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Improving outcome through two decades in childhood ALL in the Nordic countries: the impact of high-dose methotrexate in the reduction of CNS irradiation

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In this population-based material from the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden), 2860 children below 15 years of age were diagnosed with acute lymphoblastic leukemia (ALL) from July 1981 to June 1998. The annual incidence was 3.9/100 000 children and was stable throughout the study period. The development from regional or national protocols to common Nordic treatment protocols for all risk groups was completed in 1992 through a successive intensification with multidrug chemotherapy, including pulses of methotrexate in high doses and avoidance of cranial irradiation in most children. The overall event-free survival (EFS) at 5 years has increased from 56.5 ± 1.7% in the early 1980s to 77.6 ± 1.4% during the 1990s. The main improvements were seen in children with non-high risk leukemia. In high-risk patients, progress has been moderate, especially in children with high WBC (≥100 × 10^9/l) at diagnosis. During the last time period (January 1992–June 1998), only 10% of the patients have received cranial irradiation in first remission, while 90% of the patients have received pulses of high dose methotrexate (5–8 g/m^2) isolated or combined with high-dose cytosine arabinoside (total dose 12 g/m^2) plus multiple intrathecal injections of methotrexate as CNS-targeted treatment, not translating into increased cumulative incidence of CNS relapse. *Leukemia* (2000) **14,** 2267–2275.
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Introduction

The treatment results of acute lymphoblastic leukemia (ALL) in childhood have improved dramatically since the introduction of 'total therapy' by Pinkel *et al* in 1972.[1] Since then, the overall survival has increased from 25% to 75% as a result of treatment intensification and therapy adapted to risk groups.[2–5]

On 1 July 1981, the Nordic Society of Pediatric Haematology and Oncology (NOPHO) started a registration in the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) of all children below 15 years of age at diagnosis with ALL. Therapy in the different countries has developed over the years from regional or national protocols during the 1980s to common, uniform Nordic protocols. This article presents the treatment results of the complete five-country patient material of childhood ALL diagnosed from July 1981 to June 1998 and followed up until 1 January 2000.

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Patients and methods

The patient material was divided into three periods according to major changes in therapy: time period I (July 1981–June 1986; *n* = 832), time period II (July 1986–December 1991; *n* = 885) and time period III (January 1992–June 1998; *n* = 1143). The leukaemias were stratified into different risk groups (SR = standard risk; IR = intermediate risk; HR = high risk; and Infants) according to risk criteria at diagnosis (Table 1). In 1992 the HR patients were further subdivided into a HR group and a very high-risk group (VHR), which included children over 5 years of age at diagnosis with defined VHR criteria (Table 1). Mature B-ALL was excluded from the material. The diagnosis of ALL was always established at a pediatric oncology centre with analysis of bone marrow aspirates including morphology, immunophenotype and when feasible cytogenetic analysis of the leukaemic cells. Description of karyotypes and clonality criteria followed the recommendations of ISCN (1995). Modal number subgrouping reflected the bimodal distribution of chromosome number and this subgrouping was supported by differences in the pattern of whole chromosome gains and losses and the propensity of these subgroups to have additional structural aberrations. DNA index classification by flowcytometry was not done routinely.

Treatment

There was a development from regional or national protocols to uniform treatment for SR/IR patients during the first 10 years and completed in 1992 with common Nordic treatment protocols for all risk groups. During this time period therapy was successively intensified, based on multidrug chemotherapy including pulses of high doses of methotrexate alone or combined with cytosine arabinoside to avoid cranial irradiation. Details of the therapy protocols have been published earlier.[5,6]

In time period I, remission was induced for SR patients using prednisone (Pred), vincristine (Vcr) and doxorubicin (Doxo) in Finland and Sweden, or Pred, Vcr and L-asparaginase (Asp) in Denmark, Iceland and Norway. In July 1984, Asp was added to the induction treatment in Finland and Sweden. CNS consolidation consisted of three pulses of i.v. methotrexate (Mtx) 0.5–1.0 g/m^2 and eight doses of Mtx it. The maintenance therapy included oral 6-mercaptopurine (6-Mp) daily and oral Mtx weekly until 36 months from diagnosis. No reinductions were given during maintenance. In most IR patients, the induction and consolidation therapies were similar to those in the SR group. The maintenance treatment with oral 6-Mp and Mtx was intensified by pulses of Pred/Vcr with

Table 1 Risk groups for childhood ALL 1981–1998

Years	*Risk group*	*Age (years)*	*Criteria*
1981–1998	Standard	2–<10	WBC <10 × 10^9/l (<20 × 10^9/l before July 1984) No high-risk criteria
	Intermediate	2–<10 or 1–<2 or ⩾10	WBC 10–<50 × 10^9/l (20–<50 × 10^9/l before July 1984) WBC <50 × 10^9/l No high-risk criteria
1981–1991	High	⩾1	and at least one of the following criteria: WBC ⩾50 × 10^9/l T cell leukemia Mediastinal mass CNS or testicular involvement t(9;22), t(4;11)
1992–1998	High	⩾1	and at least one of the following criteria: WBC ⩾50 × 10^9/l Mediastinal mass CNS or testicular involvement t(9;22), 22q-, t(4;11) Slow response (day 15 M3 or day 29 M2/M3 bone marrow) T cell leukemia
	Very high	⩾5	and at least one of the following criteria: Lymphomatous features CNS involvement Slow response (day 15 M3 or day 29 M2/M3 bone marrow) T cell leukemia with other HR criteria
1981–1998	Infants	<1	

or without Doxo or i.v. Mtx (1.0 g/m^2) during the first year. The HR patients were treated in different ways, primarily using the intensive regimens according to Riehm *et al*[2] or Wollner *et al*.[7]

In time period II, the remission in the SR patients was induced and consolidated in the same way as during period I. The maintenance therapy included pulses of i.v. Mtx (1.0 g/m^2) and Pred/Vcr. The IR group received one early intensification course with 6-Mp, cyclophosphamide (Cyclo), cytosine arabinoside (75 mg/m^2) and Mtx it and one late intensification course (after consolidation with four times i.v. Mtx 5 g/m^2) with dexamethasone, Vcr, daunorubicine, Cyclo, Asp, 6-thioguanine and cytosine arabinoside (75 mg/m^2). Cranial irradiation of 12–18 Gy (depending on age) was given in Denmark, Finland and Sweden (NOPHO IR-1) before oral maintenance therapy with 6-Mp and Mtx. In Norway and Iceland, pulses of i.v. Mtx (1–6 g/m^2) alone or combined with high-dose cytosine arabinoside (HD-ARA-C; total dose 12 g/m^2) were administered (NOPHO IR-2) before oral maintenance therapy with 6-Mp and Mtx, which included pulses of i.v. Mtx (1–6 g/m^2) and Pred/Vcr during the first year. The HR patients were treated on intensive, national protocols. In Denmark, Finland, Iceland and Sweden treatment was more or less adapted to the BFM protocol,[2,3] including cranial irradiation. In Norway two different regimens were used: either (1) i.v. Mtx (1–6 g/m^2) or (2) i.v. Mtx (1–6 g/m^2), HD-ARA-C (total dose 12 g/m^2) and Doxo to avoid cranial irradiation.

In time period III, identical risk adapted protocols were applied throughout all five countries. For details of protocol NOPHO-ALL 92, see Table 2.

The induction therapy consisted of Pred, Vcr, Doxo (days 1, 22, 36), Asp and Mtx it. The HR and VHR groups had one extra dose of Doxo (day 8). For the SR group, consolidation therapy consisted of three pulses of i.v. Mtx (5 g/m^2) and repeat doses of i.v. Mtx (5 g/m^2) or Pred/Vcr were given at 4 weeks intervals during first year of maintenance therapy.

The IR group had two periods of intensification: one early intensification with 6-Mp, cyclophosphamide (Cyclo), cytosine arabinoside and Mtx it in repeated pulses and one late intensification (after consolidation with four times i.v. Mtx 5 g/m^2) with dexamethasone, Vcr, daunorubicine, Asp, 6-thioguanine, Cyclo, cytosine arabinoside and Mtx it. The initial treatment regimens in the HR and VHR groups were much the same as in the IR group except that i.v. Mtx was given at 8 g/m^2. Consolidation therapy included two pulses of i.v. Mtx (8 g/m^2) and HD-ARA-C (total 12 g/m^2). The delayed intensification was the same as in the IR group and was followed by one i.v. Mtx pulse (8 g/m^2), one HD-Ara-C-pulse and two pulses of Vcr and Pred before maintenance therapy with oral 6-Mp and Mtx. VHR therapy was similar to the HR protocol except that cranial irradiation of 18–24 Gy was administered before maintenance. The VHR maintenance therapy consisted of rotating pulses of cytostatic drugs according to the LSA_2L_2 regimen,[7] given in six cycles and completed with oral 6-mercaptopurine 75 mg/m^2/day and methotrexate 20 mg/m^2/week until 2 years from diagnosis. Thus, the strategy in the VHR group treatment was intensive treatment during 42 weeks followed by cranial irradiation and continued with a sequential multidrug maintenance therapy.

In period III, intrathecal Mtx doses were given 13 times in the SR group, 18 times in the IR and HR groups and 13 times before and nine times during or after cranial irradiation in the VHR group. The total duration of therapy was 2.5 years for the SR patients and 2 years for the IR, HR and VHR patients. The major change in treatment for period III was the elimination of prophylactic CNS irradiation in the IR and HR groups. During period II, 60% of all children with ALL received prophylactic CNS irradiation as compared to 10% of the children during time period III. Between January 1992 and

Table 2 Treatment protocols – NOPHO-ALL 92

Treatment element/drug	*Single or daily dose*	*Days given*	*Comments*
All risk groups			
Induction (w 0–7)			
Prednisone (orally)	60 mg/m^2/day	1–36/45	HR/VHR-prephase
Vincristine (i.v.)	2 mg/m^2 (max 2 mg)	1, 8, 15, 22, 29, 36	
Doxorubicin (i.v.)	40 mg/m^2 (24 h)	1, 22, 36	HR/VHR-1, 8, 22, 36
L-Asparaginase (i.v./i.m.)	30 000 IE/m^2 daily	36–45	
Methotrexate (IT)	10–12 mg (age adj)	1, 8, 15, 29	
Standard risk (SR)			
Consolidation SR (w 7–12)			
Methotrexate (i.v.)	5 g/m^2 (24 h)	1, 15, 29	
Methotrexate (IT)	10–12 mg (age adj)	1, 15, 29	
Maintenance (w 14–)			
6-Mercaptopurine (orally)	75 mg/m^2/day	1–until 2.5 years from diagnosis	
Methotrexate (orally)	20 mg/m^2/week	1–until 2.5 years from diagnosis	
Prednisone (orally)	60 mg/m^2/d × 7	1, 57, 113, 169, 225	
Vincristine (i.v.)	2 mg/m^2 (max 2 mg)	1, 57, 113, 169, 225	
Methotrexate (i.v.)	5 g/m^2 (24 h)	29, 85, 151, 207, 263	
Methotrexate (IT)	10–12 mg (age adj)	1, 29, 85, 151, 207, 263	
Intermediate risk (IR)			
Early intensification (w 7–14)			
6-Mercaptopurine (orally)	60 mg/m^2/day	1–14, 29–42	
Cyclophosphamide (i.v.)	1000 mg/m^2	1, 29	
Cytarabine (i.v.)	75 mg/m^2/day	3–6, 10–13, 31–34, 38–41	
Methotrexate (IT)	10–12 mg (age adj)	1, 29	
Consolidation IR (w 15–22)			
6-Mercaptopurine (orally)	25 mg/m^2/day	1–56	
Methotrexate (i.v.)	5 g/m^2 (24 h)	8, 22, 36, 50	
Methotrexate (IT)	10–12 mg (age adj)	8, 22, 36, 50	
Late intensification (w 24–30)			
Dexamethasone (orally)	10 mg/m^2/day	1–22/29	
Vincristine (i.v.)	2 mg/m^2 (max 2 mg)	1, 8, 15, 22	
Daunorubicine (i.v.)	30 mg/m^2 (24 h)	1, 8, 15, 22	
L-Asparaginase (i.v./i.m.)	30 000 IE/m^2	1, 8, 15, 22	
6-thioguanine (orally)	60 mg/m^2/day	29–42	
Cyclophosphamide (i.v.)	1000 mg/m^2	29	
Cytarabine (i.v.)	75 mg/m^2/day	31–34, 38–41	
Methotrexate (IT)	10–12 mg	31, 38	
Maintenance (w 32–)			
6-Mercaptopurine (orally)	75 mg/m^2/day	1–until 2 years from diagnosis	
Methotrexate (orally)	20 mg/m^2/w	1–until 2 years from diagnosis	
Methotrexate (i.v.)	5 g/m^2 (24 h)	1, 57, 113, 169, 225	
Prednisone (orally)	60 mg/m^2/d × 7	29, 85, 141, 197, 253	
Vincristine (i.v.)	2 mg/m^2 (max 2 mg)	29, 85, 141, 197, 253	
Methotrexate (IT)	10–12 mg (age adj)	1, 57, 113, 169, 225	
High risk (HR)			
Induction (w 0–7)			See Induction: w 0–7
Early intensification (w 7–14)			See IR: w 7–14
Consolidation-1 HR (w 16–26)			
Methotrexate (i.v.)	8 g/m^2 (24 h)	1, 43	
Cytarabine (i.v.)	2 g/m^2 × 2 daily × 3 days	22, 64	Total dose: 2 × 12 g/m^2
Methotrexate (IT)	10–12 mg (age adj)	1, 43	
Interim maintenance (w 28–35)			
Prednisone (orally)	40 mg/m^2/day	1–8, 29–35	
Vincristine (i.v.)	2 mg/m^2	1, 29	
6-Mercaptopurine (orally)	75 mg/m^2/day	1–57	
Methotrexate (orally)	20 mg/m^2/w	1–50	
Late intensification (w 36–42)			See IR: w 24–30
Consolidation-2 HR (w 44–62)			
Methotrexate (i.v.)	8 g/m^2	1, 99	
Cytarabine (i.v.)	2 g/m^2 × 2 daily × 3 days	22, 120	Total dose: 2 × 12 g/m^2
Methotrexate (IT)	10–12 mg (age adj)	1, 99	
Prednisone (orally)	60 mg/m^2/day	43–49, 71–78	
Vincristine (i.v.)	2 mg/m^2 (max 2 mg)	43, 71	
6-Mercaptopurine (orally)	75 mg/m^2/day	43–98	
Methotrexate (orally)	20 mg/m^2/w	43–91	

Table 2 Continued

Treatment element/drug	*Single or daily dose*	*Days given*	*Comments*
Maintenance (w 64–2 years)			
6-Mercaptopurine (orally)	75 mg/m^2/day	1–until 2 years from diagnosis	
Methotrexate (orally)	20 mg/m^2/w	1–until 2 years from diagnosis	
Prednisone (orally)	60 mg/m^2/d × 7	1, 57, 113, 169, 225	
Vincristine (i.v.)	2 mg/m^2 (max 2 mg)	1, 57, 113, 169, 225	
Methotrexate (IT)	10–12 mg (age adj)	1, 57, 113, 169, 225	
Very high risk (VHR)			
week: 0–42			Same as HR
CNS therapy (w 44–46)			
Cranial RT	18 Gy	1–15	
6-Mercaptopurine (orally)	50–75 mg/m^2/day	1–29	
Methotrexate (IT)	12 mg	1, 8, 15	
Maintenance-LSA$_2$L$_2$ (w 48–95)			6 cycles × d 1–56
6-Thioguanine (orally)	300 mg/m^2/day	1–4	
Methotrexate (IT)	12 mg	1	
Cyclophosphamide (i.v.)	600 mg/m^2	5	
Hydroxy-urea (orally)	2400 mg/m^2/d × cycles 1–4	15–18	Cy 5–6: Pred (d 15–22)
Daunorubicine (i.v.)	30 mg/m^2 × cycles 1–4	19	Cy 5–6: Vincristin (i.v.)
Methotrexate (orally)	10 mg/m^2/day	29–32	
Carmustin (i.v.)	30 mg/m^2	33	
Cytarabine (i.v.)	150 mg/m^2/day	43–46	
Vincristine (i.v.)	2 mg/m^2 (max 2 mg)	47	
Maintenance (w 96–)			
6-Mercaptopurine (orally)	75 mg/m^2/day	1–until 2 years from diagnosis	
Methotrexate (orally)	20 mg/m^2/w	1–until 2 years from diagnosis	

December 1996, all children with SR, IR and HR ALL were randomised to have their oral 6-Mp/Mtx maintenance therapy adjusted either (1) by the white cell counts (target: 1.5–3.5 × 10^9/l) or (2) by a combination of the white cell counts and the erythrocyte levels of 6-Mp and Mtx metabolites. Patients in the latter group were recommended to have their dose of oral 6-Mp and/or Mtx increased until the erythrocyte levels of 6-Mp and Mtx metabolites reached a certain level or their white cell count fell below 1.5 × 10^9/l.[8]

Statistical methods

SPSS software was used in the statistical analyses.[9] The probability of event-free survival (EFS) was constructed using the Kaplan–Meier method and the different subgroups were compared for significance using the Mantel–Haenszel test. The significance limit for *P* values was set to 0.05 in all tests. The hazard function was used to illustrate the risk of events as a function of time from diagnosis. Events in the analysis of event-free survival included induction failure, death in remission, relapse and second malignancy. The cumulative incidence of relapse was calculated according to the 'one minus survival' method.[9] An isolated CNS relapse was defined as a CNS relapse without relapse at other sites. A CNS relapse included any relapse with CNS involvement. All patients were followed until the first negative event and for patients in CCR (continuous complete remission) until 1 January 2000. There were eight (1%) patients diagnosed during time period I (1981–1986) who were 'lost at follow-up' (at 116–209 months), five patients period II (1986–1991; lost at 90–145 months) and three patients during period III (1992–1998; lost at 75–83 months). These patients were censored at the time of 'lost at follow-up'.

Results

The study is population-based and includes all children <15 years of age with ALL diagnosed from July 1981 to June 1998 in the five Nordic countries (4.5 million children). The annual incidence was 3.9 children/100 000 and stable throughout the study period. The male:female ratio was 1.14.

Overall treatment results

The treatment results at follow-up for the three consecutive time periods are shown in Figure 1a. The estimated event-free survival (p-EFS) at 5 years has increased from 56.5 ± 1.7% (period I) and 69.6 ± 1.5% (period II) to 77.7 ± 1.4% for period III (Table 3). The hazard function illustrates the risk of events with regard to time from diagnosis (Figure 1b). The improvement in prognosis was most evident from period I to period II with lower risk of events especially within 4 years from diagnosis. With regard to periods II and III, the decrease in events is most obvious within the first 3 years from diagnosis. The remission rates have increased from 94% to 98%, and the toxic death rates in remission have been stable at 2–3%. The cumulative incidence of all relapses has decreased from 39% in period I to 28% in period II and is 21% for period III. The cumulative incidence of bone marrow relapse has decreased significantly, but improvements have also been achieved in the cumulative incidence of isolated CNS relapses, which have decreased from 8.5% during period I (at 10 years) to <3% for period III (at 7 years).

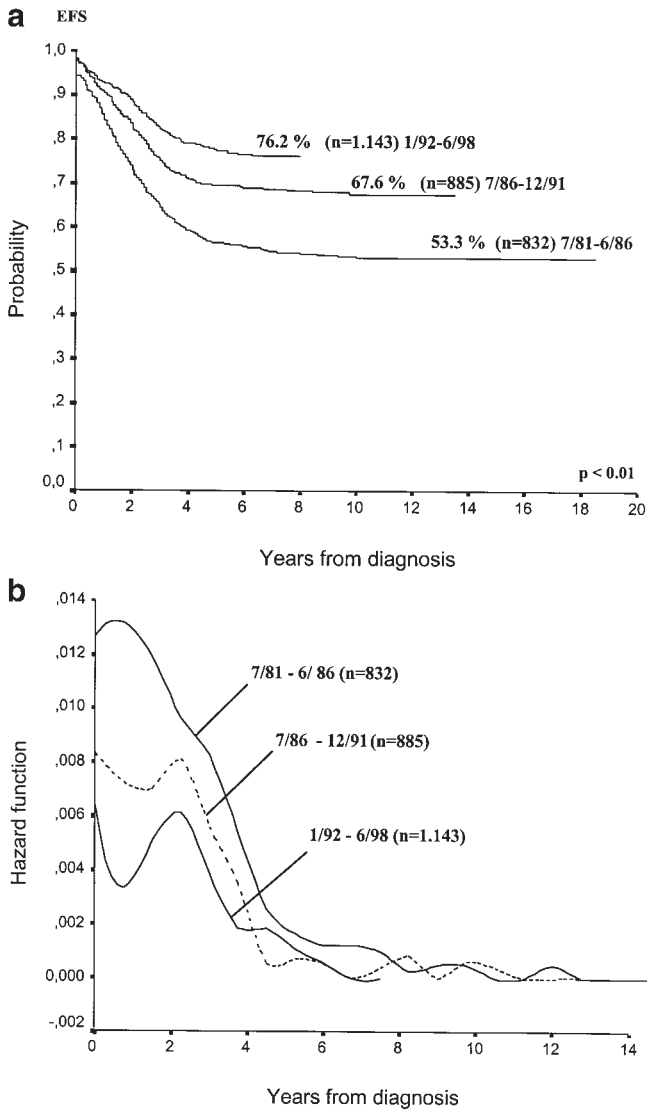

Figure 1 (a) Event-free survival (EFS) by time period. Nordic children with ALL diagnosed July 1981 to June 1998. (b) Hazard function: risk of any event from diagnosis by time period. Nordic children with ALL diagnosed July 1981 to June 1998.

Protocol-specific treatment outcome

Period I: The remission rate for all patients was 94.4% (785/832). On both NOPHO-SR protocols, which included only intermediate dose of i.v. Mtx (0.5 g/m^2) and eight Mtx it injections, the patients suffered from an unacceptable high frequency of relapses located in the bone marrow (cumulative risk for BM relapse was 29.9 ± 3.3%) or in the CNS (cumulative risk of isolated CNS relapse was 10.7 ± 2.3% and of CNS relapse in total 16.7 ± 2.7%). Thus, i.v. methotrexate (0.5 g/m^2) and eight Mtx it injections resulted in unacceptable high frequencies of bone marrow and CNS relapses among SR patients.[10]

Period II: 866/885 (97.9%) of the patients achieved remission. The overall EFS at 10 years was 67.6 ± 1.6% (Figure 1). Seventy percent of the patients were treated according to NOPHO protocols, one common SR protocol (with eight pulses of i.v. Mtx 1 g/m^2) and two different IR protocols (IR-1 with X-RT; IR-2 without X-RT) in non-randomised cohort fashion. The SR protocol had a 10-year EFS of 79.2 ± 2.6%. There was no significant difference in EFS at 10 years follow-up between the IR-1 protocol (with X-RT; EFS = 70.4 ± 2.9%) and the IR-2 (without X-RT; EFS = 69.8 ± 6.6%; $P = 0.9$). The cumulative incidence of isolated CNS relapse were 5.4 ± 1.5% for the SR protocol, 2.2 ± 0.9% for the IR-1 protocol and 4.1 ± 2.8% for the IR-2 protocol. Corresponding values for CNS relapse in total were 8.6 ± 1.9% (SR protocol), 4.3 ± 1.3% (IR-1 protocol) and 6.0 ± 3.3% (IR-2 protocol). The cumulative incidence of bone marrow relapse at 10 years was 8% for the SR protocol, 19% for the IR-1 protocol and 14% for the IR-2 protocol. Intensification of therapy improved EFS significantly for non-high risk patients and decreased the cumulative incidences of bone marrow and CNS relapses in SR/IR patients as compared to earlier protocols.

There was no difference in outcome among the NCI standard risk patients with B-precursor ALL compared to T cell ALL (EFS 74.3% and 80.0% ($P = 0.9$) (Table 3a), but among NCI high risk patients the prognosis was significantly better for B-precursor ALL (EFS = 61.1%) than for T cell ALL (EFS = 46.4%) ($P < 0.01$).

During period II, patients who were on morning schedule of their oral 6-Mp (75 mg/m^2/day) and Mtx (20 mg/m^2/week) maintenance therapy had a significantly inferior outcome compared to those on evening dosage (EFS from start of maintenance therapy 57 ± 8% *vs* 82 ± 3%; $P < 0.01$).[11] Thus, evening dosage was recommended for all patients during period III. In addition, patients with low erythrocyte levels of 6-Mp and Mtx metabolites during period II had inferior outcome.[8,11] These results constituted the basis of the randomised NOPHO ALL-92 maintenance study.

Period III: The remission rate was 98.4%. The overall EFS was 77.6 ± 1.4% at 5 years and 76.2 ± 1.5% at the follow-up on 1 January 2000 (Figure 1a). The EFS at follow-up for the different risk groups were 86.6 ± 2.1% (SR group), 82.1 ± 2.4% (IR group), 65.7 ± 5.1% (HR ⩾5 years), 59.6 ± 3.1% (HR <5 years) and 63.3 ± 4.7% (VHR group) (Figure 2). The estimated cumulative risk of isolated bone marrow relapse is 13%; of isolated CNS relapse 2.1% and that of CNS relapse in total 4.7% (Table 4).

The major improvements in outcome were observed among patients with favourable features at diagnosis, eg NCI standard risk patients, chromosomal modal number >47 and WBC $<50 \times 10^9$/l (Table 3).

As treatment became uniform throughout the Nordic countries and cranial irradiation was substituted with multiple Mtx it injections and i.v. Mtx 5 g/m^2 (SR/IR patients) and i.v. Mtx 8 g/m^2 plus HD-ARA-C (HR patients) in all children except those with VHR-ALL, patients with NCI standard risk B-lineage ALL did better than those with NCI standard risk T cell ALL (EFS 85.2% *vs* 74.8%; Table 3, $P < 0.01$). Among NCI high risk patients, the prognosis was significantly worse for T cell ALL compared to B-lineage ALL (56.9% *vs* 67.9%; Table 3, $P < 0.05$), which could be explained by a higher frequency of T cell patients with WBC ⩾200×10^9/l at diagnosis within this NCI group. Gender faded away as a prognostic factor over the three time periods. Thus, the difference in EFS between females and males was reduced from 11.9% (patients diagnosed 1981–1986) to 4.9% (diagnosed 1986–1991) and finally, to 2.8% (diagnosed 1992–1998). During time period III, the overall EFS value at follow-up (7 years) was 76.2% and

Table 3 Treatment results during different time periods (1981–1998) according to presenting features

Presenting feature	*Period I: 7/81–6/86*					*Period II: 7/86–12/91*					*Period III: 1/92–6/98*		
	n	*(%)*	*EFS (%,SE)*			*n*	*(%)*	*EFS (%,SE)*			*n*	*(%)*	*EFS (%,SE)*
			5 years	*8 years*	*10 years*			*5 years*	*8 years*	*10 years*			*5 years*
All Patients	832		56.5 ± 1.7	54.3 ± 1.7	53.3 ± 1.7	885		69.6 ± 1.5	68.5 ± 1.6	67.6 ± 1.6	1143		77.6 ± 1.4
Lineage													
Non-T lineage	734	(88.2)	58.2 ± 1.8	55.9 ± 1.8	54.6 ± 1.8	804	(90.8)	71.1 ± 1.6	70.0 ± 1.6	69.1 ± 1.6	1023	(89.5)	79.4 ± 1.4
T-lineage	68	(8.2)	51.6 ± 6.1	51.5 ± 6.1	51.5 ± 6.1	71	(8.0)	54.9 ± 5.9	53.5 ± 5.9	53.5 ± 5.9	106	(9.3)	61.3 ± 4.9
Unknown	30	(3.6)	26.7 ± 8.1	23.3 ± 7.	23.3 ± 7.7	10	(1.1)	50.0 ± 15.8	50.0 ± 15.8	50.0 ± 15.8	14	(1.2)	58.3 ± 14.2
Non-T Lineage													
NCI risk													
Standard	536		60.3 ± 2.1	57.1 ± 2.1	56.0 ± 2.1	569		76.8 ± 1.8	75.2 ± 1.8	74.3 ± 1.9	740		85.2 ± 1.5
High	182		53.9 ± 3.7	52.8 ± 3.7	52.2 ± 3.7	211		61.6 ± 3.4	61.6 ± 3.4	61.1 ± 3.4	251		67.9 ± 3.3
Infant	16		37.5 ± 12.1	37.5 ± 12.1	37.5 ± 12.1	24		20.8 ± 8.3	20.8 ± 8.3	15.6 ± 7.7	32		40.5 ± 8.7
T Lineage													
NCI Risk													
Standard	13		46.2 ± 13.8	46.2 ± 13.8	46.2 ± 13.8	15		80.0 ± 10.3	80.0 ± 10.3	80.0 ± 10.3	24		74.8 ± 8.9
High	53		52.8 ± 6.9	52.8 ± 6.9	52.8 ± 6.9	56		48.2 ± 6.7	46.4 ± 6.7	46.4 ± 6.7	79		56.9 ± 5.9
Infant	2		50.0 ± 35.4	50.0 ± 35.4	50.0 ± 35.4	—					3		66.7 ± 27.2
Unknown lineage													
Standard	6		16.7 ± 15.2	16.7 ± 15.2	16.7 ± 15.2	2		50.0 ± 35.4	50.0 ± 35.4	50.0 ± 35.4	4		100.0 ± 0
High	19		26.3 ± 10.1	21.0 ± 9.4	21.0 ± 9.4	5		80.0 ± 17.9	80.0 ± 17.9	80.0 ± 17.9	9		37.5 ± 17.1
Infant	5		40.0 ± 21.9	40.0 ± 21.9	40.0 ± 21.9	3		0.0			1		
Sex													
Male	439	(52.8)	50.6 ± 2.4	48.3 ± 2.4	47.6 ± 2.4	468	(52.9)	68.2 ± 2.2	66.5 ± 2.2	65.3 ± 2.2	617	(54.0)	76.3 ± 1.9
Female	393	(47.2)	63.1 ± 2.4	61.1 ± 2.5	59.5 ± 2.5	417	(47.1)	71.2 ± 2.2	70.7 ± 2.2	70.2 ± 2.2	526	(46.0)	79.1 ± 2.0
Age at diagnosis (years)													
<1	23	(2.8)	39.1 ± 10.2	39.1 ± 10.2	39.1 ± 10.2	27	(3.1)	18.5 ± 7.5	18.5 ± 7.5	13.9 ± 7.0	36	(3.1)	39.9 ± 8.5
1–9	669	(80.4)	57.9 ± 1.9	55.5 ± 1.9	54.3 ± 1.9	707	(79.9)	73.3 ± 1.7	71.9 ± 1.7	71.1 ± 1.7	928	(81.2)	79.9 ± 1.5
⩾10	140	(16.8)	52.9 ± 4.2	51.4 ± 4.2	50.7 ± 4.2	151	(17.1)	61.6 ± 3.9	61.6 ± 3.9	60.9 ± 3.9	179	(15.7)	72.3 ± 3.6
WBC (× 10^9/l)													
<10	434	(52.2)	65.2 ± 2.3	62.0 ± 2.3	60.6 ± 2.4	412	(46.6)	75.0 ± 2.1	73.8 ± 2.2	73.0 ± 2.2	565	(49.5)	84.5 ± 1.7
10–49	235	(28.2)	47.2 ± 3.3	46.4 ± 3.3	45.1 ± 3.3	294	(33.2)	73.5 ± 2.6	72.4 ± 2.6	70.7 ± 2.7	356	(31.1)	81.8 ± 2.3
50–99	83	(10.0)	54.2 ± 5.5	53.0 ± 5.5	53.0 ± 5.5	78	(8.8)	65.4 ± 5.4	65.4 ± 5.4	65.4 ± 5.4	103	(9.0)	67.3 ± 4.9
⩾100	80	(9.6)	38.9 ± 5.5	37.5 ± 5.4	37.5 ± 5.4	101	(11.4)	39.6 ± 4.9	38.6 ± 4.8	38.6 ± 4.8	119	(10.4)	41.3 ± 5.3
100–199	44	(5.3)	50.0 ± 7.5	50.0 ± 7.5	50.0 ± 7.5	50	(5.7)	40.0 ± 6.9	40.0 ± 6.9	40.0 ± 6.9	55	(4.8)	54.1 ± 8.5
⩾200	36	(4.3)	25.0 ± 7.2	22.2 ± 6.9	22.2 ± 6.9	51	(5.7)	39.2 ± 6.8	37.3 ± 6.8	37.3 ± 6.8	64	(5.6)	30.2 ± 6.2[a]

Table 3 Continued

Presenting feature	*Period I: 7/81–6/86*					*Period II: 7/86–12/91*					*Period III: 1/92–6/98*		
	n	*(%)*	*EFS (%,SE)*			*n*	*(%)*	*EFS (%,SE)*			*n*	*(%)*	*EFS (%,SE)*
			5 years	*8 years*	*10 years*			*5 years*	*8 years*	*10 years*			*5 years*
CNS leukemia													
Yes	38	(4.6)	42.1 ± 8.0	39.5 ± 7.9	39.5 ± 7.9	32	(3.6)	56.3 ± 8.8	53.1 ± 8.8	53.1 ± 8.8	32	(2.8)	49.9 ± 8.9
No	794	(95.4)	57.2 ± 1.8	55.0 ± 1.8	53.9 ± 1.83	853	(96.4)	70.1 ± 1.6	69.0 ± 1.6	68.2 ± 1.6	1111	(97.2)	78.3 ± 1.4
Chromosome number													
⩽44						7	(0.7)	57.1 ± 18.7	57.1 ± 18.7	57.1 ± 18.7	10	(0.9)	58.7 ± 15.9
45–46						81	(9.1)	71.3 ± 5.1	70.0 ± 5.1	70.0 ± 5.1	140	(12.2)	77.1 ± 3.9
47–51						49	(5.5)	65.3 ± 6.8	65.3 ± 6.8	65.3 ± 6.8	90	(7.9)	83.8 ± 4.5
52–60						111	(12.5)	78.4 ± 3.9	77.5 ± 4.0	77.5 ± 4.0	214	(18.7)	85.1 ± 2.8
⩾61						14	(1.6)	78.6 ± 11.0	64.3 ± 12.8	64.3 ± 12.8	32	(2.8)	87.2 ± 6.0
t(1;19)						5	(0.6)	100.0 ± 0.0	80.0 ± 17.9	80.0 ± 17.9	6	(0.5)	59.5 ± 22.9
t(9;22)						7	(0.7)	14.3 ± 13.2	14.3 ± 13.2	14.3 ± 13.2	11	(1.0)	63.6 ± 14.5[b]
MLL/11q23						11	(1.2)	27.3 ± 13.4	27.3 ± 13.4	27.3 ± 13.4	17	(1.5)	52.3 ± 12.3
Others						600	(67.8)	71.2 ± 1.9	70.8 ± 1.9	70.8 ± 1.9	623	(54.5)	83.3 ± 1.6

[a]BMT first remission in 12/64 patients.
[b]BMT first remission in 9/11 patients.

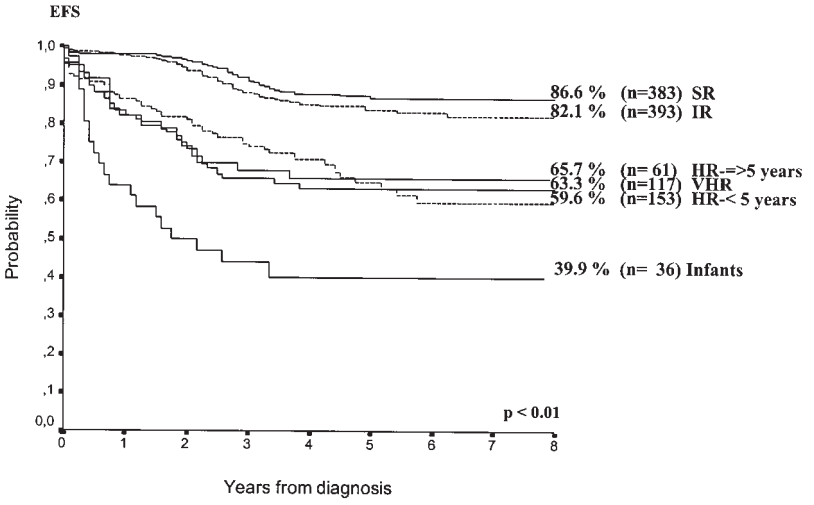

Figure 2 Event-free survival (EFS) by risk groups in Nordic children with ALL diagnosed January 1992 to June 1998.

Table 4 CNS targeted treatment and outcome in NOPHO-ALL 92 (infants excluded)

Risk group	*No. of patients*	*CNS treatment*				*Cumulative incidence of CNS events (%)*[a]	
		MTX (IT)	*MTX (i.v.)*	*Cytarabine (i.v.)*	*Cranial RT*	*CNS isolated*	*CNS total*
SR	383	13 inj	5 g/m^2 × 8 inf	—	—	0.9	4.2
IR	393	18 inj	5 g/m^2 × 9 inf	—	—	0.9	1.2
HR	214	18 inj	8 g/m^2 × 4 inf	2 × 2 g/m^2 × 3 (four times)	—	3.7	7.2
VHR	117	22 inj	8 g/m^2 × 2 inf	2 × 2 g/m^2 × 3 (twice)	18 Gy	5.7	11.4
All patients	1106					2.1	4.7

[a]Estimated according to the 'one minus survival method'. See statistical methods.

the EFS for the different countries varied between 75.8% and 76.4%, the range being within 1%, indicating that all patients had the same possibility for cure, irrespective of the country.

During the earlier time periods some differences (not significant) in EFS were seen between countries with a range of EFS at 7 years of 8.4% (patients diagnosed 1981–1986) and 9.2% (diagnosed 1986–1991), respectively. The results of the randomised NOPHO ALL-92 maintenance study remain to be analysed and published.

Discussion

Since the Nordic cooperation on childhood ALL was initiated in 1981, going from regional or national protocols to common Nordic treatment protocols for all risk groups, the overall 5-years EFS not only increased from 57% (diagnosed July 1981–June 1986) to 78% (January 1992–June 1998) but has during the latter time period become almost identical across Denmark, Finland, Norway and Sweden, which emphasizes the advantage of uniform strategies for risk-adapted therapy. Based on the results of pilot studies performed by Moe *et al* [12–14] during the 1980s, NOPHO has attempted to avoid cranial irradiation for the majority of patients. The results of the NOPHO ALL-92 protocols demonstrate that high-dose i.v. Mtx (5–8 g/m^2) may substitute cranial irradiation for the vast majority of patients still sustaining a low CNS relapse rate. Although the improvements in outcome were significant, they were mainly restricted to those subsets of patients known to have favourable features at diagnosis, such as WBC $<50 \times 10^9$/l, age $\geq$1 year and hyperdiploid ALL, including patients defined as NCI standard risk Non-T, as well as T cell ALL. In contrast, infants, those with NCI high risk T-ALL and those with Non-T and WBC $\geq 100 \times 10^9$/l still fare poorly with a predicted EFS of less than 60%. This was most noteworthy for patients with a WBC $\geq 200 \times 10^9$/l, who are candidates for bone marrow transplantation in first remission.[15]

The overall results for children diagnosed since 1992 (EFS 76.2% at 7 years) are encouraging compared with our own results during earlier time periods and seem to be comparable to the results of the trial ALL-BFM 90.[16] The EFS at 7 years for SR/IR patients (68% of the material) exceeds 80%. For HR patients (19% of the material), EFS at 7 years varies between 59.6% (patients <5 years at diagnosis) and 65.7% ($\geq$5 years at diagnosis). The VHR group (10% of the material) constitutes patients with the most serious prognostic factors in our material and has an EFS of 63.3% at 7 years. According to NOPHO risk criteria, the HR patients <5 years of age suffered from a slightly higher frequency of both early and late relapses (Figure 2). This patient group will have an intensification of therapy in the future NOPHO protocol. With the NOPHO ALL-92 protocol both gender and age (1.0–9.9 *vs* 10.0–14.9 years) as prognostic factors have decreased significantly. The inferior outcome for boys and for patients $\geq$10 years of age in earlier studies is poorly understood. It may reflect differences in disease biology (slower tumor reduction for

teenagers) or differences in drug metabolism, such as 6-mercaptopurine.[17] This has been taken into account in the next NOPHO ALL protocol, where the therapy for all patients without high risk features (T cell ALL and/or WBC $>50 \times 10^9$/l and/or CNS disease and/or a day 29 M3 bone marrow and/or certain cytogenetic features) will receive identical therapy for the first 3 months during which period minimal residual disease will be monitored by flow cytometry and/or PCR techniques to form a basis for possible subsequent treatment stratification.

Since 1992, the overall cumulative incidence of CNS relapse has been kept below 5% (isolated <3%) even though only 10% of the patients (VHR group) received cranial irradiation in first remission while all received multiple intrathecal injections of methotrexate as well as high-dose methotrexate (5–8 g/m^2) and for those with HR-ALL also high-dose cytosine arabinoside.

The high and successively improved outcome for patients with favourable features at diagnosis indicates that the vast majority of these patients have a curable disease. It is likely that improved identification of unfavourable chromosomal aberrations,[18] differences in drug sensitivity,[19] pharmacological profiles[8] and PCR and/or flowcytometry monitoring of residual disease (ie treatment response)[20,21] may identify those patients who should be upgraded to treatment intensification or even allogeneic stem cell transplantation in first remission. Effective therapy other than BMT is still lacking for patients with WBC $>200 \times 10^9$/l, high-risk chromosomal aberrations, and for some of the infants.

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References

1 Pinkel D, Simone J, Hustu O, Auer RJA. Nine years experience with 'total therapy' of childhood acute lymphoblastic leukaemia. *Pediatrics* 1972; **50**: 246–290.
2 Riehm H, Gadner H, Henze G, Kornhuber B, Lampert F, Niethammar D, Reiter A, Schellong G. Results and significance of six randomised trials in four consecutive ALL-BFM studies. *Haematol Blood Transfus* 1990; **33**: 439–450.
3 Reiter A, Schrappe M, Ludwig WD, Hiddemann W, Sauter S, Henze G, Zimmermann M, Lampert F, Havers W, Niethammer D. Chemotherapy in 998 unselected childhood acute lymphoblastic leukaemia patients. Results and conclusions of the multicenter trial ALL-BFM 86. *Blood* 1994; **84**: 3122–3133.
4 Pui CH. Childhood leukaemia. *New Engl J Med* 1995; **332**: 1618–1630.
5 Gustafsson G, Kreuger A, Clausen N, Garwicz S, Kristinsson J, Lie SO, Moe PJ, Perkkiö M, Yssing M, Saarinen-Pihkala UM on behalf of NOPHO. Intensified treatment of acute lymphoblastic childhood leukaemia has improved prognosis, especially in non-high risk patients. The Nordic experience of 2648 patients diagnosed between 1981 and 1996. *Acta Paediatrica* 1998; **87**: 1151–1161.
6 Gustafsson G, Garwicz S, Hertz H, Johannesson G, Jonmundsson G, Moe PJ, Salmi T, Seip M, Siimes MA, Yssing M, Ahstrom L for NOPHO. A population-based study of childhood acute lymphoblastic leukaemia diagnosed from July 1981 through June 1985 in the five Nordic countries. *Acta Paediatr Scand* 1987; **76**: 781–788.
7 Wollner N, Exilby PR, Liebermann P. Non-Hodgkin's lymphoma in children. *Cancer* 1979; **44**: 1990–1999.
8 Schmiegelow K, Schröder H, Gustafsson G, Kristiansson J, Glomstein A, Salmi T, Wranne L. Risk of relapse in childhood acute lymphoblastic leukemia is related to RBC methotrexate and mercaptopurine metabolites during maintenance chemotherapy. Nordic Society of Pediatric Hematology and Oncology. *J Clin Oncol* 1995; **13**: 345–351.
9 Nourusis MJ. SPSS statistical software. SPSS: Base and Advanced Statistics 10.0. SPSS Inc: Chicago, 1999.
10 Gustafsson G, Berglund G, Garwicz S, Hertz H, Jonmundsson G, Moe PJ, Salmi T, Seip M, Siimes MA, Yssing M, Ahstrom L for NOPHO. A population-based study of children with standard risk acute lymphoblastic leukaemia in the five Nordic countries. *Acta Paediatr Scand* 1989; **78**: 104–109.
11 Schmiegelow K, Glomstein A, Kristinsson J, Salmi T, Bjork O. Impact of morning versus evening schedule for oral methotrexate and 6-mercaptopurine on relapse risk for children with acute lymphoblastic leukemia. Nordic Society of Pediatric Hematology and Oncology (NOPHO). *J Pediatr Hematol Oncol* 1997; **19**: 102–109.
12 Moe PJ, Seip M, Finne PH. Intermediate dose methotrexate in childhood acute lymphocytic leukemia. *Acta Paediatr Scand* 1981; **70**: 73–79.
13 Moe PJ. Recent advances in the management of acute lymphocytic leukaemia. *Eur Paediatr Haematol Oncol* 1984; **1**: 19–22.
14 Moe PJ, Wesenberg F, Kolmannskog S. Methotrexate infusions in poor prognosis acute lymphocytic leukaemia: II. High dose methotrexate (HDM) in acute lymphocytic leukaemia in childhood. A pilot study from 1981. *Med Ped Hematol Oncol* 1986; **14**: 189–190.
15 Saarinen U, Mellander L, Nystrom K, Ringden O, Schroeder H, Glomstein A, Gustafsson G. Allogeneic bone marrow transplantation in first remission for children with very high-risk acute lymphoblastic leukaemia: a retrospective case–control study in the Nordic countries. *Bone Marrow Transplant* 1996; **17**: 357–363.
16 Schrappe M, Reiter A, Ludwig WF, Harbott J, Zimmermann M, Hiddemann W, Niemeyer C, Henze G, Feldyes A, Zintl F, Kornhuber B, Ritter J, Welte K, Gadner H, Riehm H. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. *Blood* 2000; **95**: 3310–3322.
17 Lilleyman JS, Lennard L. Mercaptopurine metabolism and risk of relapse in childhood lymphoblastic leukemia. *Lancet* 1994; **343**: 1188–1190.
18 Forestier E, Johansson B, Gustafsson G, Borgström G, Kerndrup G, Johansson J, Heim S. Prognostic impact of karyotypic findings in childhood acute lymphoblastic leukemia: a Nordic series comparing two treatment periods. *Br J Haematol* 2000; **110**: 147–153.
19 Kaspers GJ, Veerman AJ, Pieters R, Van Zantwijk CH, Smets LA, Van Wering ER, Van Der Does-Van Den Berg A. *In vitro* cellular drug resistance and prognosis in newly diagnosed childhood acute lymphoblastic leukaemia. *Blood* 1997; **90**: 2723–2729.
20 van Dongen JJ, Seriu T, Panzer Grumayer ER, Biondi A, Pongers WM, Corral L, Stolz F, Schrappe M, Masera G, Kamps W-A, Gadner H, Van Wering ER, Ludwig WD, Basso G, de Bruijn MA, Cazzaniga G, Hettinger K, Van Der Does-Van Den Berg A, Hop WC, Riehm H, Bartram C. Prognostic value of minimal residual disease in acute lymphoblastic leukemia in childhood. *Lancet* 1999; **352**: 1731–1738.
21 Coustan-Smith E, Behm FG, Sanchez J, Boyett JM, Hanook ML, Raimondi SC, Rubnitz JE, Rivera GK, Sandlund JT, Pui CH, Campana D. Immunological detection of minimal residual disease in children with acute lymphoblastic leukemia. *Lancet* 1998; **351**: 550–554.