Acta Pædiatr Scand 78: 104–109, 1989

A Population-Based Study of Children with Standard Risk Acute Lymphoblastic Leukemia in the Five Nordic Countries

A Follow-up of 230 Patients

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ABSTRACT. Gustafsson, G., Berglund, G., Garwicz, S., Hertz, H., Jonmundsson, G., Moe, P. J., Salmi, T. T., Seip, M., Siimes, M. A. and Yssing, M. (Nordic Society of Pediatric Hematology and Oncology (NOPHO), Sweden, Denmark, Iceland, Norway and Finland). A population-based study of children with standard risk acute lymphoblastic leukemia in the five Nordic countries. A follow-up of 230 patients. Acta Paediatr Scand 78: 104, 1989.

Two hundred and thirty children with standard risk acute lymphoblastic leukemia (ALL) were diagnosed during a period of 3 years from July 1, 1981 to June 30, 1984 in the five Nordic countries. Criteria for standard risk ALL were age above 2.0 and below 10 years, WBC $\leq 20\times10^9$/l, no evidence of CNS-involvement, mediastinal mass or T- or B-cell leukemia. The children were treated without prophylactic CNS irradiation, the majority (200 patients) according to two treatment programs. Follow-up of the entire group after a minimum of 30 months showed 64% of the children living in complete continuous remission with a probability of event-free survival of 0.60. The treatment results are not entirely satisfactory and intensification of therapy is required. A subgroup of patients with WBC between 10 and 20×10^9/l and with adverse prognosis was identified, justifying a change of the present criteria for risk grouping. *Key words: childhood leukemia, treatment of leukemia, prognosis in childhood leukemia.*

This investigation is a multinational study on children with standard risk acute lymphoblastic leukemia (ALL). The patient material is population-based. The study design was based on Norwegian experience indicating that intermediate dose methotrexate i.v. combined with intrathecal injections of methotrexate can be effective in prophylaxis of CNS-leukemia and thus may replace CNS irradiation (1).

The aim of the study was to investigate whether this approach (with modification of the protocol) could be applied in other Nordic countries where prophylactic CNS irradiation previously was a standard procedure.

This investigation also allowed studying the role of asparaginase compared with doxorubicin during the initial phases of therapy among the children with standard risk ALL. All patients in Denmark, Finland, Iceland, Norway and Sweden were included during a 3-year period in 1981–1984. They were followed up and analyzed as to their status on January 1, 1987.

MATERIALS AND METHODS

There were 485 children, age below 15 years, with ALL in the 5 countries between July 1, 1981, and June 30, 1984. Of the 485 patients, 230 (47%) were classified as having standard risk ALL. The criteria of standard risk leukemia at diagnosis included age above 2.0 and below 10 years, WBC below or equal to 20×10^9/l, no evidence of CNS involvement, mediastinal mass or T- or B-cell leukemia (2). The patients were observed up to January 1, 1987. No patient has been lost from the follow-up. Of the 230 patients, 200 were allocated in a non-random fashion into two treatment programmes.

Treatment programme A consisted of the following induction medication: Prednisolone (60 mg/m^2/24 h, divided into 3 oral doses) for 36 days, 6 weekly i.v. injections of vincristine (2.0 mg/m^2/dose), 5 intrathecal injections of methotrexate (12 mg/m^2/dose), 3 injections of doxorubicin (40 mg/m^2/dose) on days 1, 21, and 35. Consolidation and CNS prophylaxis consisted of 3 intravenous methotrexate infusions (500 mg/m^2/24 h) with citrovorum factor rescue and intrathecal methotrexate injections given at 3 week intervals, starting on day 50. This programme was applied in Sweden and Finland, in the treatment of 116 patients.

Treatment programme B was identical except that the doxorubicin during the induction phase was replaced by L-asparaginase (1 000 IU/kg/daily) given as consolidation for 10 days, starting day 36. This programme was used in Denmark, Iceland and half of Norway in 84 children. The maintenance therapy was identical in both groups including daily 6-mercaptopurine (75 mg/m^2) and weekly methotrexate (20 mg/m^2) both orally, up to 36 months from the time of diagnosis. No reinductions were given (2). There were no significant differences regarding sex distribution, age and WBC at diagnosis between the two treatment groups (Table 1). The median age was 4.8 and 4.7 years and the median WBC were 5.8 and 6.6×10^9/l in the treatment groups A and B, respectively. The remaining 30 children were treated according to other protocols: 19 patients according to a Norwegian pilot study (3) and 11 by different treatment protocols. The statistical methods used have been life table analyses according to the Kaplan-Meier procedure (4). The minimal and maximal observation times were 30–66 months, respectively. Event Free Survival (p-EFS) at 66 months from diagnosis, i.e.—an estimation of the proportion of children surviving in continuous complete remission, in relation to all children with ALL was used as estimation of cured children.

RESULTS

Of the 230 patients with standard risk ALL, 224 obtained remission (97%). A total of 147 patients (64%) were in complete continuous remission (CCR) after a mean of 50 months follow-up. The probability of Event-Free Survival (p-EFS) was 0.60 after 66 months. In the treatment group A, 111 of 116 children and in the treatment group B all 84 achieved initial remission. Thus, the remission rates were 96 and 100%, respectively. The event-free survival was not significantly different in the two groups (p=0.4) (Fig. 1 and Table 2). Treatment A was associated with a relatively high incidence of septicemia during the induction period, in which 36 of the children (31%) became affected. In treatment group B, only 9 children (11%) had septicemia. The difference is statistically significant (p<0.05). Of the 36 septicemic patients in treatment group A, 5 died of sepsis during the induction therapy. These fatal cases were diagnosed at the beginning of the study period.

Of the 111 patients in treatment group A with achieved remission, 38 children relapsed (34%). The relapse rate was similar among the 84 group B patients, where 27 children (32%) relapsed. There was no statistically significant difference in the distribution of relapses within

Table 1. *Some clinical data of patients in the treatment programmes A and B*

	Programme A (n=116)		Programme B (n=84)	
	n	(%)	*n*	(%)
Boys	62	(53)	40	(48)
Girls	54	(47)	44	(52)
Age				
2–<5 years	76	(66)	58	(69)
5–<10 years	40	(34)	26	(31)
WBC×10^9/l				
≤10	102	(88)	69	(82)
>10–<=20	14	(12)	15	(18)

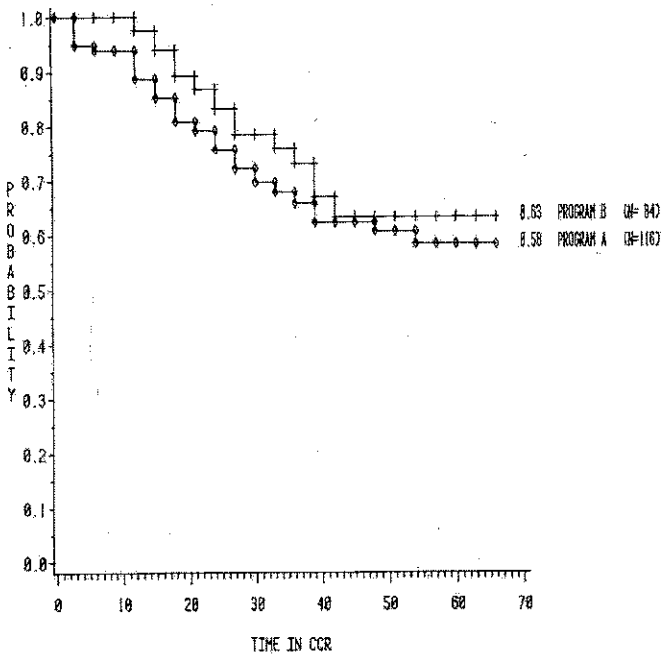

Fig. 1. Event-free survival in SR-children treated according to Programme A (n=116) and Programme B (n=84) (p=0.4).

organs, even if the frequency of CNS relapse was somewhat higher in treatment group A (Table 3).

Since there were no significant differences between treatment groups A and B we combined these data in order to analyse other prognostic factors than those which designed the patients into the standard risk group. With regard to WBC at diagnosis the data analysis showed that the patients with WBC $\leq 10\times10^9$/l had a better prognosis (p-EFS for group A 0.62 (n=102), for group B 0.67 (n=69), and for groups A+B 0.64), than those with WBC $>10-\leq 20\times10^9$/l (p-EFS for group A 0.32 (n=14), for group B 0.44 (n=15), and for groups A+B 0.38). The difference in the event-free survival between patients with higher and lower WBC in the combined material was significant with a p-value of 0.02 (Fig. 2). In this study

Table 2. *Treatment results for programmes A and B*

	Programme A	Programme B
Total patients (n)	116	84
Dead during induction (n)	5	0
Remission obtained	111	84
Dead in remission (n)	1	1
Relapsed (n)	38	27
On therapy	34	25
Off therapy	4	2
CCR (n)	72	56
CCR (%)	62	67
p-EFS	0.57	0.63

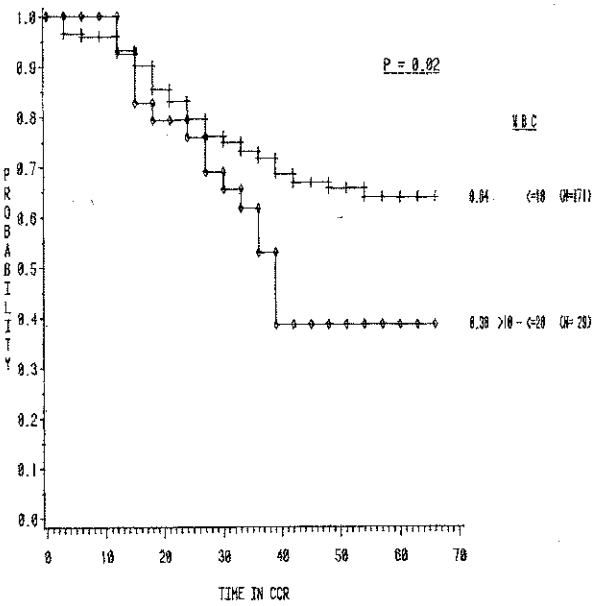

Fig. 2. Event-free survival in SR-children treated according to Programme A and B with regard to WBC$\times 10^9$/l at diagnosis.

there was no significant difference according to sex. The p-EFS values were for males 0.58 (A+B, n=102) and for females 0.63 (A+B, n=98). Of the children, 134 were aged 2–<5 years at diagnosis, 66 between 5–<10 years. There was no significant difference in prognosis for these two age-groups. (p-EFS 0.62 and 0.57 respectively.)

DISCUSSION

The Norwegian investigators have reported good treatment results, even after long follow-up periods, in children with standard risk ALL treated with an intermediate dose of methotrexate combined with intrathecal methotrexate injections, as a mean of CNS prophylaxis (3). Based on these results, the other Nordic countries which previously used prophylactic CNS irradiation changed their treatment protocols in order to avoid long-term effects of radi-

Table 3. *Frequency and organ distribution of relapses for the treatment programmes A and B*

	Programme A		Programme B	
	n	%	*n*	%
Relapses on/off therapy	38	34	27	32
Bone marrow, isolated	21	19	16	19
CNS, isolated	9	8	4	5
CNS, combined	5	5	4	5
Testes, isolated	2	2	3	3
Other	1		–	

ation therapy (5). This resulted in the first multinational, population-based study on children with standard risk ALL. The present results are comparable to those previously achieved in national studies (6, 7). There were cases of early deaths associated with septicemia in the treatment programme A in the beginning of the study. Subsequently, this mortality has decreased, probably due to increasing experience with the protocol. There were no major problems associated with the intravenous methotrexate treatment. The data analysis shows that the frequency of CNS relapses in treatment group A was slightly higher than in treatment group B, and also higher than in a previous Swedish study on the use of prophylactic irradiation (6). Furthermore, the total frequency of CNS-relapse seems to be higher than that of the POG-study (8) using three drugs intrathecal chemotherapy as CNS-prophylaxis. In the BFM-study (9) the frequency of CNS-relapses was higher in children treated with intermediate dose of Methotrexate compared to children who received prophylactic irradiation against the CNS.

Some other studies have shown that asparaginase may have some protective effect against the development of CNS leukemia (10). Our results seem to support this observation. As a consequence of this study the CNS prophylaxis in the treatment program A was later intensified by adding asparaginase in the consolidation phase and by increasing the dose of methotrexate from 0.5 g to 1.0 g/m^2.

The initial results in treatment group B were quite satisfactory but with a longer follow-up time late relapses occurred resulting in the present survival rates. The expected improvement in the treatment results was not obtained. However, the present treatment protocols differed from the previous Norwegian protocol (1), as no re-inductions were used and the dose of 6-mercaptopurine was reduced to 75 mg instead of 90 mg/m^2. On the other hand, prophylactic CNS irradiation with its adverse late effects could be omitted (5), without major negative influence on the event-free survival. The treatment programme could be performed with low therapy associated mortality, despite the fact that in the Nordic countries the treatment of standard risk ALL is not primarily centralised. Obviously, however, some patients in the entire material were undertreated (11). One such group was identified as those patients, who according to our criteria were treated as standard risk ALL and had initial WBC between 10 and 20×10^9/l.

ACKNOWLEDGEMENTS

We wish to express our most sincere thanks to all colleagues at the Departments of Pediatrics and Hematology in the Nordic countries for collecting data concerning the patients. Financial support was obtained from the Swedish Child Cancer Foundation and from the Cancer Societies in the Nordic countries.

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Submitted Jan. 27, 1988. Accepted June 29, 1988

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