Acute lymphoblastic leukemia in adolescents and young adults in Finland

Anu Usvasalo,[1] Riikka Räty,[2] Sakari Knuutila,[3] Kim Vettenranta,[1] Arja Harila-Saari,[4] Esa Jantunen,[6] Marjut Kauppila,[8] Pirjo Koistinen,[5] Katriina Parto,[10] Pekka Riikonen,[7] Toivo T. Salmi,[9] Raija Silvennoinen,[11] Erkki Elonen,[2] and Ulla M. Saarinen-Pihkala[1]

[1]Hospital for Children and Adolescents, Helsinki University Central Hospital, Helsinki; [2]Department of Hematology, Helsinki University Central Hospital, Helsinki; [3]Department of Pathology, Haartman Institute and HUSLAB, University of Helsinki and Helsinki University Central Hospital, Helsinki; Departments of [4]Pediatrics and [5]Internal Medicine, Oulu University Hospital, Oulu; Departments of [6]Medicine and [7]Pediatrics, Kuopio University Hospital, Kuopio; Departments of [8]Medicine and [9]Pediatrics, Turku University Central Hospital, Turku; Departments of [10]Pediatrics and [11]Internal Medicine, Tampere University Hospital, Tampere, Finland

Funding: this work was supported by the Foundation for Pediatric Research and the Nona and Kullervo Väre Foundation, Helsinki, Finland.

Manuscript received November 13, 2007. Revised version arrived on February 25, 2008. Manuscript accepted March 25, 2008.

Correspondence:
Anu Usvasalo, MD, Hospital for Children and Adolescents, University of Helsinki, P.O. Box 281, 00029 HUS, Helsinki, Finland.
E-mail: anu.usvasalo@helsinki.fi

The online version of this article contains a supplemental appendix.

ABSTRACT

Background

Interest has recently been paid to adolescents and young adults with acute lymphoblastic leukemia, particularly because all reports so far published indicate that these patients have a better outcome when treated with pediatric rather than adult therapeutic protocols. There are different biological subtypes of acute lymphoblastic leukemia with distinct features and prognoses; the distribution of these subtypes is not well known among adolescents. We, therefore, studied acute lymphoblastic leukemia in adolescents and young adults aged 10 to 25 years in Finland.

Design and Methods

This population-based study included 225 consecutive patients aged 10-25 years diagnosed with acute lymphoblastic leukemia during 1990-2004. One hundred and twenty-eight patients (10-16 years) were treated with pediatric Nordic (NOPHO) protocols, and 97 patients (17-25 years) with Finnish Leukemia Group National protocols. We characterized the biological subtypes, clinical features and outcome of these patients.

Results

For the whole cohort, the remission rate was 96%, 5-year event-free survival 62% and overall survival 72%. The 5-year event-free survival was 67% for the pediatric treatment group and 60% for the adult treatment group (p=n.s.). Patients with inferior outcome were those with a white bood cell count $\geq 100 \times 10^9$/L, the Philadelphia chromosome and *MLL*. Good prognostic features were *TEL-AML1*, hyperdiploidy, and pediatric intermediate risk stratification.

Conclusions

Unlike all previous studies, we found that the outcome of adolescents and young adults with acute lymphoblastic leukemia treated with pediatric or adult therapeutic protocols was comparable. The success of the adult acute lymphoblastic leukemia therapy emphasizes the benefit of central referral of patients to academic centers and adherence to research protocols.

Key words: acute lymphoblastic leukemia, adolescents, survival, treatment outcome, young adults.

Citation: Usvasalo A, Räty R, Knuutila S, Vettenranta K, Harila-Saari A, Jantunen E, Kauppila M, Koistinen P, Parto K, Riikonen P, Salmi TT, Silvennoinen R, Elonen E and Saarinen-Pihkala UM. Acute lymphoblastic leukemia in adolescents and young adults in Finland. Haematologica 2008; 93:1161-1168. doi: 10.3324/haematol.12466

Introduction

The treatment of acute lymphoblastic leukemia (ALL) in children has improved dramatically over the past three decades, such that the current 5-year event-free survival (EFS) rate is 70-80%,[1-3] being up to 87% in non-high risk patients[4,5] although below 70% in high-risk patients.[6] For adult ALL the improvement has been modest, with 5-year EFS figures in the range of 30-50%.[7-10] Within the pediatric population children over 10 years old and infants have worse outcome[6,11-13] while among adult ALL patients younger adults have better outcomes.[10,14,15] There may be multiple explanations for why adult ALL patients do more poorly. ALL is not a common disease among adults whereas it is the most common hematologic malignancy in children. In addition, adult patients may not be treated in the context of clinical trials or at academic centers, may not tolerate cytostatic drugs as well as children, and may be less compliant and adherent to treatment protocols.

Interest has recently been paid to adolescents and young adults with ALL. This age group has been rather little studied partly because these patients are treated both in pediatric and adult hematology units. There are various subtypes of ALL with different clinical features and prognoses. It is widely accepted that, in general, the frequency of favorable subtypes of ALL is higher among children, whereas adult ALL includes more of the poor prognosis subtypes such as those with high initial white blood cell count, T-ALL and Philadelphia chromosome positive (Ph^+) ALL.[15] On the other hand, the biology of ALL in adolescents is not sufficiently well known to enable a biology-based approach to designing therapy. It is striking that in all so far published reports the outcome of adolescents with ALL has been better among those treated with pediatric protocols rather than with adult ALL protocols.[16-19]

In Finland, children with ALL have been treated with Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL protocols since 1981, and adults with the Finnish Leukemia Group protocols, both of these prospectively in a population-based fashion at academic centers. Our hypothesis was that adolescence might be a transition period during which the proportion of the subtypes gradually shifts from a pediatric to an adult pattern. Our aim was to characterize ALL in adolescents and young adults aged 10 to 25 years, and to evaluate these patient's therapy and outcome.

Design and Methods

Patients

This was a population-based study in Finland. All consecutive patients aged 10-25 years diagnosed with ALL in Finland during 1990-2004 were included. In total, 128 patients were treated in pediatric hematology units and 97 in adult ones. Eight adult ALL patients were not included in this study: three with Down's syndrome, one with another form of mental retardation, one Jehovah's witness who received strongly modified therapy, and three patients who died at about the time of diagnosis without any proper therapy (*Online Supplementary Table S1*). The primary therapy for ALL was centralized to five university hospitals. Allocation to pediatric or adult programs was based on age: basically, patients 16 years or younger were treated in pediatric units and those older than 16 years in adult units although two patients under 16 years old (15.7 and 15.9 years) were treated in an adult center and five over 16 years old (16.1, 16.2, 16.7, 17.6 and 17.7 years) were treated in a pediatric center. The study was approved by the appropriate Institutional Review Boards.

Diagnostic studies

Blast cell morphology was evaluated according to the French-American-Bristish classification.[20,21] Immunophenotyping was performed by routine flow cytometry. Cytogenetic studies were based on G-banding and performed at all centers. During the study period fluorescence *in situ* hybridization, Southern blotting, chromosomal comparative genomic hybridization and reverse transcriptase polymerase chain reaction analysis became more widely applied for more detailed analyses of cytogenetic abnormalities.

Treatment protocols

Children with ALL were treated according to NOPHO protocols following stratification into standard, intermediate risk and high risk groups. Patients with standard (low) risk only included subjects aged 1 to 10 years who, by definition, were not part of this series. The risk criteria for pediatric intermediate risk ALL were initial white cell count 10-50×10^9/L, or age >10 years. Criteria for pediatric high risk ALL were white cell count >50×10^9/L, T-ALL, some cytogenetic changes associated with a poor prognosis, slow response to induction therapy, or central nervous system/testicular involvement.

Three different treatment protocols were used for the pediatric intermediate risk group during the study period: BFM-83 IR (n=9),[13] NOPHO ALL-92 IR (n=40)[22] and NOPHO ALL-2000 IR (n=7), whereas two protocols were used for the high risk group: Nalle-90 HR (n=49)[6,22] and NOPHO ALL-2000 HR (n=23). The NOPHO IR protocols consisted of induction, consolidation, delayed intensification and maintenance, the total duration of treatment being 2 to 2.5 years. In the NOPHO HR protocol induction was similar to that of the NOPHO IR protocol and the total duration of treatment was 2 years. The backbone of consolidation in all NOPHO protocols was high-dose methotrexate, together with high-dose cytarabine in NOPHO HR-protocols. Central nervous system irradiation was used in the Nalle-90 HR protocol, but was restricted to patients with special risk factors or central nervous system involvement in NOPHO ALL-2000 HR. The NOPHO HR protocol included an LSA2-L2 type of maintenance.[6,22]

No risk stratification was employed for adult ALL. Three protocols of the Finnish Leukemia Group were used during the study period: ALL90 (n=31), ALL94 (n=43), and ALL2000 (n=23). The adult ALL treatment protocols consisted of six subsequent blocks and main-

tenance (*Online Supplementary Table S2*). The total duration of treatment was 3 years. All three protocols contained relatively high total doses of vincristine, dexamethasone and metothrexate (Table 1).

The cumulative doses of drugs administered in the different protocols are given in Table 1. The major difference between the pediatric and adult protocols, including maintenance, was in the cumulative dose of methotrexate. On the other hand there were no significant differences in the doses of corticosteroids, vincristine, or asparaginase. The dose of asparaginase in the currently used adult protocol ALL2000 has been reduced because of the risk of liver toxicity and thrombotic complications associated with this drug. The total doses of anthracyclines in adult protocols were about twice those in the pediatric protocols. Epipodophyllotoxins or mitoxantrone were not included in the pediatric protocols.

Statistical methods

The number of patients studied in the two groups does not give sufficient statistical power to prove that there was no difference in outcome (statistical power of 30% with 5% significance level). On the other hand, with this cohort size it was possible to detect a difference of 16% or more (significance 5%, power 80%). SPSS software, version 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Comparisons of the clinical characteristics were performed using the Mann-Whitney U-test for continuous variables and the χ^2 test for categorized variables. EFS was defined as the time from diagnosis to the first event (relapse, death, second malignancy). Overall survival (OS) was defined as the time from diagnosis to death. If no event had occurred, the patients were censored on the day of the last follow-up. Patients who received allogeneic stem-cell transplantation in first complete remission were

Table 1. Cumulative doses (mg/m²) of cytostatic drugs in the different pediatric and adult protocols.

	Pediatric protocols					*Adult protocols*		
	BMF-83 IR	*NOPHO-92 IR-ALL*	*NOPHO-2000 IR-ALL*	*Nalle-90 HR*	*NOPHO-2000 HR-ALL*	*ALL-90*	*ALL-94*	*ALL-2000*
Intensive treatment								
Prednisolone	1680	2160	2160	2560	2160	1320	1320	
Dexamethasone	290	220	90	210	210	1280	1280	780/*620*
Prednisone equivalents	3623	3634	2763	3967	3567	9896	9896	5226/*4154*
Vincristine[a]	16	20	20	24	24	25,2	21,2	23.6/*19.6*
Doxorubicin	120	120	80	250	210	140	140	190/*140*
Daunorubicin	120	120	120			180	180	180
Mitoxantrone						48	48	*48*
Anthracycline equivalents	240	240	200	250	210	560	560	610/*560*
Cyclophosphamide IV	3000	3000	2000	3000	3000	3350	3350	4600/*2800*
Cytarabine	1800	1800	2400	25800	49800	8600	8600	12600/*20600*
L-asparaginase	12000	42000	52000	42000	52000	60000	60000	30000
Teniposide						325	325	
Etoposide						400	400	*400*
Methotrexate IV	2000	20000	15000	16000	32000	18000	15000	7000
Methotrexate PO				160	160			
6-mercaptopurine PO	3080	3200	1400	7095	5520	1080	1140	1080
6-thioguanine	840		1800	660	660			840
Carmustine						160	160	
Methotrexate IT (doses)	9	12	10	11	11	8	9	7
Cytarabine IT (doses)						10	11	4
CNS XRT prophylaxis				12 Gy	12 Gy[b]	24 Gy[b]	24 Gy[b]	
Maintenance								
Prednisolone		1920		400		8160	8160	3600
Dexamethasone			390/*150*		240			
Prednisone equivalents		1920	2613/*335*	400	1608	8160	8160	3600
Vincristine[a]		8	26/*10*	16	20			24
Vindesine						68	68	
Daunorubicin				120	60			
Cyclophosphamide IV				3600	1200			
Cytarabine				3600	600			
Methotrexate IV		25000	25000					
Methotrexate PO	1980	1460	2200	240	700	3060	3180	2120
6-mercaptopurine PO	34650	38325	57750		16800	7650	47700	44520
6-thioguanine PO				7200	2400			
Carmustine				180	300			
Hydroxyurea PO				38400	19200			
Methotrexate IT (doses)		5	6	6	2	4	4	3

IV: intra venous; PO: per os; IT: intrathecal. The equipotent doses for steroids are calculated as dexamethasone 1 mg = prednisolone 6.7 mg. The equipotent doses for anthracyclines are calculated as mitoxantrone 1 mg = doxorubicin 5 mg = daunorubicin 5 mg. CNS XRT, central nervous system radiation therapy. Italic: total dose depends on the randomization group. [a]Max. dose 2 mg/dose. [b]10 % of patients.

censored on the day of the transplant. An exception was made for Ph+ ALL since allogeneic stem cell transplantation in first complete remission was considered optimal therapy for this form of ALL. EFS and OS were estimated by the Kaplan-Meier method.[23] Survival outcomes were compared using the log-rank test.[24] The median follow-up time was 4.9 years.

Results

Patients' characteristics

The age distribution at diagnosis of the subjects indicated that the incidence of ALL decreases with age. The key characteristics of the pediatric and adult study groups are given in Table 2, showing a remarkable similarity between the groups. The distribution of initial white cell counts was quite similar, and most patients had an initial count below 50×10^9/L. The proportion of T-ALL was also similar; less than 20% of patients in both groups had T-ALL. In the adult group, the proportion of patients with T-ALL was lower among younger patients (16-20 years) than among the older ones (15% *vs.* 24%, respectively). The only difference between the pediatric and adult groups was in French-American-British morphology, with more L2 morphology in the adult study group ($p<0.001$) (Table 2).

The distribution of biological subgroups in the two treatment groups is shown in Figure 1. The proportion of *TEL-AML1* subtype ALL in the pediatric group was low, only 3%, and even lower, 1%, in the adult group. Hyperdiploidy of >50 was much more frequent in the pediatric group (18%) than in the adult group (4%) ($p=0.002$). Ph+ ALL was infrequent in both groups (8% and 4%, respectively).

Outcome

The remission rate was 96% in the pediatric group and 97% in the adult treatment group. Fifty-six percent remained in first continuous complete remission on chemotherapy, while 25% relapsed. The frequency of induction deaths was 4/128 in the pediatric group and 5/97 in the adult group ($p=0.44$). The relapse rate in the whole series (including patients treated with stem cell transplantation) was comparable in the two groups (26%, n=33, in the pediatric group, and 31%, n=30, in the adult patients, $p=0.40$). Most patients in both treatment groups were in first continuous compete remission at the end of the follow-up. Of those who relapsed, 49 (78%) achieved a second remission but only 16/49 (33%) were still in second remission at the end of the follow-up. Allogeneic stem cell transplantation was performed in second remission in 29 (46%) of the relapsed patients.

In the whole series, the 5-year and 10-year EFS rates were 62% and 57%, respectively. The corresponding OS rates were 72% and 67%, respectively. The 5-year EFS was 67% in the pediatric group, and 60% in the adult study group (p=n.s.) (Figure 2). The OS rates were not different (77% *vs.* 70%; p=n.s.) (Figure 2). In total 28 patients (14 children, 14 adults, $p=0.43$) underwent allogeneic stem cell transplantation in first remission. The indications were very high initial white blood cell count (n=6), Ph+ ALL (n=8), T-ALL (n=3), poor response to induction therapy (n=6), and unknown (n=5). Censoring those patients who underwent allogeneic stem cell transplantation on the day of the transplant did not influence either EFS or OS.

Table 2. Key characteristics of the study groups.

	Pediatric	*Adult*	*Total*	*p*
Number	128	97	225	
Gender (male/female)	79/49 (62%/38%)	58/39 (60%/40%)	137/88 (61%/39%)	0.77
Age, years (median, range)	12.9 (10.0-17.7)	18.9 (15.7-25.5)	15.4	<0.001
White cell count, $\times10^9$/L (median, range)	10.0 (0.7-524.5)	7.94 (0.5-480.0)	9.2	0.62
French-American-British classification (%)				
L1	68 (54%)	33 (34%)	101 (45%)	0.004
L2	25 (20%)	40 (41%)	65 (29%)	<0.001
Unknown	35 (27%)	24 (25%)	59 (26%)	0.66
Phenotype (%)				
T	20 (16%)	18 (19%)	38 (17%)	0.56
Precursor B	102 (80%)	57 (59%)	155 (71%)	0.001
Mixed lineage	4 (3%)	11 (11%)	15 (7%)	0.01
Unknown	2 (2%)	11 (11%)	11 (6%)	0.002
Initial risk category				
Intermediate risk	56 (44 %)			
High risk	72 (56 %)			
Follow-up, years (median, range)	5.8 (0-16.4)	3.7 (0-13.6)	4.9	
Remission rate	123 (96%)	94 (97%)	217 (96%)	0.74
Relapse rate	33 (26%)	30 (31%)	63 (28%)	0.40

Prognostic factors

There was no difference in survival between male and female patients. The 5-year EFS was 63% for males and 66% for females (p=n.s.), and the 5-year OS was 75% and 73% (p=n.s.), respectively. Only very high ($\geq100\times10^9$/L) white blood cell count was associated with a poor prognosis. Age was not a statistically significant prognostic factor within the range of 10-25 years. L2 morphology of blast cells was not related to an inferior outcome, the 5-year EFS and OS rates being similar for patients with L1 or L2 morphology. There was a trend towards an association between T-cell immunophenotype and an inferior outcome. The 5-year EFS rates were 53% and 67% ($p=0.07$), and the 5-year OS rates 65% and 77% ($p=0.12$) in the T-ALL and precursor-B-ALL groups, respectively. Interestingly, while the outcomes of patients with precursor B-ALL were similar in the pediatric and adult groups, among those with T-ALL, the EFS and OS tended to be superior in the pediatric patients, being 66% *vs.* 39% ($p=0.12$) and 77% *vs.* 51% ($p=0.09$), respectively. The number of patients with Ph+ ALL was small in this series (9 children, 4

adults). Nine out of the 13 patients (69%) underwent allogeneic stem cell transplantation in first complete remission. Most of the Ph+ patients in this series were not treated with imatinib. The 5-year EFS in the Ph+ group was 26% as compared to 64% in the other patients (p=0.02). The OS rates were not different (55% *vs.* 73%, p=0.22).

The cytogenetic subtypes of ALL with the *TEL-AML1* fusion gene and hyperdiploidy of ≥50 are considered good risk subtypes. On the other hand, Ph+ ALL, the *MLL* rearrangement and a high initial white blood cell count (≥100×10^9/L) are considered poor risk criteria. Of the pediatric patients 21% had a good risk subtype of ALL, as compared to only 5% in the adult group (p=0.001). Poor risk subtypes occurred at similar frequencies: 14% in the pediatric group and 10% in the adult group (p=n.s.). As expected, the patients with good risk subtypes of ALL had the best outcome (5-year EFS 84%, OS 88%), while those with poor risk subtypes had the poorest outcome (5-year EFS 31%, OS 28%) (p<0.001 for EFS and OS). T-ALL behaved more like poor risk ALL (Figure 3). In the adult treatment group all patients 16-25 years of age were treated with the same protocols, whereas the pediatric patients were assigned to high risk and intermediate risk groups, given different treatment protocols. The patients in the pediatric intermediate risk group had a better outcome than that of the pediatric high risk group and the adult group (Figure 4).

Discussion

Recent reports suggest that adolescents and young adults with ALL have a better outcome when treated with pediatric therapeutic protocols than with adult ALL protocols. Several groups have reported a clearly inferior outcome for adolescents treated with adult protocols. The survival of adolescents and young adults treated with pediatric protocols has ranged from 65-69%[16-19] except for a series of ALL patients aged 10-15 years old reported by the Boston group who had a 5-year EFS of as high as 77-78%.[11] Most of these data were not strictly population-based. Here we present a population-based analysis of 225 adolescents and young adults in Finland diagnosed with ALL between the ages of 10-25

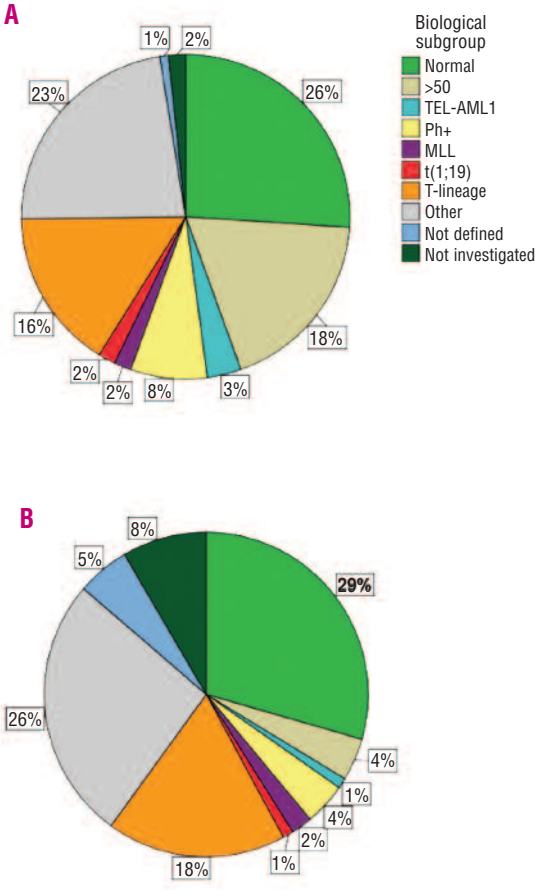

Figure 1. Distribution of biological subtypes among the (A) pediatric (n=119) and (B) adult (n=95) patients in the study.

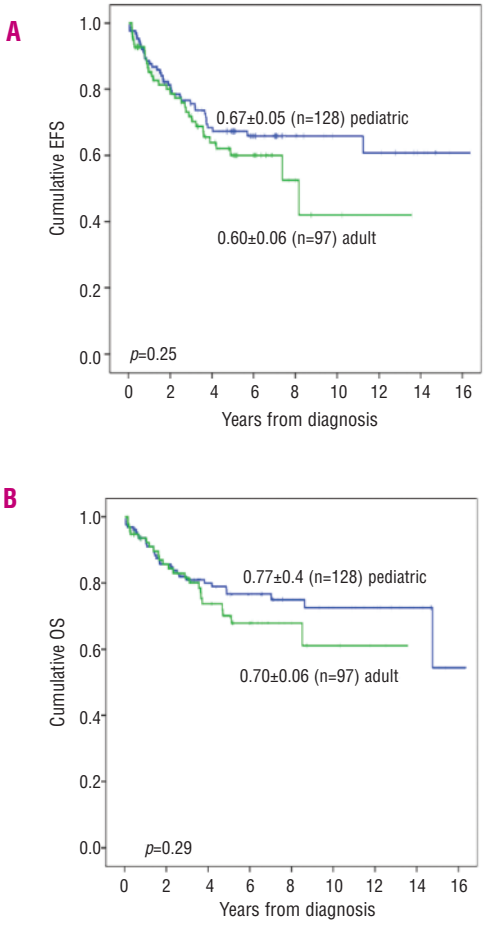

Figure 2. (A) Event-free survival (EFS) and (B) overall survival (OS) of the study patients treated with pediatric and adult protocols. The patients transplanted in first complete remission (n=28) were censored at the time of the transplant.

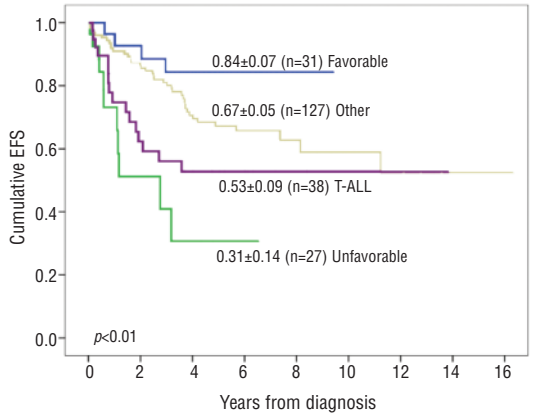

Figure 3. Outcome of the subgroups with favorable cytogenetics (hyperdiploidy ≥50 chromosomes, n=26; *TEL-AML1*, n=5), unfavorable features (Ph$^+$, n=13; MLL-rearrangement, n=4; white cell count ≥100x10^9/L, n=10) T-ALL (n=38). Significance given pooled over strata. The patients transplanted in first complete remission (n=28) were censored at the time of the transplant.

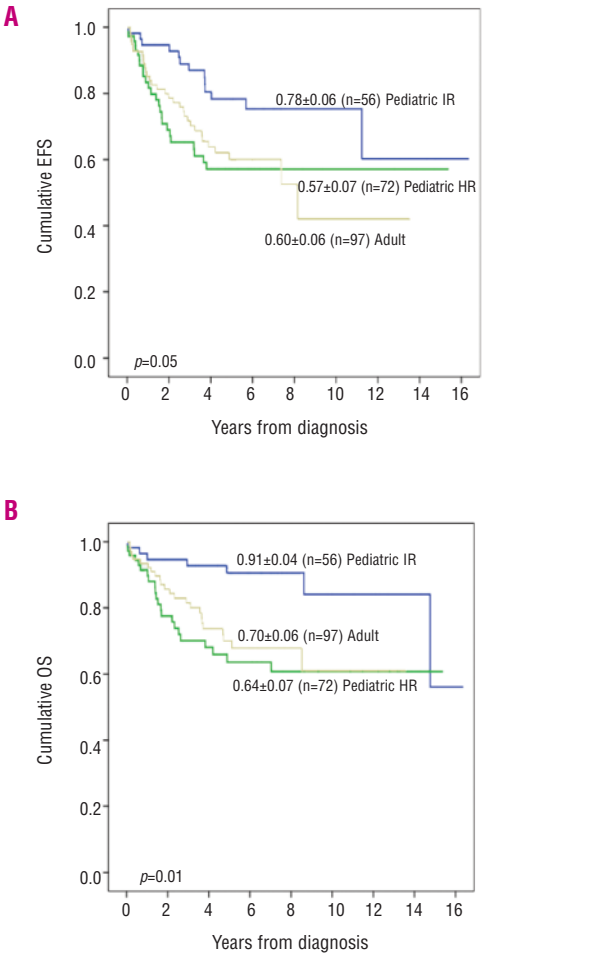

Figure 4. (A) Event-free survival and (B) overall survival according to risk stratification into pediatric intermediate risk (IR) (n=56), pediatric high risk (HR) (n=72) and adult study groups (n=97).

years. Our main finding is that there was no significant difference in outcome between those treated with pediatric or adult ALL protocols, the 5-year EFS being 67% and 60%, respectively. We did not aim to provide statistical proof that there was no difference, and, indeed, the study lacked statistical power to do so. However, our sample size would allow detection of a difference of 16% or more with 80% power. All other series so far published have found significant or even striking differences in the range of 24-35%.[16-18] Such differences would have been detected with our sample size.

Pediatric ALL is treated in Finland using population-based Nordic NOPHO-ALL protocols, the outcomes being among the best in the world.[6,22] Finnish results compare favorably with those in Europe.[25] That the results for young adults treated with adult ALL protocols in Finland are comparable to those treated with pediatric protocols is remarkable. There may be several reasons for this success. During the study period multiple protocols were used (five pediatric and three adult ones). On the other hand, the pediatric and adult protocols were not very dissimilar. The main differences between our pediatric and adult protocols were in the doses of methotrexate, anthracyclines and epipodophyllotoxins (Table 1). In the Finnish adult protocols the doses of vincristine, corticosteroids and asparaginase – traditionally considered important components of pediatric ALL treatment protocols – were relatively high as compared to those in many other protocols used for adult ALL. This might have contributed to the favorable outcome of the adult patients in our series. One regimen that has also led to good outcomes in young adults is the hyper-CVAD (5-year survival of 51% for patients <40 years old).[10,26] This regimen contains far higher doses of cyclophosphamide than the Finnish protocols, but lower doses of vincristine, methotrexate and epipodophyllotoxins. Another important factor for the good outcome of Finnish young adults is probably the fact that adults, as well as children, with ALL in Finland are treated in a centralized fashion at five academic centers, taking part in prospective, population-based studies. Furthermore, based on our culture and health care system, compliance and adherence to protocols are usually very good.

Regarding clinical features in our series, the pediatric and adult treatment groups were unexpectedly similar (Table 2). About 20% in both groups had an initial white blood cell count exceeding 50×10^9/L, in accordance with observations by others.[18,,19] Older adults more often have high white cell counts at diagnosis.[8,26] Less than 20% in both groups had T-ALL, this being a lower percentage than that reported by some others for adolescent age groups[16,17] but similar to reports from Sweden.[18] The percentage of T-ALL has been lower in NOPHO pediatric series than in, for example, the United States (8-10% *vs.* 14-17%, respectively).[22,12] The only true difference was the more frequent occurrence of the L2 FAB-type among the adult group (Table 2) though morphology was not reviewed centrally. While T-ALL and high initial white cell count are established poor prognostic factors, the role of L2 morphology in outcome remains uncertain.

The spectrum of cytogenetic changes in our patients (Figure 1) indicates that about one quarter fell within the *normal* subgroup. This probably reflects the fact that cytogenetic methods developed throughout the study period, and only G-banding data were available for the earliest cases. Of the favorable changes, hyperdiploidy was much more common in the pediatric group, while the *TEL-AML1* subtype of ALL was rare in both groups although not very systematically screened for. The unfavorable factors Ph$^+$, *MLL* and t(1;19) were infrequent in both groups (Figure 1), again partly reflecting the lack of uniformity in screening. The Ph$^+$ subtype of ALL has been more common in adult series (about 20%)[8,27] than in adolescent studies (2%-12%)[11,16,17] or the 7% in the present study.

Among our ALL series, certain factors were recognized as being of prognostic significance for EFS and OS in univariate analyses. While patient age is of prognostic value in ALL through all ages, it did not reach statistical significance within the age range of 10-25 years. Regarding initial white blood cell count, only counts exceeding 100×10^9/L were associated with a poor prognosis. T-cell immunophenotype tended to be associated with a poorer outcome. In accentuating the importance of *good* and *bad* prognostic factors, patients with hyperdiploidy or *TEL-AML1* had an excellent prognosis, while those with Ph$^+$ ALL, the *MLL* rearrangement, or a white cell count $\geq100\times10^9$/L had a clearly inferior prognosis; the rest of the series had an intermediate prognosis (Figure 3).

While no differences in outcome were found depending on the different protocols used in this study, one group of patients seemed to have a far superior prognosis compared to the others, with a 5-year EFS of 78%. This group consisted of pediatric patients initially categorized as at intermediate risk (Figure 4), treated with three successive, not very dissimilar, intermediate risk protocols. These children had an initial white cell count below 50×10^9/L, precursor-B immunophenotype, lacked lymphomatous features and poor-prognosis cytogenetics, and responded adequately to induction therapy. Our data demonstrate that these patients did very well on the antimetabolite-based, relatively non-toxic NOPHO-IR protocols used. For many treatment protocols, all children over 10 years old are categorized as high risk patients. Our results do, however, indicate that there is a group with a more favorable prognosis also within this age category, and accordingly, the NOPHO stratification seems appropriate.

There is wide debate on whether adolescents and young adults with ALL should be treated by pediatricians with pediatric protocols, or at least whether their treatment protocols should include more elements of the pediatric protocols.[28,29] Our results indicate that the survival rates of adolescents and young adults are not inevitably lower when treated with adult ALL treatment protocols. The fact remains, however, that adolescents and young adults with ALL still have a poorer outcome than children below 10 years of age. In young adults with ALL, relapse still remains the major factor responsible for a poor outcome, and, accordingly, the burden of therapy, although important, has not been considered as first priority. Follow-up of long-term adverse effects is nevertheless essential and merits prospective comparative studies. A deeper understanding of the special features of ALL in the adolescent age group is needed in order to design more efficient therapy, for which guidelines should be based more on biological subgroups than age.

Authorship and Disclosures

AU: conception and design of the study, collection and assembly of data, data analysis and interpretation, manuscript writing as first author, approval of the manuscript; RR: collection of data, manuscript writing, approval of the manuscript; SK, UMS-P: conception and design of the study, data interpretation, manuscript writing, administrative support, approval of the manuscript; KV, AH-S, EJ: provision of patients' data, manuscript writing, approval of the manuscript; MK, PK, KP, PR, TTS, RS: provision of patients' data, approval of the manuscript; EE: conception and design of the study, provision of patients' data, data interpretation, manuscript writing, administrative support, approval of the manuscript.

The authors reported no potential conflicts of interest.

References

1. Moghrabi A, Levy DE, Asselin B, Barr R, Clavell L, Hurwitz C, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. Blood 2007;109:896-904.
2. Pui CH, Sandlund JT, Pei D, Campana D, Rivera GK, Ribeiro RC, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. Blood 2004;104:2690-6.
3. Gaynon PS, Trigg ME, Heerema NA, Sensel MG, Sather HN, Hammond GD, et al. Children's Cancer Group trials in childhood acute lymphoblastic leukemia: 1983-1995. Leukemia 2000;14:2223-33.
4. Silverman LB, Gelber RD, Dalton VK, Asselin BL, Barr RD, Clavell LA, et al. Improved outcome for children with acute lymphoblastic leukemia: results of Dana-Farber Consortium Protocol 91-01. Blood 2001;97:1211-8.
5. Gustafsson G, Kreuger A, Clausen N, Garwicz S, Kristinsson J, Lie SO, et al. Intensified treatment of acute childhood lymphoblastic leukaemia has improved prognosis, especially in non-high-risk patients: the Nordic experience of 2648 patients diagnosed between 1981 and 1996. Nordic Society of Paediatric Haematology and Oncology (NOPHO). Acta Paediatr 1998;87:1151-61.
6. Saarinen-Pihkala UM, Gustafsson G, Carlsen N, Flaegstad T, Forestier E, Glomstein A, et al. Outcome of children with high-risk acute lymphoblastic leukemia (HR-ALL): Nordic results on an intensive regimen with restricted central nervous system irradiation. Pediatr Blood Cancer 2004;42:8-23.
7. Gokbuget N, Hoelzer D. Treatment of adult acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2006;133-41.
8. Thomas X, Boiron JM, Huguet F, Dombret H, Bradstock K, Vey N, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin

Oncol 2004;22:4075-86.
9. Annino L, Vegna ML, Camera A, Specchia G, Visani G, Fioritoni G, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. Blood 2002; 99:863-71.
10. Kantarjian H, Thomas D, O'Brien S, Cortes J, Giles F, Jeha S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer 2004; 101:2788-801.
11. Barry E, DeAngelo DJ, Neuberg D, Stevenson K, Loh ML, Asselin BL, et al. Favorable outcome for adolescents with acute lymphoblastic leukemia treated on Dana-Farber Cancer Institute Acute Lymphoblastic Leukemia Consortium Protocols. J Clin Oncol 2007;25:813-9.
12. Pui CH, Boyett JM, Rivera GK, Hancock ML, Sandlund JT, Ribeiro RC, et al. Long-term results of Total Therapy studies 11, 12 and 13A for childhood acute lymphoblastic leukemia at St Jude Children's Research Hospital. Leukemia 2000; 14:2286-94.
13. Schrappe M, Reiter A, Zimmermann M, Harbott J, Ludwig WD, Henze G, et al. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. Berlin-Frankfurt-Munster. Leukemia 2000; 14:2205-22.
14. Linker C, Damon L, Ries C, Navarro W. Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. J Clin Oncol 2002;20:2464-71.
15. Chessells JM, Hall E, Prentice HG, Durrant J, Bailey CC, Richards SM. The impact of age on outcome in lymphoblastic leukaemia; MRC UKALL X and XA compared: a report from the MRC Paediatric and Adult Working Parties. Leukemia 1998;12:463-73.
16. Boissel N, Auclerc MF, Lheritier V, Perel Y, Thomas X, Leblanc T, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. J Clin Oncol 2003;21:774-80.
17. de Bont JM, Holt B, Dekker AW, van der Does-van den Berg A, Sonneveld P, Pieters R. Significant difference in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric vs. adult protocols in the Netherlands. Leukemia 2004;18: 2032-5.
18. Hallbook H, Gustafsson G, Smedmyr B, Soderhall S, Heyman M. Swedish Adult Acute Lymphocytic Leukemia Group, et al. Treatment outcome in young adults and children >10 years of age with acute lymphoblastic leukemia in Sweden: a comparison between a pediatric protocol and an adult protocol. Cancer 2006;107: 1551-61.
19. Ramanujachar R, Richards S, Hann I, Goldstone A, Mitchell C, Vora A, et al. Adolescents with acute lymphoblastic leukaemia: outcome on UK national paediatric (ALL97) and adult (UKALLXII/E2993) trials. Pediatr Blood Cancer 2007;48:254-61.
20. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. The morphological classification of acute lymphoblastic leukaemia: concordance among observers and clinical correlations. Br J Haematol 1981;47:553-61.
21. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) co-operative group. Br J Haematol 1976;33:451-8.
22. Gustafsson G, Schmiegelow K, Forestier E, Clausen N, Glomstein A, Jonmundsson G, et al. Improving outcome through two decades in childhood ALL in the Nordic countries: the impact of high-dose methotrexate in the reduction of CNS irradiation. Nordic Society of Pediatric Haematology and Oncology (NOPHO). Leukemia 2000;14: 2267-75.
23. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53: 458-81.
24. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. Br J Cancer 1977;35:1-39.
25. Gatta G, Corazziari I, Magnani C, Peris-Bonet R, Roazzi P, Stiller C, et al. Childhood cancer survival in Europe. Ann Oncol 2003;14(Suppl 5):119-27.
26. Kantarjian HM, O'Brien S, Smith TL, Cortes J, Giles FJ, Beran M, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000;18:547-61.
27. Rowe JM, Buck G, Burnett AK, Chopra R, Wiernik PH, Richards SM, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 2005;106:3760-7.
28. Jeha S. Who should be treating adolescents and young adults with acute lymphoblastic leukaemia? Eur J Cancer 2003;39:2579-83.
29. Schiffer CA. Differences in outcome in adolescents with acute lymphoblastic leukemia: a consequence of better regimens? Better doctors? Both? J Clin Oncol 2003;21:760-1.