methotrexate (HD-MTX) of 8 g/m^2 with a citrovorum factor rescue system plus i.t. MTX and two infusions of HD-ARA-C of 2 g/m^2 every 12 hr six times (total 12 g/m^2), in alternate fashion (Fig. 1). An interim maintenance of oral daily 6-MP, weekly MTX, plus pulses of vincristine and prednisone was followed by delayed intensification consisting of oral dexamethasone, weekly vincristine and daunorubicin, and four doses of L-asparaginase, plus one block of cyclophosphamide, low-dose ARA-C, and oral thioguanine (Fig. 1 and Table II).

The children in the VHR subgroup received prophylactic cranial irradiation of 18 Gy and intrathecal MTX three times (Fig. 1). Thereafter they started a maintenance regimen of LSA2-L2 type [17].

The children on HR-therapy had infusions of HD-MTX and HD-ARA-C one each, interim maintenance, the HD-MTX and HD-ARA-C repeated once more, followed by a maintenance with oral 6-MP, oral weekly MTX, and five pulses q 8 weeks with vincristine plus prednisone and i.t. MTX. The total duration of therapy in all subgroups was 2 years.

Allogeneic Stem Cell Transplantation (SCT) in First Remission (1CR)

Although not an established part of the protocol, 43 children with HR-ALL were transplanted in 1CR. The indications for SCT were as follows: t(9;22), n $= 19$; t(4;11), n $= 1$; WBC $> 200 +$ other factors, n $= 11$; WBC $> 100 +$ other factors, n $= 5$; poor response, n $= 7$. Fourteen received HLA-identical sibling grafts, and 29 received unrelated donor (URD) grafts.

Statistical Methods

Event-free survival (EFS) means estimation of the final proportion of children in continuous complete remission (CCR) compared to all children in the study group. In this analysis, induction death, death in remission, relapse, or second malignancy constitute events. Overall survival (OS) is an estimation of the proportion of children

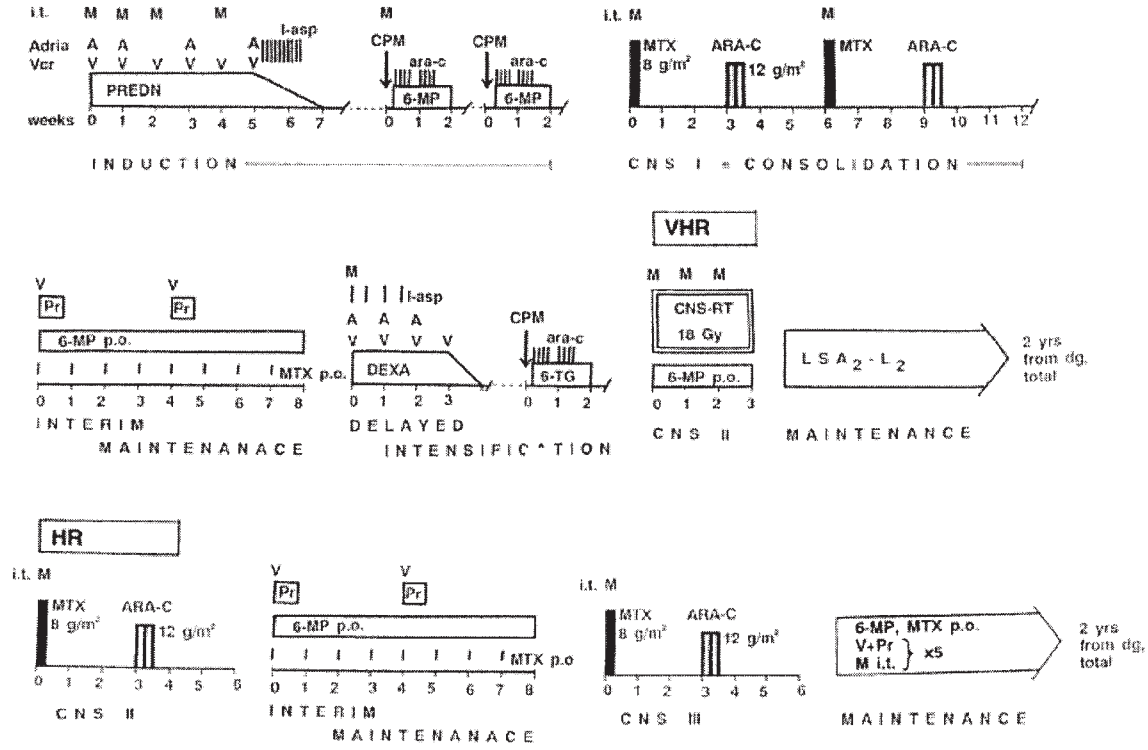

Fig. 1. Schematic presentation of the high-risk ALL (HR-ALL) chemotherapy regimen. M, methotrexate intrathecally; Adria, A, doxorubicin: Vcr, V, vincristine; PREDN, Pr, prednisone; L-asp, asparaginase; CPM, cyclophosphamide; ara-c, cytarabine low dose; ARA-C, cytarabine high-dose; 6-MP, 6-mercaptopurine; MTX, methotrexate i.v. or p.o.; DEXA, dexamathasone; 6-TG, thioguanine; CNS-RT, cranial irradiation.

surviving. Hazard function is a spline function which calculates the risk of an adverse event for a given time interval from diagnosis. The intervals in these analyses were 6 months. Statistical analyses were performed using the SPSS statistical software [23]. The life table method was used to generate graphs and the Kaplan–Meier method was used to estimate survival parameters [24]. Differences in prognosis between subgroups were compared with the log-rank test [23]. The cumulative incidence of deaths in CCR and relapse were calculated according to the ''One minus survival'' method [23]. Cox multiple regression hazard analyses were performed to evaluate prognostic factors [23]. All patients were followed up until the first event, and the patients in CCR until January 1, 2003.

RESULTS

The 9-year EFS of the HR-ALL cohort was $61 \pm 3\%$, and OS was $74 \pm 2\%$. For comparison, the 9-year EFS of the whole ALL material, all risk groups included ($n = 1{,}456$), was $75 \pm 1\%$, and the EFS of the non-high (standard and intermediate) risk groups ($n = 1030$) was $80 \pm 2\%$. No significant differences were seen in outcome between the subgroups HR < 5, HR ≥ 5, and VHR, with 9-year EFS of $63 \pm 4\%$, $61 \pm 6\%$, and $60 \pm 4\%$, respectively (Fig. 2a). The corresponding OS figures were $84 \pm 3\%$, $73 \pm 5\%$, and $67 \pm 4\%$, respectively ($P < 0.01$ between HR < 5 vs. HR ≥ 5 and HR < 5 vs. VHR).

The remission rates in the subgroups were 96% in HR < 5, 97% in HR ≥ 5, and 95% in VHR (n.s.). The cumulative incidence of death in continuous complete remission (CCR) was $4 \pm 1\%$, with no difference between the subgroups ($P = 0.7$).

The cumulative incidence of relapse was $31 \pm 4\%$ in HR < 5, $34 \pm 6\%$ in HR ≥ 5, and $34 \pm 4\%$ in VHR (Fig. 2b). In the subgroups HR ≥ 5 and VHR, most relapses occurred within 3 years of diagnosis, while the patients in HR < 5 suffered from late relapses (13 relapses $\geq$36 months after diagnosis) (Fig. 2b). Of these late relapsing patients, 5/13 had WBC ≥ 100, and 3/13 had WBC $\geq 200 \times 10^9$/L at initial presentation.

The hazard function illustrates the considerably higher risk of early events in children over 5 years of age, i.e., the VHR and HR ≥ 5 groups, as opposed to the HR < 5 (Fig. 2c). All subgroups had events after discontinuation of therapy, i.e., after 2 years from diagnosis. In addition, a late peak of events at 4–6 years after diagnosis was recognizable in the subgroup HR < 5, representing late relapses.

The types of relapses in the whole HR cohort are listed in Table III. The vast majority were bone marrow relapses. The cumulative incidence of isolated CNS relapse was 4.7%, being 3.1% in the HR < 5, 6.1% in the HR ≥ 5, and

TABLE II. The NOPHO-92 HR-ALL Treatment Protocol

Treatment phase/drug	Single or daily dose	Days (d) given	Comments
High Risk (HR < 5 and HR > 5)			
Induction (w 0–7)			
Prednisone (orally/IV)	60 mg/m^2/d	1–36/45	Optional: prephase
Vincristine (IV)	2 mg/m^2 (max. 2 mg)	1, 8, 15, 22, 29, 36	
Doxorubicin (IV)	40 mg/m^2 (24 hr)	1, 8, 22, 36	
L-asparaginase (IM)	1,000 IU/kg daily	36–45	
Methotrexate (IT)[a]	8–12 mg (age adj.)	1, 8, 15, 29	
Early intensification (w 7–14)			
6-Mercaptopurine (orally)	60 mg/m^2/d	1–14, 29–42	
Cyclophosphamide (IV)	1,000 mg/m^2	1, 29	
Cytarabine (IV)	75 mg/m^2/d	3–6, 10–13, 31–34, 38–41	
Methotrexate (IT)	8–12 mg (age adj.)	1, 29	
Consolidation (w 16–26)			
Methotrexate (IV)	8 g/m^2 (24 hr)	1, 43	Citrovorum factor rescue[b]
Cytarabine (IV)	2 g/m^2 × 2 daily × 3 d	22, 64	Total dose: 12 g/m^2/course
Methotrexate (IT)	8–12 mg (age adj.)	1, 43	
Interim maintenance (w 28–35)			
Prednisone (orally)	40 mg/m^2/d	1–8, 29–35	
Vincristine (IV)	2 mg/m^2	1, 29	
6-Mercaptopurine (orally)	75 mg/m^2/d	1–57	
Methotrexate (orally)	20 mg/m^2/w	1–50	
Late intensification (w 36–42)			
Dexamethasone (orally)	10 mg/m^2/d	1–22/29	
Vincristine (IV)	2 mg/m^2 (max. 2 mg)	1, 8, 15, 22	
Daunorubicin (IV)	30 mg/m^2 (24 hr)	1, 8, 15, 22	
L-asparaginase (IM)	1,000 IU/kg	1, 8, 15, 22	
6-Thioguanine (orally)	60 mg/m^2/d	29–42	
Cyclophosphamide (IV)	1,000 mg/m^2	29	
Cytarabine (IV)	75 mg/m^2/d	31–34, 38–41	
Methotrexate (IT)	8–12 mg (age adj.)	31, 38	
Consolidation (w 44–62)			
Methotrexate (IV)	8 g/m^2	1, 99	Citrovorum factor rescue[b]
Cytarabine (IV)	2 g/m^2 × 2 daily × 3 d	22, 120	Total dose: 12 g/m^2/course
Methotrexate (IT)	8–12 mg (age adj.)	1, 99	
Interim maintenance			
Prednisone (orally)	60 mg/m^2/d	43–49, 71–78	
Vincristine (IV)	2 mg/m^2 (max. 2 mg)	43, 71	
6-Mercaptopurine (orally)	75 mg/m^2/d	43–98	
Methotrexate (orally)	20 mg/m^2/w	43–91	
Maintenance (w 64–2 years)			
6-Mercaptopurine (orally)	75 mg/m^2/d	Until 2 years from diagnosis	
Methotrexate (orally)	20 mg/m^2/w	Until 2 years from diagnosis	
Prednisone (orally)	60 mg/m^2/d × 7	1, 57, 113, 169, 225	
Vincristine (IV)	2 mg/m^2 (max. 2 mg)	1, 57, 113, 169, 225	
Methotrexate (IT)	8–12 mg (age adj.)	1, 57, 113, 169, 225	
Very high-risk (VHR)			
Week: 0–42			Same as HR < 5 and HR ≥ 5
CNS-therapy (w 44–46)			
Cranial RT	18 Gy	1–15	
6-Mercaptopurine (orally)	50–75 mg/m^2/d	1–29	
Methotrexate (IT)	12 mg	1, 8, 15	
Maintenance: modified LSA_2L_2 (w 48–95)			6 Cycles × d 1–56
6-Thioguanine (orally)	300 mg/m^2/d	1–4	
Methotrexate (IT)	12 mg	1	
Cyclophosphamide (IV)	600 mg/m^2	5	
Hydroxyurea (orally)	2400 mg/m^2/d, cycles 1–4	15–18	Cy 5–6: pred. (d 15–22)
Daunorubicin (IV)	30 mg/m^2, cycles 1–4	19	Cy 5–6: vincristine (IV)
Methotrexate (orally)	10 mg/m^2/d	29–32	
Carmustine (IV)	30 mg/m^2	33	
Cytarabine (IV)	150 mg/m^2/d	43–46	
Vincristine (IV)	2 mg/m^2 (max. 2 mg)	47	

(*Continued*)

TABLE II. (*Continued*)

Treatment phase/drug	Single or daily dose	Days (d) given	Comments
Maintenance (w 96-			
6-Mercaptopurine (orally)	75 mg/m^2/d	Until 2 years from diagnosis	
Methotrexate (orally)	20 mg/m^2/w	Until 2 years from diagnosis	

[a]Age adjustment of IT MTX doses: 1–2 years 8 mg; 2–3 years 10 mg; ≥3 years 12 mg.
[b]Citrovorum factor rescue (Leucovorin^R): 50 mg/m^2 i.v. over 1 hr, given hr 36 from the start of MTX infusion (= 12 hr from the discontinuation). Thereafter 15 mg/m^2 i.v. push q 3 hr ×6 doses, followed by 15 mg/m^2 i.v. or p.o.q 6 hr until plasma MTX level below 8×10^{-8} molar (= 0.08 μmol/L).

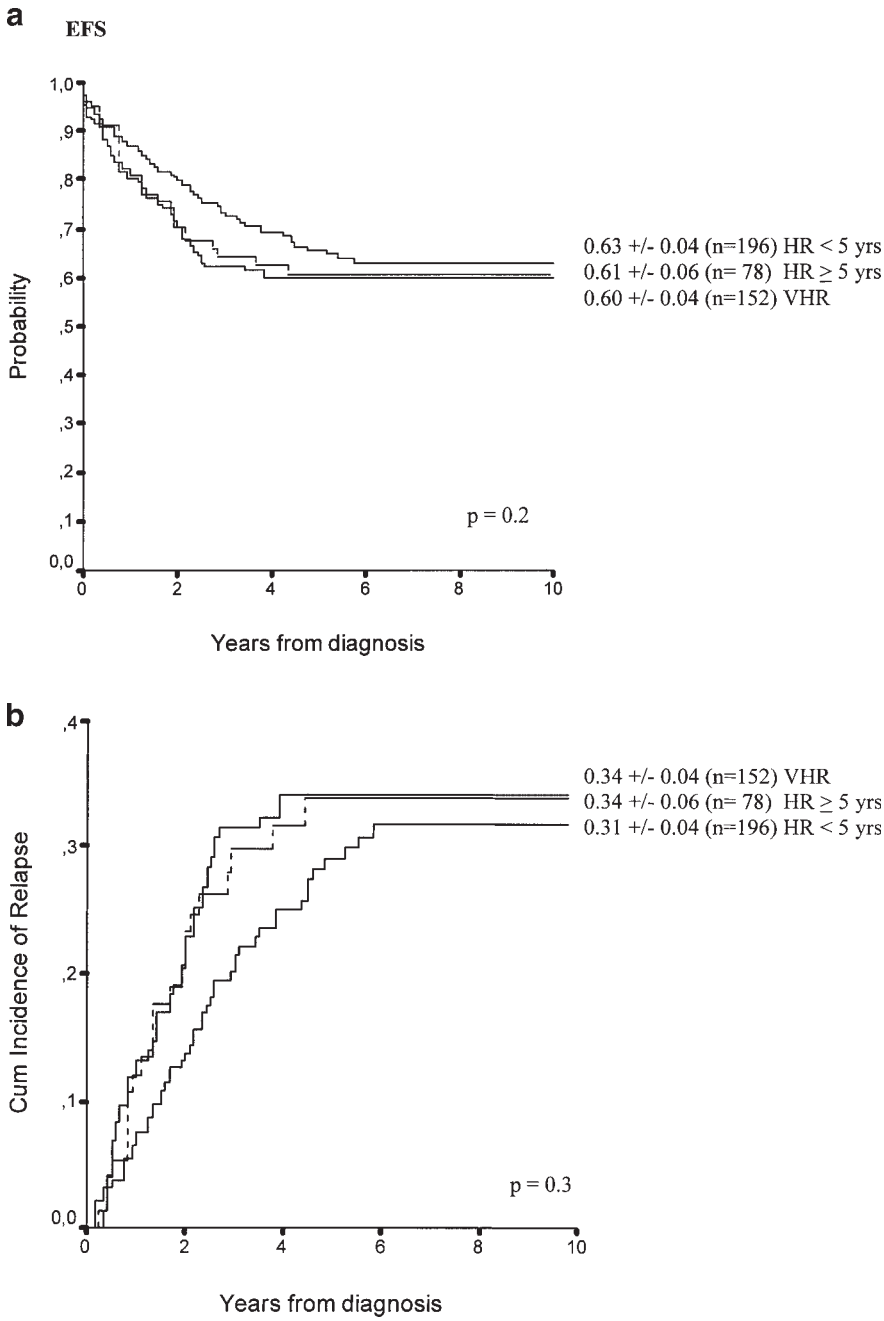

Fig. 2. Event-free survival (EFS) (**a**), cumulative incidence of relapse (**b**), and hazard function (**c**) in the three subgroups HR < 5 years of age, HR ≥ 5 years of age, and VHR. Hazard function illustrates the risk of events as a function of time.

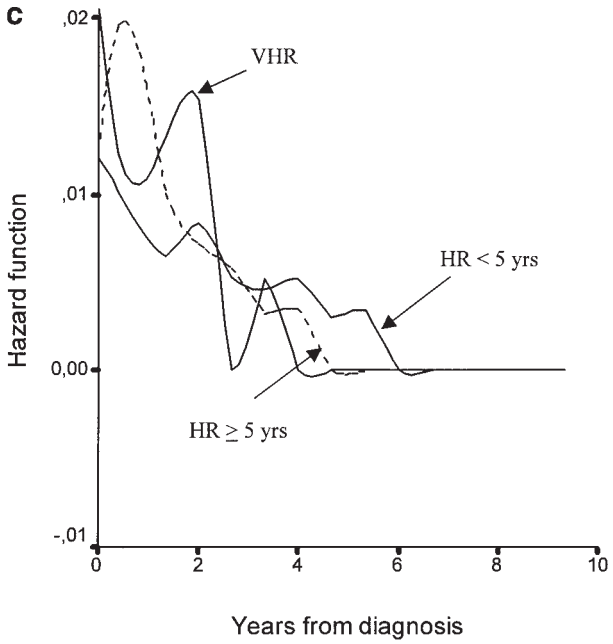

Fig. 2. (*Continued*)

6.1% in the VHR groups (Table IV). Both isolated and combined CNS relapses, together with a summary of CNS-targeted treatment given are presented in Table IV. Four out of the eight isolated-CNS events in the VHR group occurred early, before the CNS-RT had taken place.

Isolated-CNS relapses were overrepresented among those with high initial WBC. In children with WBC $> 100 \times 10^9$/L (n = 138), the cumulative incidence of isolated CNS relapse was 9.9%, as compared to 2.7% in the lower WBC categories (n = 288) ($P = 0.02$). Similarly, the cumulative incidence of any CNS relapse (combined relapses included) was 16.4% for those with WBC $> 100 \times 10^9$/L, as compared to 7.2% in those with WBC $< 100 \times 10^9$/L ($P = 0.02$). Trend to overrepresentation was also observed in those with T-cell ALL and mediastinal mass (n = 86) with a cumulative incidence of isolated-CNS relapse of 7.6%, as compared with 0% in those with T-cell ALL without mediastinal mass (n = 47; $P = 0.08$), and 4.6% in the B-precursor HR-ALL cohort (n.s.) (Fig. 3). However, in multivariate Cox analysis, no independent variable (risk category, sex, age, WBC, immunophenotype, mediastinal mass, lymphomatous features, CNS at diagnosis, response to therapy) was found to have statistical significance for isolated-CNS relapse (Table V). Regarding any CNS relapse, a trend was seen with age $\geq$10 years and with poor response (Table V). The risk category was significant ($P < 0.05$) with HR < 5 being best, HR $\geq$ 5 next, and VHR worst (Table IV).

We also evaluated the HR-ALL data by applying the NCI criteria and immunophenotype. TSR = T-cell ALL, age 1–9 years at diagnosis and WBC $< 50 \times 10^9$/L; THR = T-cell ALL, age $\geq$10 years at diagnosis or WBC $\geq 50 \times 10^9$/L; BSR = precursor B immunophenotype, age <10 years at diagnosis and WBC $< 50 \times 10^9$/L; BHR = precursor B immunophenotype, age $\geq$10 years at diagnosis or WBC $\geq 50 \times 10^9$/L. Infants were excluded from our analysis. It also needs to be notified that a proportion of BHR according to NCI criteria were not included in the HR-ALL group: those $\geq$10 years of age without other HR criteria were treated on the intermediate risk ALL protocol. We therefore also include the following data: the 9-year EFS of the whole IR-ALL group (n = 537) was $81 \pm 2\%$, being separately $75 \pm 4\%$ (n = 140) and $83 \pm 2\%$ (n = 397) for those $\geq$10 years and <10 years of age, respectively. Immunophenotypic categorization

TABLE III. Children With HR-ALL: Outcome and Relapses by Risk Groups

	HR < 5	HR ≥ 5	VHR	Total	
	n (%)	n (%)	n (%)	n (%)	*P* value
Number of patients	196	78	152	426	
Induction failures	8 (4.1)	2 (2.6)	7 (4.6)	17 (4.0)	
Remission achieved	189 (96.4)	76 (97.4)	146 (96.1)	411 (96.5)	
Relapses: total	50 (25.5)	23 (29.5)	46 (30.3)	119 (27.9)	
BM, isolated	35	16	20	71 (16.7)	
CNS, isolated	5	4	8	17 (4.0)	
Testis, isolated	1	–	–	1 (0.2)	
BM + CNS	6	2	6	14 (3.3)	
CNS + other	–	–	3	3 (0.5)	
Other localisations	3	1	9	13 (3.2)	
Death in CCR	6 (3.1)	4 (5.1)	6 (3.9)	16 (3.8)	
CCR at follow-up	132 (67.3)	49 (62.8)	93 (61.2)	274 (64.3)	
p-EFS at 5 years	66 ± 4	61 ± 6	60 ± 4	63 ± 3	0.2
p-EFS at follow-up	63 ± 4	61 ± 6	60 ± 4	61 ± 3	0.2
p-survival at follow-up	81 ± 3	69 ± 6	66 ± 4	74 ± 2	<0.01[a]
Cumul inc of relapse	31 ± 4	34 ± 6	34 ± 4	33 ± 3	0.3

[a]HR < 5 vs. HR ≥ 5/VHR.

TABLE IV. CNS-Targeted Treatment and CNS Relapses of HR-ALL Patients on the NOPHO-92 ALL Protocol (Infants Excluded)

		CNS prophylaxis				Cumulative incidence %[a] and number ( ) of CNS events	
Risk group	n	MTX (i.t., doses)	HD-MTX (i.v.)	HD-ARA-C (i.v.)	Cranial RT	CNS isolated	CNS total
HR < 5	196	18	8 g/m^2 × 4	12 g/m^2 × 4	—	3.1 (5)	7.5 (11)
HR ≥ 5	78	18	8 g/m^2 × 4	12 g/m^2 × 4	—	6.1 (4)	9.0 (6)
VHR	152	22	8 g/m^2 × 2	12 g/m^2 × 2	18 Gy	6.1 (8)	13.3 (18)
All patients	426					4.7 (17)	9.9 (35)

[a]Estimated according to the ''one minus survival'' method (see ''Statistical Methods'').

could not be performed on 12 HR-ALL patients based on very immature and/or non-classifiable phenotypes. The 9-year EFS was 69 ± 8% in the TSR (n = 33), 60 ± 5% in the THR (n = 100), 72 ± 5% in the BSR (n = 80), and 57 ± 4% in the BHR (n = 201) groups, 62 ± 4% for T-cell ALL in total, and 61 ± 3% for B-precursor ALL in total. The cumulative incidence of isolated CNS relapse was 7.1, 4.4, 1.5, and 5.5% in the TSR, THR, BSR, and BHR groups, respectively (n.s.).

Prognostic Factors Within HR-ALL Cohort

Cox analyses performed on the whole HR cohort including age, sex, WBC, platelet count, hemoglobin, mediastinal mass, CNS-ALL at diagnosis, lymphomatous features, immunophenotype, response evaluated as BM day 15 and/or day 29, and t(9;22), indicated that WBC at presentation ($P < 0.01$) and poor response ($P = 0.04$) were the only independent unfavorable prognostic factors in the model. WBC at presentation proved to be the most important risk factor, with a WBC of ≥200 × 10^9/L carrying an extra poor prognosis with an EFS of 35% only.

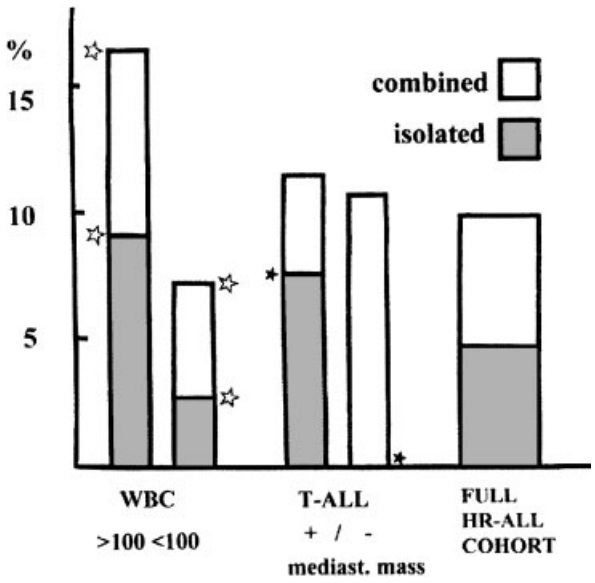

Fig. 3. Cumulative incidence of isolated- and combined-CNS relapses in HR-ALL patients, illustrating the CNS risk with high WBC and T-ALL with mediastinal mass. WBC > 100, n = 138; WBC < 100, n = 288; T-ALL, mediastinal mass+: n = 86; T-ALL, mediastinal mass−: n = 47; full HR-ALL cohort, n = 426. The large asterisks: $P = 0.02$; the small asterisk: $P = 0.08$.

The EFS by both immunophenotype and WBC is given in Figure 4, indicating that the HR-ALL patients with T-phenotype did well except for those with WBC ≥ 200 × 10^9/L (EFS 43%) (Fig. 4a), whereas those with B-precursor ALL did poorly already with a WBC of 100–200 × 10^9/L (EFS 50%), the poorest group being those with WBC ≥ 200 × 10^9/L (EFS 25%) (Fig. 4b). In the EFS figures above, censoring was not made for allogeneic SCT in 1CR. Of all children with WBC ≥ 200 × 10^9/L, 38 were T-cell ALL (21% transplanted in ICR), 23 were precursor-B ALL (26% transplanted in ICR), and 2 were unclassified. For those with initial WBC ≥ 200 × 10^9/L and treated with chemotherapy only, the 9-year EFS was 43 ± 9% for T-cell ALL (n = 30) and 15 ± 9% for precursor-B ALL (n = 17).

The response to induction therapy was evaluated on day 15 and day 29 bone marrow samples (Fig. 5). The children with M3 status (>25% blasts) on day 15 had a trend to inferior survival ($P = 0.07$; Fig. 5a), while those with M3 status on day 29 marrow had a significantly poorer outcome (EFS 25%; $P < 0.01$) (Fig. 5b) although this group was small.

For small poor-risk subgroups, the 9-year EFS was as follows: CNS-ALL at presentation (n = 31), 61 ± 8%; t(9;22) (n = 25), 44 ± 1%. Other subgroups were too small for EFS figures: t(1;19), n = 6; MLL/11q23, n = 7; hypodiploidy, n = 5.

Age was not a significant risk factor. EFS for those ≥10 years of age at diagnosis was 60 ± 5%, vs. 62 ± 3% for those 1–9 years of age ($P = 0.6$). Lymphomatous features were strongly associated with T-cell ALL, and were not recognizable as an independent risk factor. EFS for those with lymphomatous features was 67 ± 5%, vs. 60 ± 3% for the others ($P = 0.3$). Coexpression of myeloid markers CD13 and/or CD33 in at least 30% of the blast cells had no adverse effect on outcome (data not shown).

The cytogenetic and molecular genetic results were analyzed on the B-precursor ALL patients only (T-cell ALL excluded). Almost one-third (21/74) of patients

TABLE V. Five-Year EFS and Five-Year CNS-Relapse-Free Survival Separately for Isolated and any CNS Relapse for Different Subgroups in HR-ALL

				CNS-relapse-free survival		
	n	EFS	*P*	Isolated	Any	*P*, CNS−any
Sex						
Males	253	64 ± 4		95 ± 2	89 ± 2	
Females	173	62 ± 3	0.6	96 ± 2	92 ± 2	0.4
Age (years)						
1–<5	196	65 ± 4		97 ± 2	92 ± 2	
5–<10	129	60 ± 4		93 ± 3	86 ± 3	
≥10	101	60 ± 5	0.3	95 ± 2	90 ± 3	0.07
WBC × 10^9/L						
<50	165	71 ± 4		97 ± 2	92 ± 2	
50–<100	123	67 ± 4		97 ± 2	93 ± 3	
100–<200	75	60 ± 4		88 ± 4	83 ± 5	
≥200	63	35 ± 6	<0.01	94 ± 3	84 ± 5	0.1
Phenotype						
T-cell	133	62 ± 4		95 ± 2	88 ± 3	
B-precursor	281	63 ± 3		96 ± 2	91 ± 2	
Unknown	12	58 ± 14	0.4	90 ± 9	90 ± 9	0.3
Mediastinal mass						
Yes	106	69 ± 5		93 ± 3	89 ± 3	
No	320	61 ± 3	0.5	96 ± 2	91 ± 2	0.2
CNS-ALL						
Yes	31	61 ± 9		89 ± 6	85 ± 7	
No	395	63 ± 3	0.4	96 ± 2	90 ± 2	0.2
PR[a] as only HR criterion						
Yes	28	81 ± 7		100.0	100.0	
No	398	61 ± 3	0.03	95 ± 2	89 ± 2	0.08

[a]PR = poor response, M3 on day 15 and/or M2/M3 on day 29 bone marrow.

tested for TEL/AML1 were positive, with a similar frequency in the HR < 5, HR ≥ 5, and VHR subgroups. The patients positive for TEL/AML1 had a 5-year EFS of 82%, as compared to 43% in those negative for this cryptic translocation ($P < 0.05$) (Fig. 6). In total, 25 were positive for BCR/ABL (Ph+) with an EFS of 41 ± 12% (the majority of these patients were transplanted). Information about the modal chromosome number was present in 78% of the patients with B-precursor ALL, when the cases with 11q23/MLL, Ph+, and t(12;21) were excluded. The modal number of ≥52 was present in 38.7% of the patients, but it did not have any impact on survival.

Allogeneic Stem Cell Transplantation in First Remission

Allogeneic stem cell/bone marrow transplantation in 1CR was an option for selected poor-risk patients—43 HR/VHR-ALL patients were treated by this modality, 14 with related (sibling) donors, and 29 with unrelated donors (URD). The SCT indications were divided among the sibling/URD groups as follows: t(9;22) 3/16; t(4;11) 0/1; WBC > 200 + other factors 6/5; WBC > 100 + other factors 2/3; poor response 1/6, respectively. A total of 7 out of 14 sibling and 5 out of 29 URD graft recipients had T-cell ALL. The mean/median time from diagnosis to transplant was 203/210 days in the sibling donor group and 271/225 days in the URD group (n.s.). There were seven toxic deaths (sibling group 2, URD group 5) and nine post-transplant relapses. Of these nine relapses, six had Ph+ ALL and the remaining three had WBC > 200 × 10^9/L at diagnosis (2 T-cell, 1 B-precursor ALL). Five had a sibling donor and four had URD. The post-transplant EFS was 45% in the sibling donor group, vs. 65% in the URD group ($P = 0.2$; Fig. 7). Appropriate comparison of outcome with a chemotherapy group was not feasible since no group of matched controls was to be found. Nevertheless, we had 41 children with very-high-risk criteria (t(9;22), WBC ≥ 200, or poor response as M3 marrow on day 29) treated on chemotherapy only who stayed in remission for a minimum of 6 months. The 9-year EFS of these children was 41 ± 8%.

Regarding Ph+ ALL, those transplanted in first remission did significantly better than the ones treated with chemotherapy only. For the SCT group (n = 19), the p-EFS was 55 ± 13%, as compared to 17 ± 5% for the chemotherapy group (n = 6) ($P = 0.02$).

Treatment Toxicity

Among our HR-ALL cohort (n = 426), the toxic mortality was 15 (3.5%) during induction, and 16 (3.8%)

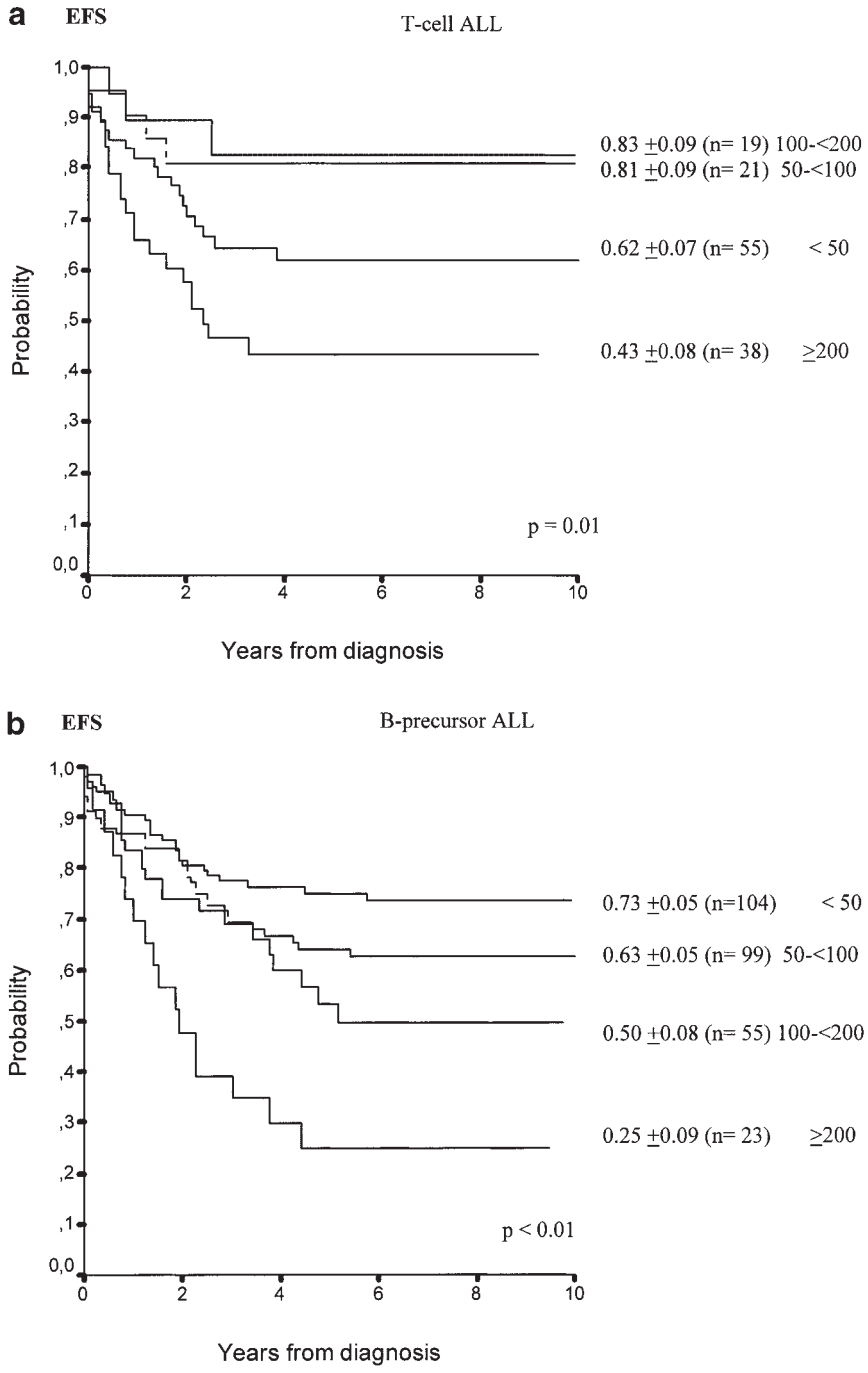

Fig. 4. EFS by immunophenotype and WBC category. **a**: T-cell ALL (n = 133). The statistical significance $P = 0.01$ was obtained in comparing >200 vs. 50–<100 and >200 vs. 100–200. **b**: B-precursor ALL (n = 281). The statistical significance $P < 0.01$ was obtained in comparing >200 vs. the others (n = 12, not classifiable, excluded from the data).

later in complete remission. Of the induction deaths, five were due to sepsis (*Candida* 2, *Pseudomonas* 1 documented), five were related to excessive blast cell burden, and the remaining ones had different kinds of other reasons or information was missing. Toxic deaths later in CCR included severe infections in six (*Pseudomonas* 2, *E. coli* 1, adenovirus 1 documented), post-transplant complications after SCT in 1CR in seven, plus other undefined causes. The CNS consolidation with HD-MTX was well tolerated. The HD-ARA-C courses were as a rule followed by profound neutropenia and acute toxicity in terms of neutropenic fever occurred, warranting the use of myeloid growth factors in addition to antibiotics.

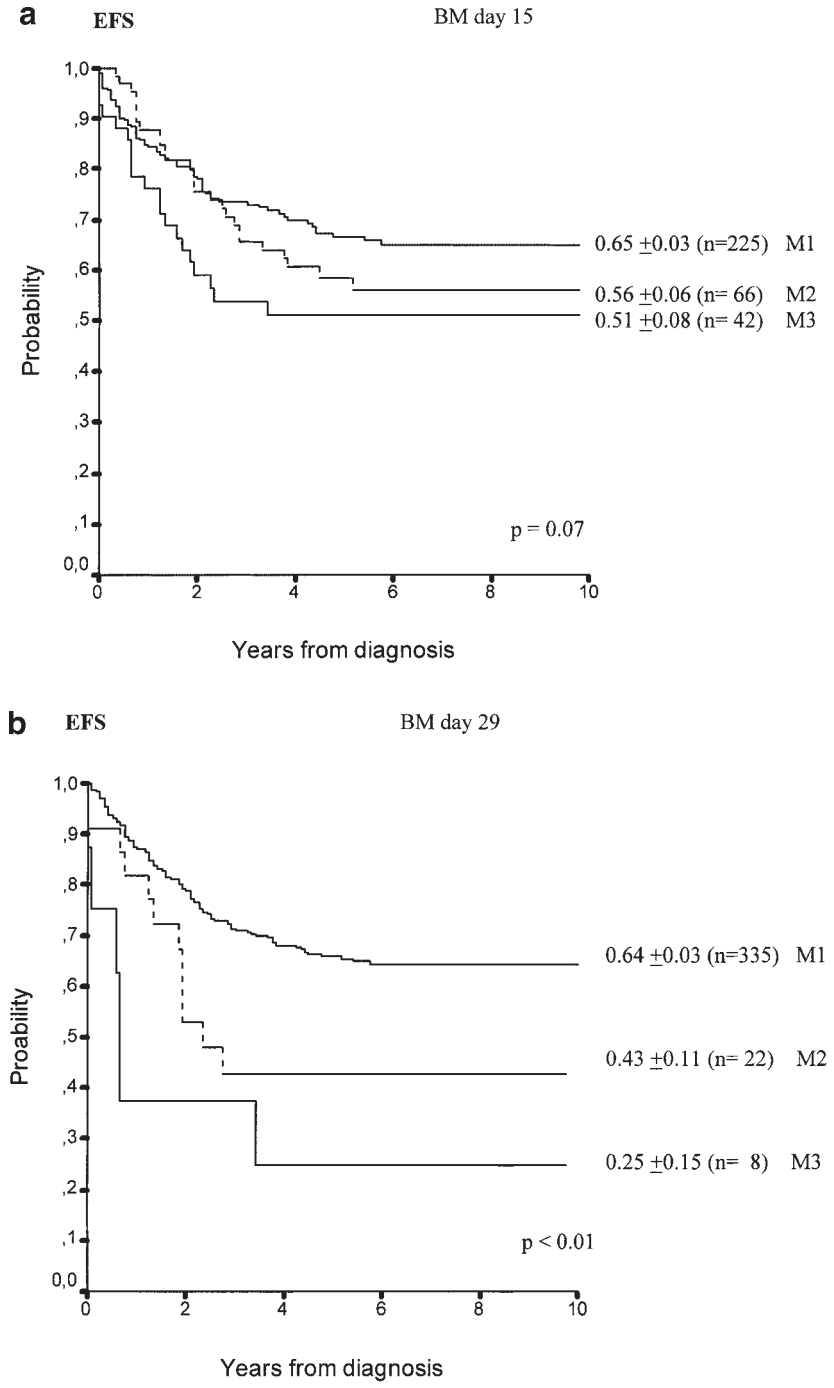

Fig. 5. EFS by initial response to therapy in children with HR-ALL. **a**: Day 15 bone marrow (data of 93 patients missing). **b**: Day 29 bone marrow (data of 61 patients missing). M1 < 5% blasts, M2 = 5–25% blasts, and M3 > 25% blasts.

DISCUSSION

The Nordic population-based NOPHO-92 ALL protocol resulted in a 9-year EFS of 61% for the HR-ALL cohort, representing 29% of the whole ALL material. Previous Nordic data from 1986–1991 gave a 5-year EFS of 60% for HR-ALL [5]. By using NCI criteria, the 9–10 year EFS has improved from 1986–1991 to the present study particularly regarding THR (from 46.4% to 60%) but has remained similar for BHR (61.1% vs. 57%) [5]. However, previous Nordic data may not be good for comparison, since HR-ALL was not uniformly treated until the NOPHO-92 protocol. Many prominent ALL study groups have reported their EFS figures for HR-ALL in the range of 60–70% [7–9,13], while others have remained within 50–60% [6,11,12,14,15].

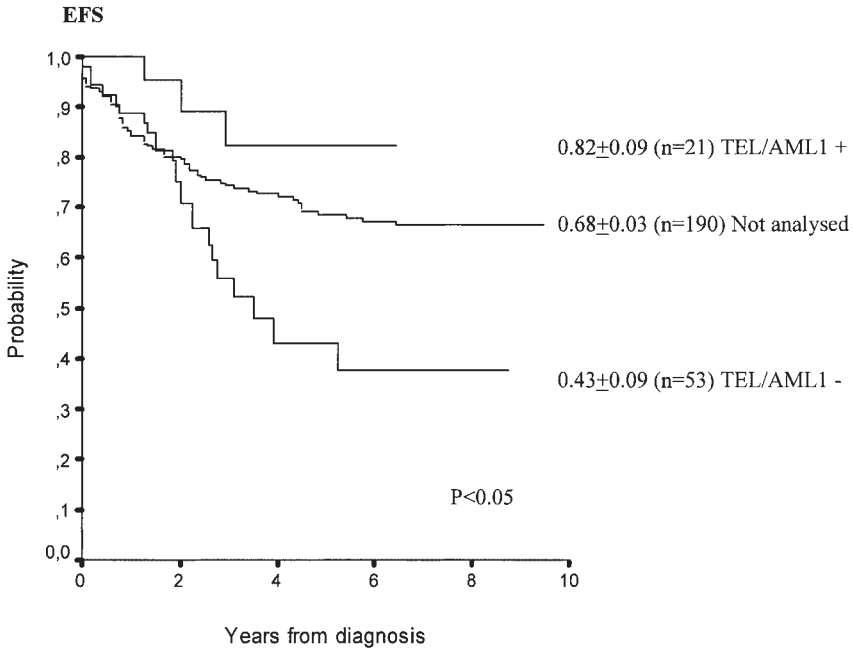

Fig. 6. EFS in children with precursor-B HR-ALL by the positivity or negativity for the TEL/AML1 fusion (the cryptic translocation t(12;21)).

In our Nordic program, only 10% of all ALL patients received prophylactic cranial RT, representing 33% of those with HR-ALL. For comparison, CCG has irradiated 10% of their ALL patients [8], St. Jude 17% [13], and BFM 70% [7] in studies during the 1990s. Our CNS-targeted therapy consisted of repeated systemic chemotherapy courses with HD-MTX at 8 g/m^2/dose and HD-ARA-C at 12 g/m^2/course, plus of a series of i.t. MTX (Table IV). The HD-MTX approach was chosen based on studies performed in Norway by Moe et al. during the 1980s [25–27]. The dose of 8 g/m^2 was selected to cover the wide range of individual metabolic variations, and this dose,

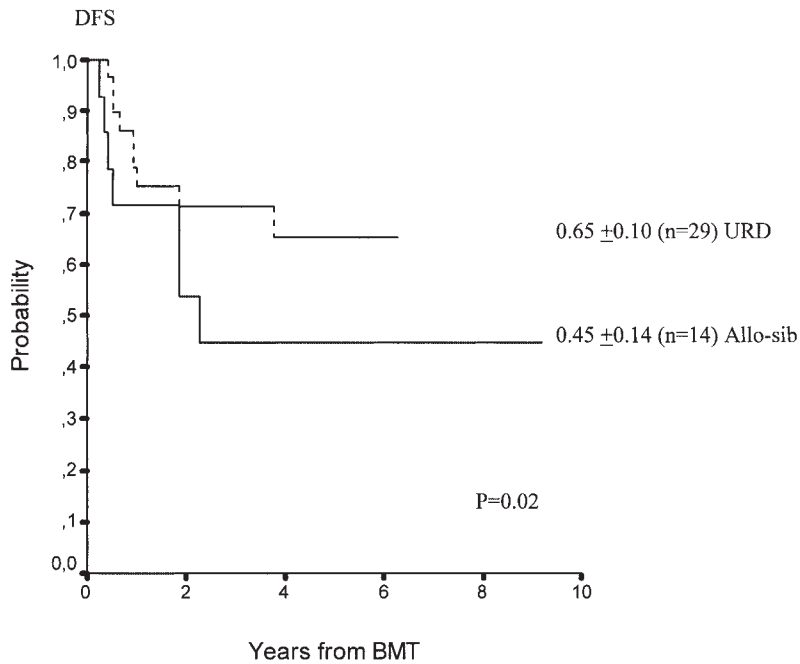

Fig. 7. Disease-free survival in children with very high-risk ALL who underwent allogeneic stem cell transplantation in first remission. URD: 29 children who received the graft from unrelated donor. Allo-sib: 14 children who received the graft from matched sibling donor. The time from diagnosis to transplant was not statistically different between the groups.

with the citrovorum factor rescue used, has been very well tolerated. There is also evidence that T-lineage blasts accumulate MTX and MTX polyglutamates less avidly than do B-lineage blasts [28,29]. Accordingly, higher serum MTX concentrations are needed for adequate response in T-cell ALL. Even extremely high MTX doses as 33.6 g/m^2 given in protracted infusions have been used in CCG infant studies. This approach appeared to control the CNS disease rather than marrow disease [30]. There is no demonstrated evidence available in favor of the 8 g/m^2 selected by us, as compared to the MTX dose of 5 g/m^2 we have used in our standard and intermediate risk ALL patients. Our Nordic HR-ALL material has been too small to address this dosage question in randomized fashion. The HD-ARA-C courses caused some acute toxicity in terms of neutropenic fever, warranting the use of myeloid growth factors. The HD-MTX and our high-dose regimen in general was well tolerated.

Based on the rather modest cumulative incidence of CNS events in our HR-ALL patients, both isolated and combined ones (Fig. 3 and Table IV), we conclude that our CNS prophylaxis has been adequate. Cranial RT has been established as a strong and effective modality for CNS prophylaxis, and interestingly, Dana Farber Cancer Institute with the best results for HR-ALL so far reported (EFS 81% and CNS relapse rate 1.0%) has still continued to irradiate all HR-ALL patients with 18 Gy to the cranium [16,31]. Nevertheless, there is general agreement that owing to the cognitive and endocrine late effects and risk of second tumors, cranial RT should be reduced to the minimum possible. Certain study groups avoid cranial RT totally [11]. In Table VI, we have summarized some available data on CNS relapses in children on HR-ALL regimens. These regimens are not entirely comparable due to different patient selection. The isolated-CNS relapse rate varied around 3–7% in regimens not utilizing prophylactic cranial RT, in accordance with 3–6% in the nonirradiated NOPHO groups. Similarly, the rate of any CNS relapse varied between 7.8–13.3%, compared to 7.5–9% in NOPHO patients. Those utilizing cranial irradiation had in general lower CNS relapse rates (Table VI). The EFS figures in Table VI are given for comprehensive view of the results. The question remains: who needs cranial RT? We believe that there exists a small subgroup of patients who still today benefit from prophylactic cranial irradiation. In our HR-ALL material, both isolated and any CNS relapses were overrepresented among those with WBC $> 100 \times 10^9$/L (Fig. 3; $P = 0.02$), with a similar trend regarding T-cell ALL with mediastinal mass ($P = 0.09$). Similar conclusions have been made—for example, at St. Jude, where cranial irradiation is confined to patients with precursor-B ALL and WBC $> 100 \times 10^9$/L, or T-cell ALL and WBC $> 50 \times 10^9$/L [36]. Furthermore, many HR-ALL protocols today, including our NOPHO-2000, use dexamethasone instead of prednisolone due to the potentially better effect in reducing the risk of CNS disease.

All children with T-cell ALL were allocated to our HR-ALL protocol, and their outcome was good with the therapy given with a 9-year EFS of $62 \pm 4\%$. The WBC limit for poorer prognosis among T-cell ALL seemed to be a WBC of $>200 \times 10^9$/L (Fig. 4a), EFS dropping to 43%

TABLE VI. International CNS Relapse Data on Children With HR-ALL Treated in the 1990s

	5-year EFS (%)			Cumul. incidence of CNS relapse			
Study	Total	T-cell (NCI)	Prec. B (NCI)	Isol.	Any	Comments	Prophyl. cranial RT
DFCI [31]	81	74	82	ND	1.0		All 18 Gy
CCG-1800 [8]	67	70	65				
RER [32]	69/75			2.3/3.6		Reg. A/B, RT±	Random±
RER, no RT				4.2			No RT
SER [33]	55/75			5.1/0	7.0/0.6	Stand./augm. tx	All 18 Gy
POG [12]							
1986–1996	53.8	48.7	55.3				
1990–1994			57.9	3.1/7.3	7.8/10.9	T-cell/prec B	97% No RT
BFM-90, HR [34]	34	64[a]	64[a]	1.6	4.1	Only poor resp. and Ph+ included	All 12 Gy
EORTC-58881 [11]	46.7	61.7	55.2	ND	11.3/13.3	All HR/T-cell	No RT
Tokyo-92 [35]	60.4	53.6	51.8	3.0	4.5	Part randomized to ±RT	73% 18 Gy
NOPHO-92:							
HR in total	61.0	60	57	4.7	9.9		35% 18 Gy
HR < 5	63			3.1	7.5		No RT
HR ≥ 5	61			6.1	9.0		No RT
VHR	60			6.1	13.3		All 18 Gy

The references are given in square brackets.
[a]The figure 64% is for T-cell and precursor-B combined.

above this WBC level. We conclude that our HR-ALL therapy was adequate for most (70%) of the T-cell ALL patients. The modified LSA2-L2 maintenance for VHR-ALL was in 1992 chosen to cover better the patients with T-ALL and lymphomatous features, and might have contributed to the favorable outcome: according to the NCI criteria, the EFS for the THR-group was now $60 \pm 5\%$, as compared to $46.4 \pm 7\%$ from the period 1986–1991 [5]. Alternating non-crossresistant combination chemotherapy represented by the original LSA2-L2 and the modifications known as the New York regimens have proven beneficial in ALL patients with bulky masses or T-cell disease [37].

Interestingly, WBC was a stronger prognostic factor for precursor-B ALL than for T-cell ALL (Fig. 4b). Unexpectedly, patients with T-cell ALL did better than those with precursor-B ALL in all WBC categories except for WBC $< 50 \times 10^9$/L (Fig. 4). The poorest outcome was observed in the group of precursor-B ALL with WBC $\geq 200 \times 10^9$/L (8% of all precursor-B ALL patients). The stem cell transplantations performed do not explain this difference, since similar proportions of T-cell ALL and precursor-B ALL patients with WBC $\geq 200 \times 10^9$/L were transplanted. In those remaining on chemotherapy, the difference in outcome was, despite of the small numbers, pronounced, indicating that it was particularly the chemotherapy regimen that benefited the T-cell ALL patients.

In considering who did not do well on our HR-ALL protocol, the group with an initial WBC of $\geq 200 \times 10^9$/L emerges as candidates to be evaluated further for allogeneic SCT in 1CR. The 9-year EFS for this group was only 35%, being 43% for T-cell ALL and 25% for precursor-B ALL separately. Another group with clearly inferior prognosis were those with very slow response to induction therapy documented as M3 status (>25% blasts) on day 29; these children had a 9-year EFS of 25% only (Fig. 5b). The prognostic impact of day 15 bone marrow status remained statistically at a trend level within HR category (Fig. 5a). The risks of slow response might to some extent be overcome by increased therapy intensity; in the CCG experience with HR-ALL and slow early response as evaluated on the day 7 bone marrow, the outcome was improved by augmented post-induction chemotherapy [33]. Certain cytogenetic changes have been established with very poor outcome: the Philadelphia translocation t(9;22) [38,39], the t(4;11) or MLL-gene rearrangement [40,41], as well as hypodiploidy [42,43]. Our patients with t(9;22) benefited from stem cell transplantation in 1CR (9-year EFS 55% vs. 17% for chemotherapy, $P = 0.02$) although these groups were small (19 SCT vs. 6 chemo). The other groups were too small for any evaluation. The above mentioned very-poor-risk patient groups are generally considered to constitute candidates for allogeneic SCT in 1CR. Benefit from allogeneic SCT is achieved on condition that the consequently reduced risk of relapse [44–46] is not counterbalanced by increased treatment-related mortality [47]. In our Nordic transplant centers, the treatment-related mortality has been acceptable, around 10–15% [44,48] even by using unrelated donors [48]. In our 43 very-high-risk ALL patients transplanted in first remission, the use of URD offered at least as good outcome as matched sibling donors (Fig. 7), supporting the similar finding we have reported on children with ALL transplanted in second remission [48].

No prognostic importance within the HR-ALL cohort was found regarding age, particularly above 10 years, gender, or coexpression of myeloid markers. Furthermore, lymphomatous features provided no independent risk factor. Also CCG/COG has abandoned the distinction between HR-ALL and lymphoma-leukemia. In the future, monitoring of minimal residual disease will probably provide a cornerstone in prognostic stratification of even HR-ALL patients.

Regarding cytogenetics, the TEL/AML1 fusion is suggested to be a good prognostic factor in childhood ALL in general. In the present study, the novel finding was that the TEL/AML1 fusion also has importance within HR-ALL category; those positive for this cryptic translocation had an EFS significantly better than those who were negative (Fig. 6). Hyperdiploidy (modal number ≥ 52), also an indicator of good outcome, did not have an impact in survival in this material. Also new factors are emerging, like the Ink4-locus deletion as a poor prognosis factor [49].

The question also arises who might not have required a treatment as aggressive as was given. The small subgroups to be pointed out might be those who had either CNS involvement at diagnosis ($n = 11$) or T-cell alone ($n = 12$) as the only HR criterion. The outcome of these groups did not differ significantly from the bulk but these are too small to be properly evaluated. The ones with TEL-AML1 ($n = 21$) were shown to have significantly better prognosis than the others.

We conclude that our Nordic HR-ALL protocol was successful with the CNS consolidation based on HD-MTX, HD-ARA-C, plus a series of i.t. MTX; only a small subgroup received cranial RT. The outcome was good with an EFS comparable to reports by several leading study groups, and the CNS relapse rate was relatively low for HR-ALL. The initial WBC of $\geq 200 \times 10^9$/L emerged as a strong prognostic factor, in addition to very slow response to therapy and Ph+ ALL, and for these patients allogeneic SCT seems an option to be further evaluated.

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