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ORIGINAL ARTICLE

Results of NOPHO ALL2008 treatment for patients aged 1–45 years with acute lymphoblastic leukemia

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Adults with acute lymphoblastic leukemia (ALL) do worse than children. From 7/2008 to 12/2014, Nordic and Baltic centers treated 1509 consecutive patients aged 1–45 years with Philadelphia chromosome-negative ALL according to the NOPHO ALL2008 without cranial irradiation. Overall, 1022 patients were of age 1–9 years (A), 266 were 10–17 years (B) and 221 were 18–45 years (C). Sixteen patients (three adults) died during induction. All others achieved remission after induction or 1–3 intensive blocks. Subsequently, 45 patients (12 adults) died, 122 patients relapsed (32 adults) with a median time to relapse of 1.6 years and 13 (no adult) developed a second malignancy. Median follow-up time was 4.6 years. Among the three age groups, older patients more often had higher risk ALL due to T-ALL (32%/25%/9%, $P < 0.001$), *KMT2A* rearrangements (6%/5%/3%, $P < 0.001$) and higher day 29 residual leukemia for B-lineage ($P < 0.001$), but not T-ALL ($P = 0.53$). Event-free survival rates ($pEFS_{5y}$) were 89 ± 1% (A), 80 ± 3% (B) and 74 ± 4% (C) with significant differences only for non-high risk groups. Except for thrombosis, pancreatitis and osteonecrosis, the risk of 19 specified toxicities was not enhanced by age above 10 years. In conclusion, a pediatric-based protocol is tolerable and effective for young adults, despite their increased frequency of higher risk features.

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INTRODUCTION

The cure rate for childhood acute lymphoblastic leukemia (ALL) is above 85% with the best contemporary treatment,[1] whereas outcome for ALL in adults has lagged significantly behind despite intensified chemotherapy and frequent use of hematopoietic stem cell transplantation (hSCT).[2–5] The use of pediatric-inspired treatment regimens has provided improvement for young adult patients,[6–11] but the upper age limit for tolerance to such intensive antileukemic therapy is still uncertain, and the higher risk of relapse for adults with ALL has led to extensive use of hSCT. When relapse or refractory disease occurs in adults, the outcome is dismal.[12] The superior cure rate for children[13] has been suggested to reflect differences in disease biology, including molecular genetics,[14] drugs administered, as well as patient adherence to treatment guidelines.[15] However, reliable comparisons of outcome have been hampered by the use of different diagnostic strategies, risk-grouping criteria and treatment protocols. To overcome these obstacles, common diagnostic work-up, risk grouping and therapy for newly diagnosed Philadelphia chromosome-negative patients aged 1–45 years with ALL since July 2008 have been implemented with the use of the NOPHO ALL2008 protocol in Denmark, Estonia, Finland (adults included from 2015), Iceland (children only), Lithuania, Norway and Sweden.[16,17] Diagnostics, treatment, toxicity and outcome data are prospectively registered in a common database.[17] We here present cure and toxicity rates in risk group-stratified analyses for 1509 childhood, and adult ALL patients reported as an observational study.

MATERIALS AND METHODS

Patients

From July 2008 to December 2014, the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol has recruited newly diagnosed patients aged 1–45 years with Philadelphia chromosome-negative B-cell precursor (BCP) or T-lineage ALL. Patients with Down's syndrome were excluded. The protocol did not open simultaneously in all centers, but once opened, all consecutive patients were included (Supplementary Table S1; Supplementary Appendix, page 2). The 1509 study patients (Figure 1) were registered in a common database and systematically updated with respect to disease characteristics, treatment response, outcome and 19 pre-selected toxicities at least every 3 months. Adherence to the protocol was facilitated by online data entry at diagnosis, treatment day 15, end of induction (day 29) and at the end of early

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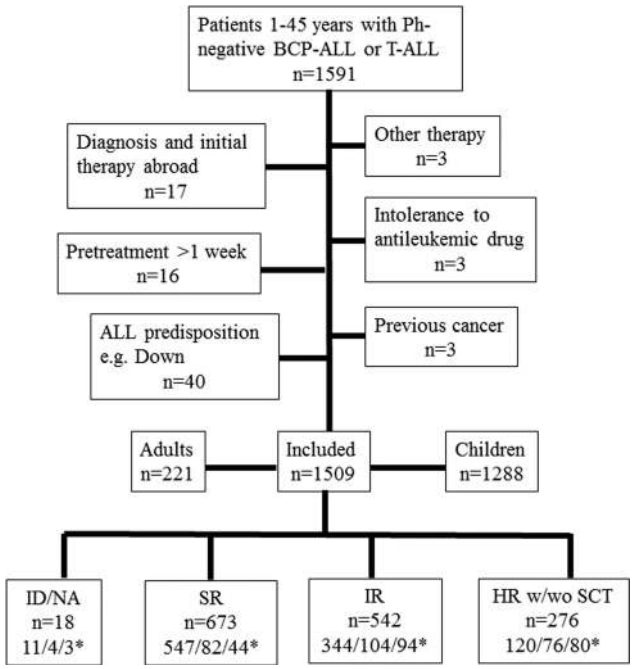


Figure 1. Consort diagram ALL patients 1–45 years. Stem cell transplantation was optional for patients with hypodiploidy. ID, induction death; NA, not available for risk grouping. *Number of patients in age groups 1–9/10–17/18–45 years.

consolidation (day 79), which then automatically provided information to the treating physician on protocol risk-group assessment and treatment allocation. In addition, patient-related questions from any participating center could be entered into an online 'help-desk' function, which were distributed by automated e-mails to all national pediatric and adult NOPHO ALL2008 principal investigators with rapid online feedback including treatment recommendations to the treating center. The regional or national ethics committees approved the protocol, and informed consent was obtained according to the Declaration of Helsinki. Adult and Baltic patients did not participate in the three randomized studies (Supplementary Table S2; Supplementary Appendix, page 4) registered with Eudract number 2008-003235-02 and at clinicaltrials.gov (NCT01678508, NCT00819351, NCT00991744).

Protocol design

NOPHO ALL2008 remission induction therapy and risk-group stratification. On the basis of leukemia characteristics at diagnosis and minimal residual disease in bone marrow (MRD) after induction therapy (vincristine, doxorubicin, glucocorticosteroid, intrathecal methotrexate) on days 15 and 29, and after consolidation therapy day 79 (or after HR-ALL blocks A1 and B1, see below), patients were assigned to standard risk (SR), intermediate risk (IR), high risk (HR), or HR therapy with hSCT indicated by poor response at MRD time points day 29 (⩾5%) or day 79 or post-block B1 (⩾0.1%) (Figures 1 and 2).[16] Except for a difference in the capping dose of vincristine (2.5 mg for patients <18 years at diagnosis; otherwise 2 mg) and an option for adult patients to be offered hSCT in case of translocation *t*(4;11)[*KMT2A/AFF1*], the treatment within each risk group was independent of patient age. Patients with SR and IR ALL received conventional post-induction ALL therapy with one or two delayed intensifications, respectively, whereas patients with HR-ALL received seven to nine very intensive ALL blocks in addition to delayed intensification and maintenance therapy. The number of HR blocks was determined by MRD after block A1. If MRD was $<0.1\%$, the patients received seven HR blocks in total (only one C block) otherwise they continued with all nine blocks. The criteria for hSCT were MRD day 29 $\geqslant 5\%$, day 79 $\geqslant 0.1\%$ or post-block B1 $\geqslant 0.1\%$. It was optional for adult clinicians to transplant patients with hypodiploidy or *KMT2A-r*. For patients allocated to HR or HR with hSCT therapy, the first three blocks would always be A1-B1-C1.

Oral mercaptopurine/methotrexate maintenance therapy was for all non-transplanted patients continued until 2.5 years from diagnosis (Supplementary Table S3; Supplementary Appendix, page 8). MRD was measured by RQ-PCR-based techniques using patient-specific clonal Ig/TCR gene rearrangements according to the BIOMED-2 guidelines[18,19] and/or by flow cytometry using protocol-defined six-color MRD panels for identification and monitoring of leukemia-associated immunophenotypes as defined by the NOPHO ALL-2000 guidelines.[20] According to the NOPHO ALL2008 protocol, BCP-ALL was risk group stratified by flow cytometry, and T-ALL by PCR assessment of clonal immune gene rearrangements, if informative markers were available (otherwise the alternative method was used).

Statistical analysis

Differences in the distribution of individual parameters were analyzed using the χ^2 test or Fisher's exact test for categorical variables and one-way ANOVA for continuous variables. Spearman's correlation coefficient (r_s) was used to identify possible associations for continuous variables. The Kaplan–Meier method was used to estimate probability of event-free survival (pEFS) and overall survival (pOS) rates, and differences were compared with the 2-sided log-rank test. For the HR-hSCT group lack of harmonized strategies across both pediatric and adult centers for donor identification, conditioning regimens and supportive care were missing which hampers reliable outcome analyses. The HR and HR-hSCT patients were thus pooled (HR w/wo hSCT) and the follow-up of patients stratified to hSCT was truncated 2 weeks prior to the hSCT date in the combined survival analyses. The duration of EFS was defined as the time from diagnosis until first occurrence of induction death, relapse, death in remission, development of a second malignancy, date of hSCT minus 2 weeks for the HR-hSCT patients or the last known follow-up for patients without events. The duration of OS was defined as time from diagnosis to death. Death in complete remission (DRC1) was defined as death without evidence of leukemia or a second malignancy. The Cox proportional hazard model was used for calculating hazard ratios (HR) with corresponding confidence limits with Wald test for *P*-values.

For patients in complete remission, the cumulative risk of any relapse, of isolated central nervous system (CNS), testicular relapse, therapy-related second malignancy or of toxic death were estimated by using a cumulative incidence perspective treating the events as competing events. *P*-values were calculated using the Gray's test. For regression modeling, a Fine-Gray model was used for calculating parameter estimates and *P*-values.[21]

Patients could change risk-group allocation until treatment day 79 (or post-block B1 for HR-ALL). When analyzing time to event within a risk group, patients were censored when allocated to another risk group and had entry to the new risk group at allocation. Equally in analyses on the entire cohort adjusting for risk-group allocation, risk-group allocation was treated as a time-dependent covariate.

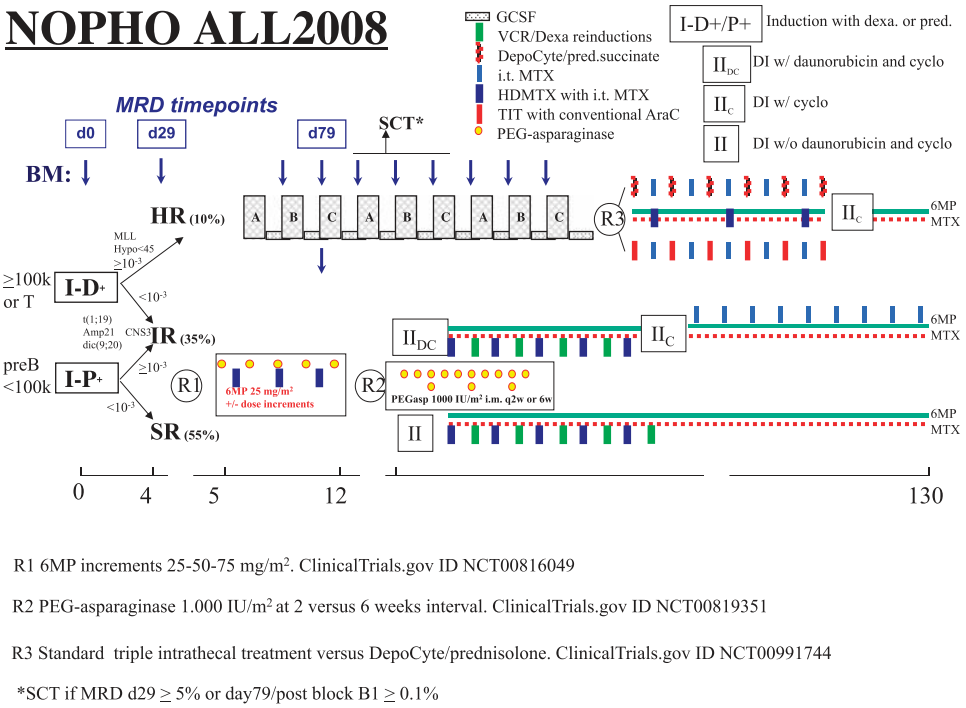
The proportional hazard assumptions were investigated using scaled Schoenfeld residuals. All the analyses were based on intention to treat. Statistical examination was carried out using the R (R Foundation for Statistical Computing, Vienna, Austria) version 3.2.3 and Statistical Packages for Social Sciences (SPSS, Chicago, IL, USA) software, version 22.0.0. Fine-Gray models and calculations including time-dependent covariates were performed using the R 'survival' package. All tests were two-sided with $P < 0.05$ considered statistically significant.

RESULTS

Of 834 males and 675 females, 1278 had BCP-ALL and 231T ALL (Table 1). T-ALL was rarer in patients aged 1–9 years than those aged 10–17 and 18–45 years (9, 25 and 32%; $P < 0.001$), with no significant difference between the two oldest age groups ($P = 0.09$). Age and WBC at diagnosis were inversely correlated in both BCP-ALL ($r_s = -0.17$, $P < 0.001$) and T-ALL ($r_s = -0.28$; $P < 0.001$). Among BCP-ALL patients, the three age groups did not differ with regard to the proportion of patients with WBC $\geqslant 100 \times 10^9$ per liter (8%, 9%, 9%, $P = 0.85$), whereas the fraction of T-ALL patients with WBC $\geqslant 100 \times 10^9$ per liter decreased significantly with increasing age (55%, 40%, 30%; $P = 0.006$). The presence of risk stratifying karyotypes differed significantly between the three age groups (Table 1).

Risk-group distribution

Owing to a higher frequency of T-cell ALL, *KMT2A-r* and poorer MRD response to induction therapy (Figure 3a), older patients were more



R1 6MP increments 25-50-75 mg/m^2. ClinicalTrials.gov ID NCT00816049

R2 PEG-asparaginase 1.000 IU/m^2 at 2 versus 6 weeks interval. ClinicalTrials.gov ID NCT00819351

R3 Standard triple intrathecal treatment versus DepoCyte/prednisolone. ClinicalTrials.gov ID NCT00991744

*SCT if MRD d29 ≥ 5% or day79/post block B1 ≥ 0.1%

Figure 2. NOPHO 2008 protocol overview. MRD, minimal residual disease; BM d0, 15, 29 and 79, bone marrow day 0, 15, 29, 79; PreB precursor, B-ALL; T, T-ALL; I-D, induction with dexamethasone; I-P, induction with prednisolone; DI, delayed intensification; SR, standard risk; IR, intermediate risk; HR, high risk; SCT, hematopoietic stem cell transplantation; HD MTX, high-dose methotrexate; 6MP, 6-mercaptopurine; VCR, vincristine; AraC, cytarabine; Dexa, dexamethasone; pred, prednisolone; TIT, triple intrathecal treatment.

often allocated to higher risk groups (Table 1; Supplementary Figure S1; Supplementary Appendix, page 15). Thus, 53.5% of all children < 10 years of age were stratified to SR therapy and 11.7% to HR w/wo hSCT, whereas only 20% of adults were stratified to SR therapy, but 31% to HR w/wo hSCT (Figure 3b).

Hematopoietic stem cell transplantation

One hundred patients were eligible for hSCT in first remission based on MRD levels measured on day 29/post A1 ($n = 61$) or day 79/post-B1 ($n = 39$). Of these 100 patients, 18 were not transplanted due to relapse ($n = 3$) or death in remission before hSCT could be performed ($n = 2$), no available donor ($n = 1$), >6 months to identify a donor and hSCT was then not chosen ($n = 1$), severe invasive fungal infection ($n = 2$), parents' refusal ($n = 1$) or the patient was treated as IR ($n = 7$) or HR ($n = 1$) due to decision by the treating physician because of MRD borderline values for risk-group assignment. Only one of the latter eight patients had a relapse. The median time from diagnosis to transplantation for the remaining 82 hSCT patients was 175 days and not influenced by age group ($P = 0.55$).

In addition, three patients with hypodiploidy (two adults and one child) and six patients with *KMT2A-r* (four adults and two children) were transplanted at the discretion of the treating physician, none of whom had an MRD indication for hSCT.

An additional 16 patients not fulfilling the protocols transplantation criteria were transplanted due to (i) MRD being only just below the threshold on day 29 ($n = 2$) or after day 79/post-B1 (or later) ($n = 7$), (ii) severe toxicity during block treatment ($n = 1$), strong request by an HR adult patient ($n = 1$), (iii) T-ALL with day 29 PCR-based MRD >5% but flow cytometry-based MRD <5% ($n = 3$), (iv) classification as hypodiploidy although with an incomplete karyotype harboring *t*(12;21)[*ETV6/RUNX1*] with DNA-index of 1 by flow cytometry ($n = 1$) or (v) severe and persistent bone marrow aplasia after the B2 HR block ($n = 1$). No change in the overall pEFS was found when these 16 patients were censored at the time of hSCT.

Events

After a median follow-up for patients in first remission of 4.6 years (IQR range: 3–6.4 years), the 5-year pEFS ($pEFS_{5y}$) and overall survival for the whole cohort was 85 ± 1% and 91 ± 1%, respectively (Figure 4a; Table 2). The risk of induction death ($N = 16$, three adults) did not differ significantly between the three age groups ($P = 0.87$). Of the remaining 1493 patients, one patient moved abroad during induction therapy, four patients had no MRD marker and two patients could not be risk grouped because of profound treatment changes including severe delays in therapy due to toxicity, and all other patients achieved complete remission (MRD <5%) after induction therapy ($n = 1376$), post HR block A1 (including patients shifted directly to block therapy day 15; $n = 85$), post HR block B1 ($n = 21$) or post HR block C1 ($n = 4$). No patient died during block therapy prior to obtaining complete remission. The 45 patients who died during remission were skewed towards patients older than 10 years ($P = 0.008$) in overall but not in risk group-adjusted analyses ($P = 0.19$).

Despite risk group-adapted therapy, the stratifying parameters (except for IR stratifying cytogenetics and *KMT2A-r* ($P = 0.059$)) were significantly associated with inferior EFS in univariate analyses, that is, higher white blood cell count (WBC) ($P < 0.001$), T-ALL immunophenotype ($P < 0.001$), CNS involvement ($P = 0.022$) and hypodiploidy ($P < 0.001$). These parameters co-varied significantly with each other (Supplementary Table S4; Supplementary Appendix, page 16)

In total, 122 patients developed a relapse after a median of 1.6 years (range: 0.11–6.6 years) from diagnosis (Table 2) of which 34 (30%) involved the CNS (22 isolated) with no significant difference in CNS involvement between age groups (overall $P = 0.12$).

The impact of age on pEFS and relapse risk differed between risk groups (Figure 4a). In both the SR and IR group, adults did significantly worse than patients aged 1–9 years of age, but did not differ significantly from patients aged 10–17 years (Figure 4a). For the HR patients with or without an indication for hSCT, no significant difference in $pEFS_{5y}$ was seen between the three age

Table 1. Demographic data for 1509 ALL patients aged 1–45 years

Age group	*1–9*	*10–17*	*18–45*	*All*	P	*pEFS ± s.e. (5 years)*
All	1022 (67.7%)	266 (17.6%)	221 (14.6%)	1509 (100%)		0.84 ± 0.01
Sex						
Male	538 (52.6%)	160 (60.2%)	136 (61.5%)	834 (55.3%)	0.012	0.84 ± 0.01
Female	484 (47.4%)	106 (39.8%)	85 (38.5%)	675 (44.7%)		0.84 ± 0.02
Cell lineage						
BCP	929 (90.9%)	199 (74.8%)	150 (67.9%)	1278 (84.7%)	< 0.001	0.86 ± 0.01
T	93 (9.1%)	67 (25.2%)	71 (32.1%)	231 (15.3%)		0.74 ± 0.03
WBC						
< 100	897 (87.8%)	221 (83.1%)	182 (84.3%)	1300 (86.4%)	0.094	0.86 ± 0.01
⩾ 100	125 (12.2%)	45 (16.9%)	34 (15.7%)	204 (13.6%)		0.70 ± 0.03
WBC[a]	11.8 (4.9; 40.8)	9.7 (4; 59.6)	12.8 (4.1; 46.3)	11.6 (4.6; 44)	0.92	—
Missing[b]	0	0	1	1		
WBC (BCP)	9.9 (4.6; 30.4)	8.1 (3.5; 30.1)	6.8 (2.9; 27)	9.1 (4.2;30)	0.013	—
Missing	0	0	1	1		
WBC (T)	134 (40;316)	71.7 (8.8; 249)	38.8 (14.4; 112)	76.3 (18.6; 226)	< 0.001	—
Hgb (g/l)[a]	72 (57; 87)	87 (70; 108)	96 (79; 118)	78 (61; 95)	< 0.001	—
Missing	1	0	2	3		
Platelets[a]	43 (20; 103)	55 (27; 118)	55 (26; 117)	47 (26; 115)	0.004	—
Missing	0	0	2	2		
CNS status						
CNS 1	888 (87.1%)	233 (87.9%)	198 (92.1%)	1319 (88%)	0.12	0.85 ± 0.01
CNS 2	91 (8.9%)	17 (6.4%)	11 (5.1%)	119 (7.9%)		0.80 ± 0.04
CNS 3	40 (3.9%)	15 (5.7%)	6 (2.8%)	61 (4.1%)		0.72 ± 0.06
Missing	3	1	6	10		
t(12;21)						
Present	287 (28.5%)	16 (6.1%)	4 (1.9%)	307 (20.8%)	< 0.001	0.91 ± 0.02
Absent	720 (71.5%)	246 (93.9%)	204 (98.1%)	1170 (79.2%)		0.82 ± 0.01
Not analyzed	13	4	10	27		
Missing	2	0	3	5		
Hyperdiploid						
Present	336 (38.4%)	42 (19.4%)	23 (13%)	401 (31.6%)	< 0.001	0.88 ± 0.01
Absent	540 (61.6%)	174 (80.6%)	154 (87%)	868 (68.4%)		0.82 ± 0.01
Not analyzed	22	5	14	41		
Missing	124	45	30	199		
t(1;19)						
Present	32 (3.1%)	9 (3.4%)	9 (4.2%)	50 (3.3%)	0.72	0.96 ± 0.03
Absent	986 (96.9%)	257 (96.6%)	203 (95.8%)	1446 (96.7%)		0.84 ± 0.01
Not analyzed	4	0	7	11		
Missing	0	0	2	2		
iAmp21						
Present	15 (1.5%)	15 (5.8%)	4 (2%)	34 (2.3%)	< 0.001[c]	0.61 ± 0.12
Absent	984 (98.5%)	244 (94.2%)	197 (98%)	1425 (97.7%)		0.85 ± 0.01
Not analyzed	22	7	18	47		
Missing	1	0	2	3		
dic(9;20)						
Present	22 (2.2%)	1 (0.4%)	2 (1.1%)	25 (1.7%)	0.11[c]	0.89 ± 0.08
Absent	975 (97.8%)	260 (99.6%)	187 (98.9%)	1422 (98.3%)		0.84 ± 0.01
Not analyzed	24	5	29	58		
Missing	1	0	3	4		
KMT2A-r						
Present	29 (2.8%)	14 (5.3%)	14 (6.5%)	57 (3.8%)	0.015	0.71 ± 0.06
Absent	990 (97.2%)	252 (94.7%)	201 (93.5%)	1443 (96.2%)		0.85 ± 0.01
Not analyzed	3	0	6	9		
Hypodiploidy [d]						
Present	11 (1.1%)	7 (2.7%)	4 (1.9%)	22 (1.5%)	0.13	0.56 ± 0.11
Absent	1008 (98.9%)	256 (97.3%)	144 (98.4%)	1473 (98.5%)		0.84 ± 0.01
Not analyzed	3	3	8	14		

Abbreviations: 5y, five year; ALL, acute lymphoblastic leukemia; BCP, B-cell precursor; CNS, central nervous system; dic(920), dicentric chromosomal aberration (920); EFS, event-free survival; Hgb, hemoglobin; iAmp21, intrachromosomal amplification of chromosome 21; *KMT2A*-r, lysine [K]-specific methyltransferase 2A; s.e., standard error; *t*(119), translocation (119); WBC, white blood cell count. [a]Median (IQR) and one-way ANOVA. [b]One patient has missing value for but confirmed from center to be below 100. [c]Fisher's exact test due to low cell counts. [d]Hypodiploidy, according to karyotype and DNA-index by flow cytometry. Tests are χ^2 except when stated otherwise. Unknown and missing patient status is not included in analyses.

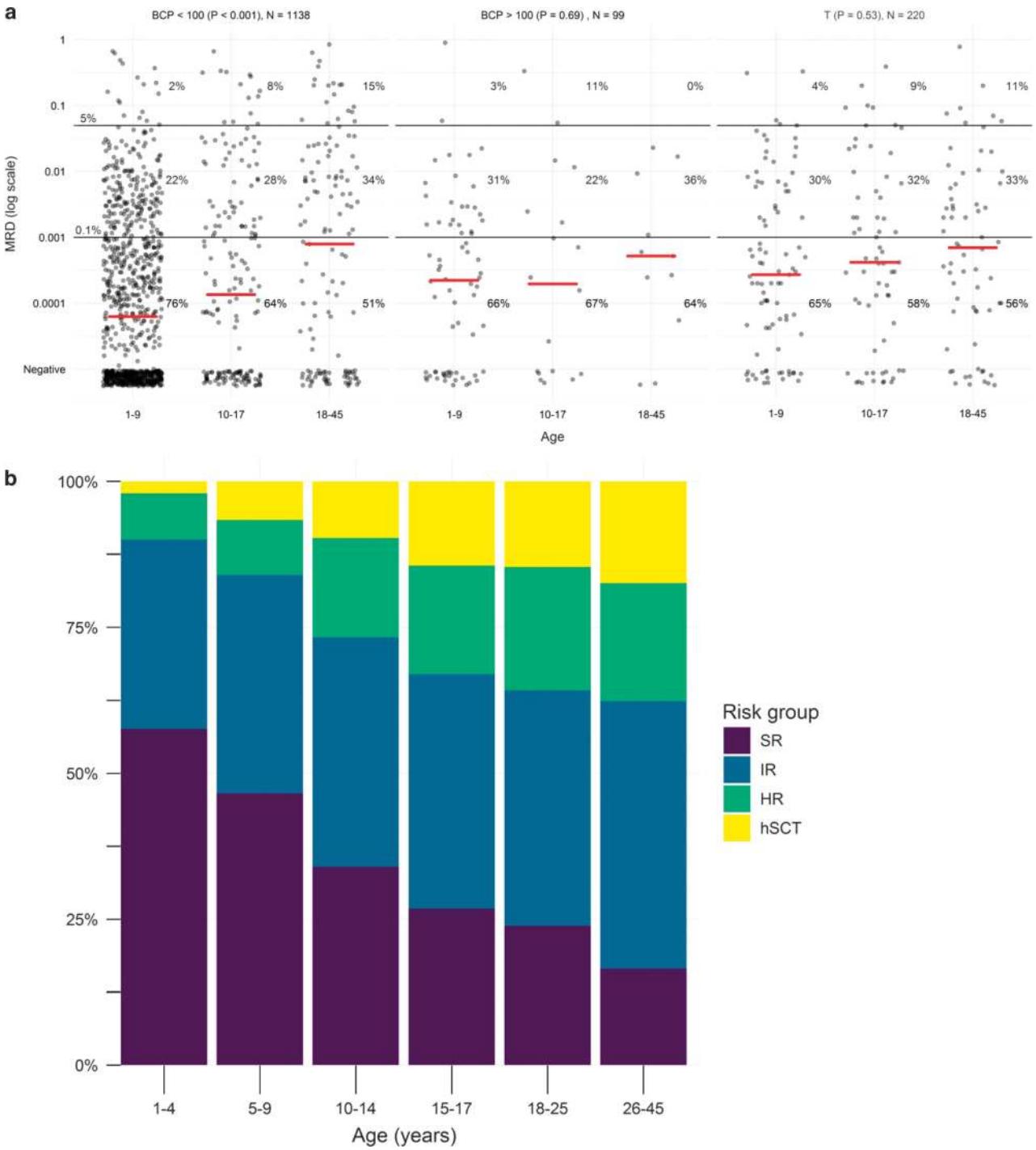
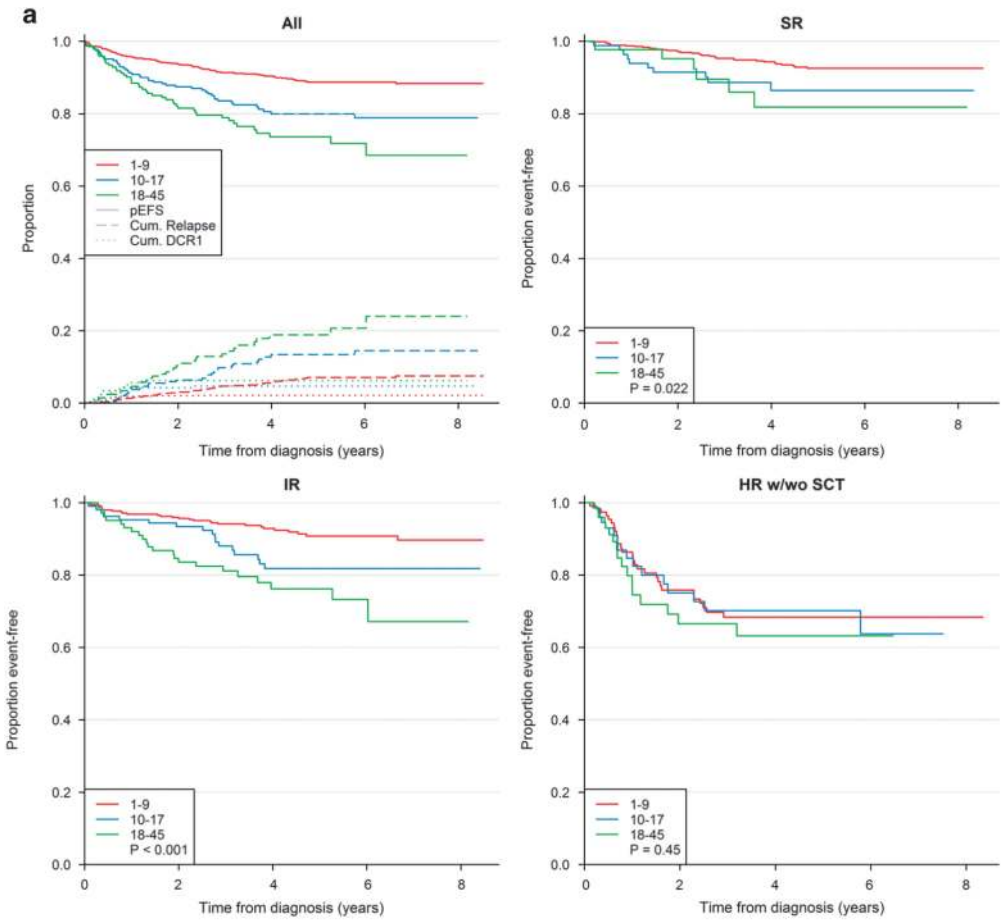


Figure 3. Early response (**a**) and risk-group distribution (**b**). (**a**) MRD day 29/post-block A1. Of 1509 patients, 16 suffered from induction death, 2 were without risk groups, 7 had no MRD value day 29/post-block A1 and 27 have missing exact values. MRD values of 10^{-5} or lower are considered MRD negative. (**b**) Final risk group distribution d79/post-block B1 for six age groups: 1–4, 5–9, 10–14, 15–17, 18–25 and 26–45 years. Standard risk (SR), intermediate risk (IR), high risk (HR) and high risk with stem cell transplantation in first remission (SCT).

groups ($pEFS_{5y}$: 70 ± 4%, 70 ± 5%, 61 ± 6%, respectively, $P = 0.45$). When comparing the HR patients who had survived until the median time to hSCT (175 days) and who had or had not an indication for hSCT, we found no difference in their $pEFS_{5y}$, and that was the case both for patients aged 1–17 years (79 ± 6% vs 71 ± 4%, $P = 0.23$) and for adults (68 ± 7% vs 60 ± 11%, $P = 0.96$). Furthermore, we found no overall significant difference between transplanted children and adults ($P = 0.2$) and no difference between non-transplanted children and adults in the HR group ($P = 0.57$). Regarding treatment-related mortality (TRM), the transplanted cohort was small ($n = 82$ of which $n = 55$ were 1–17 years, $n = 27$ were 18–45 years) and data should be interpreted with caution. In this study, we found no difference in TRM for children aged 1–17 years who were transplanted compared with non-transplanted children (9 ± 4% vs 7 ± 2%, $P = 0.73$) and no difference in the adult group either (0 ± 0% vs 10 ± 4%, $P = 0.1$). In addition, there was no difference between children and adults in neither the transplanted group ($P = 0.11$) nor the non-transplanted group



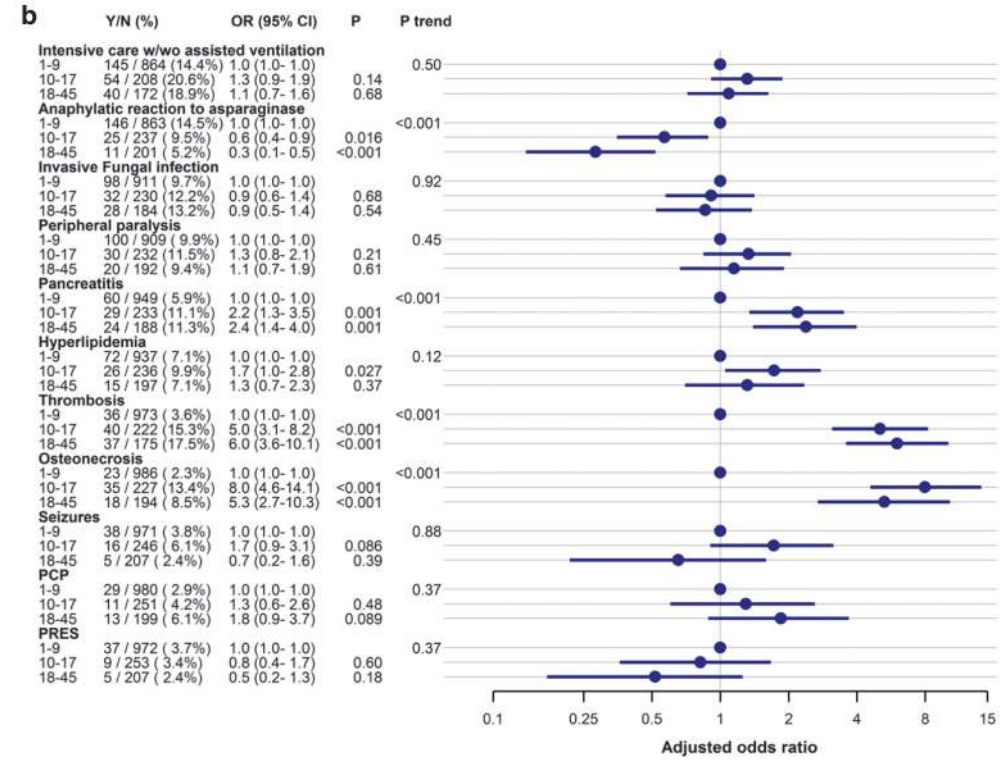


Figure 4. Response (**a**) and toxicity (**b**). (**a**) Projected event-free survival (pEFS), cumulative relapse and cumulative death in complete first remission (Cum. DCR1) in 1509 patients. Projected event-free survival (pEFS) in the four risk groups (**b**). Distribution of the 11 most common registered toxicities ($n > 50$ observations), odds ratio (OR) and trend analysis with confident intervals and *P*-values adjusted for risk group. PCP, *Pneumocystis pneumonia*; PRES, posterior reversible encephalopathy syndrome.

Table 2. Treatment outcome, pEFS, OS and cumulative risks for 1509 ALL patients aged 1–45 years

Age group	*1–9*	*10–17*	*18–45*	*Total*	*P*[a]
N	1022	266	221	1509	
Continuous CR1	920	220	174	1314	
Induction death (ID)	10	3	3	16	
Relapse					
BM only	31	16	16	63	
CNS only	11	7	4	22	
Testis only	0	0	3	3	
BM+CNS	9	1	0	10	
BM+T	1	0	0	1	
BM+CNS+T	2	0	0	2	
BM+other	0	0	3	3	
Other	1	1	1	3	
Total relapse	61	29	32	122	
SMN	10	2	0	12	
DCR1	21	12	12	45	
Median follow-up (years)[b]	4.9	4.6	3.2	4.6	
Induction death	0.01 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.00	0.87
Relapse CNS (5 years)	0.01 ± 0.00	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.00	0.12
Relapse other/BM (5 years)	0.06 ± 0.01	0.10 ± 0.02	0.16 ± 0.03	0.08 ± 0.01	< 0.001
SMN (5 years)	0.01 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.00	0.42
DCR1 (5 years)	0.02 ± 0.00	0.05 ± 0.01	0.06 ± 0.02	0.03 ± 0.00	0.006
Any relapse (5 years)[c]	0.07 ± 0.01	0.13 ± 0.02	0.19 ± 0.03	0.10 ± 0.01	< 0.001
Other event (5 years)[c]	0.04 ± 0.01	0.07 ± 0.02	0.08 ± 0.02	0.05 ± 0.01	0.046
Fine-Gray model[f]					
Relapse (HRa)	1 (ref)	2.0 (1.3; 3.2)	3.4 (2.2;5.2)		
Relapse (*P*)		0.002	< 0.001	< 0.001	
DCR1 (HRa)	1 (ref)	2.3 (1.1; 4.7)	2.9 (1.4; 5.9)		
DCR1 (*P*)		0.019	0.003	0.005	
pEFS					
5 years	0.89 ± 0.01	0.80 ± 0.03	0.74 ± 0.04	0.85 ± 0.01	
HRa (95% CI)	1 (ref)	2.0 (1.4; 2.8)	2.8 (2.0; 4.0)		
P		< 0.001	< 0.001	< 0.001	
Adjusted-HRa[d]	1 (ref)	1.7 (1.1;2.2)	2.2 (1.5; 3.3)		
Adjusted-*P*[d]		0.008	< 0.001	< 0.001	
OS					
5 years	0.94 ± 0.01	0.87 ± 0.02	0.78 ± 0.03	0.91 ± 0.01	
HRa (95% CI)	1 (ref)	2.3 (1.5; 3.5)	3.8 (2.5; 5.7)		
P		< 0.001	< 0.001	< 0.001	
Adjusted-HRa[d]	1 (ref)	1.7 (1.1;2.8)	2.8 (1.8;4.4)		
Adjusted-*P*[d]		0.021	< 0.001	< 0.001	
SR					
N[e]	547	82	44	673	
pEFS, 5 years	0.93 ± 0.01	0.86 ± 0.04	0.82 ± 0.07	0.91 ± 0.01	
pEFS, HRa (95% CI)	1	2.1 (1.0; 4.3)	2.6 (1.1; 6.2)		
pEFS, *P*		0.038	0.030	0.022	
FGM, DCR1, (HRa)		2.2 (0.4; 11.0)	2.1 (0.3; 17.7)		
FGM, DCR1, (*P*)		0.33	0.48	0.54	
FGM, relaps, (HRa)		2.6 (1.1; 6.2)	4.0 (1.5; 10.6)		
FGM, relaps (*P*)		0.028	0.006	0.006	
IR					
N	344	104	94	542	
pEFS, 5 years	0.91 ± 0.02	0.83 ± 0.04	0.77 ± 0.05	0.87 ± 0.02	
pEFS, HRa (95% CI)	1	1.9 (1; 3.5)	3.2 (1.8; 5.6)		
pEFS, *P*		0.039	< 0.001	< 0.001	
FGM, DCR1 (HRa)	1	1.9 (0.6; 6.5)	2.6 (0.8; 8.2)		
FGM, DCR1 (*P*)		0.31	0.10	0.24	
FGM, relaps (HRa)	1	2.0 (1.0; 4.1)	3.4 (1.8; 6.7)		
FGM, relaps (*P*)		0.062	< 0.001	0.001	

Table 2. (Continued)

Age group	*1–9*	*10–17*	*18–45*	*Total*	*P*[a]
HR w/wo SCT					
N	120	76	80	276	
pEFS, 5 years	0.70 ± 0.04	0.70 ± 0.05	0.61 ± 0.06	0.67 ± 0.03	
pEFS, HRa (95% CI)	1	1.0 (0.6; 1.7)	1.3 (0.8; 2.2)		
pEFS, *P*		0.91	0.23	0.45	
FGM, DCR1 (HRa)	1	1.8 (0.8; 4.2)	0.9 (0.3; 2.5)		
FGM, DCR1 (*P*)		0.19	0.85	0.29	
FGM, relaps (HRa)	1	0.7 (0.3; 1.4)	1.4 (0.8; 2.5)		
FGM, relaps (*P*)		0.26	0.23	0.12	

Abbreviations: BM, bone marrow; CI, confidence interval; CNS, central nervous system; CR, complete remission; DCR1, death in first complete remission; FGM, Fine and Gray regression model; HR, w/wo hSCT high risk with/without hematopoietic stem cell transplantation; HRa, hazard ratio; IR intermediate risk; OS, overall survival; pEFS, projected event-free survival; SMN, secondary malignant neoplasm; SR, standard risk. [a]Gray's test. [b]For patients without events. [c]Relapse: all locations; other: DCR1, SMN, IF/early death. [d]Adjusted for risk group assignment as a time-dependent covariate. 18 patients not risk grouped not included. [e]*N* indicates final risk assignment. Patients changing risk group where included and censored at time of change in risk assignment. [f]Fine and Gray regression model. SMN and induction death included in model but results not shown.

($P = 0.82$). Focusing on relapses, we found no difference between children aged 1–17 years who were transplanted compared with non-transplanted children (12 ± 5% vs 21 ± 4%, $P = 0.10$) and no difference in the adult group either (40 ± 11% vs 19 ± 6%, $P = 0.56$). However, a significant difference in risk of relapse was found between children and adults in the transplanted group ($P = 0.01$), but not in the non-transplanted group ($P = 0.42$). When looking at the latest MRD value available (post-block C1) for the 82 HR patients who were transplanted, there was for the whole group an increased HR with increasing MRD: HR 1.5 (95% CI: 1.1–2.1), $P = 0.007$ (HR per 10-fold increment in MRD).

For all patients, there were no increase in the rate of DCR1 for adolescents and adults (HR (10–17 years): 1.8, HR (18–45 years): 0.9, overall $P = 0.29$) (Table 2). Among the 45 patients aged 1–17 years with MRD day 29, ⩾5% the risk group-based strategy yielded a $pEFS_{5y}$ of 79 ± 6%, whereas for the 18 patients aged 18–45 years, the $pEFS_{5y}$ was 48 ± 12% ($P = 0.01$). When adult patients were divided into age groups 18–25 ($n = 110$) and 26–45 years ($n = 111$), no significant difference in $pEFS_{5y}$ was found (77 ± 4% and 69 ± 5%, respectively, $P = 0.60$). Furthermore, neither risk of induction death ($P = 0.57$), relapse ($P = 0.98$), remission death ($P = 0.53$) nor SMN (no events) differed between these two adult groups (Supplementary Table S5; Supplementary Appendix, page 20).

Toxicity

The incidences of 19 specified toxicities (Supplementary Table S6; Supplementary Appendix, page 21) were very similar for children and adults,[22] except for the risk of thrombosis ($P < 0.001$), pancreatitis ($P < 0.001$) and osteonecrosis ($P < 0.001$), which was higher for patients ⩾10 years (Figure 4b; Supplementary Table S7; Supplementary Appendix, page 23). In contrast, the risk of asparaginase-associated allergic reaction was significantly higher for children below 10 years compared with older patients ($P < 0.001$). Data from the randomized asparaginase study for patients aged 1–17 years are being analyzed and will be published separately. Finally, as a composite parameter of the toxicity burden, not least duration of myelosuppression, the interval between the treatment phases was almost identical for the three age groups (data not shown).[22]

DISCUSSION

The population-based use of a common treatment protocol for this, so far, largest published consecutive cohort of ALL patients aged 1–45 years adds important data to recent reports on such patients.[2,23–25] Previously, the superior outcome of children has been suggested to be linked to disease biology, treatment intensity, differences in chemosensitivity, frequency of toxicity leading to treatment modification, as well as physician compliance and patient adherence to protocol guidelines.

Compared with previous adult ALL regimens, the NOPHO ALL2008 protocol is less intensive with respect to induction treatment and SR therapy, but more intensive for HR treatment, although entirely omitting cranial irradiation. However, two of the most important differences between previous adult protocols and the NOPHO ALL2008 is the extensive use, in all risk groups, of asparaginase[23] and high-dose methotrexate with co-administration of mercaptopurine,[26] which may have contributed to the effectiveness of the protocol.

The overall worse outcome for adolescents and adults on NOPHO ALL2008 treatment seems primarily associated with the more frequent presence of T-cell ALL, *KMT2A-r* and higher post-induction MRD.[16] The risk-stratified therapy does not fully compensate for the adverse prognostic factors. Particularly in the SR/IR group, adolescents and adult patients have an increased relapse risk despite good or intermediate response to chemotherapy. However, compared with the survival in adult patients reported previously on traditional adult regimes, these results are encouraging regarding $pEFS_{5y}$.[2,27–29] Other groups have presented results of adults treated on pediatric protocols; a US intergroup trial reported 2 years EFS of 66% for patients aged 16–39 years[30] compared with EFS_{2y} 84 ± 2% for our patients aged 16–39 years. In a Dana Faber study of ALL patients aged 18–50 years treated with a pediatric protocol, the 4 years EFS was 62% for Ph-negative patients[24] compared with EFS_{4y} of 74 ± 4% in our patients aged 18–45 years. Both studies concluded that using a pediatric protocol was feasible and our results add important information to these publications.

The rate of death during induction or in remission for adults was low compared with historical data[2] and did not differ significantly from that reported for pediatric patients.[31] This finding confirms what was reported in the US intergroup trial (2% treatment-related mortality)[30] as well as the recently published UKALL14 adult study report of 0/21 induction death in a small group of Ph-negative patients below 40 years receiving treatment with asparaginase during induction (treatment-related mortality not presented).[32] The toxicities encountered during the NOPHO ALL2008 protocol seemed to affect all age groups equally and were strongly associated with HR treatment (data not shown). However, the risk of thrombosis, pancreatitis and osteonecrosis was significantly associated with age (>10 years)[22] and are most likely asparaginase related. Importantly, the incidence of these toxicities did not differ for adolescents and adults. The risk of ON in adults was in this cohort almost comparable with the adult Dana Faber study (for patients ⩾18 years 5% vs 8.5% in NOPHO ALL2008)[24] and similar to

a recent publication by the Dutch pediatric group (8% in patients aged 10–14 years and 27% in patients aged 15–18 years vs 13.4% in patients aged 10–17 years in the NOPHO ALL2008).[33] The high incidence in teenagers are well known and may be caused by extensive use of asparaginase in combination with frequent use of high-dose MTX and cumulative high doses of dexamethasone. The lower incidence of ON, thrombosis and pancreatitis in children aged 1–9 years could be explained by a lower cumulative dose of asparaginase as they may be omitted because of allergic reactions or due to more silent inactivation. Results of the randomized NOPHO ALL2008 asparaginase study (Peg-Asparaginase every 2 vs 6 week for patients aged 1–17 years) and investigation of asparaginase antibodies/silent inactivation are being analyzed and will be published accordingly. The lower incidence of anaphylactic reactions in patients above 10 years remains unexplained, however similar findings are reported for adults in the Dana Faber study (5%)[24] and the UKALL14 study (4%).[32] Except for splitting of dexamethasone to avoid osteonecrosis,[34] little is currently known how to prevent these acute toxicities associated with ALL therapy.[35]

In the wake of improved EFS with pediatric-like protocols for adult ALL, focus on acute and late side effects become increasingly important, including consensus definitions of toxicities[36] and capture strategies[17] not least for toxicities that harbor a risk of permanent sequelae such as osteonecrosis,[2,34,37] osteoporosis, chronic pancreatitis[38] or diabetes in order to improve the long-term outcome and quality of life for survivors.[35,39]

In contrast to the similar treatment outcome for HR w/wo hSCT patients across age groups, the majority of relapses among adults with IR ALL occurred while on treatment unlike that of younger patients who tended to relapse later. This did not seem to depend on toxicity-driven early treatment delays,[22] but could reflect both an increased frequency of other poor prognostic mutations not routinely included in the diagnostic work-up[14] or suboptimal adherence to maintenance treatment.[15,40,41] Few adults were for instance positive for *t*(1;19)[*TCF3/PBX1*], dic(9;20) or iAMP21, and recent studies have identified a subgroup of ALL patients with Ph-like alterations that are more frequent in adults, and have a poor prognosis.[14,30,42] Patient adherence to maintenance treatment is poorly described in adult ALL patients, but can be measured by levels of the cytotoxic metabolites of methotrexate and mercaptopurine.[34,41,43]

Future protocols for both pediatricians and adult hematologists are expected to focus more extensively on novel driver and pharmacogenetic mutations, adherence to maintenance treatment, use of immunotherapy, pathway-targeted therapy or less toxic drug combinations to improve efficacy and reduce the burden of treatment.

There are limitations to an observational study as presented in this paper for adult patients. A randomized study comparing the previously used adult regimens and the NOPHO ALL2008 protocol was considered unethical due to the inferior results derived from such therapy.[2] Patients allocated to HR w/wo hSCT group needs further investigation before conclusions can be drawn as conditioning regimes vary between centers even within the same country, and there is still no common strategy for pediatricians and adult hematologists. However, for a small subgroup of patients with a very poor response to induction therapy (MRD day 29 $\geqslant$ 5%) stratifying them to hSCT, the risk group-based strategy resulted in EFS_{5y} of 79 ± 6% for patients aged 1–17 years, which is a notable improvement compared with 45 ± 7% in the previous NOPHO ALL-2000 protocol.[4] These results are comparable with the Dutch pediatric study showing EFS_{5y} of 78 ± 8% for patients with poor end of induction response.[33] For NOPHO patients aged 18–45 years with a poor end of induction response, the EFS_{5y} was only 48 ± 12%, but MRD-based historical comparison data are not available. In a large adult UK/US study (15–55 years), transplanting all patients with an available donor the high risk-transplanted patients had an OS_{5y} of 41 vs 35% for those on chemotherapy alone (no EFS given). This was based on an adult treatment regime, and showed in addition for all Ph-negative patients an OS_{5y} of 43%. However, patient ages were higher (15–64 years) and the data are thus not completely comparable.[5]

Adult patients from Finland started recruiting later as the previous adult protocol had acceptable results compared to similar traditional adult protocols. In Iceland, only 1–2 adult patients with ALL are diagnosed each year and are not registered in the database. Both countries are similar to the remaining countries regarding health care systems and treatment availability for children and adult patients, thus we consider the results to be representative for all children and adult patients in the involved countries.

In conclusion, a common ALL strategy for adult and pediatric hematologists has shown to be feasible, it revealed similarities between teenagers and young adults and improved outcome for adults, while at the same time building a platform for future common research. Thus, the study highlights the need for risk group-stratified comparisons of age defined subsets for reliable and useful future outcome interpretations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

NT designed the study, collected, analyzed, and interpreted data, wrote and edited the manuscript; KS is principal investigator for NOPHO ALL2008, designed the study, interpreted data and critically reviewed the manuscript; HB designed the study, interpreted data, served as an investigator and critically reviewed the manuscript; TWC performed statistical analyses and interpreted data; JA designed the study, served as investigator, collected data and edited the manuscript; TF designed the study, served as investigator, supervised toxicity reporting and edited the manuscript; HH designed the study, served as investigator, collected data and edited the manuscript; LG designed the study, served as investigator, collected data and edited the manuscript; MH designed the study, served as investigator and data manager, collected data and edited the manuscript; OGJ designed the study, served as investigator, collected data and edited the manuscript; KPa designed the study, served as investigator, collected data and edited the manuscript; KPr designed the study, served as investigator, collected data and edited the manuscript; PQP designed the study, served as investigator, collected data and edited the manuscript; GV designed the study, served as investigator, collected data and edited the manuscript; KV designed the study, served as investigator, collected data and edited the manuscript; AÅ designed the study, served as investigator, collected data and edited the manuscript; HM served as flow cytometry investigator, collected data and edited the manuscript; HOM served as PCR investigator, collected data and edited the manuscript; UNN served as cytogenetic investigator, collected data and edited the manuscript. All authors approved the final manuscript.

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Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)