Relapsed childhood acute lymphoblastic leukemia in the Nordic countries: prognostic factors, treatment and outcome

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	No. of patients (%)	NOPHO ALL-92 freq (%)	NOPHO ALL-2000 freq (%)	p-value	NOPHO ALL-92 5-year EFS % ± s.e.	NOPHO ALL-2000 5-year EFS % ± s.e.	p-value	NOPHO ALL-92 5-year OS % ± s.e.	NOPHO ALL-2000 5-year OS % ± s.e.	p-value
Overall	485 (17.0)	324 (19.7)	161 (14.8)		0.42 ± 0.03	0.44 ± 0.04	0.533	0.50 ± 0.03	0.53 ± 0.05	0.422
Gender										
Boys	299 (64.2)	206 (63.6)	108 (67.1)	0.447	0.42 ± 0.04	0.51 ± 0.05	0.245	0.50 ± 0.04	0.59 ± 0.06	0.114
Girls	167 (35.7)	118 (36.4)	53 (32.9)		0.41 ± 0.05	0.31 ± 0.07	0.481	0.49 ± 0.05	0.42 ± 0.08	0.416
Age at primary diagnosis										
1-9 years	388 (80.0)	257 (79.3)	131 (81.4)	0.596	0.45 ± 0.03	0.47 ± 0.05	0.536	0.54 ± 0.03	0.56 ± 0.05	0.464
≥10 years	97 (20.0)	67 (20.7)	30 (18.6)		0.30 ± 0.06	0.25 ± 0.09	0.440	0.35 ± 0.06	0.36 ± 0.09	0.813
WBC at primary diagnosis										
<50 x 10^9/l	358 (73.8)	231 (71.3)	127 (78.9)	0.139	0.47 ± 0.03	0.43 ± 0.05	0.524	0.54 ± 0.03	0.52 ± 0.05	0.702
50-99 x 10^9/l	55 (11.3)	38 (11.7)	17 (10.6)		0.37 ± 0.08	0.40 ± 0.13	0.953	0.42 ± 0.08	0.44 ± 0.14	0.655
≥100 x 10^9/l	72 (14.8)	55 (17.0)	17 (10.6)		0.26 ± 0.06	0.39 ± 0.15	0.087	0.33 ± 0.06	0.58 ± 0.12	0.126
Primary risk group[1]										
Standard risk	130 (26.8)	84 (25.9)	46 (28.6)	0.165	0.54 ± 0.05	0.55 ± 0.09	0.820	0.57 ± 0.05	0.63 ± 0.09	0.507
Intermediate risk	154 (31.8)	112 (34.5)	42 (26.1)		0.47 ± 0.05	0.42 ± 0.09	0.965	0.58 ± 0.05	0.55 ± 0.10	0.988
≥High risk	201 (41.4)	128 (39.5)	73 (45.3)		0.31 ± 0.04	0.37 ± 0.06	0.378	0.39 ± 0.04	0.50 ± 0.06	0.303
NCI risk group[2]										
Standard risk	281 (57.9)	180 (55.6)	101 (62.7)	0.132	0.51 ± 0.04	0.55 ± 0.05	0.472	0.60 ± 0.04	0.60 ± 0.05	0.618
High risk	204 (42.1)	144 (44.4)	60 (37.3)		0.31 ± 0.04	0.34 ± 0.06	0.567	0.38 ± 0.04	0.45 ± 0.07	0.366
Immuno-phenotype										
Pre-B ALL	417 (86.0)	277 (85.8)	140 (87.0)	0.129	0.46 ± 0.03	0.43 ± 0.05	0.867	0.54 ± 0.03	0.53 ± 0.05	0.946
T-cell ALL	60 (12.4)	39 (12.0)	21 (13.9)		0.15 ± 0.06	0.38 ± 0.11	0.114	0.21 ± 0.07	0.48 ± 0.11	0.076
Unknown	8 (1.6)	8 (2.5)	0		-	-	-	-	-	-
Cytogenetics[3]										

Unfavorable	28 (5.8)	15 (4.6)	13 (8.1)	0.001	0.33 ± 0.12	0.08 ± 0.07	0.376	0.33 ± 0.06	0.15 ± 0.10	0.252
Favorable	173 (35.7)	105 (32.4)	68 (42.2)		0.46 ± 0.05	0.50 ± 0.07	0.345	0.57 ± 0.05	0.59 ± 0.07	0.326
Other	123 (25.4)	77 (23.8)	46 (28.6)		0.36 ± 0.06	0.42 ± 0.08	0.693	0.46 ± 0.06	0.54 ± 0.08	0.815
Normal/missing	161 (33.2)	127 (39.2)	34 (21.1)		0.44 ± 0.04	0.44 ± 0.10	0.941	0.50 ± 0.05	0.52 ± 0.11	0.515
Site of relapse										
Bone marrow	300 (61.9)	205 (63.3)	95 (59.0)	0.514	0.37 ± 0.03	0.39 ± 0.06	0.957	0.46 ± 0.04	0.41 ± 0.06	0.763
Combined	82 (16.9)	55 (17.0)	27 (16.8)		0.44 ± 0.07	0.34 ± 0.12	0.945	0.52 ± 0.07	0.55 ± 0.12	0.413
Extramedullary	103 (21.2)	64 (19.8)	39 (24.2)		0.56 ± 0.06	0.54 ± 0.09	0.947	0.63 ± 0.06	0.76 ± 0.07	0.584
Time to relapse										
<18 months	104 (21.4)	67 (20.7)	37 (23.0)	0.089	0.21 ± 0.05	0.22 ± 0.07	0.516	0.22 ± 0.05	0.32 ± 0.08	0.161
18-36 months	149 (30.7)	91 (28.1)	58 (36.0)		0.29 ± 0.04	0.50 ± 0.07	0.010	0.39 ± 0.05	0.61 ± 0.07	0.020
≥36 months	232 (47.8)	166 (51.2)	66 (41.0)		0.63 ± 0.04	0.50 ± 0.09	0.172	0.72 ± 0.04	0.55 ± 0.10	0.221
Relapse risk group										
Standard-risk	293 (60.4)	201 (62.0)	92 (57.1)	0.299	0.56 ± 0.04	0.58 ± 0.06	0.063	0.65 ± 0.03	0.66 ± 0.06	0.058
High-risk	192 (39.6)	123 (38.0)	69 (42.9)		0.20 ± 0.04	0.33 ± 0.06		0.26 ± 4.0	0.39 ± 0.06	
Secondary events										
Alive in CR2	204 (42.1)	123 (38.3)	66 (49.7)	0.028	-	-	-	-	-	-
Second relapse	186 (38.4)	135 (41.7)	49 (31.7)		-	-	-	-	-	-
Dead in ≤ CR2	84 (17.3)	55 (17.0)	27 (18.0)		-	-	-	-	-	-
SMN	11 (2.3)	10 (3.1)	1 (0.7)		-	-	-	-	-	-

Table A. Characteristics of patients that relapsed after initial NOPHO ALL-92 and ALL-2000 protocol treatment, five year event-free survival (5-year EFS) and five year overall survival (5-year OS) according to presenting features at diagnosis and at relapse. Patients undergoing stem cell transplantation in first complete remission (n=31) are excluded. [1]Standard Risk (SR), Intermediate Risk (IR), ≥ High Risk (HR). The ≥HR group contains patients initially stratified to the NOPHO ALL-92 and ALL-2000 Intensive, Very Intensive and Extra Intensive arms. [2] National Cancer Institute (NCI) standard risk group: WBC count less than 50,000/μL and age 1 to younger than 10 years, NCI high risk group: WBC count 50,000/μL or greater and/or age 10 years or older. [3] Unfavorable cytogenetics: MLL rearrangements n=7, hypodiploidy n=10, t(9;22) n=5, t(1;19) n=6, Favorable cytogenetics: High hyperdiploidy n=106, t(12;21) n=67. Hypodiploidy: modal chromosomal number <45. High hyperdiploidy: modal chromosomal number >50.

Definition of relapse and second complete remission

Bone marrow relapse was not uniformly defined, since there was no common relapse-protocol. However, there has been a Nordic consensus to define bone marrow relapse as reappearance of ≥5% of lymphoblasts in the bone marrow, confirmed by flow-cytometry. Central nervous system (CNS) relapse was defined as ≥5 lymphoblasts per µl of cerebrospinal fluid. Since data on MRD were only available for a very limited number of patients, M1 marrow status (<5% lymphoblasts in bone marrow) together with restoration of hematopoiesis has generally defined complete remission after relapse diagnosis.

Hematopoietic stem cell transplantation in second complete remission

We used two different methods to estimate the association of HSCT on survival. First, we excluded patients that died before reaching CR2 since they were not eligible for HSCT at the time of death (n=44). Furthermore, patients that only received chemotherapy but died in CR2 before the median time from relapse diagnosis to HSCT (landmark day 162, n=15) were also excluded in the Kaplan-Meier survival analyses. This was done to avoid the overestimation of the effect of HSCT on survival since patients who died in the post-induction phase or the HSCT conditioning phase were not coded as HSCT patients in the NOPHO ALL registry. Analyzing patients from the Intention to Treat (ITT) perspective would have been the method of choice but information on ITT in the ALL registry was not reliable in all cases. The information was missing in a large number of patients and the ITT is likely to have changed during the course of the treatment. Furthermore, since the criteria for HSCT in CR2 were not universal the decision of performing HSCT was often made on individual basis. For the second subgroup analysis of the standard-risk patients we used a stratified Cox proportional hazards regression model and included HSCT in CR2 as a time-dependent covariate instead of excluding patients by the landmark method.

Isolated extramedullary relapses			
Time to relapse	**Very early** **<18 months from diagnosis** freq (%)	**Early** **18-36 months from diagnosis** freq (%)	**Late** **≥36 months from diagnosis** freq (%)
Total n=103	27	48	28
Primary risk group			
Standard risk	2 (7.4)	23 (47.9)	13 (46.4)
Intermediate risk	0	16 (33.3)	11 (39.3)
≥ High risk	25 (92.6)	9 (18.8)	4 (14.3)
CNS involvement at diagnosis			
Yes	9 (33.3)	1 (2.1)	0
No	18 (66.6)	47 (97.9)	28 (100)
Site of relapse			
CNS	22 (81.5)	39 (81.3)	11 (39.3)
Testicular	1 (3.7)	5 (10.4)	11 (39.3)
Other	3 (11.1)	2 (4.2)	5 (17.9)
CNS + other	1 (3.7)	2 (4.2)	1 (3.6)
Relapse treatment			
NOPHO HR	7 (25.9)	11 (22.9)	5 (17.9)
ALL-REZ BFM	14 (51.9)	32 (66.7)	17 (66.7)
RALLE	1 (3.7)	3 (6.3)	0
Other	5 (18.5)	2 (4.2)	6 (21.4)
HSCT in CR2			
Yes	11 (40.7)	13 (27.1)	4 (14.3)
No	16 (59.3)	35 (72.9)	24 (85.7)

Table B. Description of patients with isolated extramedullary relapses. Very early relapses: occurring <18 months from primary diagnosis. Early relapses: occurring ≥18 months from diagnosis and <6 months after completion of primary therapy. Late relapses: occurring ≥6 months after completion of primary therapy. NOPHO High Risk (HR) arms, ALL-REZ Berlin Frankfurt Münster (BFM) relapse protocols, Relapse in Acute Lymphoblastic Leukemia (RALLE) pilot protocol, "Other treatment"; combinations of protocols, the Children´s Cancer and Leukemia Group (CCLG) ALLR3 relapse protocol, Children´s Cancer Group (CCG) relapse protocols and non-protocol treatment. HSCT in CR2: Hematopoietic stem cell transplantation in second complete remission.

Relapse period	1992-2001 freq. (%)	2002-2011 freq. (%)	p-value
Total number	239	246	
Primary risk group			
Standard risk	51 (21.3)	79 (32.1)	0.01
Intermediate risk	75 (31.4)	79 (32.1)	
≥ High risk	113 (47.3)	88 (35.8)	
Immunophenotype			
Pre-B ALL	197 (82.4)	220 (89.4)	0.062
T-cell ALL	36 (15.1)	24 (9.8)	
Unknown	6 (2.5)	2 (0.8)	
Site of relapse			
Bone marrow	148 (61.9)	152 (61.8)	0.732
Combined	43 (18.0)	39 (15.9)	
Extramedullary	48 (20.1)	55 (22.4)	
Time to relapse			
<18 months	64 (26.8)	40 (16.3)	0.002
18-36 months	78 (32.6)	71 (28.9)	
≥36 months	97 (40.6)	135 (54.9)	
Relapse risk group[1]			
Standard-risk	126 (52.7)	167 (60.4)	0.001
High-risk	113 (47.3)	79 (32.1)	

Table C. Pattern of relapse compared between the relapse periods 1992-2001 and 2002-2011. [1]Relapse risk groups according to the IntReALL trial.