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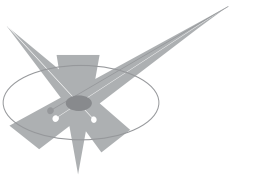

Preliminary Communication

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Comparison of treatment results in children with non-high risk acute lymphoblastic leukaemia treated according to ALL-BFM 90 and ALL-IC BFM 2002 regimens – single centre preliminary experience

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background Acute lymphoblastic leukaemia (ALL) represents about 30% of cancer in children and thus is the most common childhood malignancy. Despite the great progress, further improvement of treatment results remains an important problem.

Aim A comparison of the results of standard risk and intermediate risk group regimens ALL-BFM 90 and ALL IC-BFM 2002 was the subject of our study.

Materials/Methods A retrospective analysis of 41 (18 males and 23 females) children aged 2–15 years (median: 6 years) diagnosed from 25.01.1994 to 9.04.1997 and treated according to ALL-BFM 90 (group A), and 44 (22 males and 22 females) children aged 0-18 years (median: 7 years) diagnosed from 12.10.2002 to 31.12.2005 and treated according to ALL IC BFM-2002 regimen (group B) was performed. For statistical evaluation Kaplan–Meier methods and the log-rank test were used.

Results Remission on time (day +33) was achieved in 39/41 (94%) children from group A and in 43/44 (98%) children from group B (p=0.07). The average day of achieving remission was 49 (range: 28–109; median: 46) in group A and 39 (range: 31–71; median: 35) in group B (p<0.001). Treatment failures observed in both groups were as follows:

- death during induction therapy: 0/41 (0%) – group A, 1/44 (2%) – group B; p=0.954;
- relapse: 2/41 (5%) – group A, 3/43 (7%) – group B; p=1.000;
- death after relapse: 2/2 (100%) – group A, 0/3 (0%) – group B; p=0.100.

Probability of 43 months event-free survival (pEFS) was 95.2% in ALL-BFM 90 and 92.7% in ALL IC-BFM 2002 (p=0.452).

Conclusions

1. The average day of achieving remission was significantly shorter in children treated according to ALL IC–BFM 2002.
2. Although the number of relapses increased, there were no cases of death in relapsed patients observed in the ALL IC–BFM 2002 group.
3. The follow-up was too short to evaluate the long-term effects of ALL treatment. Further observation of investigated groups of patients is necessary.

Key words **childhood acute lymphoblastic leukaemia • treatment results**

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Background

Acute lymphoblastic leukaemia (ALL) represents about 30% of cancer in children and thus is the most common childhood malignancy. The prognosis of ALL has improved greatly over recent decades. More than 95% of patients achieve complete remission (i.e. blast cells <5% in the bone marrow and disappearance of clinical symptoms related to the disease) and about 80% are expected to be cured with current chemotherapy regimens [1–3]. In the ALL-BFM 90 trial the standard-risk group (SRG) was defined by prednisolone good response (PGR) and initial WBC lower than 50 000/µl [4] and the high-risk group (HRG) by inadequate response to the cytoreductive steroid prephase, WBC more than 50 000/µl induction failure, or Philadelphia-chromosome-positive ALL t(9;22) [5] (Table 1). Age, leukocyte count, translocations t(9;22) (BCR/ABL) and t(4;11) (MLL/AF4), as well as response to pretreatment with corticosteroids and to remission-induction therapy are used for risk group classification in children treated according to the ALL IC-BFM 2002 protocol (Table 1) [6].

Despite the great progress, further improvement of treatment results remains an important problem.

In Poland due to a decision of the Polish Pediatric Leukemia/Lymphoma Study Group (PPLLSG), between 1993 and 2002, patients from the standard-risk (SR) group were treated according to modified ALL-BFM 90 and from the high-risk (HR) group according to the New York regimen [7]. The ALL-BFM 90 trial was designed to improve final outcome in patients with childhood SR-ALL by using a reduced treatment regimen. To achieve this purpose central nervous system (CNS) radiotherapy was substainted by high dose of methotrexate HD-MTX (3 or 5g/m^2) and intrathecal therapy [8]. Since December of 2002 patients have been treated according to ALL IC-BFM 2002. This regimen was designed to answer the question whether treatment intensity in the newly defined standard risk group may be safely reduced [9]. The aim was to reduce the risk of late complications without decreasing anti-leukaemic effect by adjustment of treatment intensity to risk group. Contrary to the group of patients treated according to ALL-BFM 90, patients treated according to ALL IC-BFM 2002 were randomized. In our study we focused on patients from the SR and IR group treated according to ALL IC-BFM 2002 to make the group comparable with the standard risk group treated according to ALL-BFM 90.

Aim

A comparison of the results of standard risk and intermediate risk group regimens ALL-BFM 90 and ALL IC-BFM 2002 was the subject of our study.

Materials and Methods

From 25/01/1994 to 09/04/1997, forty-one children (18 males and 23 females) with newly diagnosed SR-ALL were treated according to standard risk modified ALL-BFM 90 (Figure 1). Median age at diagnosis was 6 years, range 2–15 years.

Between 12/10/2002 and 31/12/2005 forty-four patients with ALL (22 males and 22 females) aged between 1 and 18 years (median: 7 years) were treated according to the standard (SR) and intermediate risk (IR) arm of the ALL IC-BFM 2002 protocol. All children were diagnosed and treated in the Department of Pediatric Hematology, Oncology and Transplantology, Poznań University of Medical Sciences. Tables 2 and 3 show the comparison of prognostic criteria in patients treated according to ALL-BFM 90 and ALL IC-BFM 2002 protocols and patient characteristics, respectively.

Table 1. Prognostic criteria and risk groups of children with ALL treated according to ALL-BFM 90 and ALL IC-BFM 2002 protocols.

Risk group	ALL-BFM 90	ALL IC-BFM 2002
Standard risk	• for ALL except B-ALL • age of patients >1 year and <18 years • WBC <50 000/μl • PGR*	• age of patients >1 year and <6 years • WBC <20 000/μl • <1000 blasts/μl on day 8 of treatment
Intermediate risk	—	• age of patients <1 year and >6 years and/or WBC >20 000/μl • <1000 blasts/μl on day 8 of treatment
High risk	• WBC >50 000/μl • PPR**	• translocation t(9;22) [bcr/abl] or t(4;11) [MLL/AF4] • >1000 blasts/μl on day 8 of treatment • on day 33 of treatment bone marrow M2 or M3

* PGR – prednisolone good responders (number of blasts in blood <1000/μl on day +8 of induction);
** PPR – prednisolone poor responders (number of blasts in blood >1000/μl on day +8 of induction).
M2 – 5–25% of leukaemic blasts in bone marrow; M3 – more than or equal to 25% of leukaemic blasts in bone marrow.

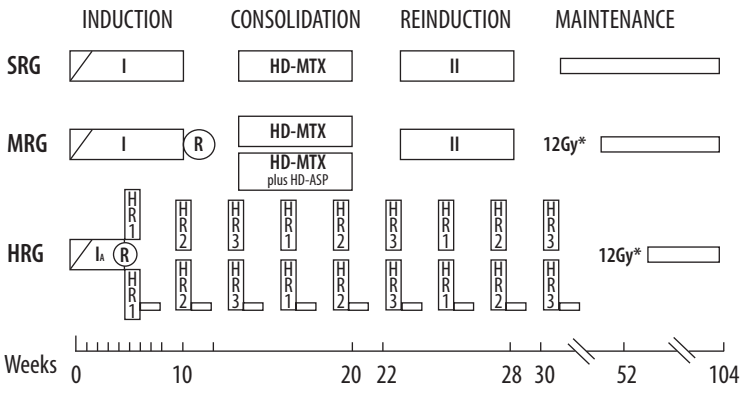

Figure 1. Outline of ALL-BFM 90 protocol [10].

Table 2. Characteristics of patients.

Patients	Treatment protocol	
	ALL-BFM 90	ALL IC-BFM 2002
Number	41	44
Sex	18 males and 23 females	22 males and 22 females
Age range	2–15 years	1–18 years
Mean age	7 years	8 years
Median age	6 years	7 years
Risk group	SRG-	SRG-; IRG-

The outlines of protocols ALL-BFM 90 and ALL IC-BFM 2002 are presented in Figures 1 and 2. In the ALL-BFM 90 protocol all patients qualified for SRG therapy receive induction protocol I, consolidation/ extracompartmental protocol M, reinduction (delayed intensification) protocol II, and maintenance therapy. Patients treated according to the ALL IC-BFM 2002 protocol who did not qualify for HRG therapy were stratified into standard- and intermediate-risk groups. Both groups received protocols I and mM at first and then were randomized to the newly investigated treatment group or control group with known performance and outcome (Figure 2).

Also there were differences of drug dosages in each trial. In ALL IC-BFM 2002, during induction, daunorubicyn was given only twice at a dose of 30mg/m^2 for SRG BCP-ALL patients. The L-asparaginase dose was decreased from 10 000U/m^2 (in ALL-BFM 90) to 5000U/m^2 (in ALL IC-BFM 2002). In protocol mM of ALL IC-BFM 2002, intravenous methotrexate was given at a dose of 2g/m^2/24h. Patients from SRG and IRG received lower doses of cyclophosphamide (500mg/m^2) during reinduction. Preventive CNS irradiation was given not only to patients who initially had CNS disease, but also to all patients with T-ALL, while according to ALL-BFM 90, CNS radiotherapy in such patients was omitted [9]. These differences are presented in Table 3.

Table 3. Differences between ALL-BFM 90 protocol and ALL IC-BFM 2002 treatment arm for SRG- and IRG-patients with ALL.

Phase of treatment	ALL-BFM 90	ALL IC-BFM 2002
Induction		
Daunorubicin (DNR)	for all patients 30 mg/m^2 (4 times)	only in BCP-ALL patients 30 mg/m^2 (2 or 4 times)
L-asparaginase (ASP)	10 000 U/m^2 (8 times)	5000 U/m^2 (8 times)
Consolidation		
Methotrexate (MTX) I.V.	3 g/m^2/24h	2 g/m^2/24h
Reinduction		
Cyclophosphamide (CPM)	for all patients 1000 mg/m^2	for SR-2 and IR-2 group 500 mg/m^2
Maintenance therapy		
Methotrexate (MTX) I.T.	4 times for all patients: 8 mg (patients 1–2 years old) 10 mg (patients 2–3 years old) 12 mg (patients above 3 years old)	in SR-1 and IR-1 group 4 times for BCP-ALL patients: 8 mg (patients 1-2 years old) 10 mg (patients 2-3 years old) 12 mg (patients above 3 years old)
Vincristine (VCR) Prednisolone (PRED)	4 times	not given
Cranial irradiation	in patients with CNS involvement	in patients with T-ALL and patients with CNS involvement

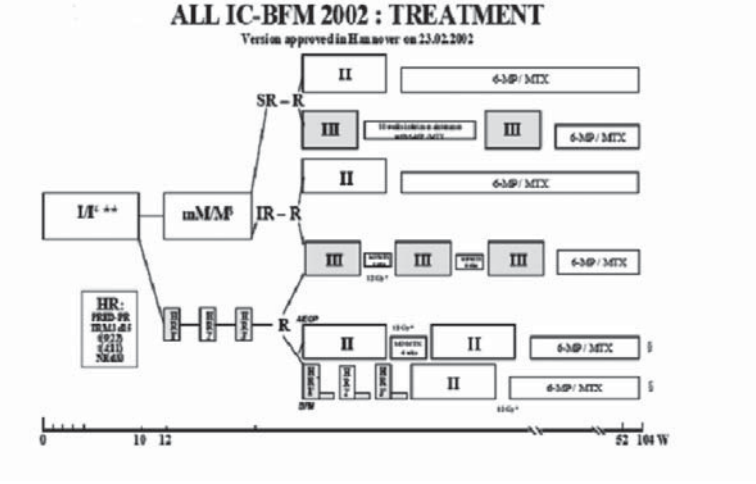

Figure 2. Outline of ALL IC-BFM 2002 protocol [9].

Range and mean day of first complete remission (CR) achievement were assessed. In addition, occurrence of ALL relapse and probability of event-free survival (pEFS) at 43 months were analyzed and compared in both study groups. The duration of event-free survival (EFS) was defined as the time from diagnosis until the date of treatment failure (induction failure, relapse, non-relapse death).

For statistical evaluation Kaplan-Meier methods and the log-rank test were used. For bi-variable analysis alpha error probability of 0.05 was adopted. Data were processed and analyzed using Statistica software version 6.0.

Results

Tables 4 and 5 show time of first CR, occurrence of relapses and pEFS at 43 months. In the ALL-BFM 90 group time of observation was 5–43 months (mean: 21 months, median: 21 months) and in the ALL IC-BFM 2002 group 6–43 months (mean: 23 months, median: 22 months).

Remission induction

In the group treated according to modified ALL-BFM 90 94% (39 out of 41 children) achieved remission on time, day +33 while in the

Table 4. Time of first complete remission achievement in patients with ALL treated according to ALL-BFM 90 and ALL IC-BFM 2002.

	ALL-BFM 90 (n=41)	ALL IC-BFM 2002 (n=44)	P
First CR on day +33	39/41 (94%)	43/44 (98%)	0.07
Mean day of first complete remission achievement	49	39	**<0.01**
Range of days of achieving first complete remission	28–109	31–71	–

Table 5. Treatment results in SRG-patients treated according to ALL-BFM 90 and SRG- and IRG-patients ALL IC-BFM 2002.

Events	ALL-BFM 90 (n=41)	ALL IC-BFM 2002 (n=44)	P
Death during induction therapy	0/41 (0%)	1/44 (2%)	0.954
Relapse	2/41 (5%)	3/43 (7%)	1.000
Death due to ALL progression	2/2 (100%)	0/3 (0%)	0.000
Death in first continuous complete remission	0/41 (0%)	0/43 (0%)	1.000
pEFS at 43 months	95.2%	92.7%	0.452

ALL IC-BFM 2002 treatment group the remission induction rate was 98% (43 out of 44 children).

Time of remission achievement

The mean day of I CR achievement was 49 (median: 46) and 39 (median: 35) in patients treated according to ALL-BFM 90 and ALL IC-BFM 2002, respectively. This difference attained statistical significance in analysis by the log-rank test ($p<0.01$).

One patient from the ALL IC-BFM 2002 group did not obtain remission because of early death due to Waterhouse–Friedrichsen syndrome, whereas there was no death before remission in the ALL-BFM 90 group (Table 5).

Relapses and non-relapse deaths

A total of five patients relapsed following initial remission. Two patients on ALL-BFM 90 protocol suffered bone marrow (BM) relapse at 22 and 28 months from diagnosis. In the group treated according to ALL IC-BFM 2002 protocol, 3 patients had relapse: 2 had BM relapse at 4 and 6 months, and 1 suffered from combined bone marrow/central nervous system relapse at 34 months from diagnosis. Of those patients, both from the first group died due to progression of the disease.

None of the patients died in first CR from complications in both compared groups.

Event-free survival

After 43 months of observation, the estimate probability of event-free survival (pEFS) was 95.2% for patients treated according to ALL-BFM 90 and 92.7% for patients from the ALL IC-BFM 2002 group ($p=0.452$) (Table 5).

Conclusions

One major focus of designing new trials for ALL therapy is to answer the question whether risk of early and late therapy related complications may be reduced while having the same anti-leukaemic effect. On protocols ALL-BFM 90 and ALL IC-BFM 2002, patients are classified to different risk groups by applying new criteria. Some doses of drugs have been decreased in an effort to reduce side effects in children treated for ALL. The most important changes were: reduction of methotrexate dose in consolidation therapy and decrease of L-asparaginase during induction therapy in ALL IC-BFM 2002. As a result of all these modifications there are differences in treatment results between ALL-BFM 90 and ALL IC-BFM 2002. In children with SR-ALL and IR-ALL the mean day of remission achievement was significantly shorter in those treated according to ALL IC-BFM 2002. This is especially important because of the fact that remission induction is the most important prognostic factor in childhood ALL. In contrast to deaths observed in relapsed patients from the ALL-BFM 90 group, there was

no death in patients demonstrating relapse in the ALL IC-BFM 2002 group. This could be the result of both better trials for relapses of ALL and the possibility of haematopoietic stem cell transplantation (HSCT) in this group of patients. Overall, event-free survival at 43 months for the standard risk group ALL-BFM 90 was 95.2% in ALL-BFM 90 and 92.7% in the standard risk and intermediate risk ALL IC-BFM 2002 group.

Discussion

The results of pEFS for patients treated according to ALL-BFM 90 are comparable with other authors, but the follow-up was short and the long-term effects cannot be evaluated. Some patients are still continuing the therapy. Further observation of the investigated groups of patients is necessary. This is especially important in the context of the high rate of cure in children with ALL.

Because of the short time of observation it is difficult to compare our results with other recent studies.

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