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Intensified treatment of acute childhood lymphoblastic leukaemia has improved prognosis, especially in non-high-risk patients: the Nordic experience of 2648 patients diagnosed between 1981 and 1996

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In a multinational, population-based study from the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden), 2648 children below 15 y of age were diagnosed with acute lymphoblastic leukaemia (ALL) in the years 1981–1996. 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 of therapy, based on multidrug chemotherapy including pulses of methotrexate in high doses and avoidance of cranial irradiation in most children. For children with non-B-cell ALL ($n = 2602$), the event-free survival (p-EFS) increased from 0.53 ± 0.02 (diagnosed 7/81–6/86) to 0.67 ± 0.02 (7/86–12/91) to 0.78 ± 0.02 (1/92–12/96). The corresponding p-EFS values at 5 y were 0.57, 0.70 and 0.78, respectively. The main improvements were seen in the group of children with non-high risk leukaemia, with 5-y p-EFS values increasing from 0.60 to 0.76 and 0.85 for the three periods. In high-risk patients, progress has been moderate, especially in children with high white blood cell values at diagnosis. During the last 5-y period, only 10% of the patients received cranial irradiation in first remission while 90% of the patients received high doses of cytostatic infusions (methotrexate isolated or combined with cytarabinoside) and multiple intrathecal injections of methotrexate as CNS-adjusted treatment without any indication of an increased CNS relapse rate. □ *Childhood acute lymphoblastic leukaemia, incidence, prognosis in childhood acute lymphoblastic leukaemia, prognostic factors, treatment results*

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The treatment results of acute lymphoblastic leukaemia (ALL) have improved dramatically since 1972 when Pinkel et al. introduced ''total therapy'' (1). Since then, the overall survival in first remission has increased from 25% to 75% as a result of intensification of therapy and treatment adapted to risk groups (2).

On July 1, 1981 the Nordic Society of Paediatric Haematology and Oncology (NOPHO) started a registration in the five Nordic countries of all children below 15 y of age at diagnosis with ALL. Treatment protocols have developed over the years through a successful change from different regional and national treatment protocols to uniform common treatment protocols in the five Nordic countries.

The changes followed international experiences regarding the treatment of ALL and were based on earlier experiences within NOPHO (2–6). This article presents and summarizes the treatment results of the complete five-country patient material of childhood ALL diagnosed from July 1981 to December 1996 and followed up in January 1998.

Patients and methods

The patient material was divided into three periods; period I (July 1981–June 1986), period II (July 1986–December 1991) and period III (January 1992–December 1996) according to major changes in therapy. The leukaemias were stratified into different treatment risk groups [standard risk (SR), intermediate risk (IR), high risk (HR), special groups (SG), infants and B-cell ALL] according to prognostic factors at diagnosis. In 1992 the HR patients were subdivided into a traditional HR group and a very high risk (VHR) group, which includes children over 5 y of age at diagnosis and with defined criteria at diagnosis (Table 1).

Table 1. Risk groups for childhood ALL 1981–1996.

Years	Level of risk	Criteria	
1981–1996	Standard	Age 2– <10 y and no high-risk criteria	WBC $<10 \times 10^9$ l^{-1} ($<20 \times 10^9$ l^{-1} before July 1984)
	Intermediate	Age 2– <10 y and no high-risk criteria or age 1– <2 y or ≥10 y	WBC 10– $<50 \times 10^9$ l^{-1} (20– $<50 \times 10^9$ l^{-1} before July 1984) WBC $<50 \times 10^9$ l^{-1}
1981–1991	High	Age ≥1 y	and at least one of the following criteria: WBC $\geq 50 \times 10^9$ l^{-1} T-cell leukaemia CNS or testis involvement Mediastinal mass
1992–1996	High	Age ≥1 y	and at least one of the following criteria: WBC $\geq 50 \times 10^9$ l^{-1} Mediastinal mass CNS or testis involvement Chromosomal translocation (9; 22), (4; 11), (22q-) Slow responder T-cell leukaemia without any other high-risk criterion
	Very high	Age ≥ 5 y	and at least one of the following criteria: Lymphomatous leukaemia CNS involvement Slow responder T-cell leukaemia with other high-risk criteria
	Special groups:	Infants (< 1 y) B-cell ALL	

In period I, the SR patients were divided into two groups according to therapy: SR patients in Finland and Sweden; and SR patients in Denmark, Norway and Iceland.

In period II almost all children with SR-ALL in the five countries were treated on the same protocol. There were two different IR-ALL protocols; children from Denmark, Finland and Sweden were treated according to one protocol, and those from Norway and Iceland according to another in non-randomized fashion.

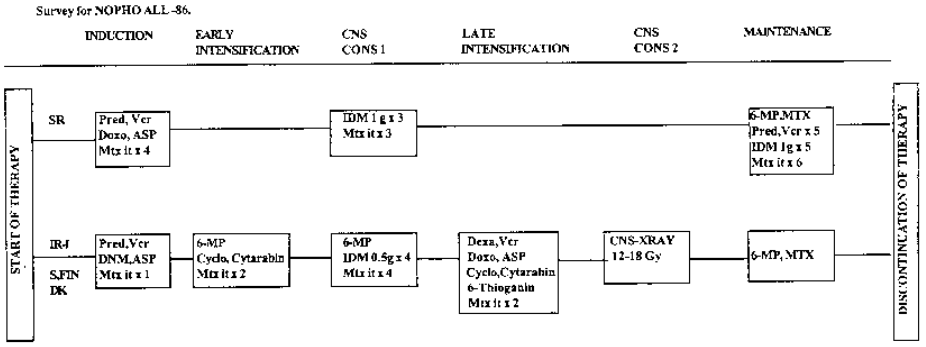
In period III almost all children in the five Nordic countries were treated according to common protocols, comprising separate protocols for SR-ALL, IR-ALL, HR-ALL and VHR-ALL. Infants and children with B-cell ALL (4% of the patients) were still treated on national protocols. Although the treatment has been heterogeneous, particularly during the first period, the total population-based treatment results, according to the different risk criteria and protocols, have been evaluated continuously. Some of the protocols have emerged as pilot studies before acceptance as a NOPHO protocol. The diagnosis of ALL was always established at a paediatric oncology centre with analysis of bone marrow aspirates including morphology, immunophenotype and, preferably, cytogenetic analysis of the leukaemic cells. Seven patients from period I were lost at follow-up at 116–181 months from diagnosis and one patient from period II was lost at 90 months from diagnosis, while the other 2640 patients were followed until death or until the closing date (January 1, 1998).

Treatment in period I

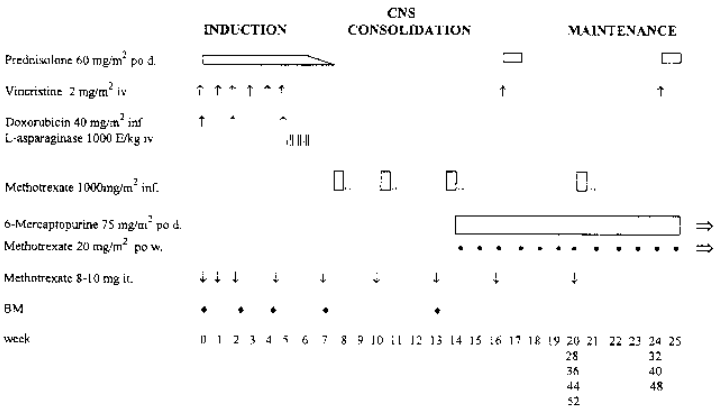
In period I remission was induced and consolidated for SR patients using prednisolone (Pred), vincristine (Vcr) and doxorubicin (Doxo) in Finland and Sweden, or Pred, Vcr and L-asparaginase (Asp) in Denmark, Iceland and Norway. In July 1984, Asp was added to the induction treatment in Finland and Sweden. CNS consolidation consisted of three pulses of i.v. methotrexate (Mtx) 0.5 g m^{-2} (1.0 g Mtx m^{-2} after July 1984) and eight doses of Mtx i.t. 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 a small pilot study, Doxo was not used during induction but alternating pulses of i.v. Mtx and Vcr were added to the maintenance therapy during the first year. In most IR children, 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 and Vcr with or without Doxo or Mtx during the first year. The HR children were treated in many different ways (3), primarily using the intensive regimens according to Riehm et al. (4) or Wollner et al. (5).

Treatment in period II

In period II the remission in the SR patients was induced and consolidated in the same way as during period I and the maintenance therapy included i.v. pulses of Mtx and Vcr. The IR group was treated with additional early and late intensification chemotherapy courses. Cranial irradiation of 12–18 Gy was given in Denmark, Finland and Sweden (NOPHO IR-1) before oral maintenance therapy with 6-Mp and Mtx (Fig. 1). In Norway and Iceland pulses of high-dose Mtx (HD-Mtx) and/or high-dose cytarabinoside (HD-Ara-C) were administered (NOPHO IR-2) before oral maintenance therapy with 6-Mp and Mtx, which included



NOPHO ALL-86; SR PROTOCOL



NOPHO ALL-86; IR-1 PROTOCOL

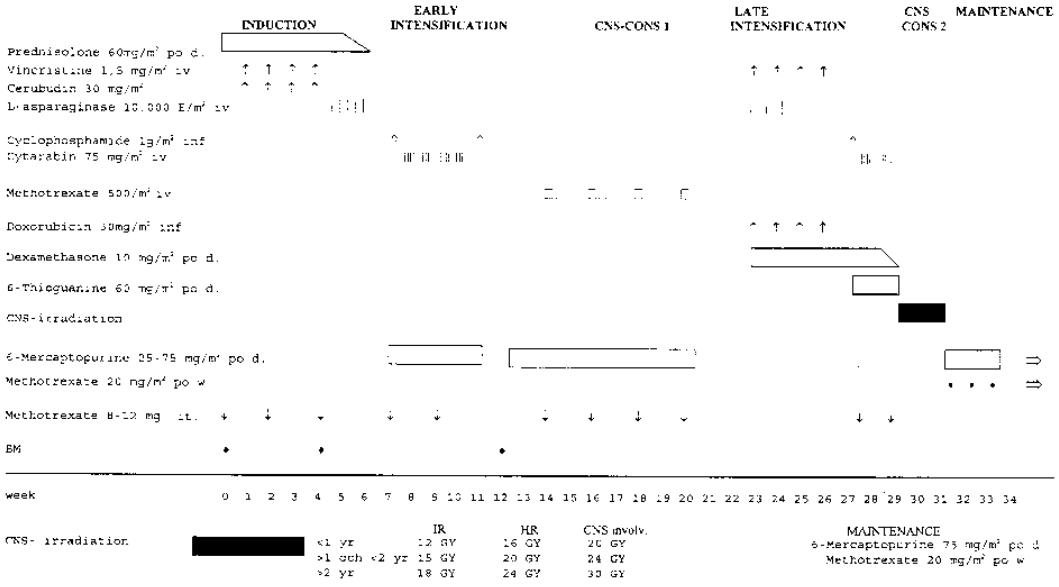


Fig. 1. Treatment protocols in childhood ALL in period II (7/86–12/91).

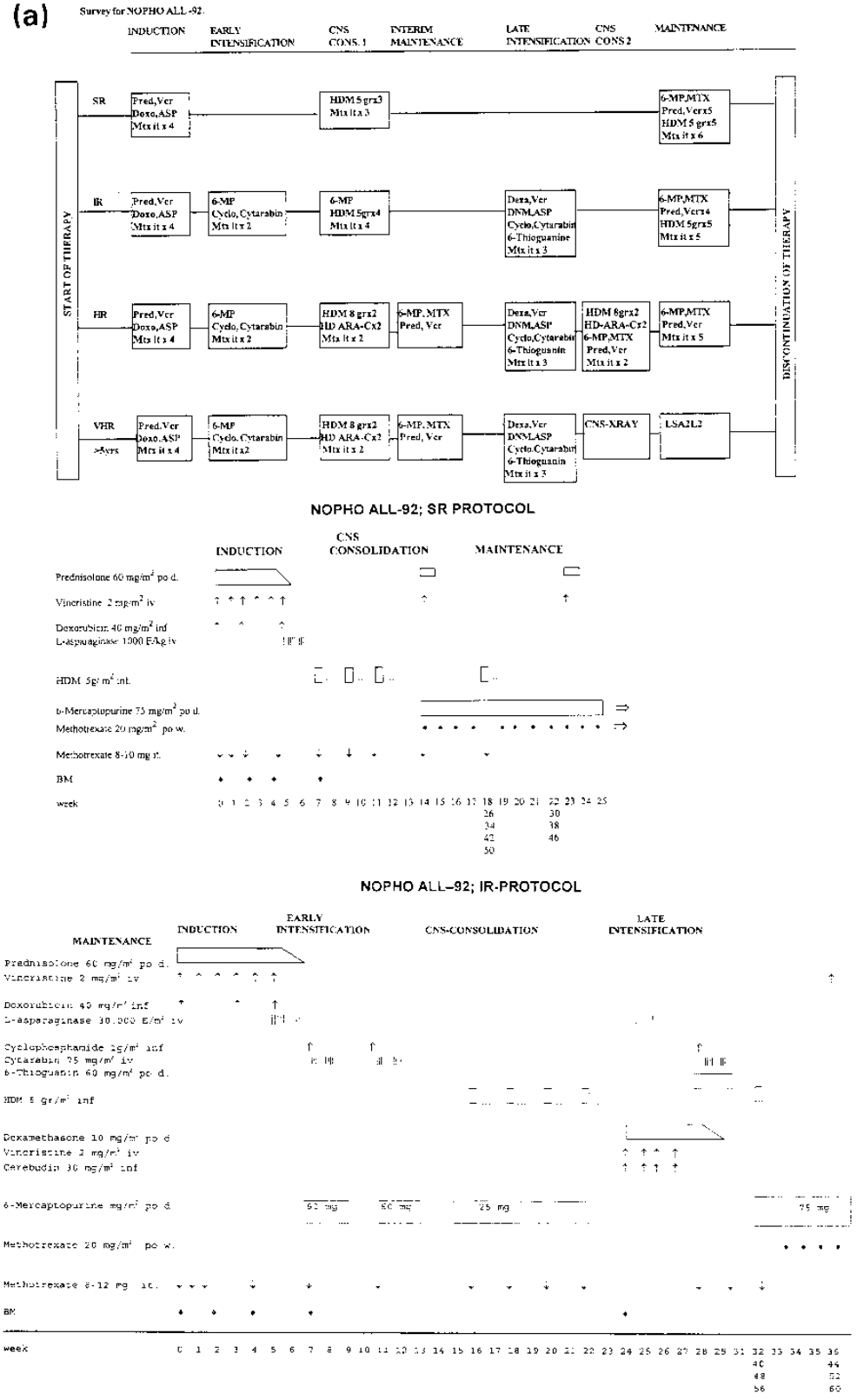


Fig. 2. Treatment protocols in childhood ALL in period III (1/92–12/96).

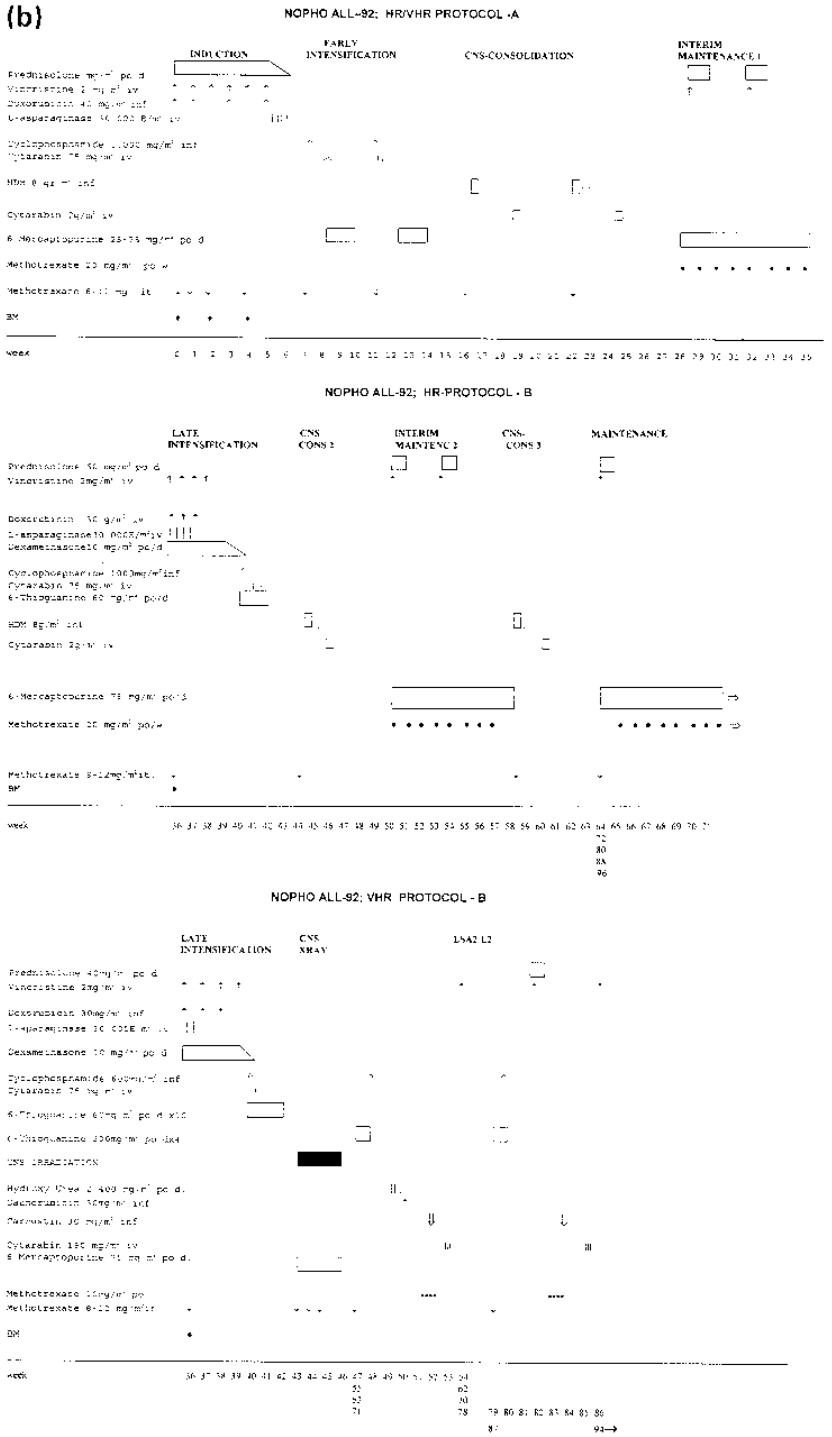


Fig. 2. (Continued).

repeat pulses of HD-Mtx and Vcr and Pred during the first year. The HR children were treated on intensive, national protocols. In Denmark, Finland, Iceland and Sweden treatment was more or less adapted to the German HR protocol according to Riehm et al. (6), which includes cranial irradiation. In Norway two different regimens were used: HD-Mtx without Doxo, and HD-Mtx and HD-Ara-C with Doxo (Seip M, personal communication, 1986). None of the Norwegian regimens used cranial irradiation.

Treatment in period III

In period III all five countries had identical protocols for each risk category. The induction consisted of Pred, Vcr, Doxo, Asp and Mtx i.t. The HR and VHR groups received one extra dose of Doxo. The treatment of the SR group was much the same as that during period II, except that HD-Mtx was given at 5 g m^{-2}, and repeat doses of HD-Mtx and Vcr were given in the maintenance therapy during the first year (Fig. 2a). The IR group had two periods of intensification: one early intensification for 6 weeks with 6-Mp, cyclophosphamide (Cyclo), Mtx i.t. and Ara-C in repeat pulses and one delayed intensification (after the consolidation with HD-Mtx) with dexamethasone, Vcr, daunorubicine, Cyclo, Asp, 6-thioguanine and Ara-C for 6 weeks (Fig. 2a). The initial treatment regimens in the HR and VHR groups were much the same as in the IR group except that Mtx was given at 8 g m^{-2}, as opposed to 5 g m^{-2} in the IR group. There was a consolidation with two pulses each of HDM (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 HD-Mtx pulse, one HD-Ara-C pulse and two pulses of Vcr and Pred before maintenance therapy with oral 6-Mp and Mtx. In the VHR group cranial irradiation of 18 Gy was administered before maintenance. The maintenance therapy consisted of five rotating pulses of cytostatic drugs according to the LSA2L2 regimen (5), given until 2 y from diagnosis (Fig. 2b). In period III, intrathecal Mtx doses were thus given 13 times in the SR group, 18 times in the IR and HR groups and 13 times before cranial irradiation in the VHR group. The total duration of therapy was 2.5 y for the SR patients and 2 y 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, almost 60% of the children received prophylactic CNS irradiation, compared with <10% of the children during period III. Leucovorin rescue was given in the dose of 15 mg m^{-2} i.v. every sixth hour starting 36 h from the beginning of HD-MTX infusion and adjusted continuously according to serum Mtx concentrations. L-Asparaginase was given as Crasnithin during period I and was successively changed during period II to Erwinia for all patients.

Statistical methods

SPSS software was used in the statistical analyses (7). Life-table analyses were constructed using the Kaplan–Meier method and the different subgroups were compared for significance using the log-rank test (7, 8). 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 (7). The eight patients lost at follow-up were censored at the time when they were lost. The probability of deaths in CCR and the probability of relapse were calculated according to the ''one minus survival'' method (7). This implies censoring of patients dying in remission when analysing the probability of relapse. In the same way, patients who relapsed were censored when analysing the probability of deaths in remission. Events in the analysis of event-free survival (EFS) included induction failure, death in remission and relapse.

Results

Epidemiology and subject characteristics

The annual incidence of ALL was 3.9/100 000 children below 15 y of age at diagnosis and was stable throughout the study period. The age distribution demonstrates the well-known prominent peak in frequency at 2–5 y, with most cases being B-precursor ALL (Fig. 3).

From July 1981 to December 1996, 2648 children were diagnosed with ALL. After exclusion of 46 (2%) patients with mature B-cell ALL, 2602 children were left for further analysis. Clinical characteristics of the subjects are given in Table 2. The male:female ratio was 1.14 and 50% were below 5 y of age at diagnosis. In 50% of the children, the white blood cell (WBC) count at diagnosis was $<10\times10^9 l^{-1}$ and in 11% of the children it was $\geq100\times10^9 l^{-1}$. At diagnosis, 8% of the children had a mediastinal mass, 4% had CNS leukaemia and 9% were classified as T-cell ALL.

Overall treatment results

The treatment results from the three consecutive periods

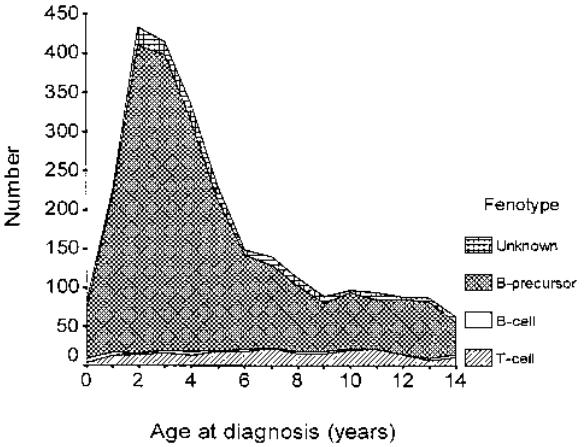


Fig. 3. Phenotype with regard to age at diagnosis in all cases of childhood ALL ($n = 2648$).

Table 2. Clinical characteristics at diagnosis of children aged 0– <15 y.

	Period I (7/81–6/86)		Period II (7/86–12/91)		Period III (1/92–12/96)		Total (7/81–12/96)	
	n = 832	(%)	n = 885	(%)	n = 885	(%)	n = 2.602	(%)
Country								
Denmark	177	(21)	178	(20)	183	(21)	538	(21)
Finland	209	(25)	212	(24)	209	(24)	630	(24)
Iceland	11	(1)	13	(1)	8	(1)	32	(1)
Norway	154	(19)	156	(18)	155	(18)	465	(18)
Sweden	281	(34)	326	(37)	330	(37)	937	(36)
Gender								
Males	439	(53)	466	(53)	481	(54)	1386	(53)
Females	393	(47)	419	(47)	404	(46)	1216	(47)
Age (y)								
<1	23	(3)	26	(3)	24	(3)	73	(3)
1– <2	53	(6)	77	(9)	79	(9)	209	(8)
2– <10	614	(74)	631	(71)	637	(72)	1882	(72)
≥10	142	(17)	151	(17)	145	(16)	438	(17)
WBC $\times 10^9$ l^{-1}								
<10	444	(54)	421	(48)	429	(48)	1291	(50)
10 – <20	95	(11)	135	(15)	131	(15)	364	(14)
20 – <50	130	(16)	151	(17)	147	(16)	428	(16)
50 – <100	83	(10)	78	(9)	83	(9)	244	(9)
≥100	80	(10)	100	(11)	95	(11)	275	(11)
Phenotype								
T-cell	68	(8)	75	(9)	82	(9)	225	(9)
B-precursor	732	(88)	799	(90)	789	(89)	2320	(89)
Other/missing	32	(4)	11	(1)	14	(2)	57	(2)
Mediastinal mass								
Present	64	(8)	68	(8)	66	(8)	198	(8)
CNS involvement								
Present	38	(5)	32	(4)	22	(2.5)	92	(4)

B-cell ALL excluded.

are shown in Fig. 4a. The estimated event-free survival (p-EFS) increased from 0.53 at 16 y during period I to 0.67 at 11 y for period II to 0.78 at 6 y for period III. The corresponding p-EFS values at 5 y were 0.57, 0.70 and 0.78, respectively (Table 3). The hazard function illustrates the risks of events with regard to time from diagnosis (Fig. 4b). The improvement in prognosis was most evident from period I to period II with lower risk of events, especially during the first 4 y from diagnosis. With regard to periods II and III, there seemed to be a decrease in events within the first 3 y from diagnosis. The distribution of events is shown in Table 3. The remission rate increased from 94% to 98% and the toxic death rates in remission were 1.7% for period I, 1.5% for period II and, so far, 2.1% for period III.

The relapse rate decreased from 39% in period I to 28% in period II and, based on the probability of relapse, the estimated relapse frequency for period III will be about 20% (see Table 3). Bone marrow relapses were the most frequent, but the major improvement was seen in isolated CNS relapse rates, which decreased considerably in each risk group and for the whole material from 8.5% to <4% (Table 3). There were 20 secondary malignant events (1 non-Hodgkin lymphoma, 2 cerebral tumours, 10 acute myeloblastic leukaemias and 7 myelodysplastic syndromes) in the whole material, evenly distributed among the periods (Table 3). The overall survival figures at 5 y were 0.71 ± 0.02 for period I, 0.81 ± 0.02 for period II and 0.88 ± 0.03 for period III (Table 3).

Treatment results from period I

The p-EFS for all children was 0.53 (Fig. 4a, Table 3). The SR patients on the two first NOPHO protocols suffered from a high frequency of early relapses located in the bone marrow or the CNS (3, 9). As a consequence, these two protocols were already intensified in July 1984. Almost 20% of all children suffered from an isolated bone marrow relapse and 8.5% had an isolated CNS relapse (Table 3). The p-EFS for the SR, IR, HR and infant groups were 0.57, 0.55, 0.48 and 0.30, respectively.

Treatment results from period II

During the second period, 70% of the children were treated according to NOPHO protocols. Most of the SR patients (236/284) were on the common protocol. Of the IR children, 259 were treated on a protocol which included cranial

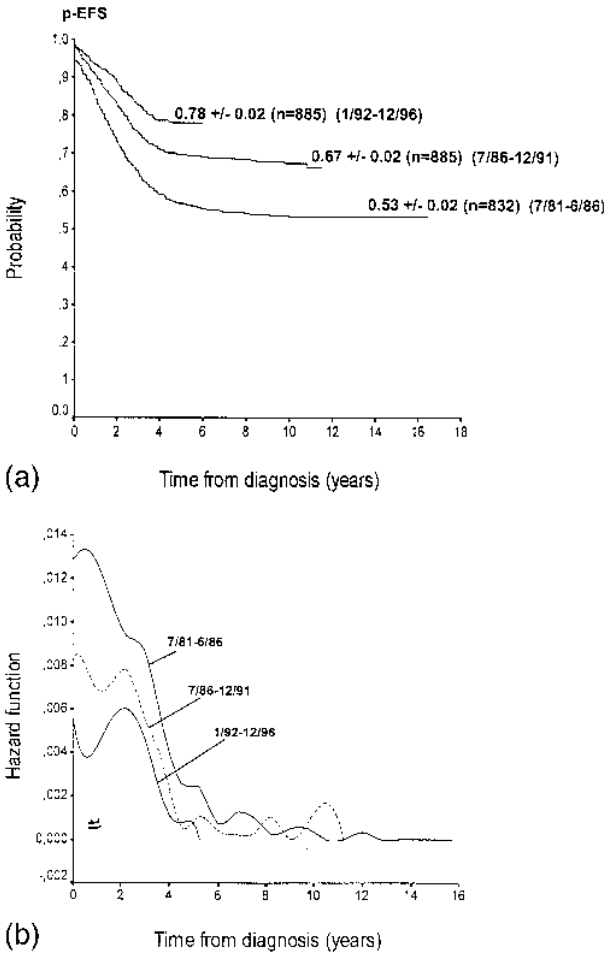


Fig. 4. (a) Event-free survival of Nordic children with ALL, diagnosed and treated during different periods. Period I: 7/81–6/86; period II: 7/86–12/91; period III: 1/92–12/96. B-cell ALL excluded. (b) Hazard function demonstrating the risk of events as a function of time from diagnosis. The patients are Nordic children with ALL diagnosed and treated during different periods. B-cell ALL excluded.

irradiation as part of the CNS prophylaxis (NOPHO IR-1). Fifty-six patients were on NOPHO IR-2 without cranial irradiation. The p-EFS was 0.68 for the whole group (SR 0.77, IR 0.71, HR 0.60 and infants 0.19). In the SR group treated according to the NOPHO protocol, the p-EFS was 0.79 (Fig. 5), bone marrow relapse rate was 8% and isolated CNS relapse rate was 5%. Combined relapses occurred in 3% of the children. The comparison between the NOPHO IR-1 (with cranial irradiation) and NOPHO IR-2 (without cranial irradiation) protocols showed no difference in outcome (Fig. 5). The CNS relapse rate was 3% in the NOPHO IR-1 and 6% in the NOPHO IR-2 study, while the bone marrow relapse rates were 19% and 14%, respectively.

Treatment results from period III

The observation time for this period is still too short for a confident estimation of the final p-EFS; however, the p-EFS value of 0.78 at 5 y for the whole material indicates improved prognosis. The p-EFS at 5 y is 0.84 for SR, 0.85 for IR, 0.68 for HR and 0.67 for VHR. If only patients treated on NOPHO protocols are included in the analyses, the results are almost identical and the p-EFS at 5 y is 0.84 for SR, 0.85 for IR, 0.69 for HR and 0.67 for VHR (Fig. 6). The distribution of events at this point is shown in Table 3. The number of events will increase with longer follow-up and events may, in time, affect 25–30% of the patients.

Comparison among periods I, II and III

Improvement in the p-EFS (at 5-y follow-up) has been most prominent in children with WBC counts <50, with p-EFS figures of 0.60, 0.75 and 0.85 throughout the study period ($p < 0.01$). In children with WBC ≥ 50 at diagnosis improvement has been less evident (p-EFS values of 0.48, 0.55 and 0.55, respectively; not significant). The prognosis for B-precursor ALL has significantly improved over time (p-EFS at 5 y 0.59, 0.73 and 0.81; $p < 0.01$). Patients with T-cell ALL have all been treated on HR protocols and the improvement in prognosis for these children is less evident, as indicated by the p-EFS values at 5 y of 0.52, 0.53 and 0.63, respectively ($p = 0.1$). For children diagnosed during period III with T-cell ALL without other HR criteria the p-EFS was 0.84 ($n = 14$), compared with 0.60 ($n = 66$; $p = 0.2$.) for patients with T-cell ALL with other unfavourable criteria (infants excluded). Forty-nine T-cell ALL children were classified as VHR and received cranial irradiation and the p-EFS in this group was 0.70, compared with the 31 non-irradiated children where the p-EFS was 0.55 (not significant). However, children with T-cell ALL and WBC $\geq 200 \times 10^9 l^{-1}$ had significantly inferior prognosis ($n = 26$, p-EFS $= 0.33$) compared with both WBC $< 100 \times 10^9 l^{-1}$ ($n = 43$, p-EFS 0.76) and WBC $100-<200 \times 10^9 l^{-1}$ ($n = 11$, p-EFS 0.78) ($p < 0.01$). During period I there was a significant difference in gender favouring females (p-EFS at follow-up 0.59 for females and 0.48 for males, $p < 0.01$) (10). During periods II and III there were no significant differences in prognosis between the genders ($p = 0.3$ and 0.4; data not shown), which could thus be ascribed to the intensification of therapy. Infants have the worst prognosis, with no significant improvement in p-EFS at 5 y, being 0.35, 0.19 and 0.40 for the three periods.

Further relapse analysis shows that progress in treatment between periods I and II is explained by a reduced frequency of isolated CNS relapses followed by combined bone marrow and CNS relapses and by isolated bone marrow relapses, in that order (Table 3).

Prognosis after relapse

The survival after relapse reached a plateau at 25–30%, with no differences between the three periods. Children with early relapses, especially if located in the bone marrow, had the worst prognosis. The prognosis after relapse in the Nordic material has been described previously (11).

Table 3. Outcome in children with ALL from different periods of diagnosis and therapy.

	Period I (7/81–6/86)		Period II (7/86–12/91)		Period III (1/92–12/96)	
	$n = 832$	(%)	$n = 885$	(%)	$n = 885$	(%)
Induction failures	47	(5.6)	19	(2.1)	14	(1.6)
Remission	785	(94.4)	866	(97.9)	871	(98.4)
Deaths in CCR	14	(1.7)	13	(1.5)	19	(2.1)
Relapses						
BM isolated	165	(19.8)	151	(16.7)	66	
CNS isolated	70	(8.5)	34	(3.8)	15	
Testis isolated	25	(3.0)	18	(2.0)	3	
BM combined	57	(7.0)	34	(3.8)	20	
AML/MDS/SMN	6	(0.7)	7	(0.8)	7	
Other localization	5	(0.6)	7	(0.8)	4	
Children in CCR	443	(53.2)	602	(68.7)	737	
Children in ≥CR-2	109	(13.2)	86	(9.4)	62	
p-EFS at follow-up	0.53 (16 y)		0.67 (11 y)		0.78 (6 y)	
p-EFS at 5 y	0.57 ± 0.02		0.70 ± 0.02		0.78 ± 0.02	
Probability of deaths in CCR	0.02 ± 0.01		0.02 ± 0.01		0.03 ± 0.01	
Probability of relapse at follow-up	0.42 ± 0.02		0.31 ± 0.02		0.19 ± 0.02	
Probability of relapse at 5 y	0.39 ± 0.01		0.27 ± 0.01		0.18 ± 0.01	
p-Survival at follow-up	0.66 (16 y)		0.76 (11 y)		0.86 (6 y)	
p-Survival at 5 y	0.71 ± 0.02		0.81 ± 0.02		0.88 ± 0.03	

B-cell ALL excluded. Follow-up January 1, 1998.

Discussion

The Nordic population-based 15-y material clearly illustrates how gradual advances in the therapy of childhood ALL have been translated into improved survival figures. The health-care system in the Nordic countries has made it possible to follow almost every child with ALL, and analysis of the material has yielded both incidence figures and outcome between 1981 and the end of 1997. During the 15-y period described, there has been a development from different national protocols in the Nordic countries to uniform ALL protocols. Optimal treatment would be the lowest amount of therapy to cure the maximum number of children with a minimum risk of acute and long-term side-effects. Individualization of treatment through risk-adapted therapy is the means to pursue that goal. The major therapeutic interventions have been the introduction of high-dose methotrexate infusions, strong reduction of

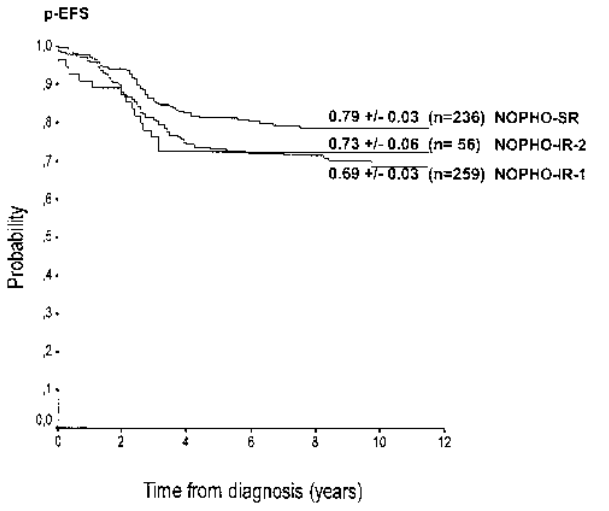


Fig. 5. Event-free survival of Nordic children with ALL, diagnosed between 7/86 and 12/91 and treated according to the NOPHO ALL-86 protocols for SR patients, IR-I patients (with cranial irradiation) and IR-2 patients (without cranial irradiation).

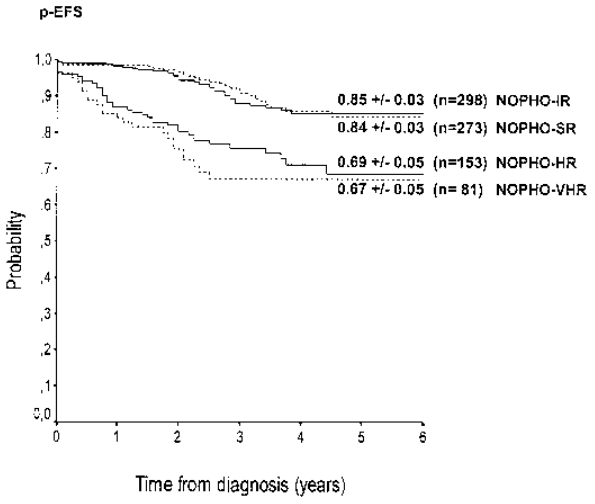


Fig. 6. Event-free survival of Nordic children with ALL, diagnosed between 1/92 and 12/96 and treated according to the NOPHO ALL-92 SR, IR, HR and VHR protocols.

cranial irradiation and the introduction of early and/or delayed intensification courses in the IR and HR regimens. The overall EFS has increased from 53% in the early 1980s to 75% in the 1990s, a result which is in accordance with other international studies (2, 12). The intensification of treatment has resulted in a reduction in the relapse rate but has not given an increase in toxic deaths, as the remission rate has increased and the mortality of children in remission has been stable (1.5–2.1%) during the whole period. The potential risk of secondary malignant events may increase with more intensive treatment; so far, this risk is below 1% in all periods; but the time of follow-up must be extended. The frequency of other late effects is beyond the scope of this study and will be presented in future studies.

An important strategy in the Nordic countries has been to avoid cranial irradiation. Based on the experiences of Moe et al. (13), the first common SR protocols included i.v. pulses of Mtx as a part of the consolidation and CNS treatment. With these protocols, however, it turned out that there was an unacceptably high proportion of bone marrow and CNS relapses compared with other international studies in the 1980s (6, 14, 15). With increasing doses of Mtx, based on new Norwegian protocols (16, 17) and further intensification of therapy, there was a substantial improvement in the prognosis for all risk groups. So far, there is no indication for increased CNS relapse rate during the last 5-y period, in spite of the reduction in the number of children receiving cranial irradiation. The results of the ongoing study are promising, with good p-EFS values and a relative lack of serious toxicity in most patients. The ultimate outcome is unclear and will be evaluated within a couple of years, but some improvement should be expected compared with the earlier periods.

The development of therapy through the three periods is illustrated as the hazard function, i.e. the risk of events as a function of time from the diagnosis of ALL (Fig. 4b). Intensification of treatment has decreased the risk of events, but in periods II and III there are new hazard peaks after treatment intensification, possibly reflecting subgroups of ALL resistant to therapy. Next to treatment intensity, the WBC count at diagnosis is the strongest prognostic factor in all ALL series and forms the basis for risk classification in this material. At diagnosis, 80% of the children had WBC <50 and, consequently, the results of this low WBC group have the strongest impact in the overall figures. The prognosis is most favourable in the age group of 1– <10 y, while infants have the worst prognosis, with p-EFS values at 5 y of 0.35, 0.19 and 0.40 for the three periods. Older children (≥ 10 y) have almost as good prognosis as younger children, probably attributable to the treatment intensification for this age group. As a consequence of the improved results among non-high-risk patients, progress has mainly occurred among B-precursor ALL patients. Among the children with T-cell ALL, the prognosis is still poor compared with the B-precursor ALL. There is a difference, although not significant, between T-cell ALL with additional high-risk criteria and T-cell ALL without other high-risk criteria. However, T-cell ALL and WBC $\geq 200\times10^9\,l^{-1}$ had significantly worse prognosis than the WBC groups $<200\times10^9\,l^{-1}$ ($p < 0.001$). According to treatment, there was no significant difference in this material between T-cell ALL treated with or without cranial irradiation. Karyotyping of the malignant cells in part of this patient material has been described previously (18) but the incomplete examinations, especially in the early periods, decreased the possibility of analysing data in this respect.

Future aspects

In the future, therapy with cytostatic drugs may not change dramatically. New risk categories may be identified with particularly good or bad prognoses. With modern ALL treatment 25–35% of all patients may be overtreated since the true good prognosis group cannot be defined accurately. It may be desirable to reduce or avoid treatment with anthracyclines and/or alcylating agents for some of the patients. The small subgroup of very high-risk patients who would benefit from allogeneic bone marrow transplantation in the first remission would also have to be identified (19). Selected children with chromosomal abnormalities and/or phenotypic criteria are known to have a poor prognosis with conventional treatment and should be offered other front-line therapies. During the past few years, the response to therapy has emerged as an important prognostic factor (6, 20). New methods to detect minimal residual disease (MRD)-residual malignant cells in the bone marrow after initial treatment include fluorescent activated cell sorting (FACS) and polymerase chain reaction (PCR) (21). *In vitro* resistance, which tests the sensitivity of the leukaemic cells to different cytostatic agents, may also offer prognostic information (22). Novel additional approaches such as immunotherapy achieved by experiences from graft versus leukaemia studies (23) may be used during maintenance therapy to improve the results from the current status.

A detailed diagnostic work-up, including morphology, immunophenotyping and cytogenetic analysis is essential, but a careful follow-up of the MRD status throughout the treatment period may also become routine policy in the future.

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