



Long-term Outcome of Children with Acute Lymphoblastic Leukemia Treated with IC-BFM2002 Regimen

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Background: Changes in pediatric chemotherapy regimens over the last three decades have introduced a variety of protocols to increase the survival of patients with acute lymphoblastic leukemia (ALL). Intercontinental Berlin-Frankfort-Munich (IC-BFM) 2002 is one of the protocols widely used in countries that could not perform minimal residual disease by polymerase chain reaction (MRD PCR) method. Evaluation the results of these regimens is very effective in improving their quality.

Materials and Methods: Children with newly diagnosed ALL in Ali Asghar Children's Hospital were randomly divided into two groups. Patients in both groups underwent chemotherapy according to IC-BFM 2002 protocol. Patients were divided into two groups based on the type of reinduction regimen, so that patients in-group A received protocol II and patients in-group B received protocol III as a reinduction regimen. Then demographic information and patient outcome were statistically analyzed with SPSS 23.

Results: Sixty-three patients were included in the study. There were 32 patients in-group A (18 boys and 14 girls) and 31 patients in-group B (11 boys and 20 girls). The number of high-risk patients was higher in-group A, but this difference was not statistically significant. The recurrence

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rate in-group B patients was about seven times higher than the recurrence rate in group A patients, and this difference was statistically significant. In-group A, no patients had an early relapse, while about half of the recurrences in-group B occurred as early relapse and the rest as late relapse. CNS recurrence occurred in only two patients. 5-yr EFS of all enrolled patients was $88.90 \pm 8.00\%$ (95% CI). This rate for group A and B was $96.90 \pm 6.20\%$ (95% CI) and $80.60 \pm 14.20\%$ (95% CI), respectively (P=0.022).

Conclusion: It seems that IC-BFM 2002 protocol is an appropriate treatment regimen with acceptable results for children with ALL in developing countries, a workable protocol with significant consequences. Protocol II seems to be suitable for reinduction and increasing the Methotrexate dose may not be necessary for non-high-risk groups.

Keywords: Acute lymphoblastic leukemia; IC-BFM 2002; outcome.

1. INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer and the outcome of has significantly improved over the past 40 years [1]. This is due to the redoubled efforts of medical research teams around the world. One of the oldest and most famous of these groups is the International Berlin-Frankfurt-Münster study group (I-BFM-SG). It has over 30 member countries, and in the form of various working committees, it conducts research on various basic and clinical aspects of pediatric leukemia and lymphoma². Over the past 30 years, this group has introduced several protocols to improve the outcome of children with ALL, including ALL BFM-83, BFM-90, BFM-95, and finally BFM2002 and BFM2009 [2-7]. BFM and AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) groups showed that measurement of minimal residual disease (MRD) by polymerase chain reaction (PCR) at weeks 5 and 12 of the protocol is very useful in identifying high-risk patients who are not detectable by bone marrow morphology [8-11]. Because this method is expensive and its technology does not exist in most developing and low-income countries, BFM used peripheral blood smear morphology examination on day 8 and bone marrow aspiration morphology examination on days 15 and 33, instead of using PCR-MRD, and introduced the IC-BFM 2002 protocol for these countries [10,12].

On the other hand, evaluation the outcome of children with ALL treated with this treatment regimen in developing countries such as Iran can be very helpful in improving the treatment protocol in the coming years. Therefore, in this study, we report the results of the treatment of these patients from Ali-Asghar Children hospital.

2. MATERIALS AND METHODS

A retrospective case-control analytical study from 2009 to 2015, in which children with B-precursor ALL (1-16 years old) referred to Ali Asghar Children's Hospital in Tehran of Iran University of Medical Sciences after confirmation of diagnosis with BMA and flow cytometry. All patients were included into two groups and treated with IC-BFM 2002 chemotherapy regimen. As you can find in Table 1, patients in-group A routinely received protocol II as a reinduction during the treatment (one time for the standard and intermediate risk groups and two times for the high-risk group). While patients' in-group B received protocol III as reinduction (twice for standard and intermediate risk groups and three times for high-risk group). Then demographic data and risk groups defined according to IC-BFM 2002 protocol for each patient were extracted.

2.1 Data Analysis

Patients' information was entered into SPSS v23.0. Descriptive data were analyzed by descriptive tests. The Kaplan-Meier test was used to determine event-free survival (EFS). Log-Rank method was employed to measure the survival rate and P-value less than 0.05 was considered as significant. Based on the median follow-up months, the estimated long term EFS values were determined for patients.

3. RESULTS

Sixty-three patients were included in the study. All patients in the study had B-precursor ALL and none of them had t (4; 11) or t (9; 22). Thirty-two patients were in-group A (18 boys and 14 girls) and 31 patients were in-group B (11 boys and 20 girls). The number of boys was higher in-group A, but this difference was not statistically

significant [P = 0.08 with Odd ratio = 2.33 (0.84-6.44)]. There was no statistically significant difference between the two groups in terms of mean age at diagnosis and initial WBC (Table 2).

The number of patients older than 10 years at the time of diagnosis was 17.5 in total and about

8.3% of the patients in the study had an initial WBC count greater than 50,000/ μ l and there was no significant difference between the two groups, neither of the two groups had CNS involvement at the time of diagnosis. The number of high-risk patients was higher in-group A, but this difference was not statistically significant (Fig. 1).

Table 1. IC-BFM 2002 Protocol used for all enrolled patients

Treatment element/drug	Treatment method	Single dose	Per-day dose	Days of administration ^a
Induction				
Protocol I' (SR BCP-ALL only) and protocol I (SR T-ALL, all IR and HR patients)				
Phase 1	PO		60 mg/m ²	1-28b
Prednisone	IV	1.5 mg/m ²		8, 15, 22, 29
Vincristine		(max. 2 mg)		
Daunorubicin	PI over 1 hour	30 mg/m ²		8, 15, 22c, 29c
L-asparaginase	PI over 1 hour	5,000 IU/m ²		12, 15, 18, 21, 24, 27, 30, 33
Methotrexate	PI over 1 hour	5,000 IU/m ²		12, 15, 18, 21, 24, 27, 30, 33
Phase 2				
Cyclophosphamide	IT	12 mgd		1, 12, 33
Cytarabine	PI over 1 hour	1,000 mg/m ²		40, 75
GCSF	IV	75 mg/m ²		47-50, 54-57, 61-64, 68-71
6-mercaptopurine	SC	5 μ g/kg		41-46, 51-53, 58-60, 65-67, 72-74, 76-81
Methotrexate	IV	75 mg/m ²		47-50, 54-57, 61-64, 68-71
	SC	5 μ g/kg		41-46, 51-53, 58-60, 65-67, 72-74, 76-81
	PO		60 mg/m ²	40-68
	IT	12 mgd		54, 68
Consolidation				
Protocol mM (only BCP-ALL, SR/IR)				
6-mercaptopurine	PO		25 mg/m ²	1-56
Methotrexate ^e	PI over 24 hour	2,000 mg/m ²		8, 22, 36, 50
GCSF	SC	5 μ g/kg		15, 29, 43, 57
Methotrexate	IT	12 mgd		8, 22, 36, 50
				1-56
Protocol M (only T-ALL, SR/IR)				
6-mercaptopurine	PO		25 mg/m ²	8, 22, 36, 50
Methotrexate ^e	PI over 24 hours	5,000 mg/m ²		8, 22, 36, 50
Methotrexate	IT	12 mgd		
Delayed intensification				
				1-21b
Protocol II ^f				
				8, 15, 22, 29
Phase 1				8, 15, 22, 29
Dexamethasone	PO/IV	1.5 mg/m ²	10 mg/m ²	8, 11, 15, 18
		(max. 2 mg)		
Vincristine	IV	30 mg/m ²		
Doxorubicin	PI over 1 hour	10,000 IU/m ²		
L-asparaginase	PI over 1			

Treatment element/drug	Treatment method	Single dose	Per-day dose	Days of administration ^a
				hour
Phase 2: Cyclophosphamide				36
Cytarabine		1,000 mg/m ²		43-46, 50-53
6-thioguanine	PI over 1 hour IV	75 mg/m ²		36-49
Methotrexate	PO IT	12 mg ^d	60 mg/m ²	43, 50
Interim maintenance therapy				
Methotrexate	PO	20 mg/m ²		
6-mercaptopurine	PO	50 mg/m ²		
Maintenance therapy ^h				
Methotrexate	PO	20 mg/m ²		
6-mercaptopurine	PO	50 mg/m ²		

Table 2. Comparison between two groups in terms of age at diagnosis, duration of follow-up and initial WBC

	Groups	N	Mean	Std. deviation	Std. error mean	P value
Age at diagnosis (mo)	A	32	63.28	45.821	8.100	0.84
	B	31	65.47	41.355	7.428	
Duration of follow-up (mo)	A	32	113.81	23.788	4.205	0.03
	B	31	97.45	34.304	6.161	
Initial WBC	A	32	11906.67	16885.189	3082.800	0.13
	B	31	21713.33	30742.902	5612.860	

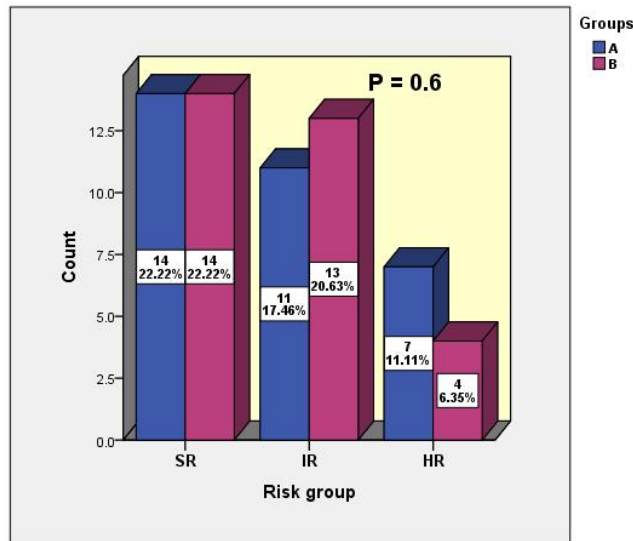


Fig. 1. Comparison between two groups for distribution of patients with different risk groups (SR= standard risk; IR= intermediate risk; HR= high risk)

In terms of response to prednisolone during the first week of remission induction period, 17.5% of all patients had prednisolone poor response and there was no significant difference between the two groups in this regard. The recurrence rate (relapses) in-group B patients was about seven

times higher than the recurrence rate in group A patients, and this difference was statistically significant (Fig. 2).

In-group A there was no early relapse (recurrence in the first 18 months after

diagnosis). About half of the recurrences in-group B occurred as early relapse and the rest as late relapse (recurrence after 18 months from diagnosis); Of course, this difference was not statistically significant (Fig. 3).

The most common recurrence was in bone marrow, which occurred in-group B patients.

CNS recurrence occurred in only two patients (Table 3).

The median follow-up of all enrolled patients was about 112 months. According to this finding, the 5-yr EFS of all patients studied was $88.90 \pm 8.00\%$ with 95% confidence interval (95% CI), (Fig. 4).

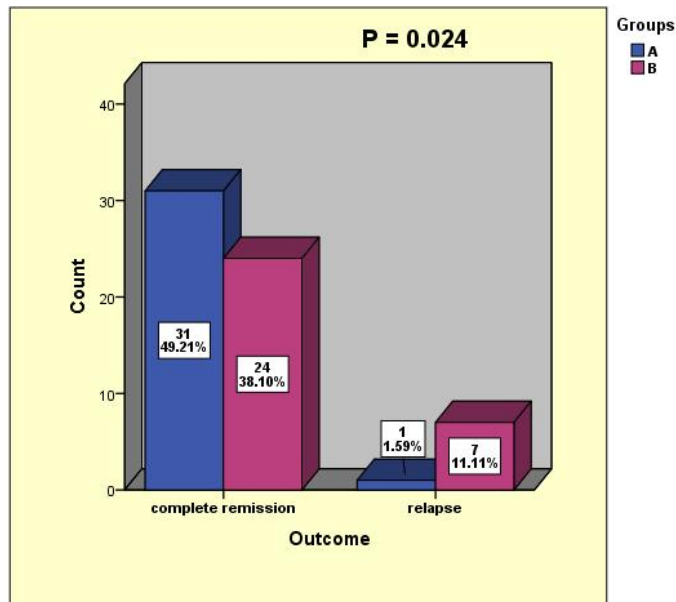


Fig. 2. Comparison between two groups for outcome

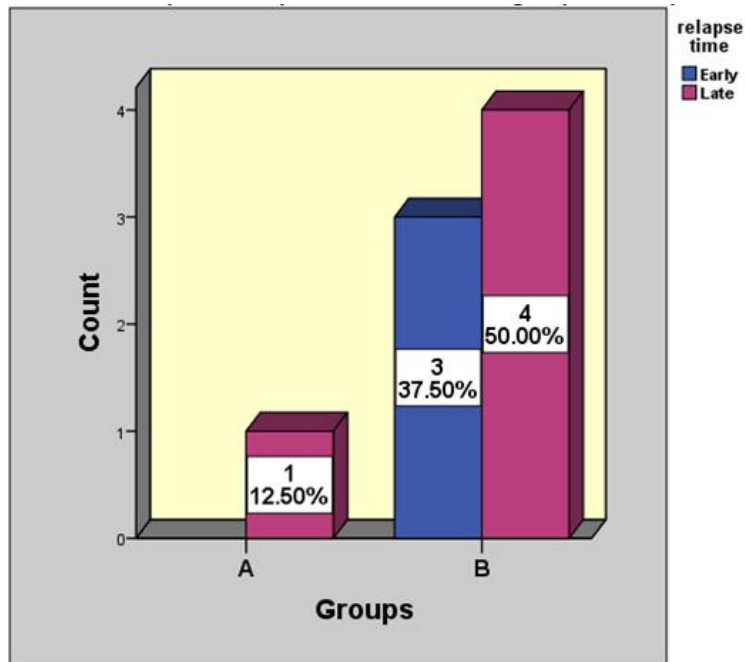
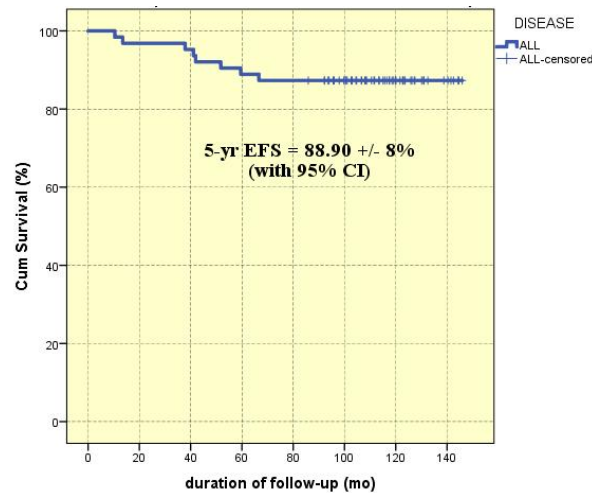


Fig. 3. Comparison between the two studied ALL groups for relapse time

Table 3. Comparison between the two studied groups in terms of relapse site

P = 0.13			Relapse site				Total
			no relapse	BM	CNS	BM & CNS	
Groups	A	Count	31	0	1	0	32
		% within Groups	96.9%	0.0%	3.1%	0.0%	100.0%
	B	Count	25	4	1	1	31
		% within Groups	80.6%	12.9%	3.2%	3.2%	100.0%
Total		Count	56	4	2	1	63
		% within Groups	88.9%	6.3%	3.2%	1.6%	100.0%

BM = Bone Marrow; CNS = Central Nervous System

**Fig. 4. Event-free survival of all enrolled patients**

In terms of the effect of gender on the outcome of all enrolled patients, the 5-yr EFS was $94.10 \pm 8.00\%$ (95% CI) for girls and $82.80 \pm 14.00\%$ (95% CI) for boys; but this difference was not statistically significant. The level of 5-yr EFS was $96.90 \pm 6.20\%$ (95% CI) for group A and $80.60 \pm 14.20\%$ (95% CI) for group B and this difference was statistically significant (Fig. 5).

4. DISCUSSION

Chemotherapy has long been the mainstay of treatment for children with ALL, and various research groups around the world have developed a variety of chemotherapy regimens with varying implications. One of the oldest of these protocols is provided by the BFM group and is in fact one of the most popular chemotherapy regimens in the world for this group of patients. A comparison of popular chemotherapy regimens for children with ALL presented by SIOP in 2010 found that the BFM protocol had one of the best outcomes for this group of patients by 2000 [13]. Due to the increasing use of MRD in improving the outcome

of these patients in the first decade of the 21st century, the BFM group presented its new protocol in 2002 under a clinical trial based on the main use of MRD results. Due to the inability of developing countries to perform accurate MRD, this group presented another protocol based on peripheral blood and bone marrow morphological findings during a treatment called IC-BFM 2002. In this article, we present and analyze the outcome of patients treated with this treatment regimen who referred to one of the most prestigious and oldest pediatric oncology centers in Iran, and compared to the results of other countries, especially developed countries, we achieved significant results.

In a study presented in 2016 from Czechoslovakia, the estimated 5-yr EFS of 24 patients was about 83% [14]. An initial study reported from IC-BFM 2009 by Nath et al. in 2019 showed an increase in disease-free survival of 88% [7]. Evaluating the results of other protocols presented by well-known research groups also shows the results of IC-BFM 2002 comparable. Gaynon et al. in 2010

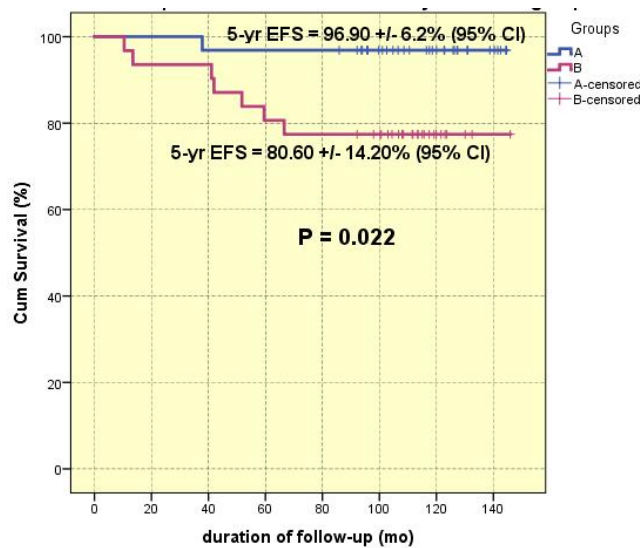


Fig. 5. Event-free survival analysis of both groups

reported the outcome of children with B-precursor ALL treated with CCG-1900 regimen at 5-yr EFS 82% for the standard risk group and 70% for the high-risk group [15]. In a 2010 study, Salzer et al reported that the rate of 10-yr EFS in patients with standard risk (NCI standard risk with DNA index ≤ 1.16 or lacking trisomies 4 and 10; or NCI higher risk with DNA index > 1.16 or trisomies 4 and 10) B-precursor ALL treated with the ALinC16 chemotherapy regimen was about 73%, and the rate was about 86% for the low-risk group [16]. In 2013, a report was published from Egypt on the outcome of 14 children with T-cell ALL treated with the CCG1991 protocol had a 5-yr EFS of 77% [17]. In 2016, Trehan et al. reported a 65% EFS outcome of treatment using the UKALL 2003 (known as protocol 2) chemotherapeutic regimen [18]. In comparison to all these results and despite the small number of patients in the high-risk group in our study, the results obtained are not only comparable to other developed countries, but as a developing country is quite brilliant and thought provoking.

In 2007, Zając et al. presented the results of the treatment of 41 children with ALL treated with this protocol with a very brilliant result of estimated 5-yr EFS of about 92% [19]. Federico G. et al. presented a report from a very low-income country, Guatemala, on 787 children treated with IC-BFM 2002 protocol, despite the fact that about 450 patients were in the intermediate risk group and 177 patients were in the high-risk group. Their estimated 5-yr EFS was about 56% [20]. In 2012, Gao et al.

described the treatment outcome of 92 Chinese children with ALL treated with IC-BFM 2002 with a 6-yr EFS of approximately 75.5% [21]. However, the first valid report published by the BFM group in early 2014 included 5060 patients treated with IC-BFM 2002. Of these, 26.5% were at the age of diagnosis more than 10 years, about 20% in all initial WBC patients had more than 50,000/ μ l, 13% T-cell type, 2.8% t(9;22) and 1% t(4;11). Under these conditions, the 5-yr EFS of all patients was about 74%². Interestingly, patients treated with protocol II as a reinduction of EFS were better than patients treated with Protocol III in our study, which was statistically significant. This was confirmed by doing not use of Protocol III in IC-BFM 2009 for standard and intermediate risk groups and using only Protocol II [22]. On the other hand, CNS recurrence due to the use of high dose Methotrexate at 2 g/m² for four consecutive cycles has been minimized and its increase to 5 g/m² in four consecutive cycles for non-high-risk groups does not seem reasonable. Of course, our study with a limited number of samples may not be a definitive answer to this question.

5. CONCLUSION

The IC-BFM2002 protocol seems to be an appropriate treatment regimen with acceptable outcomes for children with ALL in developing countries, a workable protocol with significant consequences. Protocol II seems to be suitable for reinduction and increasing the MTX dose may not be necessary for non-high-risk groups.

CONSENT AND ETHICAL APPROVAL

Patients' written consent has been collected and preserved by the author(s). Patient information was only available to the executor and the name of the patient remained confidential. Research team members were aware of the details of Helsinki statement about ethic principles in medical research and were strictly committed to follow them in this study. This project was approved at the Ethics Committee of the University of Medical Sciences.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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