

Acute lymphoblastic leukemia in adolescents between 10 and 19 years of age in Denmark – secondary publication

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ABSTRACT

Introduction: Data seem to indicate that young adults with acute lymphoblastic leukemia (ALL) have a better survival when treated with pediatric protocols compared with adult ALL protocols. The purpose of the study was to report the clinical characteristics and outcome of all children and young adults 10-19 years of age diagnosed with ALL in Denmark between 1992 and 2001.

Material: The study includes 99 patients 10-19 years of age with ALL in Denmark during a ten year period found in the complete NOPHO (Nordic Society of Pediatric Hematology and Oncology) registry and through the Danish Cancer Registry and local pathology databases. Data were retrieved by reviewing medical charts of the patients. A total of 61 children (10-14 years) treated on pediatric protocols and 38 young adults (15-19 years) were diagnosed with ALL. Data were reported as of January 1st 2005.

Results: There were no difference with respect to the distribution of T-ALL, CNS-leukemia, total white blood count and high risk chromosomal abnormalities between the two groups. There was a statistical significant lower event free survival ($p < 0.01$) and lower overall survival ($p < 0.01$) in young adults compared with 10-14 year-old children (0.38 vs 0.60 and 0.47 vs 0.67). There were more transplant-related deaths in the young adults. Higher treatment intensity in children may be an additional explanatory factor. Children received more prednisone, vincristine and high-dose methotrexate than young adults.

Conclusion: Young adult patients with ALL might benefit from therapy with pediatric NOPHO ALL protocols.

Acute lymphoblastic leukemia (ALL) is the most common cause of leukemia in children with an annual incidence of 3.5 cases per 100,000 children below 15 years of age. Event free survival (EFS) is about 80% for the two thirds of children without clinical high risk criteria at diagnosis (1). In Denmark patients with ALL below 15 years of age at the time of diagnosis have been treated at the four Danish centers for pediatric oncology, whereas patients 15 years or older at diagnosis have been treated at five Departments of Hematology traditionally. Since 1981 all cases of childhood ALL have been reported to the Nordic ALL database, and since 1992 >95% of children below 15 years of age have been treated according to uniform Nordic ALL protocols (2).

60% of ALL is diagnosed in children below 15 years of age, and about 7% are diagnosed in young adults 15-20 years of age (3). The prognosis for ALL in adults is worse than for children with decreas-

ing EFS rates with increasing age (3, 4). The difference may be caused by increased incidence of adverse risk factors (eg t(9;22) and T-ALL) decreased incidence of good-risk cytogenetic abnormalities (eg t(12;21) and hyperdiploidy), poorer sensitivity of leukemia cells to chemotherapy and poorer tolerance to intensive chemotherapy compared with younger patients with ALL (5).

The distinction between children and adults at 15 years of age is an arbitrary one, mostly dictated by tradition and by the practical organization of the treating departments. Childhood ALL protocols are often quite different from treatment protocols used in adult patients. Because of increasing intolerance of chemotherapy with increasing age protocols are designed to be tolerated by the entire adult ALL population. However, young adults may tolerate more dose-intensive chemotherapy than older patients.

Recently four papers have demonstrated that young adults with ALL being treated on "adult ALL-protocols" had a significantly worse prognosis compared to young adults treated on "pediatric ALL-protocols" although the initially known risk factors did not vary (6-9). It was suggested that young adult patients with ALL might benefit from treatment with pediatric protocols (6).

The purpose of this paper is to report the clinical characteristics and outcome of all Danish patients 10-19 years of age with ALL treated over a ten year period with either pediatric or adult protocols with special emphasis on the two age groups, 10-14 years of age and 15-19 years of age.

MATERIAL AND METHODS

During the ten year period 1992-2001 99 children 10-19 years of age were diagnosed with ALL in Denmark. The diagnosis was made by standard analysis of bone marrow biopsies and aspirates and flow-cytometry of peripheral blood and bone marrow aspirates. Metaphases of bone marrow blasts were analysed for cytogenetic abnormalities. The diagnosis of ALL was made when there were more than 25% leukemic cells in the bone marrow. CNS infiltration was diagnosed when there were more than five leucocytes/microliter in the spinal fluid and unequivocal blasts were detected on cytopsin preparations. Patients were divided into two groups according to treatment. Group 1 were diagnosed and treated in four pediatric departments according to the Nordic pediatric ALL protocols, and group 2 were treated in five adult hematological departments.

GROUP 1

Sixtyone children 10-14,99 years of age with ALL treated at one of the four departments of pediatrics according to the common Nordic ALL 1992 protocol (2). Treatment was stratified according to risk criteria. All children were by definition treated either as intermediate risk (IR) (because of age ≥ 10 years of age at diagnosis) or high risk (HR). High risk criteria were, white blood count (WBC) $\geq 50 \times 10^9/l$, T-ALL, mediastinal mass, CNS leukemia, testicular leukemia, translocation t(9;22) and t(1;19) and >5% leukemic blast in the bone marrow four weeks after start of the induction therapy.

Induction treatment lasted six weeks and consisted of six weekly injections of vincristine, three infusions of doxorubicin, six weeks of oral prednisone and four intrathecal instillations of methotrexate. Consolidation and reinduction-maintenance therapy lasted from day 36 to 200 (IR) and from day 36 to 430 (HR). The therapy consisted of frequently rotating pulses of chemotherapy, asparaginase, vincristin-prednisone reinductions, high-dose methotrexate (HD-MTX) infusions 5 g/m² (IR) or 8 g/m² (HR) and high dose cytarabine (HR). Children with IR ALL received a total of 17 intrathecal MTX injections. Children with HR ALL had 16 intrathecal MTX injections and cranial irradiation 18 Gy. From day 200 (IR) and day 430 (HR) maintenance therapy consisted of daily 6-mercaptopurine orally and weekly oral MTX until 24 months after the time of diagnosis. Four children had an allogeneic stem cell transplantation (SCT) in first complete remission (CR). All data were registered prospectively in the Nordic ALL database.

GROUP 2

Thirtyeight patients 15-19 years of age at diagnosis were diagnosed with ALL in the ten year period. Patients were retrieved from the Danish Cancer Registry and from local pathology databases at the five centers of hematology in Denmark. All medical records were reviewed for relevant clinical data. Two patients (15 years of age) were treated at pediatric departments with NOPHO-ALL protocols. Their data regarding clinical characteristics are included in the group of children >14 years of age, but information regarding their survival is not included in either group. Two patients were excluded from the survival analyses in this group because of very limited or no therapy (one patient with Down's syndrome and congenital cyanotic heart disease and one patient who was a Jehova's witness, both patients have died). That leave 34 patients 15-19 years eligible for the survival analyses.

The treatment protocols for ALL varied in the five departments of hematology but were mainly based on protocols from the Cancer and Acute Leukemia Group B (CALGB) or CHOP-like protocols followed by delayed intensification as for lymphoblastic lymphoma (10). The CNS-directed therapy consisted of 4-7 intrathecal injections of cytostatics and cranial irradiation. Following consolidation therapy maintenance therapy with daily oral 6-mercaptopurine and weekly oral MTX was given until 24 months after the time of diagnosis. Patients with initial high risk criteria were candidates for allogeneic SCT. High risk criteria were, WBC >30 × 10⁹/l in patients with pre-B-ALL, pro-B-ALL, translocation t(9;22) and t(4;11) and other translocations including the 11q23 region, and CR later than four weeks after start of induction therapy. Seven patients had an allogeneic SCT in first CR.

STATISTICAL ANALYSES

The statistical analyses were performed with SPSS version 12.0. EFS and overall survival (OS) were calculated from the date of diagnosis until the time of last follow-up or the time of event (death during induction therapy before remission, relapse or death in CR). EFS and OS were calculated according to the Kaplan-Meier method and statistical differences were examined with the log-rank test. Differences in mean values between the two groups were tested with the ANOVA analysis of variance, and differences in the distribution of the clinical parameters between the two groups were tested by the Chi-square test. P-values <0.05 were considered as statistically significant.

RESULTS

CLINICAL CHARACTERISTICS

The most important clinical characteristics are shown in Table 1. It is seen that there are no significant differences between the two groups of patients with respect to the distribution of various high risk criteria, except for the median age.

COMPLETE REMISSION

In group 1 59/61 (97%) obtained CR within 4-5 weeks after start of treatment. One child never achieved remission, and another one died from infection before CR was reached. During first CR two children died from toxicity, one child after allogeneic SCT and another one from a fulminant septicaemia caused by *E. coli*.

In group 2 all patients achieved CR, but in three patients it was not reached until after 4-6 months of intensive chemotherapy. Four patients died during first CR all following allogeneic SCT (Table 2)

RESULTS OF ALLOGENEIC STEM CELL TRANSPLANTATION

Group 1

Four children were transplanted in CR 1 all with a matched unrelated donor (MUD). One child died from toxicity and one from relapse; two children are alive in first CR 43 and 63 months after SCT.

After 1. relapse 7/17 children were transplanted in CR 2. Three children have died from a new recurrence of their disease and four

children are alive in CR 2 26, 53, 101 and 104 months after SCT (Table 3).

Group 2

Seven young adults were transplanted in CR1, of whom five have died, three from toxicity within three months after SCT and two patients from disease recurrence. Two patients are alive in CR 1 72 and 122 months after SCT. Besides, two patients had an autologous bone marrow transplant, of whom one died from encephalitis and one patient is alive 132 months later.

After first relapse seven patients were transplanted in CR 2. Six patients died, three from acute graft versus host disease (GVHD) and three from a second relapse. One patient is alive 18 months after an isolated testicular relapse (Table 3).

RELAPSE

29% of the children in group 1 developed a recurrence of their leukemia at a median time of 27 months after diagnosis. Among the young adults 47% experienced disease recurrence at a median time

Table 1. Patient characteristics.

	10-14 years group 1	15-19 years group 2
Number	61	38
Median age, years	12	17
Males, n	37 (61%)	27 (71%)
Median/mean WBC, × 10 ⁹ /l	5.0/32	8.0/51
WBC ≥ 50, n	12 (20%)	7 (18%)
WBC ≥ 100, n	6 (10%)	7 (18%)
T-ALL, n	15 (24%)	4 (12%)
CNS leukemia, n	1 (2%)	4 (12%)
Cytogenetics		
t (9;22)	3/50 (6%)	2/22 (9%)
t (4;11)	0	0
hypodiploidy <45 chromosomes	1/50 (2%)	2/22 (9%)
hyperdiploidy	10/50 (20%)	3/22 (14%)
Cytogenetics non available	11/61 (18%)	15/37 (40%)
Treatment protocol		
Increased risk	36 (59%)	-
High risk	25 (41%)	-

WBC: white blood count.

Table 2. Overall results.

	10-14 years group 1	15-19 years group 2
Number	61	34
Induction failure, n	2	0
Dead during induction, n	1	0
Resistant disease, n	1	0
Complete remission, n	59	34
Relapse, n	17 (29%)	16 (46%)
Dead in first complete remission	2/59	4/34
Number in continuous complete remission	40/61 (66%)	14/34 (41%)
Number alive 010104	44/61 (72%)	15/34 (44%)

Table 3. Results after allogeneic bone marrow transplantation. Number of patients*.

	Group 1	Group 2
Allo-BMT first remission total	4 (2)	7 (2)
Sib	-	4 (2)
MUD	4 (2)	3 (0)
Other	-	-
Allo-BMT second remission total	7 (4)	7 (1)
Sib	2 (1)	1 (1)
MUD	5 (3)	4 (0)
Other	-	2 (0)

* number of survivors in parantheses. BMT: Bone marrow transplantation. Sib: Fully matched sibling donor; MUD: Matched unrelated donor; Other: haploidentical family donor.

of 14 months after diagnosis. There were no obvious differences in the localisation of the relapses between the two groups. After first recurrence four children below 15 years of age and one young adult are alive in continuous CR 2.

EVENT FREE SURVIVAL AND OVERALL SURVIVAL

There was a significantly higher EFS and OS among the 10-14 year old patients compared with the young adults (0.60 vs 0.38 and 0.67 vs 0.47, $p < 0.01$) (Figure 1 and Figure 2). For comparison the EFS and OS are shown in Figure 1 and Figure 2 for all Danish children with ALL between 1 and 10 years of age treated during the same period with the same treatment protocol.

DISCUSSION

The prognosis for ALL in children has improved considerably within the last 20-25 years. No corresponding improvement has been observed in adults with ALL (3, 4). It may be caused by the fact that adults do not tolerate the same intensification of the chemotherapeutic treatment as children do, and that adults with ALL have more high risk criteria. Besides it is a wellknown fact that only few adult patients with ALL are enrolled into clinical trials (11, 12).

This Danish study including all children and young adults between 10 and 19 years of age with ALL over a ten year period has shown that young adults between 15 and 19 years of age do not have an increased prevalence of high risk criteria compared with children 10-14 years of age as demonstrated also by others (6, 7, 13). Our study has also demonstrated a significantly better EFS and OS for children compared with the young adults. Thus we have confirmed the findings of other recent reports of the survival of young adults with ALL reporting better results for those young adults who were treated with pediatric protocols compared with those being treated with "adult" ALL protocols (6, 7, 9, 13). In contrast to other studies we report the results for two different age groups. Considering the fact, that the two groups are comparable with respect to all known risk factors we think that the comparison of our two groups of patients is relevant, in as much as the "age-limit" of 15 years for treatment according to pediatric versus adult protocols is an arbitrary

one not dictated by pharmacokinetic or toxicological differences between patients below or over 15 years of age. Our conclusions are also supported by the fact that international groups are using common ALL treatment protocols for patients up till 18 (14) or even 21 years of age (13, 15). In Germany children and young adults up till 18 years of age are treated according to pediatric protocols and the EFS for 10-13 year-old patients is 66% and 64% for the 14-18-year-old patients (14).

During the same period 57 patients with ALL between 15 and 19 years of age were treated in the Nordic countries (predominantly Sweden) with the pediatric Nordic ALL protocols. This group of patients had the same distribution of risk criteria as described in the present study. When comparing this group of young adults with the Danish group of 15-19 year-old patients the EFS was significantly higher for the young adults who had been treated with pediatric NOPHO ALL protocols (0.68 vs 0.38, $p < 0.01$), whereas there was no difference between Danish children 10-14 years of age and the Nordic young adults treated by the same protocols (EFS 0.68 vs 0.60, $p = 0.7$) (16).

The difference in outcome between the Danish children and young adults treated on adult protocols may be explained by different treatment intensity of the most important cytostatic drugs. The consolidation period after induction lasted only $2\frac{1}{2}$ - $3\frac{1}{2}$ months in the young adults whereas it lasted $6\frac{1}{2}$ (intermediate risk) and 15 months (high risk) in children. The total dose of prednisone per surface area was twice as high in children and the dose of vincristine was 75% higher in children compared with the young adult patients. Furthermore 24 hour high dose methotrexate infusions $5-8 \text{ g/m}^2$ is part of the NOPHO ALL protocols whereas it was used only very sporadically in the adult patients. With respect to the other drugs there were no obvious differences between the two patient groups.

The use of allogeneic SCT in the two groups was also different. A total of 14 out of 34 adult patients were transplanted either in first or second CR compared with 11/61 children. There was a trend towards higher mortality due to complications in the young adults, which was not significant, however, because of small number of patients. This study seems to implicate that part of the poorer survival

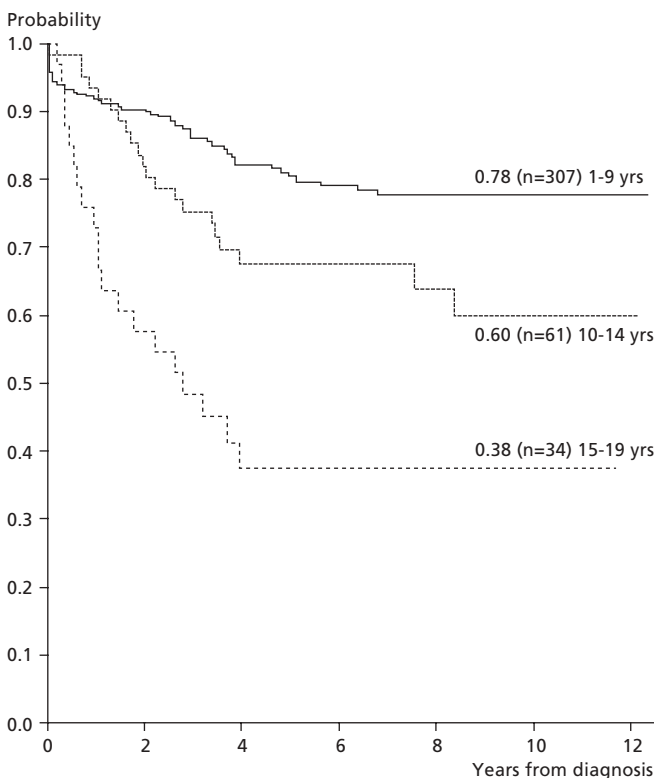


Figure 1. Event free survival for all Danish patients 1-19 years of age with acute lymphoblastic leukemia.

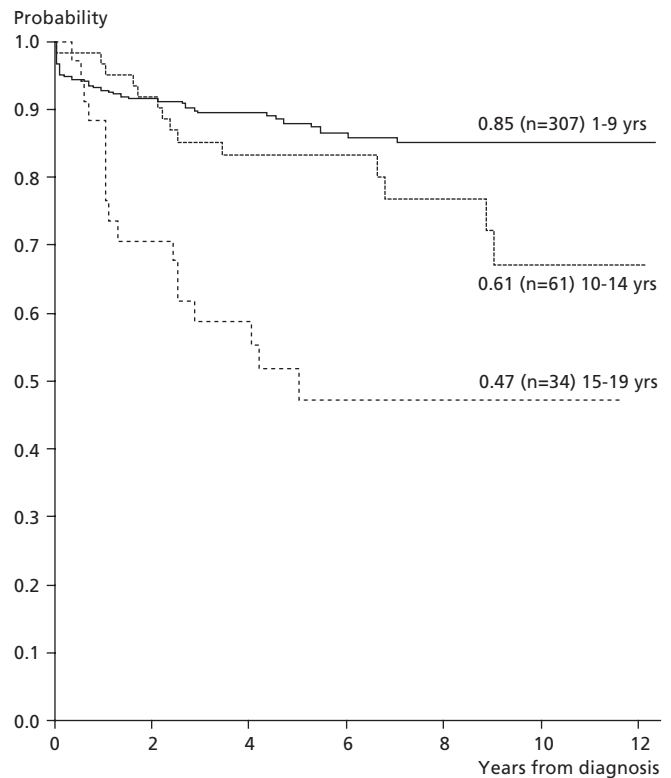


Figure 2. Overall survival for all Danish patients 1-19 years of age with acute lymphoblastic leukemia.

in young adults was caused by a higher transplant related mortality. Thus there is a need for a conventional ALL treatment regime in the young adults which will reduce the need for allogeneic SCT in both first and second CR and thus presumably reduce the toxic death rate in these patients.

In this small material differences in treatment intensity is presumed to play a role for the observed difference in EFS and OS which has also been stated by others (6-9). In some other smaller studies the EFS has been increased to about 50% in adults with ALL by intensifying conventional cytostatic therapy (17-20). This option thus seems possible in the Danish young adult patients in as much as none of these died from complications to conventional therapy, only after allogeneic SCT.

We suggest that all Danish children and young adults up till 18-20 years of age should be treated according to pediatric ALL protocols based on our results and the preliminary results of 15-18 year-old Nordic patients treated with the Nordic pediatric ALL protocols. The risk criteria for allocation to intermediate and high risk treatment and to transplantation of the NOPHO-ALL protocol should be respected and patients should be prospectively reported and followed closely for toxicity and outcome.

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