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

Helene Hallböök, MD, PhD[1]
Göran Gustafsson, MD, PhD[2]
Bengt Smedmyr, MD, PhD[1]
Stefan Söderhäll, MD, PhD[2]
Mats Heyman, MD, PhD[2]
for the Swedish Adult Acute Lymphocytic Leukemia Group and the Swedish Childhood Leukemia Group

[1] Department of Hematology, Uppsala University Hospital, Uppsala, Sweden.

[2] Childhood Cancer Research Unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden.

BACKGROUND. Several studies have reported a more favorable outcome for teenagers and young adults with acute lymphoblastic leukemia (ALL) when they were treated in pediatric oncology departments compared with adult hematology departments. However, biased risk grouping and high treatment-related mortality have hampered some of those comparisons.

METHODS. In Sweden during the 1990s, adolescents with ALL were treated in a pediatric oncology unit or in an adult hematologic unit, depending on the initial referral. In the current national, comparative, retrospective study, patients with ALL aged 10 years to 40 years who were treated either according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL protocol (1992–2000) (NOPHO-92 protocol) or according to the Swedish Adult ALL Group protocol (1994–2000) (Adult protocol) were included. None of the protocols had age as a high-risk criterion.

RESULTS. In total, 243 patients with B-precursor and T-cell ALL were treated according to the protocols. There was a significant difference in the remission rate between the NOPHO-92 protocol (99%; $n = 144$ patients) and the Adult protocol (90%; $n = 99$ patients; $P < .01$), and the event-free survival (EFS) was also superior for the NOPHO-92 protocol compared with the Adult protocol ($P < .01$). However, EFS was higher for patients aged 15 years to 25 years compared with patients aged 26 years to 40 years within the Adult protocol group ($P = .01$). The treatment protocol itself was identified as an independent risk factor.

CONCLUSIONS. The NOPHO-92 protocol resulted in a better outcome than the Adult protocol; therefore, adolescents may benefit from the pediatric protocol treatment strategy. Prospective trials are warranted to determine whether young

Supported by the Children's Cancer Foundation in Sweden.

The following are participating centers in the Swedish Adult Acute Lymphocytic Leukemia Group: Department of Haematology, Karolinska University Hospital, Huddinge; Department of Haematology, Karolinska University Hospital, Solna; Department of Haematology, University Hospital, Linkoping; Department of Haematology, University Hospital, Lund; Section of Haematology and Coagulation, Department of Medicine, Malmo University Hospital, Malmo; Haematology Section, Department of Internal Medicine, Sahlgrenska University Hospital, Goteborg; Department of Medicine, Division of Haematology, University Hospital, Umea; Department of Haematology, University Hospital, Uppsala; and Department of Medicine, Division of Haematology, University Hospital Orebro, Sweden. The following are participating centers in the Swedish Pediatric Leukemia Group: Department of Paediatric Haematology and Oncology, Astrid Lindgren's Children's Hospital, Karolinska University Hospital, Stockholm; Department of Paediatric Haematology and Oncology, Queen Silvia's Children's Hospital, Sahlgrenska University Hospital, Goteborg; Department of Paediatric Haematology and Oncology, Children's Hospital, Uppsala University Hospital, Uppsala; Department of Paediatric Haematology and Oncology, University Hospital, Umea; Department of Paediatric Haematology and Oncology, Children's University Hospital, University Hospital, Lund; and Department of Paediatric Haematology and Oncology, Paediatric Clinic, University Hospital, Linkoping, Sweden.

Address for reprints: Mats Heyman, MD, PhD, Childhood Cancer Research Unit, Astrid Lindgren's Children's Hospital, Karolinska Institute, Karolinska University Hospital, SE-171 76 Stockholm, Sweden; Fax: (011) 46 851773184. E-mail: mats.heyman@ki.se

Received May 19, 2006; revision received June 29, 2006; accepted July 6, 2006.

© 2006 American Cancer Society
DOI 10.1002/cncr.22189
Published online 5 September 2006 in Wiley InterScience (www.interscience.wiley.com).

adults would benefit from similar treatment. ***Cancer*** **2006;107:1551–61.** © *2006 American Cancer Society.*

KEYWORDS: acute lymphoblastic leukemia, treatment outcome, teenager, young adult.

Acute lymphoblastic leukemia (ALL) is most common in childhood but may occur at all aged. It has a bimodal age distribution, with the main peak in children between aged 2 years and 5 years and another peak in adults age >40 years. In recent decades, survival has improved dramatically for patients with ALL. However, this improvement has occurred mainly in children, resulting in a 5 year event-free survival (EFS) rate of 63% to 78%[1–4]; whereas adults have a 5-year survival rate of 30% to 39%.[5–11] In many countries, adolescents (aged 15–20 years) with ALL may be treated in a pediatric unit or in an adult unit, depending on where the first consultation takes place. Several studies have indicated that outcomes were better for teenagers who were treated on pediatric protocols compared with patients who were treated on adult protocols.[12–15] However, it is noteworthy that adolescents are considered as high-risk patients in some pediatric protocols, although not usually in adult protocols, which may affect their stratification into protocols of different treatment intensity. Conversely, stem cell transplantation (SCT) is used more frequently in adult treatment protocols, especially for patients with high-risk criteria. In at least 1 study, high treatment-related mortality in the adult group hampered the comparison.[13]

In Sweden, both children and adults have been treated according to national treatment protocols since the 1980s. Adolescents (aged 15–20 years) are treated either in a pediatric unit according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) protocols or in an adult hematology unit according to the Swedish Adult ALL Group protocols (Adult protocols). Children age >10 years are excluded from the least intensive pediatric treatment protocol. Age itself, however, is not used otherwise for treatment stratification in the pediatric or adult protocols.

The objective of the current study was to determine, on a national basis, how many adolescents had been treated in pediatric units and adult units and which treatment protocols had been used. We also compared treatment outcomes, taking clinical characteristics and treatment protocol/treating unit into consideration.

MATERIALS AND METHODS

Patients

Patients aged 10 years to 18 years who were diagnosed with ALL between January 1992 and December 2000 in a pediatric unit and patients aged 15 years to 40 years who were diagnosed with ALL between January 1994 and December 2000 in an adult unit in Sweden were included in the study. The patients were identified in the NOPHO register and in the Swedish Adult ALL Group register. For patients who were treated in pediatric units, repeated comparisons with the mandatory Swedish Cancer Register have shown that the voluntary pediatric registration is virtually complete. The patients aged ≥16 years also were identified in the national Swedish Cancer Register. Data concerning clinical characteristics, treatment administered, and outcomes were obtained from the patient records for patients who were not registered previously. All regional ethical committees approved the study both for children and for adults.

Therapy

Children (aged ≤18 years) who were diagnosed in a pediatric unit were included and were treated according to the NOPHO ALL-92 protocol (described in Table 1, and reported in refs. 2 and 4), which consisted of continuous treatment after remission induction up to 2 years or 2.5 years but with different treatment intensity for different risk groups. Approximately 7% of patients received cranial irradiation. For most patients, central nervous system (CNS)-directed prophylactic treatment consisted of intrathecal and high-dose methotrexate. High risk was defined as the presence of Philadelphia chromosome, t(4,11), a white blood cell count (WBC) $>50 \times 10^9$/L, mediastinal mass, testicular involvement, or T-cell leukemia. Very high risk was defined as slow response, CNS involvement, lymphomatous features, or T-cell leukemia combined with 1 more high-risk factor. In the current study, leukemia with either of those features is referred to as "higher risk" leukemia. Patients without high-risk criteria were stratified into a standard-risk (SR) group if they were aged 2 to 9.99 years at diagnosis and had a WBC $\leq 10.0 \times 10^9$/L. Patients aged 1 year to 1.99 years or aged ≥10 years or patients who had a WBC from 10.1×10^9/L to $\leq 50.0 \times 10^9$/L were stratified into an intermediate-risk group. Thus, all adolescents without high-risk features were considered intermediate-risk patients and are referred to in this report as patients with "lower risk" leukemia.

Adults with B-precursor or T-cell ALL were treated according to the 1994 Swedish ALL Group protocol (Adult protocol), described in Table 2 and reported in

TABLE 1
The Pediatric Nordic Society of Pediatric Hematology and Oncology 92 Treatment Protocol

Treatment phase and drug	Days given	Comments
All risk groups		
Induction (Weeks 0–7)		
Prednisone (orally), 60 mg/m^2	1–36/45	High-risk/very high-risk prephase
Vincristine (IV), 2 mg/m^2 (maximum, 2 mg)	1, 8, 15, 22, 29, 36	
Doxorubicin (IV), 40 mg/m^2	1, 22, 36	High-risk/very high-risk given on Days 1, 8, 22, 36
L-asparaginase (IV/IM), 30.000 IE/m^2	36–45	
Methotrexate (IT), 10–12 mg (age adjusted)	1, 8, 15, 29	
Intermediate-risk group*		
Early intensification (Weeks 7–14)		
6-mercaptopurine (oral), 60 mg/m^2	1–14, 29–42	
Cyclophosphamide (IV), 1000 mg/m^2	1, 29	
Cytarabine (IV), 75 mg/m^2	3–6, 10–13, 31–34, 38–41	
Methotrexate (IT), 10–12 mg (age adjusted)	1, 29	
Consolidation: Intermediate-risk group (Weeks 15–22)		
6-mercaptopurine (oral), 25 mg/m^2	1–56	
Methotrexate (IV), 5 g/m^2	8, 22, 36, 50	
Methotrexate (IT), 10–12 mg (age adjusted)	8, 22, 36, 50	
Late intensification (Weeks 24–30)		
Dexamethasone (oral), 10 mg/m^2/d	1–22/29	
Vincristine (IV), 2 mg/m^2 (max 2 mg)	1, 8, 15, 22	
Daunorubicin (IV), 30 mg/m^2	1, 8, 15, 22	
L-asparaginase (IV/IM), 30,000 IE/m^2	1, 8, 15, 22	
6-thioguanine (oral), 60 mg/m^2	29–42	
Cyclophosphamide (IV), 1000 mg/m^2	29	
Cytarabine (IV), 75 mg/m^2	31–34, 38–41	
Methotrexate (IT), 10–12 mg (age adjusted)	31, 38	
Maintenance (Week 32 to Year 2)		
6-mercaptopurine (oral), 75 mg/m^2	Until 2 years after diagnosis	
Methotrexate (oral), 20 mg/m^2	Once weekly until 2 years after diagnosis	
Methotrexate (IV), 5 g/m^2	1, 57, 113, 169, 225	
Prednisone (oral), 60 mg/m^2 × 7 days	29, 85, 141, 197, 253	
Vincristine (IV), 2 mg/m^2 (maximum, 2 mg)	29, 85, 141, 197, 253	
Methotrexate (IT), 10–12 mg (age adjusted)	1, 57, 113, 169, 225	
High-risk group		
Induction (Weeks 0–7)		See induction, Weeks 0–7
Early intensification (Weeks 7–14)		See intermediate-risk group: Weeks 7–14
Consolidation-1 HR (Weeks 16–26)		
Methotrexate (IV), 8 g/m^2	1, 43	
Cytarabine (IV), 2 g/m^2 × 2 daily	22–24, 64–66	
Methotrexate (IT), 10–12 mg (age adjusted)	1, 43	
Interim maintenance (Weeks 28–35)		
Prednisone (oral), 40 mg/m^2	1–8, 29–35	
Vincristine (IV), 2 mg/m^2	1, 29	
6-mercaptopurine (oral), 75 mg/m^2	1–57	
Methotrexate (oral), 20 mg/m^2	1–50 (Once weekly)	
Late intensification (Weeks 36–42)		See intermediate-risk group, Weeks 24–30
Consolidation 2 (Weeks 44–62)		
Methotrexate (IV), 8 g/m^2	1, 99	
Cytarabine (IV), 2 g/m^2 × 2 daily	22–24, 120–122	
Methotrexate (IT), 10–12 mg (age adjusted)	1, 99	
Prednisone (oral), 60 mg/m^2	43–49, 71–78	
Vincristine (IV), 2 mg/m^2 (maximum, 2 mg)	43, 71	
6-mercaptopurine (oral), 75 mg/m^2	43–98	
Methotrexate (oral), 20 mg/m^2	43–91 (Once weekly)	

(*continued*)

TABLE 1
(*Continued*)

Treatment phase and drug	Days given	Comments
Maintenance (Week 64 to Year 2)		
Prednisone (oral), 60 mg/m^2 × 7 days	1, 57, 113, 169, 225	
Vincristine (IV), 2 mg/m^2 (maximum, 2 mg)	1, 57, 113, 169, 225	
Methotrexate (IT), 10–12 mg (age adjusted.)	1, 57, 113, 169, 225	
6-mercaptopurine (oral), 75 mg/m^2	Until 2 years after diagnosis	
Methotrexate (oral), 20 mg/m^2	Once weekly until 2 years after diagnosis	
Very-high-risk group		
Weeks 0–42		Same as high-risk group
CNS therapy (Weeks 44–46)		
Cranial RT, 18 Gy	1–15	
6-mercaptopurine (oral), 50–75 mg/m^2	1–29	
Methotrexate (IT), 12 mg	1, 8, 15	
Maintenance (Weeks 48–95)		6 Cycles on Days 1–56
6-thioguanine (oral), 300 mg/m^2	1–4	
Methotrexate (IT), 12 mg	1	
Cyclophosphamide (IV), 600 mg/m^2	5	
Hydroxyurea (oral), 2400 mg/m^2	15–18	Cycles 1–4
Daunorubicin (IV), 30 mg/m^2	19	Cycles 1–4
Methotrexate (oral), 10 mg/m^2	29–32	
Carmustine (IV), 30 mg/m^2	33	
Cytarabine (IV), 150 mg/m^2	43–46	
Vincristine (IV), 2 mg/m^2 (maximum, 2 mg)	47	
Maintenance (Week 96 to Year 2)		
6-Mercaptopurine (oral), 75 mg/ m^2	Daily until 2 years after diagnosis	
Methotrexate (oral), 20 mg/m^2	Once weekly until 2 year after diagnosis	

IV indicates intravenous; IM, intramuscular, IT, intrathecal, Gy, grays.

* Intermediate risk in the Nordic Society of Pediatric Hematology and Oncology-92 protocol included pediatric patients age ≥10 years who were without other high-risk criteria.

ref. 16. The treatment consisted of an induction course that included high-dose cytarabine, a reinduction course in case the first induction course had not resulted in complete remission (CR), and 2 consolidation courses. CNS prophylaxis consisted of intravenous, high-dose cytarabine and 6 doses of intrathecal methotrexate without CNS irradiation. Higher risk was defined as the presence of Philadelphia chromosome, t(4,11); WBC $> 30 \times 10^9$/L, CNS-involvement, and/or remission after >1 course. For these patients, SCT was recommended in first CR (CR1). An allogeneic SCT using a related donor as a stem-cell source or an unrelated donor was recommended as a first option, and autologous SCT was recommended if a suitable allogeneic donor could not be found. The lower risk patients received maintenance chemotherapy for 2 years. The preparative regimens for SCT were determined according to institutional guidelines at each transplantation center.

Because the protocols differed significantly concerning induction treatment intensity, and because the response to induction was included in the risk stratification of both protocols, uniform pretreatment risk criteria were defined as follows: WBC $> 30 \times 10^9$/L, the presence of Philadelphia chromosome, t(4,11), or CNS involvement. Patients with mature B-ALL were treated according to the non-Hodgkin lymphoma Berlin-Frankfurt-Munster protocol (NHL-BFM 90) in both pediatric and adult hematology units.

In total, 144 patients with B-precursor ALL or T-cell ALL were treated according to the NOPHO-92 protocol in pediatric units, and 99 patients were treated according to the Adult protocol in adult units and were included in the protocol evaluation. Nine patients with mature B-cell ALL who were treated according to the NHL-BFM 90 protocol and 1 patient with natural killer cell ALL were excluded from the analyses. The evaluated patients represented 95% of all patients aged 10 to 40 years who were diagnosed with ALL in Sweden during the period (representing 100% of patients treated in the pediatric units and 89% of patients treated in adult units; $P < .01$; chi-square test). The median follow-up for patients who were alive at follow-up was 89 months (range, 29–144 months) for the NOPHO protocol group and 84 months (range, 28–126 months) for the Adult protocol group.

TABLE 2
Treatment Protocol: The Swedish Adult Acute Lymphoblastic Leukemia Group

Treatment phase and drug	Days given
Remission induction	
Methotrexate, 10 mg/m^2 (maximum, 15 mg) IT	1
Cyclophosphamide, 600 mg/m^2 IV	1
Vincristine, 2 mg IV	1
Cytarabine, 3 g/m^2 IV every 12 hours	1–3
β-methasone, 20 mg/m^2 orally	1–5
Consolidation I or 2nd induction	
Vincristine, 2 mg IV	1
Amsacrine, 200 mg/m^2 IV (2 hours)	1–3
Cytarabine, 3 g/m^2 IV	1–4
β-methasone, 20 mg/m^2 orally	1–5
Consolidation II	
Cyclophosphamide, 1000 mg/m^2 IV	1
Daunorubicin, 30 mg/m^2 IV	1–2
Etoposide, 100 mg/m^2 IV	1–5
β-methasone, 20 mg/m^2 orally	1–5
Consolidation*	
Vincristine, 2 mg IV	1
Amsacrine, 200 mg/m^2 IV	1–2
Cytarabine, 3 g/m^2 IV	1–3
β-methasone, 20 mg/m^2 orally	1–5
Maintenance (2 y)†	
6-mercaptopurine, 50–75 mg/m^2 orally	Daily
Methotrexate, 5–10 mg/m^2 orally	Once weekly
Reinductions first y	Every 2nd month
Daunorubicin, 40 mg/m^2 IV	1
Vincristine, 2 mg IV	1
Prednisone, 60 mg/m^2 orally	1–7
Reinductions 2nd y	Every 3rd month
Cytarabine, 60 mg/m^2 SC	1–5
Thioguanine, 80 mg/m^2 orally	1–5
Prednisone, 60 mg/m^2 orally	1–5

IT indicates intrathecal; IV, intravenous; SC, subcutaneously.

* The 2nd consolidation course was given if a second induction was required.

† Maintenance was given only to patients who did not undergo stem cell transplantation. Central nervous system prophylaxis consisted of the inclusion of IV high-dose cytarabine in the treatment blocks and 6 doses of IT methotrexate.

TABLE 3
Comparison of Nordic Society of Pediatric Hematology and Oncology-92 Protocol and Adult Protocols for Lower Risk Leukemia

	Protocol	
Drug	NOPHO-92	Adult
Prednisone*	4260 mg/m^2	3720 mg/m^2
Dexamethasone*	220 (290) mg/m^2	
β-methasone*		300 mg/m^2
Vincristine (total dose)	30 mg	16 mg
Doxorubicin	120 mg/m^2	
Daunorubicin	120 mg/m^2	390 mg/m^2
Cyclophosphamide	3000 mg/m^2	1600 mg/m^2
Cytarabine	1800 mg/m^2	31,200 mg/m^2
L-asparaginase	420,000 IE/m^2	
Etoposide		500 mg/m^2
Amsacrine		600 mg/m^2
Methotrexate, IV or oral	46,400 mg/m^2	740 mg/m^2
6-mercaptopurine	41,400 mg/m^2	38,850 mg/m^2
6-tioguanine	840 mg/m^2	1600 mg/m^2
Methotrexate IT	17 (number)	6 (number)
Steroids in all (expressed as predisone)*	5734 mg/m^2	6232 mg/m^2

NOPHO indicates Nordic Society of Pediatric Hematology and Hematology; IV, intravenous; IT, intrathecal.

* Total doses of steroids are expressed as predisone. The equipotent doses beta methasone 0.8 mg = dexamethasone 1 mg = prednisone 6.7 mg were used for the calculations.

Differences between the Pediatric and Adult Protocols

A comparison of the total doses of chemotherapeutic drugs for lower risk patients in the NOPHO-92 and Adult protocols is presented in Table 3. The main differences were 1) the exclusive use of asparaginase in the NOPHO-92 protocol; 2) the use of prednisone and dexamethasone in the NOPHO-92 protocol instead of beta methasone and prednisone in the Adult protocol; 3) cumulative doses of vincristine and cyclophosphamide approximately twice as high in the NOPHO-92 protocol; 4) doxorubicin instead of daunorubicin in the NOPHO-92 induction phase; 5) a generally more extensive use of methotrexate (both as intravenous high-dose infusions and intrathecal injections) in the NOPHO-92 protocol; and 6) the exclusive use of etoposide and amsacrine in the Adult protocol, and the use of high-dose cytarabine for all patients (only for high-risk patients on the NOPHO-92 protocol). The total dose of equipotent steroids was similar between the protocols. There also were differences in the disposition of the treatment. Patients with lower risk leukemia who were treated according to the NOPHO-92 protocol received a longer induction and consolidation therapy in a continuous fashion, with the start of maintenance at Week 32; whereas the Adult protocol included a block-based, intensive, but short induction and consolidation phase with the start of maintenance after approximately 15 weeks.

A similar comparison between the 2 protocols for patients with higher risk leukemia was difficult to make. In the NOPHO-92 protocol, the treatment strategy still was continuous therapy but with higher treatment intensity for a longer time and with the start of maintenance after 64 weeks or 95 weeks. The Adult protocol started with block-based induction and consolidation phases (similar to what was used for standard-risk patients, except for a reinduction course for slow responders) and recommended SCT instead of maintenance therapy.

Statistical Analysis

The likelihood of EFS was calculated based on the time from diagnosis to recurrence or death in CR, and

patients in continuous remission were censored. Patients who died during remission induction or who did not achieve CR on the prescribed protocol were classified as having an event at the time point zero. EFS was estimated using the Kaplan–Meier method, and differences in outcome distribution between the patient subgroups were tested using the log-rank test. Prognostic factors for EFS were evaluated by univariate and multiple analyses using the Cox proportional hazards regression method. Ninety-five percent confidence intervals (95% CIs) were obtained both for the regression analyses and for the survival probability estimates. Comparisons of patient characteristics between subgroups were performed by using the chi-square test or the Fisher exact test for comparison of proportions and the Mann–Whitney *U* test or Kruskall–Wallis test for comparison of continuous parameters. Two-tailed tests with $P < .05$ were considered significant.

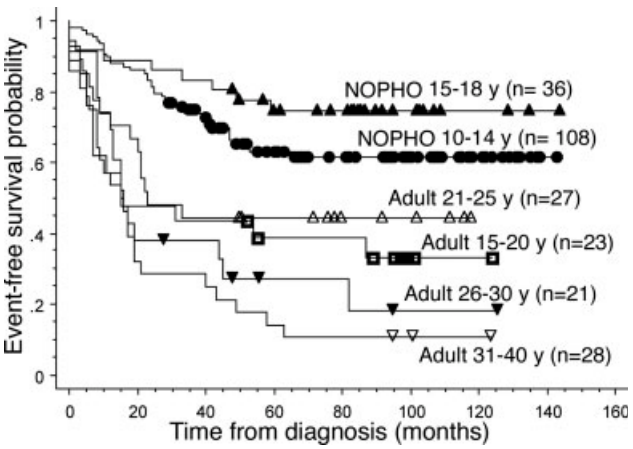

FIGURE 1. Event-free survival is illustrated for patients divided according to age and treatment protocol. NOPHO indicates Nordic Society of Pediatric Hematology and Oncology.

RESULTS

Treatment of Adolescents and Basis for Division into Age Groups

The group of 59 adolescents (aged 15–20 years) included 36 patients who were treated in pediatric units (mean age 15.6 years; range, 15–18 years) and 23 patients who were treated in adult units (mean age, 18.2 years; range, 15–20 years. The 5-year EFS was 74% (95% CI, 60–89%) for patients who were treated according to the NOPHO-92 protocol and 39% (95% CI, 19–59%) for patients who were treated according to the Adult protocol ($P < .01$). Five of 36 patients in the pediatric group (14%) and 9 of 23 patients in the adult group (39%) had pretreatment high-risk factors ($P = .03$; chi-square test). Because there was an uneven distribution of patients who had high-risk factors and the numbers of patients in each group were relatively small, an alternative grouping of patients for further statistical analyses was used.

The patients who were treated according to the NOPHO-92 protocol initially were divided into 2 groups (aged 10–14 years and 15–18 years), and the adults were initially divided into 4 groups (aged 15–20 years, 21–25 years, 26–30 years, and 30–40 years), and the EFS rates for each of these groups were calculated (Fig. 1). Because we did not want to bias the comparison by the "dilution" of NOPHO adolescents with younger children who had lower risk features and better outcomes, we compared the groups aged 10 to 14 years and 15 to 18 years. However, neither clinical characteristics nor outcomes were better in the younger group. The same comparison was used for the groups aged 15 to 20 years and 21 to 25 years who received the Adult protocol; the clinical characteristics were similar, and the outcomes were not better for younger group. Therefore, we believed it was justified to form 3 prognostic groups with comparable EFS: 1) patients aged 10 to 18 years who were treated on the NOPHO-92 protocol, 2) patients aged 15 to 25 years who were treated on the Adult protocol, and 3) adult patients aged 26 to 40 years. These age groups were used in the subsequent analyses.

Patient Characteristics According to Age Group and Protocol

The patient characteristics according to age group and protocol are shown in Table 4. The median WBC values were significantly higher in the adult groups compared with the pediatric group, but the proportion of patients with WBC $> 30 \times 10^9$/L or $>50 \times 10^9$/L did not differ between the groups. There were significantly more patients with hyperdiploidy (51–61 chromosomes) but fewer with the Philadelphia chromosome ($P < .01$) or t(4,11) in the pediatric group compared with the adult groups. In the adult group aged 15 to 25 years, T-cell phenotype was less common. Four patients with Mb Down were included in the pediatric group.

Response to Initial Treatment and Induction Deaths

The CR-rate for patients who were treated according to the NOPHO-92 protocol was 99% (CR on Day 29 during induction), and it was 90% for patients who were treated according to the Adult protocol (CR after 1 or 2 courses; $P < .01$). There was no difference between the 2 adult age groups. The frequency of in-

TABLE 4
Patient Characteristics According to Protocol and Age

Characteristic	*P**	NOPHO protocol (Aged 10–18 years)	Adult protocol	
			Aged 15–25 years	Aged 26–40 years
No. of patients		144	50	49
Median age, y	<.01†	13	21	32
Gender (male/female)	NS*	86/58	26/24	30/19
WBC (median, range)	.03†	5.5 (0–400)	13 (1.1–308)	14 (1.7–460)
WBC >30 × 10^9/L	NS*	38	14	16
WBC >50 × 10^9/L	NS*	31	11	12
CNS involvement	NS*	4	4	5
Immunophenotype	.02*			
B precursor		112	46	35
T cell		31	4	14
Unknown		1		
Cytogenetics				
t(9,22)/bcr/abl	<.01*	5	8	11
t(4,11)	<.01*	0	4	3
Hyperdiploid (51–62)	<.01*	21	0	2

NOPHO indicates Nordic Society of Pediatric Hematology and Hematology; NS, not significant; WBC, white blood cell count; CNS, central nervous system.

* Chi-square test.

† Kruskall–Wallis test.

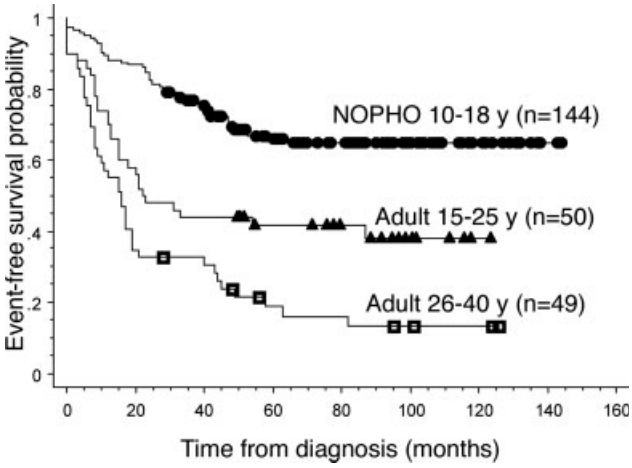

FIGURE 2. Outcomes are illustrated for patients who were treated according to the Nordic Society of Pediatric Hematology and Oncology (NOPHO) protocol and the adult protocols. The 5-yearevent-free survival rate was 66% (95% confidence interval [95% CI], 58–74%) for the NOPHO-92 group (aged 10–18 years), 42% (95% CI, 28–56%) for the adult protocol group aged 15 to 25 years, and 19% (95% CI, 7–31%) for the adult protocol group aged 26 to 40 years.

duction deaths was 1% for the NOPHO-92 protocol versus 2% for the Adult protocol (not significant).

Survival Analyses

Significant differences in EFS were observed between the NOPHO-92 protocol group (aged 10–18 years) and both Adult protocol groups (aged 15–25 years and 26–40 years) (Fig. 2). In addition, a significant difference was observed between the adult groups aged 15 to 25 years and 26 to 40 years. There were no significant differences in EFS between patients with B-precursor All and T-cell ALL within the groups: The 5-year EFS rate for the NOPHO-92 protocol group aged 10 to 18 years was 67% (95% CI, 58–76 %) for patients with B-precursor ALL versus 65% (95% CI, 48–81%) for patients with T-cell All; for the Adult protocol group aged 15 to 25 years, the 5-year EFS rate was 43% (95% CI, 29–58%) for patients with B-precursor ALL versus 25% (95% CI, 0–67%) for patients with T-cell ALL; and, for the Adult protocol group aged 26 to 40 years, the 5-year EFS rate was 22% (95% CI, 9–36%) for patients with B-precursor ALL versus 9% (95% CI, 0–25%) for patients with T-cell ALL. For the group without pretreatment risk criteria, for the NOPHO-92 protocol group aged 10 to 18 years, the 5-year EFS rate was 71% (95% CI, 62–80%); for the Adult protocol group aged 15 to 25 years, the 5-year EFS rate was 47% (95% CI, 29–66%); and, for the Adult protocol group aged 26 to 40 years, the 5-year EFS rate was 22% (95% CI, 4–40%; $P < .01$; log-rank, overall test) (Fig 3A). For the group with pretreatment risk criteria, the 5-year EFS rate was 53% (95% CI, 37–68%) for the NOPHO-92 protocol group aged 10–18 years, 33% (95% CI, 13–54%) for the Adult protocol group aged 15 to 25 years, and 17% (95% CI, 2–32%) for the Adult protocol group aged 26 to 40 years ($P < .01$; log-rank test) (Fig. 3B). There was no significant difference in outcome between the 2 Adult protocol groups in the high-risk population.

The cause of death was associated mainly with recurrence of leukemia. The most common site of relapse was bone marrow in both protocol groups, and 4.9% of relapses involved the CNS in the pediatric group. The reporting of relapse site was incomplete in the adult group, but CNS relapses did not seem more common than in the NOPHO group. In fact, of 37 reported relapse sites, 3 involved the CNS, corresponding to an estimated CNS recurrence frequency of approximately 5%. The frequency of deaths in CR1 was low for all groups (range, 3–8%).

SCT in first remission was a part of the treatment for 14 of 144 patients (10%) in the pediatric group and for 41 of 99 patients (41%) in the adult group. All pediatric patients received an allograft (7 of 14 from a related donor, 6 of 14 from an unrelated donor, and 1 from an unreported donor); whereas, in the adult

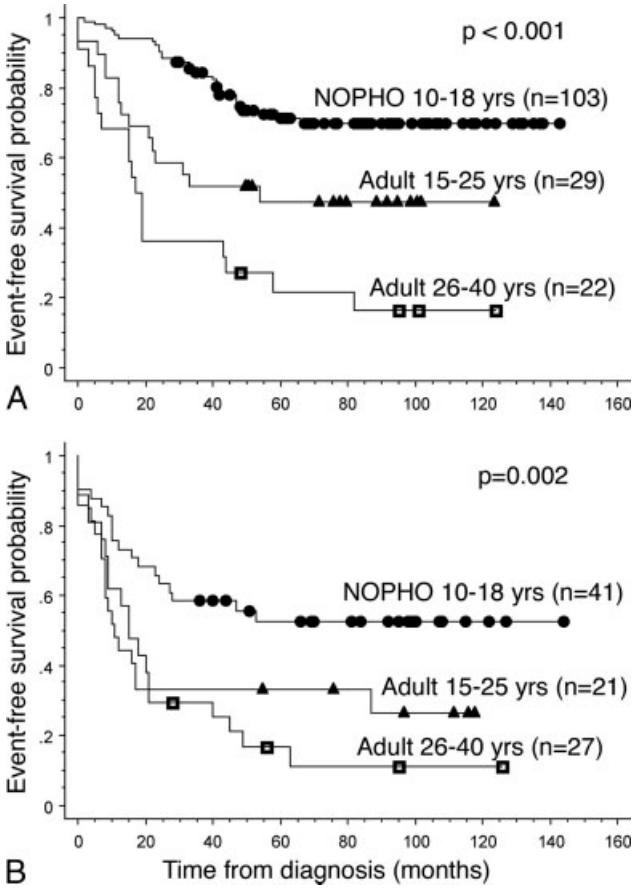

FIGURE 3. Five-year event-free survival for (A) lower risk patients and (B) higher risk patients according to pretreatment characteristics (white blood cells $> 30 \times 10^9$/L, the presence of Philadelphia chromosome, t[4,11], or central nervous system leukemia). NOPHO indicates Nordic Society of Pediatric Hematology and Oncology.

group, 10 patients (24%) underwent autologous SCT, and 31 patients (76%) underwent allogeneic SCT (16 from a related donor and 15 from an unrelated donor): The 5 year EFS rates were 42% (95% CI, 15–68%) and 29% (95% CI, 15–43%), respectively ($P = .41$). The treatment-related mortality for patients who underwent SCT was 21% for the pediatric group and 17% for the adult group.

Regression Analysis of Prognostic Factors

Univariate and multivariate regression analyses were used to evaluate the impact of prognostic factors on EFS. In the multivariate analysis of the entire cohort, WBC, CNS involvement, the presence of Philadelphia chromosome, and treatment protocol were identified as independent risk factors (Table 5). When the group aged 15 to 20 years ($n = 59$ patients) was analyzed separately, treatment protocol remained as the only significant factor.

When the pediatric and adult groups were analyzed separately in a multiple model, only WBC count remained an independent risk factor in the pediatric group (Table 5). In the adult patients, age group (26–40 years vs. 15–25 years), CNS leukemia, and the presence of Philadelphia chromosome were identified as independent risk factors. The impact of CNS leukemia and age should be interpreted with caution because of the multiple comparisons.

DISCUSSION

We evaluated the clinical characteristics and outcomes of patients with ALL aged 10 to 40 years from a population-based national perspective. Like previous studies, the proportion of adult patients who were treated according to the national protocol (89%) was lower than the proportion of adolescents with ALL who reportedly were treated on protocol in pediatric units (100%).[17,18] However, the reported adherence to protocol was high in both groups. Several explanations for the differences in prognosis between children and adults have been considered: higher WBC values and more frequent T-cell phenotype in adults, more common favorable cytogenetics (such as hyperdiploidy) in young children, and more frequent adverse karyotypes (t[9;22] and t[4;11]) with increasing age.[19] In addition, ALL cells from adults have shown reduced sensitivity to chemotherapy and steroids in vitro[20] as well as decreased concentrations of methotrexate polyglutamates compared with leukemic cells from children.[21] Furthermore, poor performance status hampers the administration of intensive chemotherapy in elderly patients.[22]

In the current investigation, the 2 adult groups had a higher incidence of Philadelphia chromosome and t(4,11) and a lower incidence of hyperdiploidy compared with the pediatric group, similar to previous studies. The median WBC was, as expected, was higher in the adult groups, but the fraction of patients with high WBC did not differ between the groups. However, chemotherapy was tolerated relatively well, and the frequency of induction death and death in CR was low in all 3 groups.

The NOPHO-92 protocol resulted in better survival compared with the Adult protocol for adolescents aged 15 to 20 years. The comparison was complicated by the uneven distribution of clinical and genetic pretreatment high-risk factors. These differences were less pronounced but remained significantly different when patients aged 10 to 14 years were included in the pediatric group and when the

TABLE 5
Multiple-Model Cox Regression Analyses of Factors Associated With Event-Free Survival

	Entire cohort		Teenage cohort (Aged 15–20 years)			Pediatric cohort (Aged 10–18 years)		Adult cohort (Aged 15–40 years)	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**Variable**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Entire cohort and teenage cohort (aged 15–20 y)					Pediatric cohort (aged 10–18 y) and adult cohort (aged 15–40 y)				
Age group (continuous)	1.02 (0.99–1.06)	.20			Aged 15–18 years (vs. aged 10–14 years)	0.79 (0.37–1.68)	.54		
					Aged 26–40 years (vs. aged 15–25 years)			1.68 (1.02–2.77)	.04
Male gender (vs. female)	1.10 (0.74–1.63)	.63	0.99 (0.40–2.45)	.98	Male gender (vs. female)	1.16 (0.62–2.16)	.64	0.83 (0.48–1.43)	.51
WBC (continuous)	1.003 (1.001–1.005)	.009	1.002 (0.996–1.008)	.57	WBC (continuous)	1.005 (1.001–1.009)	.009	1.002 (0.998–1.005)	.33
CNS leukemia present (vs. absent)	1.94 (0.996–3.79)	.05			CNS leukemia present (vs. absent)	1.26 (0.28–5.60)	.76	2.22 (1.01–4.83)	.04
t(9,22) or bcr/abl present (vs. absent)	2.62 (1.53–4.50)	<.001	2.58 (0.61–11.0)	.20	t(9,22) or bcr/abl present (vs. absent)	1.87 (0.55–6.36)	.32	2.74 (1.48–5.07)	.001
Precursor B (vs. T immunophenotype)	0.87 (0.52–1.47)	.61	0.35 (0.09–1.38)	.14	Precursor B (vs. T immunophenotype)	1.80 (0.65–5.02)	.26	0.61 (0.30–1.23)	.17
Adult protocol (vs. pediatric protocol)	2.30 (1.24–4.25)	.008	4.01 (1.48–10.90)	.006					

HR indicates hazards ratio; 95% CI, 95% confidence interval; WBC, white blood cell count; CNS, central nervous system.

corresponding adult group was expanded to include patients aged 15 to 25 years. However, when common pretreatment risk criteria were applied, a significant difference in outcome remained between the pediatric group aged 10 to 18 years and the adult group aged 15 to 25 years, both for higher risk patients and lower risk patients. Because of the difference in risk factors, the comparison carried more weight for the "lower risk" patients. Cox regression analysis, which included multiple models, confirmed that treatment protocol (together with the presence of Philadelphia chromosome) was the factor that had the most pronounced impact on the outcome, and treatment protocol remained the only significant factor in a multiple-factor Cox model when patients aged 15 to 20 years were analyzed separately.

The NOPHO-92 and Adult protocols differed in several ways. The NOPHO-92 protocol had longer induction and consolidation phases and more continuous treatment with a later start of maintenance compared with the Adult protocol. Asparaginase and high-dose methotrexate were prominent features in the NOPHO-92 protocol and are well recognized as efficacious drugs for the treatment of ALL.[23] The absence of these drugs was not counterbalanced by the extensive use of high-dose cytarabine. The high cumulative dose of vincristine in the NOPHO-92 protocol also may be important, because vincristine is a prominent part of many ALL treatment protocols. It should be noted that, for the patients with adverse cytogenetics, e.g., t(9;22) and t(4;11), it is not likely that these changes alone would alter the treatment results drastically. The outcome of these selected high-risk patients in current pediatric protocols is much worse than the outcome for other pediatric patients. Ongoing studies (both in adults and children) that include tyrosine kinase inhibitors such as imatinib, is likely will contribute more to the improved outcome of these groups.

SCT was a part of the treatment strategy for a much greater fraction of the adult patients compared with the pediatric patients. However, 25% of SCT procedures were autologous transplantations. Furthermore, the indication for SCT in CR1 in the Adult protocol was a combination of pretreatment high-risk criteria and poor response, which, together with the uneven distribution of high-risk factors at diagnosis, makes the comparison difficult. With these factors in mind, it appears that the adult high-risk treatment based on SCT in CR1 was relatively more successful than the protocol for lower risk leukemia, because the difference in outcome between the pediatric and adult protocols was less pronounced for the high-risk patients. Only prospective studies of adults treated with the pediatric strategy will elucidate whether response to initial treatment will increase the fraction of "lower risk" patients by a reduction of poor responders. It is noteworthy that the outcome in the adult high-risk group was not hampered by a high treat-

ment-related mortality rate, although both protocols had acceptable toxicity. The adult CNS-directed therapy that was based mainly on high-dose cytarabine in the Adult protocol did not appear to be associated with a higher CNS-involved recurrence rate, but this was offset by the high rate of bone marrow recurrence.

The current investigation is in accord with the previously published comparisons from France[12] and the Netherlands.[13] Treatment protocols are always difficult to compare; however, in both the French and Dutch adult protocols (as in the Swedish comparison), the total doses of vincristine and asparaginase were lower than in the corresponding pediatric protocols. In the Dutch adult protocol, treatment-related mortality was considerably higher than in the corresponding pediatric protocol. Recurrence remained the main cause of treatment failure, especially in the adult group. The significant difference observed between the adult protocol groups aged 15 to 25 years and aged 26 to 40 years (especially for the pretreatment "lower risk" patients) may have been caused by decreased sensitivity to chemotherapy with increased age, as discussed earlier.

In conclusion, the results of the current study demonstrated that the treatment of older children and adolescents with ALL using the Nordic Pediatric protocol resulted in higher CR rates and increased survival compared with adolescents and young adults who were treated according to a Swedish national Adult ALL protocol. The death rates in CR1 were comparable, but the recurrence rate was significantly higher for the Adult protocol. These results confirm previous comparisons between pediatric and adult protocols for adolescents and support the notion that other risk factors and treatment protocols contribute more to the outcome than age. However, older age does seem to remain a risk factor within the adult group, and the distribution of leukemia characteristics (Philadelphia chromosome and CNS leukemia) indicates a different biology of the disease with increasing age.

The results indicate that adolescents may benefit from a treatment strategy more in line with the NOPHO-92 protocol. Prospective trials are warranted to confirm these results and to determine whether young adults would benefit from similar treatment. These results have lead to a reconsideration of treatment protocols for adolescents and young adults with ALL in Sweden.

REFERENCES

1. Pui CH, Boyett JM, Rivera GK, 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;14:2286–2294.
2. Gustafsson G, Schmiegelow K, Forestier E, 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: 2267–2275.
3. Gaynon PS, Trigg ME, Heerema NA, et al. Children's Cancer Group trials in childhood acute lymphoblastic leukemia: 1983–1995. *Leukemia.* 2000;14:2223–2233.
4. Gustafsson G, Kreuger A, Clausen N, 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;87:1151–1161.
5. Thomas X, Boiron JM, Huguet F, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. *J Clin Oncol.* 2004;22:4075–4486.
6. Rowe JMB, Burnett G, Chopra AK, et al. Induction therapy for adults with acute lymphoblastic leukemia ALL: results of nearly 1400 patients from the International ALL Trial (MRC UKALLXII/ECOG E2993. *Blood.* 2003;102:785a. Abstract.
7. Gokbuget NA, Buechner R, Ganser TA, et al. Intensification of induction and consolidation improves only subgroups of adult ALL: analysis of 1200 patients in GMALL study 05/93. *Blood.* 2001;98:802a. Abstract.
8. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol.* 2000;18:547–561.
9. Larson RA, Dodge RK, Linker CA, et al. A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. *Blood.* 1998; 92:1556–1564.
10. Annino L, Vegna ML, Camera A, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. *Blood.* 2002;99: 863–871. Abstract.
11. Dekker AW, van't Veer MB, van der Holt B, et al. Postremission treatment with autologous stem cell transplantation (auto-SCT) or allogeneic stem cell transplantation (allo-SCT) in adults with acute lymphoblastic leukemia (ALL). A Phase II clinical trial (HOVON 18 ALL). *Blood.* 2001;98: 3567a. Abstract.
12. Boissel N, Auclerc MF, Lheritier V, 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;21:774–780.
13. 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 versus adult protocols in the Netherlands. *Leukemia.* 2004;18:2032–2035.
14. Horibe K, Tsukimoto I, Ohno R. Clinicopathologic characteristics of leukemia in Japanese children and young adults. *Leukemia.* 2001;15:1256–1261.
15. Stock W, Sather H, Dodge RK, Bloomfield CD, Larson RA, Nachman J. Outcome of adolescents and young adults with ALL: a comparison of Children's Cancer Group (CCG) and Cancer and Leukemia Group B (CALGB) regimens. *Blood* 2000;96:467a. Abstract.
16. Hallbook H, Simonsson B, Ahlgren T, et al. High-dose cytarabine in upfront therapy for adult patients with acute lymphoblastic leukaemia. *Br J Haematol.* 2002;118:748–754.

17. Benjamin S, Kroll ME, Cartwright RA, et al. Hematologists' approaches to the management of adolescents and young adults with acute leukaemia. *Br J Haematol.* 2000;111:1045–1050.
18. Stiller CA, Eatock EM. Patterns of care and survival for children with acute lymphoblastic leukaemia diagnosed between 1980 and 1994. *Arch Dis Child.* 1999;81:202–208.
19. 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;12:463–473.
20. Styczynski J, Pieters R, Huismans DR, Schuurhuis GJ, Wysocki M, Veerman AJ. In vitro drug resistance profiles of adult versus childhood acute lymphoblastic leukaemia. *Br J Haematol.* 2000;110:813–818.
21. Goker E, Lin JT, Trippett T, et al. Decreased polyglutamylation of methotrexate in acute lymphoblastic leukemia blasts in adults compared to children with this disease. *Leukemia.* 1993;7:1000–1004.
22. Hussein KK, Dahlberg S, Head D, et al. Treatment of acute lymphoblastic leukemia in adults with intensive induction, consolidation, and maintenance chemotherapy. *Blood.* 1989; 73:57–63.
23. Abromowitch M, Ochs J, Pui CH, et al. High-dose methotrexate improves clinical outcome in children with acute lymphoblastic leukemia: St. Jude Total Therapy Study X. *Med Pediatr Oncol.* 1988;16:297–303.