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Superior treatment results in females with high-risk acute lymphoblastic leukemia in childhood

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In this population-based study, 808 children aged 1–15 years from Denmark, Finland, Iceland, Norway and Sweden, were diagnosed between July 1981 and June 1986 as suffering from non-B-cell acute lymphoblastic leukemia (ALL). The total population was 4.5 million children. Remission was achieved in 770/808 of the patients (95%). No sex difference in the remission rate was observed. The event free survival (EFS) at 102 months was 0.47 for males and 0.62 for females ($p < 0.001$). There was no difference in EFS between males and females with standard-risk (0.58 and 0.60) or intermediate-risk (0.47 and 0.60) ALL, respectively. The EFS for females with high-risk ALL (0.68) was superior to that of males with high-risk ALL (0.31). Cox multivariant analysis showed that white blood cell count, sex, age and thrombocyte count were significant prognostic factors in all children. The intensified treatment according to the prognostic factors used in this study led to equal EFS for females with ALL from all risk groups. Males with high-risk ALL, however, did not benefit from the intensified treatment. □ *Childhood leukemia, prognosis in childhood leukemia, prognostic factors*

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Progress in the therapy of children with acute lymphoblastic leukemia (ALL) is well documented. Much of the progress has been achieved as a result of risk-adjusted treatment (1). The major risk factors include total white blood cell count (WBC) and age at the time of diagnosis (1). Sex, however, is a controversial prognostic factor (1–3). This population-based study in the Nordic countries carried out by the Nordic Society of Pediatric Hematology and Oncology (NOPHO) (4) indicates that male sex ia a negative prognostic factor in children with high-risk leukemia.

Materials and methods

Non-B-cell ALL was diagnosed in 808 children aged 1–15 years between July 1, 1981 and June 30, 1986 in the five Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) with a population of 4.5 million children. Table 1 shows the clinical characteristics of females and males with ALL included in the study. The 808 patients were divided into three risk groups according to risk criteria at diagnosis (Table 2). Table 3 shows the number and percentage of patients in each risk group.

In almost all standard-risk (SR) patients, 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 treatment included three pulses of methotrexate 0.5 g/m^2 or (after July 1984) 1.0 g/m^2 and eight intrathecal doses of methotrexate (5, 6). Maintenance therapy included oral doses of mercaptopurine daily and methotrexate weekly up to 36 months after diagnosis. No reinduction was given. In a pilot study, doxorubicin was not used during induction, but iv pulses of methotrexate were added to the maintenance therapy during the first year of therapy (6). In most of the intermediate-risk (IR) children the induction therapy, its consolidation and CNS therapy were as in the SR group. However, the maintenance treatment was intensified by pulses of predinisolone and iv vincristine with or without doxorubicin or methotrexate during the first year. The high risk (HR) children were treated in different ways, using primarily the intensive protocols of Riehm et al. (7), Wollner et al. (8), Moe et al. (9), Seip (personel communication) or bone marrow transplantation after the first remission. There was no difference in treatment according to sex.

The statistical methods included Cox regression analysis (10) and life table analysis (11). Event free survival (EFS), i.e., an estimation of the proportion of children surviving in continuous complete remission in relation to the total number of children in the respective group, was used as a measure of cure rate. All children were followed up in January 1990 giving an observation time of 42–102 months.

Results

No difference between males (408/428) and females (362/380) was observed in the remission rate, achieved in

Table 1. Clinical data of patients with ALL on admission.

	Males		Females	
	n	(%)	*n*	(%)
Total number	428	(53)	380	(47)
Age (years)				
1–<2	56	(13)	51	(13)
2–<10	304	(71)	272	(72)
≥10	68	(16)	57	(15)
White blood cell ($\times 10^9$/l)				
≤10	216	(40)	217	(57)
11–≤20	53	(12)	44	(12)
21–≤50	63	(15)	62	(16)
51–≤100	46	(11)	34	(9)
>100	50	(12)	23	(6)
CNS leukemia	24	(6)	10	(3)
Mediastinal mass	47	(11)	17	(4)
T-cell leukemia	46	(11)	20	(5)

Table 2. Criteria for risk grouping of children aged over 1 year with non-B-cell ALL.

High risk (HR)	WBC > 50×10^9/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 21–50×10^9/l Age <2 years or ≥10 years and WBC ≤ 50×10^9/l
Standard risk (SR)	No HR criteria Age 2–<10 years and WBC ≤ 20×10^9/l

Table 3. Number, percentage and event free survival (EFS) of patients with ALL in each risk group. *p* indicates significance of EFS between males and females.

	Males			Females			
	n	(%)	EFS	*n*	(%)	EFS	*p*
SR	179	(41)	0.58	187	(49)	0.60	0.3
IR	114	(27)	0.47	110	(29)	0.60	0.9
HR	135	(32)	0.31	83	(22)	0.68	0.0001
Total	428		0.47	380		0.62	0.001

770/808 (95%) of the patients. The remission rate was 98% in SR (359/366), 96% in IR (214/224) and 90% in HR patients (197/218). The induction failures were due to death as a result of aplasia and/or septicemia, and were not related to the patient's sex. Cox multivariant regression analysis showed that WBC count ($p < 0.001$), sex ($p < 0.001$), age ($p < 0.004$) and thrombocyte count ($p < 0.023$) at diagnosis were significant prognostic factors. HR leukemia was diagnosed more frequently in

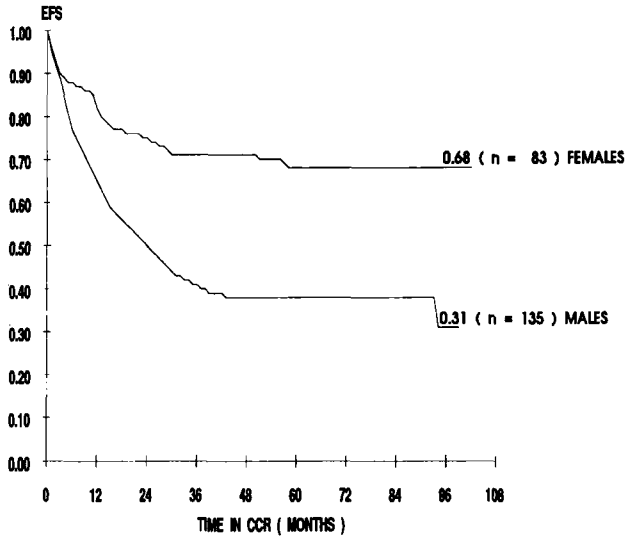

Fig. 1. Event free survival (EFS) in high-risk ALL with regard to sex ($p < 0.001$).

Table 4. Number of children who died during induction and in continuous complete remission (CCR) and localization of first relapse with regard to sex in high-risk ALL

	Males	Females	Total
Total number	135	83	218
Dead during induction	13	8	21
Dead in CCR	5	2	7
Localization of relapse			
Bone marrow	32	11	43
CNS isolated	15	3	18
Testis isolated	5	—	5
CNS combined	9	1	10
Testis combined	4	—	4
Other localization	2	1	3
CCR at follow-up	50	57	107

Table 5. Event free survival (EFS) of males and females with high-risk ALL divided into subgroups according to clinical criteria on admission. *p* indicates significance of EFS between males and females

	Males		Females		
	N	EFS	N	EFS	*p*
CNS leukemia	24	0.29	10	0.78	0.01
Mediastinal mass	47	0.38	17	0.76	0.01
T-cell ALL	46	0.41	20	0.75	0.02
HR < 2 years	9	0.20	8	0.88	0.03
HR 2–<10 years	98	0.38	60	0.70	0.002
HR ≥ 10 years	28	0.39	15	0.52	0.1

males (32% and 22%). A significant difference in EFS between males and females was observed. This was explained by the difference in prognosis in patients with HR leukemia (Table 3, Fig. 1). Of the 12 deaths in complete continuous remission, seven had HR leukemia

(Table 4). We observed isolated testicular relapse in five males. After exclusion of these five patients, the significance of sex difference in EFS remained. The males with HR ALL had a higher relapse rate in all localizations, but a significant difference was observed only in the frequency of CNS relapse (15/135 males, 3/83 females, $p < 0.01$) (Table 4). As shown in Table 5, females with HR ALL, irrespective of the type of prognostic factor, had a significantly better prognosis than males. In order to exclude the possibility that the difference was due to T-cell disease alone, a special subgroup was formed consisting of children with known non-T-cell leukemia and WBC $> 50 \times 10^9$/l as the only criteria for entering the HR group. The difference between the sexes was also significant ($p < 0.01$) in this subgroup. The difference between sexes in EFS was significant in all age groups for HR ALL, except for patients aged over 10 years at the time of diagnosis (Table 5).

Discussion

The Nordic study on ALL is population-based and includes all children suffering from ALL in the five Nordic countries. The remission rate of 95% and the EFS of the whole sample at 102 months are comparable with other recent studies (12–14). Our finding that the prognosis of females with ALL as a whole group is superior to that of males is also in agreement with some earlier studies (3, 15, 16). Risk-adjusted treatment in the Nordic countries has led to the use of more intensive induction treatment in HR patients compared to SR/IR patients. In our sample the remission rate did not differ between sexes in any of the risk groups but the EFS of males was inferior to that of females in the HR group. Intensified treatment, according to the known risk factors in females, led to equal EFS in each risk group. In HR males treated according to the same protocols, the EFS was inferior compared to that of SR and IR males, or to that of females in any risk group. Could the inferior prognosis of the male sex and the higher incidence of ALL among males have a common genetic background?

The difference in therapeutic effectiveness between females and males has been explained by more serious complications of treatment in females compared to males, indicating that females are more susceptible to treatment than males (3). The complications leading to death did not differ significantly between the sexes and could not explain the difference in EFS in our study. None of the known risk factors or high-risk criteria used in the Nordic countries could specifically explain the difference in prognosis of females and males with HR ALL. We suggest that males with HR ALL may need even more intensified treatment than females with HR ALL. Further intensification of chemotherapy may lead to unacceptable toxicity, in which case bone marrow transplantation in first remission could be an alternative in some cases. However, further investigations are needed to explain fully the sex difference in the prognosis for childhood leukemia.

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