Çocukluk Çağı Akut Lenfoblastik Lösemilerinde, ALL-BFM Protokolleri ile İnduksiyon Ölümleri ve Tedavi-İlişkili Ölümler

Induction Deaths and Treatment-Related Mortality in Childhood Acute Lymphoblastic Leukemia with ALL-BFM Protocols

Duygu Köse, Nazan Sarper, Emine Zengin, Sema Aylan Gelen
Kocaeli Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Kocaeli,Türkiye

ÖZ

GİRİŞ ve AMAÇ: *Çocukluk çağı akut lenfoblastik lösemilerinde (ALL), Berlin-Frankfurt-Münster (BFM) çalışma grubu çok iyi sonuçlar elde edilmiştir. Burada, BFM-ALL çalışma grubuna göre daha kötü sonuçlar alınmasının nedenlerinin açıklanması için lösemilerin biyolojik özellikleri ve BFM tabanlı protokollerle tedavi edilmiş çocuk ve ergenlerin tedavi sonuçları değerlendirilmiştir.*

YÖNTEM ve GEREÇLER: *Ocak 2001-Aralık 2014 döneminde tanı konmuş hastaların bilgileri hastane kayıtlarından alındı. BFM- Türkiye ALL 2000 (TRALL-2000) (BFM-ALL 95 ten türetilmiş), BFM-ALL 95 ve BFM-ALL-Intercontinental-2009 tedavi protokolleri art arda kullanıldı. Down sendromlu hastalar dışındaki 1-18 yaştaki tüm hastalar çalışmaya alındı.*

BULGULAR: *Ortalama yaşı 6,64 ± 4,35 yıl olan 207 hasta vardı. Hastaların standart, orta ve yüksek risk grubundaki dağılımları sırasıyla %27,5, %54,9 ve %16,2 idi. İmmünofenotip sırasıyla hastaların %84,3, %13,7 ve %1,0 inde B-ALL, T-ALL ve bifenotipik lösemiydi. İndüksiyon ölümü 9 hastada (%4,3) saptandı ve 33. günde remisyon oranı %94,2 idi. On üç hasta (%6,5) ilk tam remisyonda kaybedildi. İndüksiyon+ tam remisyondaki ölümlerin 16 sı (%7,7) enfeksiyonla ilişkiliydi. Relaps oranı %19,3 tü. Ölüm oranı %20,1 idi. Yedi-yıllık olaysız sağkalım ve genel sağkalım sırasıyla %73,0 ve %79,4 idi.*

TARTIŞMA ve SONUÇ: *BFM-ALL çalışma grubunun BFM-ALL 95 çalışmasına kıyasla, bu çalışmada indüksiyon ölümleri ve ilk remisyondaki ölümler daha yüksekti. Sağkalım oranları Türkiye'deki benzer merkezler gibiydi. Enfeksiyonlara bağlı ölümlerin azaltılması için, hematoloji ünitelerinin şartlarının iyileştirilmesi, daha iyi destek bakım, çalışanların ve refakatçilerin eğitilmesi gerekmektedir.*

Anahtar Kelimeler: *Akut lenfoblastik lösemi, çocuklar, indüksiyon ölümleri, tedavi ilişkili ölümler, olaysız sağkalım, genel sağkalım*

ABSTRACT

INTRODUCTION: *Favorable results were achieved in childhood acute lymphoplastic leukemia (ALL) by Berlin-Frankfurt-Münster (BFM) study group trials. Here, biological features of leukemia and treatment results of children and adolescents treated with BFM-based protocols were analysed to explain relatively inferior outcomes compared to BFM-ALL study group*

METHODS: *Data of the patients diagnosed between January 2001-December 2014 were collected from hospital records. BFM- Turkey ALL 2000 (TRALL-2000) (modified BFM-95), BFM-ALL 95 and BFM-ALL-Intercontinental -2009 treatment protocols were used consecutively. All patients 1-18 year-old, excluding patients with Down syndrome were included in the study.*

RESULTS: *There were 207 patients with a mean age of 6.64 ± 4.35 years. Distribution of the patients were 27.5%, 54.9% and 16.2% in standard, medium and high risk groups, respectively. Immunophenotype was B-ALL, T-ALL and biphenotypic leukemia in 84.3%, 13.7% and 1% of the patients respectively. There were 9 (4.3%) induction deaths and remission rate was 94.2% on day 33. Thirteen patients (6.5%) died in the first complete remission. Sixteen of the deaths (7.7%) in induction plus first complete remission were infection related. Relapse rate was 19.3%. Mortality was 20.1%. Seven-year event –free survival and overall survival were 73% and %79.4 respectively.*

DISCUSSION AND CONCLUSION: *Compared to multicenter trial BFM-95 of BFM-ALL study group, induction deaths and death in first CR were high. Survival rates were similar to other Centers of Turkey. Improvement in conditions of the Hematology Units, better supportive care, training of the staff and caregivers will be required to decrease infection related mortality.*

Keywords: *Acute lymphoblastic leukemia, children, induction deaths, treatment- related- mortality, event-free-survival, overall survival*

İletişim / Correspondence:

Prof.Dr.Nazan Sarper
Kocaeli Üniversitesi Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları Anabilim Dalı, Kocaeli, Türkiye,
E-mail:nazan_sarper@hotmail.com
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INTRODUCTION

Childhood acute lymphoblastic leukemia (ALL) treatment was a success story of collaborating pediatric hematologists. The story started with "West-Berlin study" performed from 1970 to 1976 trying multi-agent chemotherapy (1). Previous observations showed that drug combinations would overcome drug resistance and irradiation would prevent central nervous system disease (2). Berlin-Frankfurt-Münster (BFM) study group reported treatment results of 5 consecutive multi-center trials enrolling more than 6000 patients and randomized arms answered important questions and provided balance between effective therapy and toxicity (3). Probability of 10-year event-free survival (EFS) increased to 85% in ALL-BFM 95 study (4). Quantitative assessment of blast count on day 15 bone marrow by multiparameter flow cytometry (FCM) was found as a strong evidence of minimal residual disease (MRD) (5). In this cohort it was also shown that polymerase chain reaction (PCR) based MRD on day 33 and 78 was highly predictive for relapse in childhood precursor B ALL (pB-ALL) (6). Allogeneic hematopoietic stem cell transplantation (HSCT) also contributed to survival of patients with poor prognostic features or patients in second or further remissions.

In the last two decades number of Pediatric Hematology Centers in Turkey increased and access of children to leukemia treatment improved throughout country. In Turkey, pediatric HSCT facilities started in 1988 with only one Center in İstanbul. Our Pediatric Hematology Center was established in 2000 by one hematologist as the only pediatric hematology center of the city and the district. The center developed in the succeeding years increasing number of the hematologists, capacity and laboratory facilities. Here, biological features of leukemia, and treatment results of children and adolescents treated with BFM based ALL protocols were analysed to explain relatively inferior outcomes compared to trials in West Europe.

MATERIAL AND METHODS

Patients

A retrospective analysis of 1-18 year-old patients with ALL, diagnosed from January 2001 to December 2014 was performed. Follow-up was updated at the end of 2018. Patients with Down syndrome and mature B-cell leukemia were not included in the study. Approval of the institutional ethical committee was obtained for the study. Approval of the legal guardians of the patients for using medical data was also obtained during admission to the hospital.

Risk stratification

BFM-TR ALL 2000 (BFM-Turkey ALL 2000) and ALL BFM-95 risk groups (3).

HR group: Prednisolone poor response (PPR) on day 8, and/no complete remission (CR) on day 33, and/or presence of t (9; 22) or BCR/ABL, and/or presence of t (4; 11) or MLL/AF4

MR group: No HR criteria and initial (white blood cell) WBC ≥ 20 000/μL and/or age at diagnosis ≥ 6 years, and or T-ALL

SR group: No HR criteria and initial WBC <20 000/μL, and age at diagnosis between 1-6 years and no T-ALL.

BFM-ALLIC-2009 risk groups: (7)

In addition to above criteria 15th day bone marrow morphology and/FCM-MRD analysis was also used for post-induction stratification.

SR: 15th day bone marrow FCM-MRD<0.1% or M1/M2 morphology

MR: 15th day bone marrow FCM-MRD between 0.1-10% or M1/M2

HR: 15th day bone marrow FCM-MRD>10% and M1/M2/M3 morphology

T-cell phenotype was not a risk group criterion in ALLIC- BFM-2009 protocol.

Definitions

Patients who died within the first 4–5 weeks after primary diagnosis of ALL (end of induction therapy) were defined as suffering from induction deaths. Death in first CR included all children who died after having achieved CR. EFS was defined as the time from diagnosis to the date of last follow-up in CR or the first event. Events were resistance to therapy (nonresponsive), abandonment of treatment, and relapse or death from any cause. If CR could be achieved after one block in HR arm after induction failure, it was not accepted as an event. Resistance to therapy was defined as not having achieved CR by the end the third HR block.

OS was defined as time from initiation of treatment to death or the date of the last follow-up.

Treatment

In succeeding years three chemotherapy protocols were used: BFM- TR ALL-2000 between 2001-2010, ALL BFM-95 protocol between 2010-2012 and BFM- ALLIC-2009 protocol between 2012-2014 (4, 8, 9). In two patients with BCR/ABL expression EsPhALL 2010 protocol was administered (10).

BFM-TR ALL-2000 was the first Turkish multi-centre study in the treatment of pediatric ALL (8, 9). This was a modified version of BFM-ALL 95 protocol. Major modification was substitution of methotrexate (mtx) 5g/m2/24 h with 1g/m2/36 h. Only T-ALL patients in MR arm received mtx 5g/m2/24 h. Due to reduction in mtx dose, prophylactic cranial irradiation (pcRT) could not be omitted from MR arm; 12 Gy in pBALL >2 years and T-ALL >1 year was administered. Rational for this modification was lack of laboratory facilities for monitoring mtx drug level in many centers and hematologists' anxiety about high dose mtx toxicity.

From 2010 to 2012, original BFM-95 protocol was used without MCA arm randomization (4). In this protocol 12 Gy pcRT was introduced only to T-ALL patients in MR group and HR patients >1year. BFM-ALLIC 2009 protocol was introduced without any randomization (7). But FC-MRD was only performed in pB-ALL, because laboratory was not accredited in FC-MRD of T-ALL. In MR and HR arm Augmented IB consolidation was administered only in T-ALL. All patients except pB-ALL in SR group received mtx 5g/m2/24h. In SR group pB-ALL patients received mtx 2 g/m2/24h. In this protocol 12 Gy pcRT was limited to non-transplanted HR patients and patients with T-ALL+ WBC > 100 000/µL in MR group >1year. pcRT was also omitted from treatment of patients with pB-ALL who are in HR group only due to PPR. In the maintenance phase, patients who had no pcRT, received additional intrathecal mtx.

Before June 2005, unit had 3-bed rooms and patients used common bathroom of the unit. Then new unit had 2-bed rooms with private bathrooms. The rooms had no high particulate efficacy air (HEPA) filters. In the first 4 years there was no intensive care Unit and no pediatric intensive care specialist throughout the study. In 2015, HSCT unit was established and matched-family-donor (MFD) transplants were started.

Statistical Analysis

Statistical Package for Social Science software version 13.0 was used. Descriptive statistics was used for calculation of mean, median and percentage. For comparison of groups Mann-Whitney U and Kruskal Wallis tests were used. For survival analysis Kaplan-Meier method and two-way log-rank is used. $p<0.5$ is accepted as significant.

RESULTS

Clinical and biological features and treatment response of the 207 patients were given on table 1. Genetic study could not be performed in 6 of the patients.

Table 1. Clinical and biological features of patients with ALL

Characteristics	N 207 (%)
Age (year)	
mean	6.6±4.38
median	5.16 (13 month-17.66 year)
Sex	
Male	112 (53.1%)
Female	95 (46.9%)
White blood cell(median)/ µL	14 000(458-743000)
<20 000/ µL	119 (57.5%)
20 000-<100 000/ µL	61 (31.4%)
≥100 000/ µL	23 (11.1%)
Initial Central Nervous system involvement	5 (2.4%)
mediastinal mass	13 (6.3%)
Immunophenotype	
Precursor B-ALL	174 (84.1%)
T-cell	28 (13.5%)
Biphenotypic	2 (1%)
Not defined	3 (1.4%)
t(9:22) or BCR/ABL positive	5 (2.4%)
t(4;11) or MLL/AF4 positive	5 (2.4%)
Response to pednisone	
Good	188 (90.8%)
Poor	18 (8.7%)
Not defined	1 (0.4%)
15 day bone marrow morphology	188
M1	127(61.5%)
M2	41 (19.8%)
M3	24 (11.6%)
Remission achieved	195 (94.2%)
Risk group	
Standard	55 (27%)
Medium	115(56.4%)
High	34(16.7%)
Not defined	3 (1.44%)
Induction deaths	9 (4.3%)
Death in first Complete Remission	13(6.5%)

Treatment outcomes of the patients were shown in the flow-diagram (Figure 1). During BFM-TR ALL chemotherapy, day 15 bone marrow was not performed in a few patients but it had no role in

post-remission stratification. There were 9 (4.3%) induction deaths; 6 were due to infection, one due to leukostasis related cerebral hemorrhage, one due to venooclusive disease and one due to resistant disease. One of the patients that died with infection had ataxia telangiectasia. Two patients abandoned treatment in CR1 (one in consolidation, one in maintenance). Death in CR1 was 6.5% (n=13). Relapse rate was 19.3%; one early relapse was after treatment abandonment. Median relapse time was 25 months (4-110 months). Among these relapses there were 29 (72.5%) isolated bone marrow, 2(5%) isolated CNS, 2(5%) isolated testis, 3(7.5%) marrow+CNS, and 4(10%) marrow+testis relapses. One patient developed Hodgkin's disease and she was alive and disease free after chemotherapy and autologous transplantation. Seven (3.8%) patients were transplanted in CR1 whereas 11(5.3%) patients were transplanted in CR2. Among 18 transplanted patients 15 were alive and disease-free. Risk Factors for poor EFS were given on table 2. High WBC count at diagnosis, T-cell immunophenotype, PPR, ≥ 5% blast on marrow smear on day 15 and day 33 were significantly related to inferior 7-year EFS. Although female sex and 1-9 years had better EFS, this difference was not significant from male sex and patients ≥10 years, respectively.

Table 2. Risk Factors for Poor Event-Free- Survival

	7- year EFS(%)	Log rank test p value
Age (year)		
1-9 years	74.5	>0.05
≥10yr	66.7	
Sex		
Female	76.8	>0.05
Male	69.1	
WBC count (per/µL)		
<20 000	81.4	0.001
20 000- <100 000	71.9	
≥100 000	30.4	
Immunophenotype		
pB-cell	75.6	0.004
T-cell	53.6	
Response to prednisolone		
Good	75.4	0.001
Poor	47.1	
15 day bone marrow morphology		
M1	78.6	0.014
M2	65.9	
M3	52.2	
33 day bone marrow morphology		
M1	76.7	0.001
M2	20.0	
M3	0.48	

There were 41deaths (19.8%) during study. Causes of deaths: 1 (0.4%) cerebral hemorrhage due to leukocytosis, 1 resistant disease (0.4%), 2(%1.0) transplant-related, 4 (1.9%) chemotherapy toxicity, 16 (7.7%) infection, and 17(8.2%) relapse-resistant. EFS according to risk groups were calculated in 204 patients due to early deaths before identification of the risk group. Total number of events was 54 and 7-year-EFS was 83.6%, 73.9% and 55.9%, in SR, MR and HR groups respectively (p=0.02) (Figure 2).

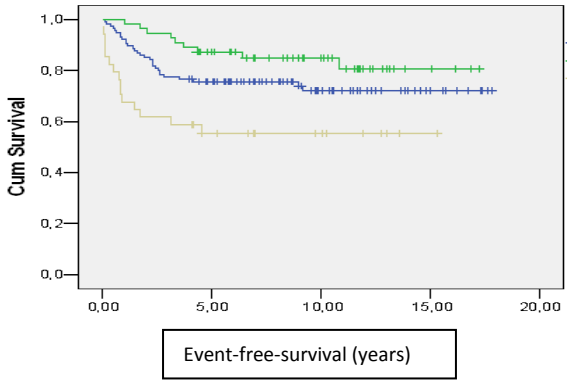

Figure 2. Event-free-survival according to risk groups SR n=55, events= 9 EFS 83.6_ MR n=115, events=30 EFS 73.9_ HR n=34, events=15 EFS 55.9_ All patients=204 events=54 7- year EFS 73.5_ p=0.02

Out of 5 patients with t(4; 11), 2 had induction deaths (VOD and cerebral hemorrhage due to leukostasis). One patient had successful matched-sibling donor (MSD) transplant in CR1. Finally 3/5 patients were alive in CR1. Out 5 patients with t (9; 22), 3 were also alive in CR1 (only 1 had MSD transplant). Two patients relapsed and died; one of these deaths was transplant related. As a result, 6/10 of these high risk patients were alive and two of them were transplanted in CR1.

In a mean follow-up of 7-year, EFS, relapse-free-survival (RFS) and OS were 72.5%, 79.3%, and 80.2%, respectively. EFS and OS were 69.1% and 78.2% in males versus 76.8% and 83.2% in females. (p>0.05)

Comparison of some risk factors and outcomes of the patients receiving different chemotherapy protocols were given on table 3. EFS of patients receiving ALLIC-2009 protocol was superior to other protocols (p=0.001). OS of patients receiving ALL BFM-95 protocol was inferior to other protocols (p=0.001). In the last 57 patients treated with BFM-ALLIC-2009 protocol, 7-year EFS and OS increased to 78.9% and OS 84.2%, respectively. Distribution of the patients into risk groups was also different between the three chemotherapy protocols. In TR ALL-2000 cohort SR group was larger, but HR was smaller; in ALL-BFM-95 cohort SR was small (p<0.01). (Table 3).

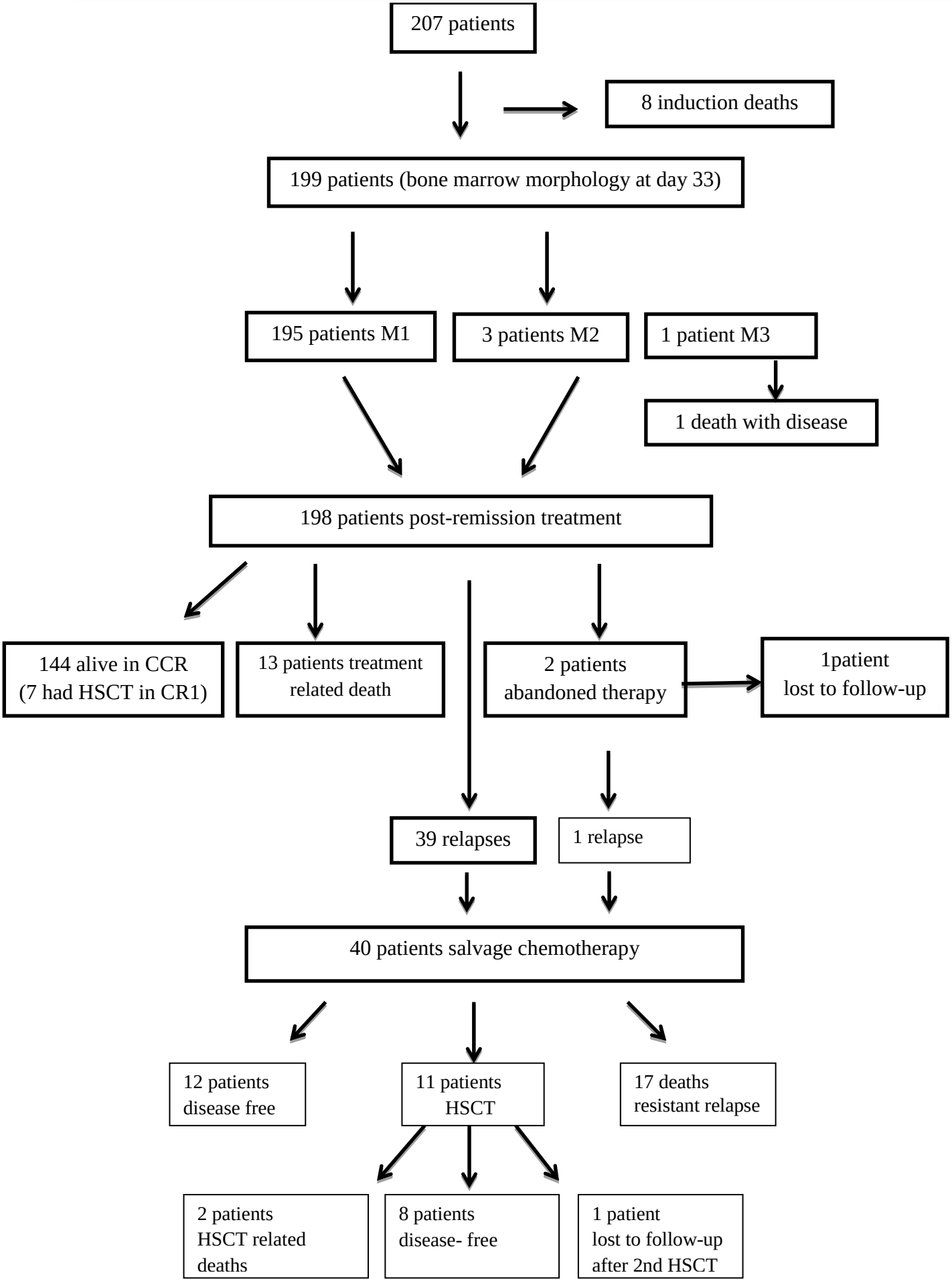

Figure 1.Flow diagram showing treatment outcome;

Table 3. Comparison of risk factors and outcomes of three consecutive chemotherapy protocols

Patients	**BFM TR ALL-2000 n=117 56.5%**	**BFM ALL-95 n=31 15%**	**BFM ALLIC-2009 n=57 27.5%**	**p**
T-ALL	12%	12.9%	17.5%	>0.05
WBC>100 000/µl	7.7%	22.6%	12.3%	>0.05
≥10 yaş	21.4%	41.9%	26.3%	>0.05
Standard Risk Group	34.2%	6.7%	23.6%	
Medium Risk Group	57.3%	66.7%	50.9%	**<0.001***
High Risk Group	8.5%	26.7%	25.5%	
Induction deaths	3.4%	3.2%	5.3%	
Treatment related deaths	7.6%	6.4 %	3.5%	**
Relapse rate	22.4%	25.0%	15%	>0.05
HSCT in 1st remission	3.4%	3.2%	5.4%	>0.05
HSCT in 2nd remission	5.1%	3.2%	5.4%	
EFS (7-year)	70.9%	67.7%	78.9%	**<0.001*** **
OS (7 year)	81.2%	71.0%	84.2%	**<0.001 **** **
RFS	77.6%	75.0%	84.9%	>0.05

Difference was between TRALL-2000 and the other chemotherapy protocols .
****Small figures were not suitable for statistical evaluation***
***** Difference was between ALLIC-2009 and other chemotherapy protocols.***
****** Difference was between ALL-95 and other chemotherapy protocols.***

DISCUSSION

In the present study there was male predominance in children with ALL (M/F=1.17) similar to other studies (3, 6, 11-13). Mean age was 6.6±4.38 year similar to other studies from Turkey (11, 13). Similar to ALL-BFM 95 cohort of the BFM-ALL study group, 11.1% of the patients had WBC ≥100 000/µl (3). T-cell immunophenotype, BCR/ABL and MLL/AF4 incidences were 13.5%, 2.4%, and 2.4% respectively, very similar to ALL-BFM 95 cohort, where incidences were 13.3 %. 2.1% and 2.2% respectively (3). Initial CNS involvement was 2.4% similar to BFM group studies (3.3% in ALL-BFM 95 and 2.6% in ALL-BFM 90 cohort) (3). Distribution of the patients in SR, MR and HR groups were 27.0%, 56.4%, and 16.7% respectively. In ALL-BFM 95 cohort distribution of these groups were 34.9%, 53.3% and 11.7%. In both cohorts majority of the patients were in the MR group and minority in HR group. EFS and OS were inferior in boys compared to girls, but these differences were not significant. In ALL-BFM 95 cohort also inferiority of EFS was not statistically different in boys whereas in ALL-BFM 83, 86 and 90 trials EFS of males was significantly lower. Demographic characteristics of the patients and biological characteristics of the leukemic cell were similar to cohorts of BFM group study (3).

In this cohort, PPR was 8.7%, very similar to prednisone response in ALL-BFM 95 trial of the ALL-BFM study group (3). But in the same study, induction death was only 0.7%. In the present study induction death rate was 4.3%; among these 9 patients there was one patient with ataxia telangiectasia and one patient with malnutrition who could not tolerate chemotherapy. Another patient with leukostasis and cerebral hemorrhage on admission also died despite supportive care. During induction, one patient developed venooclusive disease and died; defibrotide was not available. Induction deaths were between 1.5-12.3% in different pediatric ALL series from Turkey (11-15). Highest induction death was from Centers in the east and south-east of the country where socioeconomic status, school literacy, hygiene, health literacy, compliance to treatment was poor (14). In these Centers there was also shortage of hematologists and less optimal laboratory facilities. Improvement in hospital conditions, one-bed, HEPA filtered rooms with private bathrooms, and better hand hygiene of staff may decrease infection related mortality. In the present study, there were only 2 patients (0.9%) that abandoned treatment in CR1. Some Centers from Turkey reported abandonment rates as 2.8% and 3.5% (14, 15).

Providing temporary housing and transportation support for poor families who live far from the treating Centers may decrease abandonment rates. In Turkey, during long hospitalization, care of siblings was also a challenge for families. Thirteen patients (6.5%) died in the first CR; in BFM-ALL 95 trial of BFM study group death in first CR was only 2.1% (3). Sixteen of the deaths (7.7%) in induction plus first CR were infection related. Better supportive care may decrease these events.

Relapse rate was 19.8% in this cohort, higher than ALL-BFM-95 study group relapse rate which were 16.9% (3). Compared to BFM-ALL-95 protocol, lower mtx doses were used in some protocols and risk groups. In late-relapsed pB-ALL patients (ALL-REZ BFM-90), mtx infusion 5g/m2/24 hr was randomized with 1 g/m2/36 hr and did not show any difference in 10-year EFS and OS (16). In studies from Turkey relapse rate ranged from 12.9% to 20.4% (11-13, 15). There was not a central morphological evaluation for prednisolone response or remission evaluation of 15 and 33 day marrow smears in multi-center ALLIC-BFM study. HSCT beds and MUD transplant facilities increased in pediatric hematology centers of the country after 2015. In the same year National Stem Cell Donor Bank (TÜRKÖK) was founded and dependency to foreign donor banks and expenses decreased. In this cohort, patients without MSD, did not have chance for transplantation.

In ALL-BFM 95 trial of the BFM study group, 6 year-pEFS was 81.4% (SR 88.7%, MR79.7% and HR 53.2%). In the present study 7-year EFS was 73.5%. EFS of SR, MR and HR groups were 83.6%, 73.9% and 55.9% respectively. RFS was higher in BFM-ALLIC-2009 compared to previous protocols in this study. Day 15 bone marrow evaluation by morphology and FC-MRD may contribute to risk stratification in addition to using higher mtx doses and improving conditions of the Center and increasing experience of the staff. Compared to BFM-TR ALL 2000 protocol, stratification to SR group decreased but HR group increased in BFM-ALLIC protocol (Table 3). In 31 patients treated with ALL-BFM-95 protocol, relapse rate was higher, EFS and OS was lower compared to other protocols but there were more patients presenting with WBC ≥100 000/μL in this cohort. Follow-up time was longer in patients treated with BFM-TR ALL 2000. It was shown in AIEOP studies that EFS of the patients with ALL has an absolute decrease of 3.2% and of 0.6% in the second and third 5-year period after diagnosis, respectively (17). When outcomes of the present study was compared with reports of similar Pediatric Hematology Centers from Turkey, there was similar EFS and OS rates with BFM protocols (11-13,15).

Secondary malignancy was low similar to ALL-BFM 95 study group results (1.7% in 9 year follow-up) (3). A large retrospective study showed that in a median duration of 18.7 years, the cumulative incidence of secondary malignancy was 4% overall at 15 years and was increased to 11% at 30 years (18). Cranial irradiation increases risk of brain tumors, impairs neurocognitive and endocrine functions. Limitation of pcRT in BFM-95 and BFM-ALLIC-2009 protocols to some patients with high-risk features or T-ALL immunophenotype was an important step.

There were limitations in the laboratory facilities which impaired risk stratification of the patients. DNA-index of the patients could not be determined and enough metaphases were not obtained in many diagnostic samples. Quantitative PCR-MRD at day 33 and 78 was the most sensitive method for prediction of relapses in childhood ALL (6). But resources for this expensive methodology were not available in Turkey. FCM-MRD was relatively less sensitive but cheaper method but requires standardization. In this study, 15 day FCM-MRD was performed in only patients with pB-ALL receiving BFM-ALLIC 2009 protocol and some patients were stratified to higher risk groups but never to less intensive chemotherapy arms.

There were limitations of this study. As this was the result of a single Center, number of the enrolled patients was not high. Patients receiving interfant protocol and patients with Down syndrome were not included in the study which would probably further decrease survival rates. Patients receiving BFM-ALLIC 2009 protocol showed superior EFS, RFS and OS compared to previous patients in this report. Compared to ALL-BFM 95 results of BFM study group, outcomes were inferior but similar to outcomes of tertiery Centers from Turkey. To improve the survival rates, the first aim must be decreasing induction deaths and infection-related deaths in CR1 by training of the staff and caregivers and by improving the conditions of the Units. Treatment protocols should be also updated in the light of the developments in this area.

Conflict of Interest: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/ or affiliations relevant to the subject matter or materials included.

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