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A Population-Based Study of Childhood Acute Lymphoblastic Leukemia Diagnosed from July 1981 through June 1985 in the Five Nordic Countries

Incidence, Patient Characteristics and Treatment Results

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ABSTRACT. Gustafsson, G., Garwicz, S., Hertz, H., Johanesson, G., Jonmundsson, G., Moe, P. J., Salmi, T., Seip, M., Siimes, M. A., Yssing, M. and Åhström, L. (Nordic Society of Pediatric Hematology and Oncology (NOPHO), Sweden, Denmark, Iceland, Norway and Finland). A population-based study of childhood acute lymphoblastic leukemia diagnosed from July 1981 through June 1985 in the five Nordic countries. Incidence, patient characteristics and treatment results. Acta Paediatr Scand, 76: 781, 1987.

Six hundred and fifty-six children with acute lymphoblastic leukemia (ALL) have been diagnosed in the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) during the period from July 1981 through June 1985. Annual incidence of ALL was 3.6/100 000 children aged <15 years, with an incidence for males of 3.8 and for females of 3.4 respectively. Half of the children were younger than 5 years of age at diagnosis, with a peak incidence between 2–3 years of age. The leukemias were classified as Standard Risk (SR), Intermediate Risk (IR) or High Risk (HR) leukemia according to prognostic criteria at diagnosis. The remission rate was 95%. In children ≥1 year of age with non-B-cell ALL at diagnosis, the Event-Free Survival (EFS) was 0.58; 0.65 for SR-children, 0.51 for IR-children and 0.52 for HR-children. WBC count at diagnosis was the most important prognostic factor and a WBC count of 11–20×10^9/l was associated with the worst prognosis of all WBC values (EFS=0.30), independent of other prognostic factors. Male sex was the second most important adverse prognostic criterion. The follow-up in January 1986 (observation time 6–54 months), showed that 442 of the 656 children (67%) were in complete continuous remission. The total results indicate a possibility to improve the prognosis for most of the risk groups of ALL with a more intensive treatment. *Key words: childhood leukemia, incidence of leukemia, prognosis in childhood leukemia, prognostic factors.*

On July 1, 1981 the Nordic Society of Pediatric Hematology and Oncology (NOPHO) started a cooperative study with registration of all children with acute lymphoblastic leukemia (ALL). This was done in connection with the introduction of intermediate dose Methotrexate (IDM) as consolidation treatment of SR-children in all the Nordic countries, based on the preceding Norwegian experience (1). The aim of the present investigation was to study the incidence of ALL in the Nordic countries. In addition the preliminary treatment results with regard to some prognostic factors are presented.

MATERIAL AND METHODS

There were 656 children (<15 years of age at diagnosis) in the Nordic countries (Denmark, Norway, Iceland, Finland and Sweden) with ALL diagnosed in the 4-year-period from July 1981 through June 1985. The population of the five Nordic countries is 23 million people, including about 4.5 million children <15 years of age. Information concerning the children was obtained by annual reports, the latest in January 1986, from all Departments of Paediatrics and Internal Medicine treating childhood leukemia in these countries. The diagnosis was based and the remission was confirmed on representative bone-marrow smears. The ALL were classified as Standard Risk (SR) (n=295), Intermediate risk (IR) (n=176) or High Risk (HR) (n=185) according to criteria at diagnosis shown in Table 1.

In almost all SR-children the remission was induced and consolidated with prednisolone and vincristine, and doxorubicin (Finland and Sweden) or asparaginase (Denmark, Iceland and Norway). In July 1984 asparaginase was added to the induction treatment in Finland and Sweden. CNS prophylaxis was performed with three pulses of intravenous methotrexate 0.5 or (after July 1984) 1.0 g/m^2 and 8 intrathecal doses of methotrexate (1, 2). The maintenance therapy included oral 6-mercaptopurine daily and methotrexate weekly until 36 months from diagnosis. No re-induction was given. In a pilot study, doxorubicin was not used during induction, but intravenous pulses of methotrexate were added to the maintenance therapy during the first year of therapy (2). In most of the IR-children the induction therapy, its consolidation and CNS-prophylaxis were as in the SR-group. However, the maintenance treatment with oral 6-mercaptopurine daily and methotrexate weekly was intensified by pulses of prednisolone and intravenous vincristine with or without doxorubicin or methotrexate during the first year. The HR-children were treated in many different ways, using primarily the intensive regimens of Riehm (3), Wollner (4), Moe (2), Seip (5) or bone-marrow transplantation after achieved first remission.

RESULTS

Incidence. The incidence figures are given in Table 2, for the whole material as well as for each country separately. An incidence of 3.6/100 000 children/year was found, 3.8 for boys and 3.4 for girls. The male/female ratio was 1.17 in this material. Denmark had a higher male/female ratio compared to the other countries ($p<0.05$). Half of the children were <5 years of age at diagnosis with a peak incidence between 2–3 years. The incidence (per 100 000 children aged <15 years) was 6.0 and 5.7 (ages 0–4 years), 3.9 and 3.4 (ages 5–9 years) and 2.0 and 1.5 (ages 10–14 years) in males and females, respectively.

Clinical characteristics. Table 3 illustrates the distribution of sex and the risk criteria at diagnosis. 3% of the children were <1 year of age. A mediastinal mass was diagnosed in 8% of the children, CNS-involvement at diagnosis in 5% of the children. In the 556 children analysed with regard to immunological markers, 47 were classified as T-cell ALL. WBC-

Table 1. *Criteria for risk-grouping of children with ALL*

High risk (HR)	WBC $>50\times10^9$/l and/or CNS-involvement and/or Mediastinal mass and/or T- or B-cell ALL
Intermediate risk (IR)	No HR-criteria Age 2–<10 years and WBC 21–50×10^9/l or Age <2 years or ≥10 years and WBC ≤50×10^9/l
Standard risk (SR)	No IR/HR-criteria Age 2–<10 years and WBC ≤20×10^9/l

Table 2. *Annual incidence of ALL in the Nordic countries*

Per 100 000 children <15 years

	Males	Females	Total	Ratio M/F
Denmark[a]	4.6	2.6	3.6	1.8
Norway	3.3	4.0	3.6	0.9
Finland	4.3	4.2	4.2	1.1
Sweden	3.3	3.2	3.3	1.1
Total	3.8	3.4	3.6	1.17

[a] Including Iceland.

distribution showed that 10% of the children had a WBC count $>100\times10^9$/l at diagnosis. As shown in Table 4, 45% of the children were classified as having a SR-ALL, 27% an IR-ALL and 28% a HR-ALL with criteria used in this study.

Treatment results. In agreement with international recommendation (6), 19 children <1 year of age at diagnosis, 7 children with B-cell ALL at diagnosis and 3 children with both these criteria, were excluded from the subsequent analysis. Of these 29 children, 18 achieved a complete remission, 12 children have so far relapsed and thus, only 6/29 children were in complete remission at the follow-up, none of the children with B-cell ALL.

Of the remaining 627 children aged ≥1 year at diagnosis and with Non-B-cell ALL, 596 (95%) achieved complete remission. The remission rate for the SR-group was 98% (289/295), for the IR-group 96% (160/167) and for the HR-group 89% (147/165). Thus, 31 children (15 boys, 16 girls) died during induction before achieved remission. By January 1986, 143 children (96 boys, 47 girls) on therapy had relapsed and 9 children (6 boys, 3 girls) after discontinuation of therapy. The bone-marrow was involved in 107 relapses, 35 children had isolated CNS relapse. Eight of the boys had isolated testicular relapse. Two children had relapses in other localisations. CNS-relapse had occurred in 22/289 SR-children with achieved

Table 3. *Sex, age and clinical characteristics at diagnosis in 656 children with ALL*

	N	(%)
Sex		
Males	353	(54)
Females	303	(46)
Age		
<1 year	22	(3)
1–<2 years	42	(6)
2–<10 years	478	(74)
≥10 years	114	(17)
Mediastinal mass present	52	(8)
CNS-involvement present	36	(5)
WBC-count $\times10^9$/l		
≤10	353	(54)
11–20	77	(12)
21–50	99	(15)
51–100	63	(9)
>100	64	(10)
Immunological markers		
T-cell	47	(7)
B-cell	10	(2)
Non-T-cell	499	(77)
Unknown	100	(14)

Table 4. *Risk-grouping at diagnosis in children with ALL in the Nordic countries*

	All children	≥1 year, non-B ALL
Standard risk (SR)	295 (45%)	295
Intermediate risk (IR)	176 (27%)	167
High risk (HR)	185 (28%)	165
Total	656	627

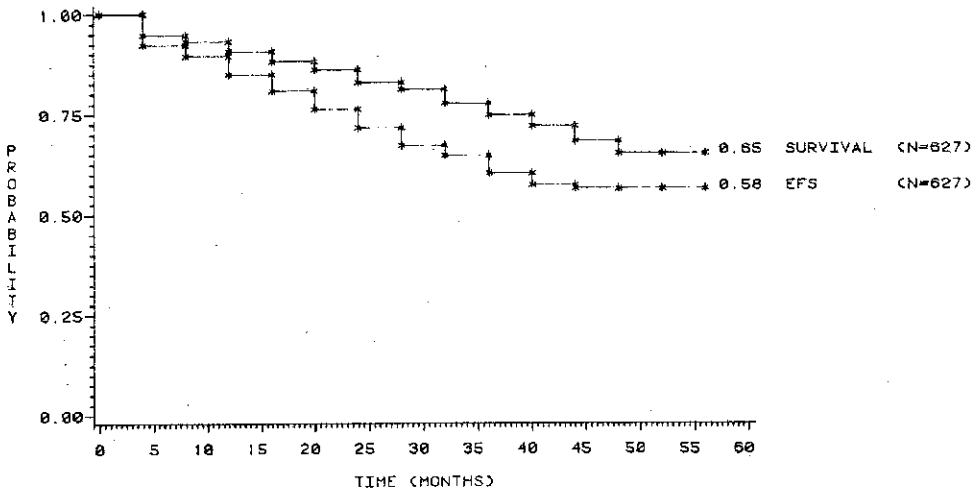

Fig. 1. Event Free Survival versus Survival for children ≥1 year of age and non-B ALL at diagnosis (n=627).

remission (13 isolated, 9 CNS-relapses combined with other manifestations). CNS-relapse had occurred in 18/160 IR-patients (9 isolated, 9 combined). Corresponding figures for HR-children were 19/147 CNS relapses (13 isolated, 6 combined). Thus, so far the total frequency of CNS-relapses (isolated and combined) is 9% for the SR/IR groups and 13% for the HR group. These figures should increase with a longer follow-up period. Eight children (2 boys, 6 girls) have died in complete continuous remission due to infections or other causes. Remaining 436 patients (70%) were in complete continuous remission.

Life-table analyses according to the Kaplan-Meier procedure (7) have been performed for the 627 children (≥1 year of age, Non-B ALL) followed up in January 1986, with an observation time of 6–54 months. The estimation of the prognosis is established with the expres-

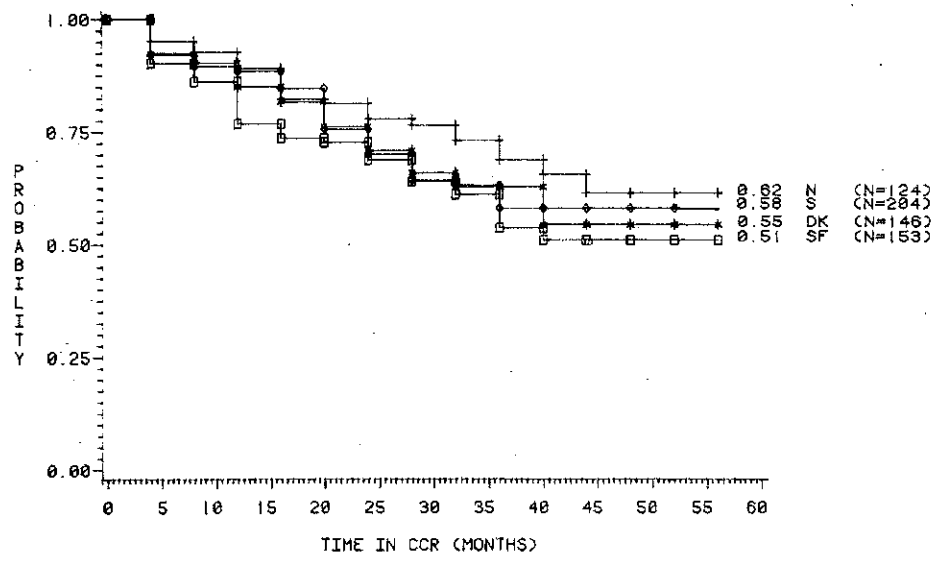

Fig. 2. Event Free Survival in the separate countries for children ≥1 year of age and non-B ALL at diagnosis (n=627). DK=Denmark+Iceland, N=Norway, S=Sweden, SF=Suomi-Finland.

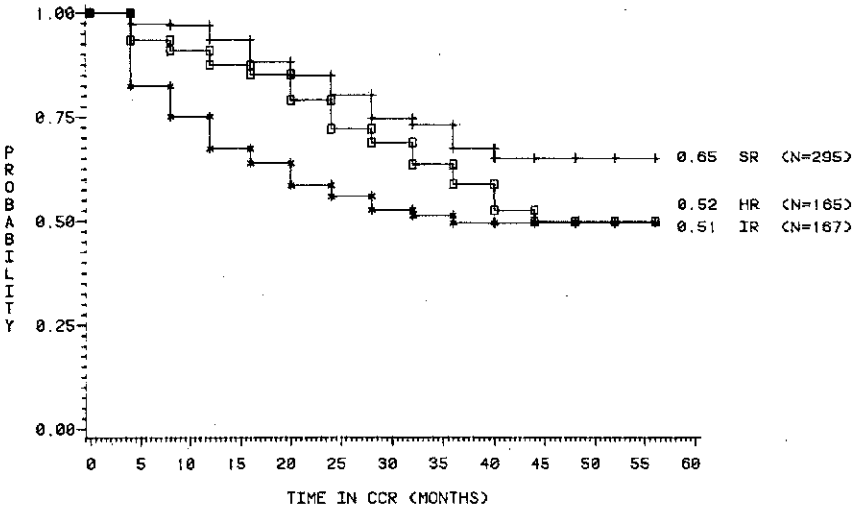

Fig. 3. Event Free Survival for children ≥1 year of age and non-B ALL with regard to risk group at diagnosis (n=627). +–+–+=SR, □–□–□=IR, ∗–∗–∗=HR.

sion Event-Free Survival (EFS), which means the proportion of children who will survive in complete continuous remission, in relation to all children with the diagnosis ALL. Fig. 1 shows that the Event-Free Survival (EFS) and Survival are almost similar indicating a poor prognosis after relapse. The EFS in the separate Nordic countries are shown in Fig. 2 with differences in EFS varying between 0.51 and 0.62. Denmark and Iceland are analysed as one group in this analysis. Fig. 3 shows EFS for the same patients according to risk-group at diagnosis. The EFS-values for the SR-, IR- and HR-groups are estimated to 0.65, 0.51, and 0.52, respectively. There was a significant difference in prognosis favouring females in this material. This difference was most pronounced in the HR-group (Fig. 4) and persisted even if boys with testicular relapse were excluded from the analysis. For HR-males the EFS-value

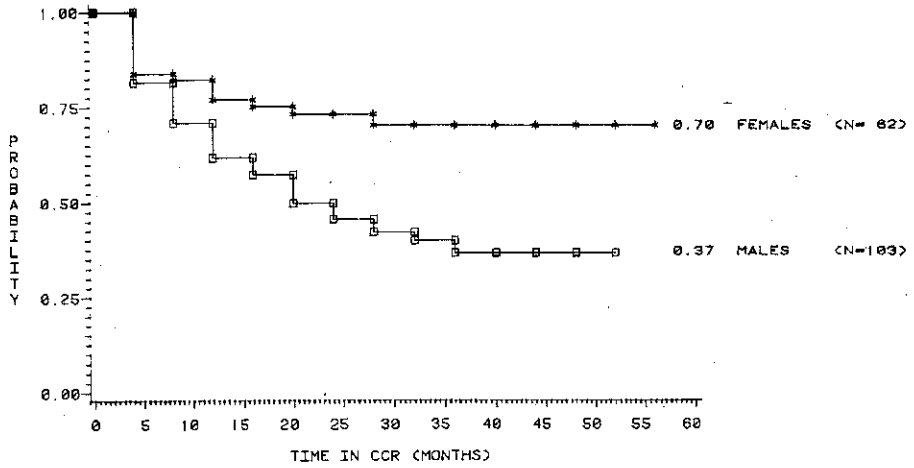

Fig. 4. Event Free Survival for children with HR-leukemia and ≥1 year of age, non-B ALL with regard to sex at diagnosis (n=165).

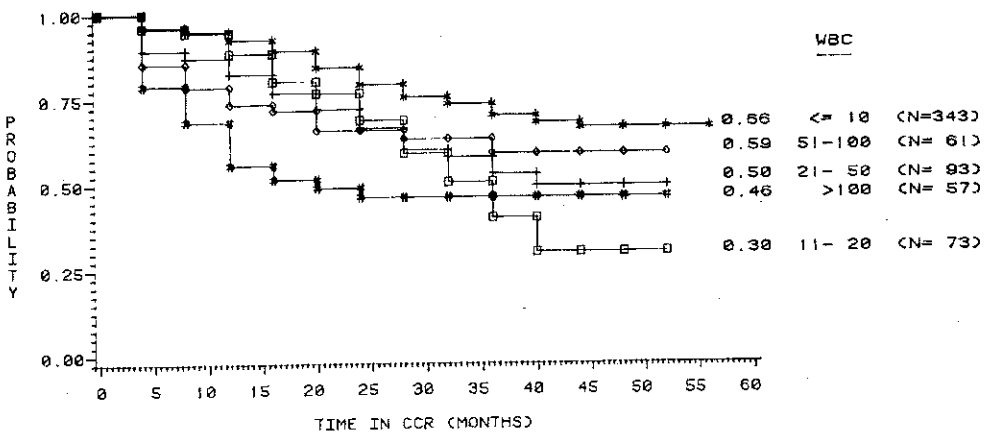

Fig. 5. Event Free Survival for children ≥1 year of age and non-B ALL with regard to WBC-value at diagnosis (n=627).

was 0.37 compared to 0.70 for HR-females ($p<0.001$). The prognosis, with regard to different WBC-values at diagnosis, are illustrated in Fig. 5. The 73 children with WBC-values $11–20\times10^9$/l had the worst prognosis with an EFS-value of 0.30. This is the worst WBC category in all risk-groups and for both sexes (figures not shown). Only 42 of the 73 children (57%) were in complete remission in January, 1986. Three children died during induction treatment and 28 children have so far relapsed. The children in this WBC-group have a high relapse-rate, especially after 2 years from diagnosis.

DISCUSSION

The Nordic countries have a well developed health- and welfare service, especially for children, which makes it highly probable that in fact all children with ALL were diagnosed and included in these series. The incidence rates are in agreement with earlier results from the Nordic countries (8, 9, 10). Finland had a comparatively high incidence in this study, explained by the fact that the birth rate in Finland has recently increased compared to the other countries, where a decrease of 10–20% has been recorded during the last 10 years. As half of the children are <5 years of age at diagnosis, these changes will influence the incidence figures. The sex distribution shows a lower male/female ratio than in most other materials (11), but it is in accordance with earlier Nordic studies (8, 10). The distribution of children with regard to WBC counts, age, and the proportion of children with a mediastinal mass or CNS-involvement at diagnosis are in agreement with other studies (11) but the proportion of T-cell leukemia is low. This cannot be explained by the 14% of the children who were not analysed at the time of diagnosis. T-cell leukemia may have been underdiagnosed due to use of older techniques, but it is more probable that the frequency of T-cell leukemia really is lower in the Nordic countries compared to other regions. A third possibility is that earlier, often selected materials, tend to overestimate the frequency of T-cell ALL. For exact comparison large population-based studies are necessary.

The treatment results indicate that the long term survival may be 55–60% of all children, with only moderate differences between the risk-groups as defined in this investigation. Sex is a significant prognostic factor in this material, as in other materials described from Sweden (12) and Denmark (13). Nevertheless, it is in the HR-group that the influence of sex is most pronounced. Analysis of the WBC-values as prognostic factor shows some unexpected find-

ings for the WBC-group 11–20×10^9/l. The reason for the bad prognosis in this group is so far unclear. The explanation is not that these children have other IR/HR-criteria, as the prognosis for this WBC-group is equally as poor through all three risk-groups. The poor prognosis is not explained by sex differences either, as both sexes have equally bad prognosis in this particular WBC-group.

The main aim of this investigation has not been to compare different treatment protocols, but rather to show the total results in the Nordic countries for treatment of ALL, with no loss or selection of patients. However, some conclusions regarding the therapy seem justified. As CNS-prophylaxis, almost all of the SR/IR-patients received pulses of methotrexate intravenously and intrathecally in the consolidation phase avoiding CNS irradiation. The CNS-relapse rate seems to become somewhat higher with most of these regimens compared to CNS-prophylaxis with cranial irradiation and methotrexate intrathecally, where figures below 5% isolated CNS-relapses have been reported (14). In previous Norwegian studies, where the patients received methotrexate intravenously and intrathecally as CNS-profylaxis the relapse rate was 7–8% (2). For the HR-children the relapse rate is in agreement with other studies with intensive treatment (15).

As a consequence of the results, the Nordic Society of Pediatric Hematology and Oncology has decided to change risk-grouping by including the children with WBC 11–20×10^9/l in the Intermediate Risk-group and to intensify the treatment for most of the children with ALL in order to improve treatment results. However, the pilot studies (2) will continue with the same protocols as before.

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