

CENTRAL NERVOUS SYSTEM DISEASE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA: Prognostic Factors and Results of Treatment

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This study was sponsored by the Nordic Society of Paediatric Haematology and Oncology.

This investigation has been supported by grants from the Swedish Child Cancer Foundation and from the Cancer Societies in the Nordic countries.

Pediatric Hematology and Oncology, 8:291-299, 1991
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In the five Nordic countries, 808 children 1 to 15 years of age (428 boys, 380 girls) were diagnosed with non-B acute lymphoblastic leukemia (ALL) from July 1981 through June 1986. Complete remission was achieved in 770 children (95%). Central nervous system (CNS) involvement at diagnosis was noticed in 34 children, of whom 26 achieved remission. Of these 26 patients 11 subsequently relapsed, 5 in the central nervous system. An interim analysis in January 1990 (observation time 3 1/2 to 8 1/2 years) revealed that isolated CNS relapse had occurred in 70 children (9.0%). Of these 70 patients, 12 out of 142 children (8.5%) had initially received irradiation and 58 out of 628 children (9.2%) only chemotherapy as CNS-prophylaxis. There was a significant higher risk for boys (12%) than for girls (6%) to relapse in the CNS compartment. Unfavorable prognostic factors for survival after isolated CNS relapse were short duration of first remission and male sex. In high-risk patients after an isolated CNS relapse, there was no difference in prognosis related to treatment with or without irradiation as initial CNS prophylaxis.

KEY WORDS: acute lymphoblastic leukemia, CNS involvement, prognostic factors, treatment results.

INTRODUCTION

A population-based registry of childhood acute lymphoblastic leukemia (ALL) has been running since 1981 in the five Nordic countries. This material offers the unique opportunity to follow every child with a malignant disorder over time in societies where "lost to follow up" is virtually nonexistent. This material thus avoids the bias sometimes impossible to avoid in large studies from multicenter studies in many countries.

The present study focuses on the frequency and outcome of central nervous system (CNS) disease in ALL. Occurrence of CNS disease in this sanctuary has always been regarded as a bad prognostic factor. In spite of differences between some national protocols, the present material illustrates both the incidence and outcome. We concentrated on the role of CNS leukemia at diagnosis and as an isolated site of relapse in regard to prognosis in various patient groups.

MATERIALS AND METHODS

A population-based study in the five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) was conducted by the Nordic Society of Paediatric Haematology and Oncology (NOPHO). Out of a population of 4.5 million children aged 1 to 15 years, 808 children (428 boys and 380 girls) were diagnosed with non B-cell ALL between July 1, 1981 and June 30, 1986. The leukemias were classified as standard risk (SR; $n = 368$), intermediate risk (IR; $n = 224$) or high risk (HR; $n = 218$), according to criteria at diagnosis (Table 1). All patients were evaluated in January 1990.

Treatment was given according to the Nordic ALL protocols for SR patients and for IR and HR patients according to both Nordic and national ALL protocols.¹ In almost all SR children the remission was induced and consoli-

TABLE 1. Criteria for Risk Grouping of Children Over 1 Year Old and with Non-B-Cell ALL

Group	Criteria
High risk (HR)	WBC $>50 \times 10^9/l$ and/or CNS involvement and/or Mediastinal mass and/or T-cell ALL
Intermediate risk (IR)	No HR criteria Age 2- < 10 years and WBC $21-51 \times 10^9/l$ Age < 2 years or ≥ 10 years and WBC $\leq 50 \times 10^9/l$
Standard risk (SR)	No IR/HR criteria Age 2- < 10 years and WBC $\leq 20 \times 10^9/l$

dated 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 and 8 intrathecal doses of methotrexate. The maintenance therapy included oral 6-mercaptopurine daily and methotrexate weekly for 36 months after diagnosis. No reinduction 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. 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, Wollner, or Seip, or bone marrow transplantation after achieved first remission.¹

CNS prophylaxis was given as cranial irradiation and intrathecal methotrexate injections to 4 SR patients, 15 IR patients, and 123 HR patients who achieved remission. The other 628 children were treated with intrathecal methotrexate injections and intravenous pulses of methotrexate (0.5-8.0 g/m²) with or without intravenous ARA-C (1-2 g/m² \times 6) as CNS prophylaxis.

The statistical methods used involved Cox regression analysis and life table analysis according to the PHGLM procedure.²

RESULTS

Of the 808 patients with ALL, complete remission was obtained in 770 children (95%): 359 SR patients (98%), 214 IR-patients (95%), and 197 HR

patients (90%). There was no sex difference in the frequency of remission: 408 boys and 362 girls achieved remission. At diagnosis 34 patients (4.2%; 24 boys and 10 girls) presented with CNS leukemia. Of these 34 patients, 71% of the boys and 90% of the girls obtained primary remission; 5 patients later experienced CNS relapse and 6 patients relapsed in the bone marrow.

Of the 770 patients, 297 (38%) have relapsed (Table 2) and 12 have died in continuous complete remission (CCR). Of the 297 relapsed patients, 110 have had CNS relapse; 70 had an isolated CNS relapse (9%) and 40 had combined relapses. Of the 70 patients, 32 (8.9%) had SR, 20 (9.3%) had IR, and 18 (9.1%) had HR leukemia (Table 2). Thus no difference was observed between the risk groups with regard to frequency of isolated CNS relapses.

Cranial irradiation as CNS prophylaxis was given to only 19 children with SR leukemia and IR leukemia compared to 123 children in the HR group (Table 2). We found no difference between patients in the HR group who had received cranial irradiation and patients who had not received cranial irradiation in CNS prophylaxis (Table 2, Fig. 1).

Overall, isolated CNS relapses were significantly more common in boys (49/408 boys = 12%) than in girls (21/362 = 6%), ($p < 0.05$). Table 3 shows that 10/91 boys (11%) and 2/51 girls (4%) with cranial irradiation had isolated CNS relapses compared to 39/317 boys (12%) and 19/311 girls (6%) with isolated CNS relapses in the nonirradiated group. This finding implies a greater risk for boys than for girls to relapse in the CNS, regardless of the kind of CNS prophylaxis given ($p < 0.01$, Fig. 2).

A Cox regression multivariate analysis of prognostic risk factors after an isolated CNS relapse revealed significantly impaired prognosis for short duration of first remission and for male sex. However, impaired prognosis could *not* be associated with the following parameters at diagnosis: risk group; CNS involvement; presence of mediastinal mass; age; and white blood cell counts, platelet counts, and hemoglobin values in peripheral blood or initial treatment.

The prognosis after isolated CNS relapse was independent of the treatment given whether CNS irradiation was used or not. Thus, in 35 children with less than 24 months in CCR before CNS relapse, the estimated survival was 0.34 compared to an estimated survival of 0.68 in 35 children with more than 24 months in CCR before CNS relapse ($p < 0.001$; Figure 3). Finally, after an isolated CNS relapse (Figure 4), there was a significantly lower survival rate for boys than for girls ($p < 0.005$).

DISCUSSION

In children with ALL, CNS leukemia has always implied an impaired prognosis. Before institution of CNS prophylaxis, the CNS was the most com-

TABLE 2. First Relapse in 297 Children with ALL. Localization Risk Group and Relation to Cr+ or Cr- in Children with Achieved Remission ($n = 770$)

	Standard Risk		Intermediate Risk		High Risk		Total (770)
	Cr+ (4)	Cr- (355)	Cr+ (15)	Cr- (199)	Cr+ (123)	Cr- (74)	
CNS	—	32	2	18	10	8	70
CNS combination	—	17	—	13	5	5	40
Non-CNS	—	81	4	47	35	20	187
Total	—	130	6	78	50	33	297

Cr+ = cranial irradiation. Cr- = no cranial irradiation. Total number of children in the group is in parentheses.

mon (75%) place for relapses in childhood ALL, thus representing the most frequently diagnosed sanctuary for ALL cells.³ An involvement of the CNS with lymphoblasts was almost always followed by a hematological relapse. The first reports of cure in childhood ALL consequently comprised prophylactic CNS irradiation.⁴

From the population-based NOPHO study reported here, we have analyzed the results obtained in the Nordic countries with special emphasis on

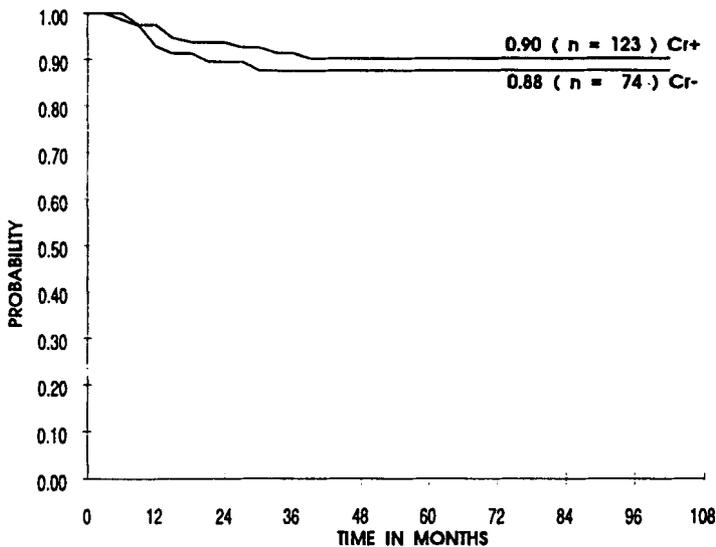


FIGURE 1. CNS disease free survival in children with HR ALL and achieved remission with or without cranial irradiation as CNS prophylaxis. Curves show an estimation of the proportion of children surviving without CNS relapse. Cr+ = patients receiving cranial irradiation. Cr- = patients not receiving cranial irradiation.

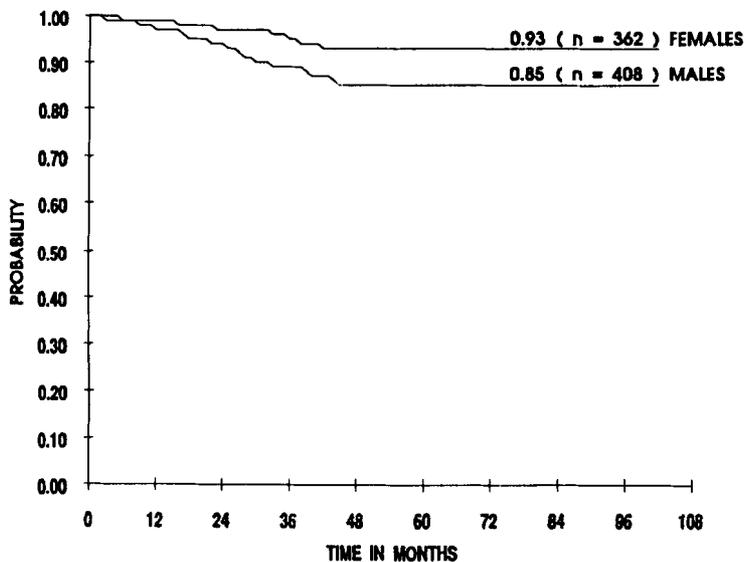
TABLE 3. Sex Distribution of 70 Isolated CNS Relapses in Children with Achieved Remission

Group	Boys		Girls		Total
	Cr+	Cr-	Cr+	Cr-	
Standard risk	0 (3)	20 (173)	0 (1)	12 (182)	(359)
Intermediate risk	2 (10)	12 (100)	0 (5)	6 (99)	(214)
High risk	8 (78)	7 (44)	2 (45)	1 (30)	(197)
Total	10 (91)	39 (317)	2 (51)	19 (311)	(770)

Total number of children in the group is in parentheses.

prognostic factors and treatment results of CNS disease in childhood ALL. Although slightly different protocols have been used, these uniformly treated and carefully controlled patients will constitute patient data suitable for analysis of CNS involvement in ALL and a comparison of irradiation and high doses of systemic and intrathecal chemotherapy as CNS prophylaxis.

Today, CNS prophylaxis has reduced isolated CNS relapses to less than 10% in children with ALL and has considerably improved treatment results.⁵ The long-term effects of CNS prophylaxis in irradiated children cannot be overlooked, however. This has also resulted in attempts to decrease the dose of CNS irradiation and to give CNS irradiation to fewer children with ALL.⁶

**FIGURE 2.** CNS disease free survival in boys and girls with achieved remission of ALL.

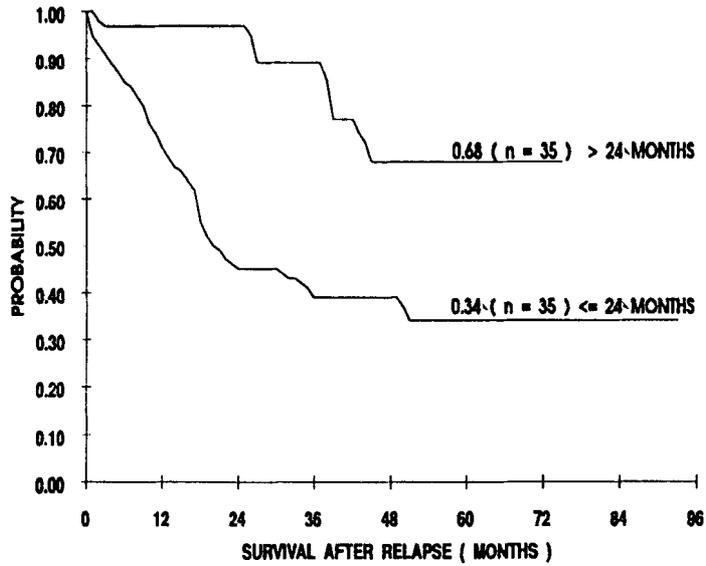


FIGURE 3. Estimated survival after relapse of children with more or less than 24 months in first remission before isolated CNS relapse, ($p < 0.001$).

For example, the radiotherapy in children with standard risk ALL has been avoided or substituted with systemic and intrathecal chemotherapy.⁷

In this study the frequency of CNS relapses has been reduced to less than 10% in all risk groups in both irradiated and nonirradiated children. How-

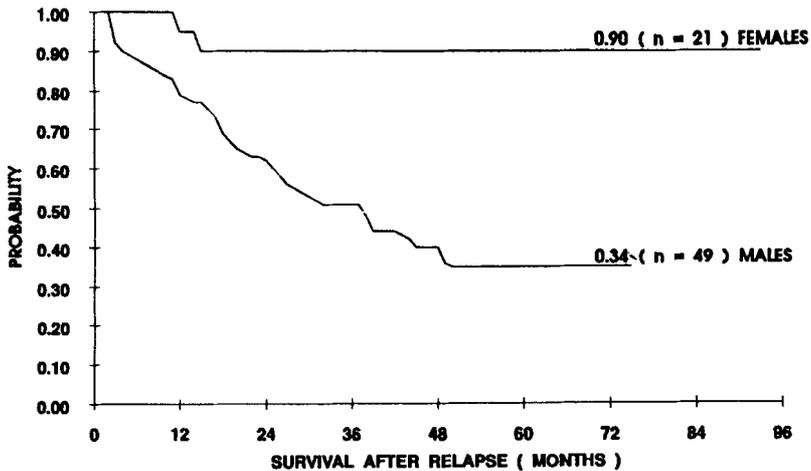


FIGURE 4. Estimated survival after relapse for boys and girls with isolated CNS relapse, ($p < 0.005$).

ever, there was a significantly higher risk for boys (12%) than for girls (4% to 6%) to relapse in the CNS. In the SR and IR risk groups, the dose of intravenous methotrexate used was 0.5 g/m² to 1.0 g/m². The frequency of CNS relapses for boys in all risk groups was more than 10%, indicating the CNS protection was not sufficient. Other studies indicate that intravenous methotrexate doses exceeding 3 g/m², in addition to intrathecal methotrexate injections, will give sufficient protection against CNS relapses in the SR risk group.⁸ In the HR risk group, the frequency of CNS relapses was low for girls but high for boys, especially for boys treated without CNS irradiation (7/44; Table 3). It has been proposed that methotrexate given in repeated intrathecal injections, in addition to repeated systemic doses of 3 g/m² to 5 g/m², would also be sufficient as CNS prophylaxis in the HR groups.^{8,9} Further, the small risk of developing a second malignancy following prophylactic CNS irradiation¹⁰ may well balance the slightly increased risk for CNS relapse if prophylactic CNS irradiation is substituted with intrathecal and systemic chemotherapy.

As seen in Fig. 1, the frequency of CNS relapses is the same for children in the HR group whether treated with cranial irradiation or not as CNS prophylaxis. Our study indicates it may be possible to avoid irradiation as CNS prophylaxis in most children with ALL, even in the HR groups (Fig. 1).

We could not find any differences in prognosis after isolated CNS relapses between the various patient risk groups treated with irradiation or systemic chemotherapy as initial CNS prophylaxis. However, CNS involvement in ALL was more frequent in boys than in girls, regardless of when the diagnosis occurred, implying an overall impaired prognosis for the boys. In addition, as shown by our multivariate analysis, short duration of first remission and male sex were the only prognostic factors indicating impaired prognosis after isolated CNS relapse. A significant number of the CNS relapses can be explained by the fact that a proportion of boys do not benefit from the therapy given in the present Nordic protocols. Other treatment modalities such as further intensification of chemotherapy intrathecally and systemically should be tried with these boys.

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Received January 25, 1991

Accepted May 2, 1991

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