Pediatric Chemotherapeutic Regimen (BFM-95) is Superior for Overall Survival in Adult Acute Lymphoblastic Leukemia

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is a neoplastic disease characterized by clonal malignant proliferation of the lymphoid blast cells. The aim of this study is to compare chemotherapy, pediatric regimen BFM-95 protocol with adult ALL protocols in our patient cohort. We retrospectively collected data of patients aged 17 and older who were registered to database of our Hematology Department as acute lymphocytic leukemia between the years 2003-2016. Demographic data,chemotherapy protocols,side effects due to chemotherapy,disease free survivals (DFS) and overall survivals(OS) of remaining 101 patients were compared. The mean age of the patients was 33.6±14.5 ages.80% of patients were B-ALL,15% were T-ALL, 5% were in Ph+ ALL phenotype.Coagulopathy was seen more in patients receiving BFM-95 (p= 0.002). There was no significant difference among the protocols except for the coagulopathy. The complete remission rate (CR) was 100% in the BFM-95 protocol group, 70% in the Hyper-CVAD group and 60% in the CALGB receiving group. Three-year OS rate was 89% in patients receiving BFM-95, 41% in patients receiving Hyper-CVAD and 53% in CALGB group (p= 0.022).Since patients receiving BFM-95 are under 40 years of age, in order to be able to evaluate the BFM-95 protocol more clearly, OS is examined separately in patients under 40 years of age and it was found that OS was again significantly high in BFM-95 group (p= 0.014). The BFM-95 protocol has been shown to be well tolerated and to improve survival in adult patients when careful in terms of L-asparaginase and steroid-dependent side effects.

Keywords: Adult Acute Lymphoblastic Leukemia, Prognosis, adult protocol, BFM

ÖZET

Pediatrik Kemoterapi Protokolü (BFM) Erişkin Akut Lenfoblastik Lenfomada Genel Sağkalımda Üstündür

Akut lenfoblastik lösemi (ALL), lenfoid blast hücrelerinin klonal malign proliferasyonu ile karakterize neoplastik bir hastalıktır. Bu çalışmanın amacı, hasta kohortumuzda erişkin ALL protokolleri ile kemoterapiyi, pediatrik rejim BFM-95 protokolünü karşılaştırmaktır. Hematoloji Anabilim Dalı veritabanına 2003-2016 yılları arasında akut lenfositik lösemi olarak kaydedilmiş 17 yaş ve üstü hastaların verilerini geriye dönük olarak derledik. Demografik veriler, kemoterapi protokolleri, kemoterapiye bağlı yan etkiler, hastalıksız sağkalımlar (DFS) ve geri kalan 101 hastanın genel sağkalımları (OS) karşılaştırıldı. Hastaların yaş ortalaması 33.6 ± 14.5 idi. Hastaların %80'i B-ALL, %15'i T-ALL,% 5'i Ph+ ALL fenotipinde idi. Koagülopati BFM-95 alan hastalarda daha fazla görüldü (p= 0.002) Koagülopatinin dışında protokoller arasında anlamlı bir fark yoktu.

Tam remisyon oranı (CR), BFM-95 protokol grubunda% 100, Hyper-CVAD grubunda %70 ve CALGB alan grupta %60 idi. Üç yıllık OS oranı, BFM-95 alan hastalarda %89 idi. Hyper-CVAD alan hastalarda% 41 ve CALGB grubunda %53 (p= 0.022) idi. BFM-95 alan hastaların 40 yaşın altında olması nedeniyle BFM-95 protokolünü daha net bir şekilde değerlendirebilmek için OS; 40 yaşın altındaki hastalarda ayrı ayrı incelendi ve BFM-95 grubunda OS'nin tekrar anlamlı derecede yüksek olduğu bulundu (p= 0.014). BFM-95 protokolünün iyi tolere edildiği ve yetişkin hastalarda L-asparaginaz ve steroid bağımlı yan etkiler açısından dikkatli olduğunda sağkalımı iyileştirdiği gösterilmiştir.

Anahtar Kelimeler: Erişkin akut lenfoblastik lösemi, Prognoz, Erişkin protokol, BFM

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a neoplastic disease characterized by clonal malignant proliferation of the lymphoid blast cells. The 5-year survival rates of children reached up to 85% while the survival rate is around 40% despite high full remission rates in adults.[1,2] More intensive pediatric ALL protocols are recently used in adult ALL considering the lower survival of young adult patients. In some studies, the survival of adult patients with pediatric regimens was found to be increased.[3-5] However, pediatric regimens are usually more toxic to the adult ALL patients. The aim of this study is to compare chemotherapy, pediatric regimen (Berlin-Frankfurt-Munster-95) BFM-95 protocol with adult ALL protocols in our patient cohort.

PATIENTS AND METHODS

One hundred and twenty-three patients with ALL who were 17 years of age or older located at the database system of our Hematology Department between the years 2003-2016 were enrolled into the study. The patients with Burkitt ALL, patients with missing data, and patients receiving other chemotherapies prior to the BFM-95 protocol were excluded. A total of 101 patients were included for statistical evaluation.

Patients were scanned retrospectively from the database system of the Hacettepe University. Demographic information was recorded. Bone marrow biopsy revealed less than 5% blast, improvement in extramedullary involvement, and total blood count reaching normal limits were evaluated as complete remission. The last control date for living patients and the exitus dates for the patients who died, was accepted as the final status day. Disease free survival (DFS) and overall survival (OS) time of the patients were calculated. Patients with allogeneic stem cell transplantation were censored from the date of allogeneic transplantation for a more accurate comparison of chemotherapy protocols with each other. The pediatric protocol, BFM-95, was compared with adult protocols in terms of side effects, remission rates and survival.

The BFM-95 protocol consisted of four phases: induction, consolidation, re-induction, and maintenance therapy. The protocol contains prednisolone, vincristine, daunorubicine, L-asparaginase. The protocol Cancer and Leukemia Group B (CALGB) contains cyclophosphamide, daunorubicine, vincristine, prednisolone and L-asparaginase. The Hyper-Cylophosphamide-vincristin-adriamycin-dexamethasone (Hyper-CVAD) protocol contains cyclophosphamide, adriamicine, vincristine and dexamethasone.

This study was approved by the Ethical Committee of the Hacettepe University. All of the ethical considerations had been strictly followed in accordance with the Helsinki declaration. As a standard care/action of the hospitals of the Hacettepe Medical School, it has been recognized from the patient records that all of the studied patients had given informed consents at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standard of care. Statistical analyses were performed via using Statistical Package for Social Sciences (SPSS) version 23.0 for Windows. Numerical variables (minimum-maximum) were expressed as mean ± standard deviation. Categorical and continuous variables were compared with Chi-square and Mann-Whitney U, respectively, and independent variables were compared with Student's t test. Survival analyzes were performed by the Kaplan-

Table 1. Sex, ALL type, extramedullary involvement, allogenic BMT status according to the induction therapy

	BFM95	Hyper-CVAD	CALGB	OTHER	TOTAL	p
Sex						0.14
Female	5 (21%)	18 (48%)	16 (40%)	1 (100%)	40	
Male	18 (79%)	19 (52%)	24 (60%)	0 (0%)	61	
Age (mean)	23±5.3	35±13.5	39±16.2	27		
Extramedullary involvement					0,25	
CNS	4 (17%)	7 (18%)	3 (7%)	0 (0%)	14	
Other	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1	
No involvement	19 (83%)	29 (80%)	37 (93%)	1 (100%)	86	
Allogenic BMT						0.57
Yes	7 (30%)	6 (19.3%)	12 (42.8%)	0 (0%)	25	
No	16 (70%)	31 (80.7%)	28 (57.2%)	1 (100%)	76	
ALL type						0.85
B-ALL	18 (78%)	28 (75%)	33 (82%)	1 (100%)	80	
T-ALL	5 (22%)	7 (18%)	4 (10%)	0 (0%)	16	
Ph+ ALL	0 (0%)	2 (7%)	3 (8%)	0 (0%)	5	
Total						
23	37	40	1	101		

BFM95: Berlin-Frankfurt-Munster-95, Hyper-CVAD:Hyper-Cylophosphamide-vincristin-adriamycin-dexamethasone, CALGB: Cancer and Leukemia Group B, CNS: Central nervous system, ALL: Acute lymphoblastic leukemia BMT: Bone marrow transplantation, B-ALL: B-cell acute lymphoblastic leukemia, T-ALL:T-cell acute lymphoblastic leukemia , PH+ ALL: Philedelphia chromosome positive acute lymphoblastic leukemia

Meier method. Survival rates were calculated by log-rank test. $p< 0.05$ was considered statistically significant.

RESULTS

The mean age of diagnosis for a total of 101 patients was 33.6 ± 14.5 years. 40% percent of the patients were female and 60% were male. 80% of the patients were B-ALL, 15% were T-ALL and 5% were Philadelphia chromosome positive (pH +) ALL. Central nervous system (CNS) involvement was detected in 14% of the patients while 86% of patients had no extramedullary involvement. A total of 25% of the patients (n: 25) underwent allogeneic stem cell transplantation. The chemotherapy protocol was BFM-95 at 23 patients (23%), Hyper-CVAD at 37 patients (37%), and CALGB at 40 patients (40%). One patient has received the HAM protocol (Table 1). Hepatic side effects were the

Table 2. Side effects due to chemotherapy

	BFM95		Hyper-CVAD		CALGB		p
Hepatic	11/23	47,8%	7/26	26,9%	10/22	45,4%	0,38
Renal	1/23	4,3%	0/26	0%	1/22	4,5%	0,76
CNS+Neuropathy	6/23	26,0%	2/26	7,6%	3/22	13,6%	0,35
Coagulopathy	8/23	34,7%	0/26	0%	1/22	4,5%	0,002
Pancreatitis	2/23	8,6%	0/26	0%	0/22	0%	0,23
Other	1/23	4,3%	1/26	3,8%	0/22	0%	0,80

BFM95: Berlin-Frankfurt-Munster-95, Hyper-CVAD:Hyper-Cylophosphamide-vincristin-adriamycin-dexamethasone, CALGB: Cancer and Leukemia Group B, CNS: Central nervous system

Table 3. Induction results according to chemotherapy protocols

Induction Result	BFM	Hyper-CVAD	CALGB	HAM	p
Complete Remission	23 (100%)	26 (70%)	24 (81%)	1 (100%)	
No response	0	6 (16.3%)	1 (2%)	0	
Could not be assessed	0	1 (2.7%)	0 (0%)	0	0.172
Exitus	0	4 (11%)	15 (38%)	0	

BFM95: Berlin-Frankfurt-Munster-95, Hyper-CVAD:Hyper-Cylophosphamide-vincristin-adriamycin-dexamethasone, CALGB: Cancer and Leukemia Group B

most common side effects in all of the induction chemotherapies. There was no significant difference among the protocols except for the coagulopathy (Table 2).

When the results of induction were taken into account, it was seen that 74% of the patients had a complete remission and 7% of the patients had no response. In 19 patients (19%), induction-associated death was seen. Mortality rate was the highest in patients receiving CALGB (38%). Induction-related mortality was significantly higher in the CALGB group in comparison to the other groups (p= 0.001). The most frequent cause of death in induction was infection (75%). When non-infectious causes of death are examined; active disease in 10% of patients, other causes in 10% and hemorrhage in 5% were the cause of deaths. The complete remission rate was 100% in patients receiving BFM-95, 70% in patients receiving Hyper-CVAD, and 60% in CALGB (Table 3).

The mean follow-up period of patients was 56.5 ± 3.9 months for BFM-95 group, 22.6 ± 14.8 months for Hyper-CVAD and 90.2 ± 56.5 months for CALGB regimen. The mean follow-up period was 42.9 ± 27.1 months. The OS of the patients who received BFM-95 protocol was significantly higher than patients who received CALGB and Hyper-CVAD (p: 0.022). The 3-year OS rate for BFM-95 patients was 89% while for Hyper-CVAD patients was 41% and for CALGB patients was 53% (Figure 1). The duration of DFS was 55.2 ± 3.9 months for BFM-95, 34.1 ± 14.8 months for Hyper-CVAD and 62.5

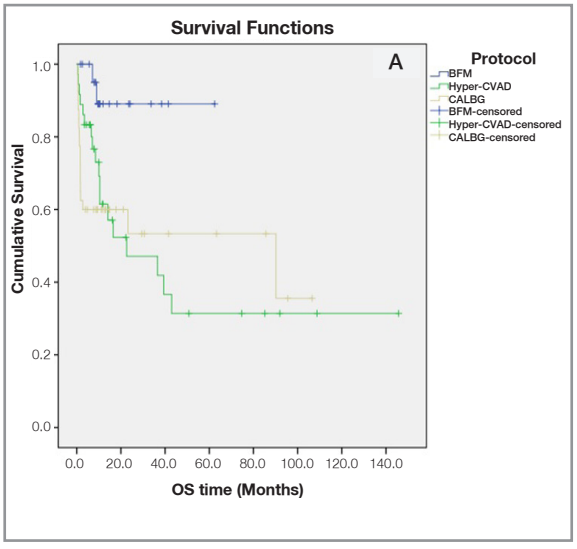

Figure 1. Total survival according to protocols. BFM95: Berlin-Frankfurt-Munster-95, Hyper-CVAD:Hyper-Cylophosphamide-vincristin-adriamycin-dexamethasone, CALGB: Cancer and Leukemia Group B, OS: Overall survival, DFS: Disease free survival

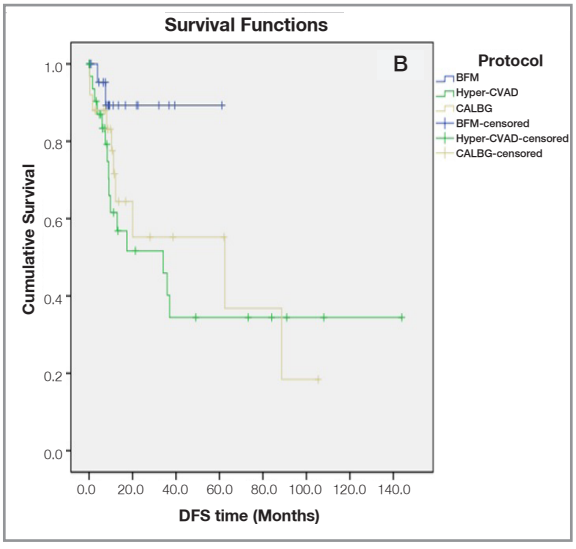

Figure 2. Duration of disease-free survival according to protocols. BFM95: Berlin-Frankfurt-Munster-95, Hyper-CVAD:Hyper-Cylophosphamide-vincristin-adriamycin-dexamethasone, CALGB: Cancer and Leukemia Group B, OS: Overall survival, DFS: Disease free survival

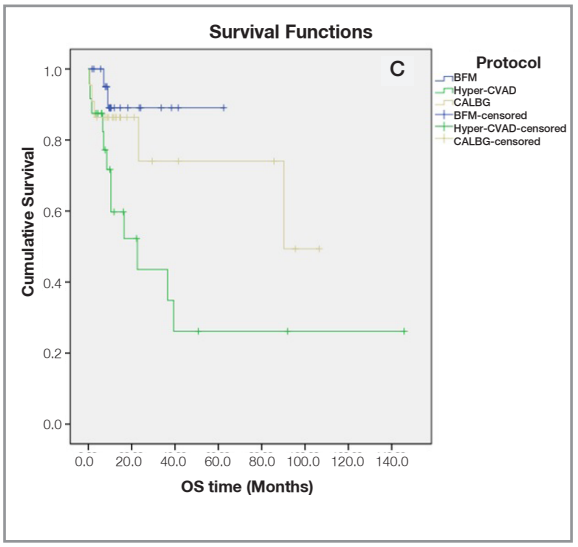

Figure 3. Total survival in patients under 40 years of age. BFM95: Berlin-Frankfurt-Munster-95, Hyper-CVAD:Hyper-Cylophosphamide-vincristin-adriamycin-dexamethasone, CALGB: Cancer and Leukemia Group B, OS: Overall survival, DFS: Disease free survival

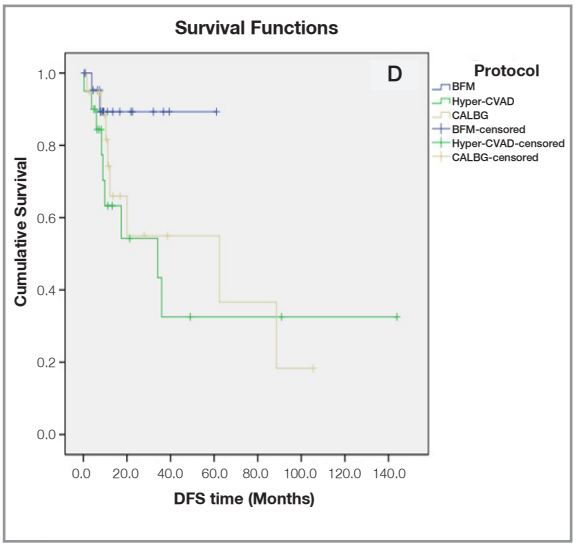

Figure 4. Disease-free survival in patients under 40 years of age. BFM95: Berlin-Frankfurt-Munster-95, Hyper-CVAD:Hyper-Cylophosphamide-vincristin-adriamycin-dexamethasone, CALGB: Cancer and Leukemia Group B, OS: Overall survival, DFS: Disease free survival

± 39.9 months for CALGB. The median duration of DFS was 62.5 ± 18.9 months all of patients. The 3-year DFS rates were 89% in the BFM-95 group but not statistically significant. This rate was 40% for patients receiving Hyper-CVAD, 55% for patients receiving CALGB (Figure 2).

Since patients receiving BFM-95 are under 40 years of age, in order to be able to evaluate the BFM-95 protocol more clearly, OS is examined separately in patients under 40 years of age and it was found that OS was again significantly higher in BFM-95 group. (p= 0.014). The 3-year OS rate was 89% for BFM-95 group, 34% for Hyper-CVAD group and 74% for CALGB group (p: 0.014). The median follow-up duration was 90.2 ± 56 months (Figure 3). In patients under 40 years of age, DFS was more prominent in patients who received BFM-95, but there was no significant difference between Hyper-CVAD and CALGB. The 3-year DFS was found to be 89% in the BFM-95 group, 32% in the Hyper-CVAD group, and 55% in the CALGB group. The average DFS duration for those receiving the Hyper-CVAD protocol was 34.1 ± 17.6 months, while 62.5 ± 21.6 months for the CALGB protocol (Figure 4).

DISCUSSION

The results of our present study indicated that better complete remission rates and survival could be obtained with pediatric BFM-95 regimen in comparison to adult ALL protocols. Despite more common adverse effects of steroid and L-asparaginase with BFM-95; side effects were usually tolerable. There is a general concern regarding adverse effects and survival rates of pediatric protocols that given to adult ALL patients. High toxicity profiles of pediatric protocols represent the great challenge for adult patients.[6]

In a study with 288 patients who had received Hyper-CVAD (Ph+ 17%, T-ALL 17%), CR was 92%, mortality related to induction was %5 (at ≤ 60 age 15%, at age > 60 2%). The prognosis was poor in the patients with high ECOG scores or abnormal liver functions.[7] Mortality rates linked to the induction chemotherapy was similar with our present study. In a study of Abbasi and colleagues that compared Hyper-CVAD and CALGB; there was no statistical differences between two protocols in terms of OS and DFS.[8] However, we detected that Hyper-CVAD was slightly better than CALGB

regimen. In our previous study the patients who received Hyper-CVAD had shorter OS and DFS in comparison to CALGB.[9] We assessed BFM-95 protocol also under 40 ages. In De Angelo and colleagues' study that compared adult ALL protocols and pediatric protocols. They detected 85% CR rates with pediatric protocol and CR rates was lower (78%) in the Ph+ ALL patients.[10] Our present results were better because of the lower numbers of Ph+ ALL patients. Rytting and colleagues' study disclosed that there was no difference among BFM-95 and Hyper-CVAD in terms of OS and DFS.[11] In a previous study that compared BFM-95 and Hyper-CVAD, 5 year survival was 59% for BFM-95 and 34% for Hyper-CVAD. There was no difference between two protocols in terms of adverse effects.[12] In our present study, BFM-95 was better than Hyper-CVAD as well.

Rytting and colleagues indicated that adverse effects depending on L-asparaginase were much higher with BFM-95, whereas Hyper-CVAD side effects were mostly related to myelosupression.[3,11] In a study of McNeer and calleagues' there was no difference between BFM-95 and other protocols in terms of side effects.[13] In our study, most common adverse effect was hepatic toxicity. Adverse events of L- asparaginase were also higher in the BFM-95 group. In our study, coagulopathy was higher in BFM group and this finding was likely to be related with the use of L-asparaginase in BFM protocol. Induction mortality was significantly higher in CALGB group in our study. This observation may be ascribed to the older ages (39 year) and probably higher ECOG scores in the CALGB group. Abbasi and colleagues' implied that induction mortality rate of CALGB was only 5% in a younger population cohort of ALL.[8] The most common cause of death was bacterial infections in our study. Prophylactic antibiotic using during ALL chemotherapy is controversial subject. In our clinic, we give trimethoprim-sulfamethoxasole prophylaxis against *P. Carinii*. However, the studies that recommend antiviral and antifungal antibiotics are also presents. Antibiotic prophylaxis may be necessary for adult ALL patients.[14] In our study, Ph+ ALL patients were not separately evaluated because they constituted 5% of all patients (5 patients). However, in different our retrospective study of 46 patients with Ph+ ALL at our center; the CR rate was 85% and the rate of CR was higher in patients receiving concurrent tyrosine kinase inhibitor (TKI) than in patients receiving only chemotherapy. In the patients who went transplantation; TKI taking patients had longer survival.[15] Survival of ALL is increased in relation to allogeneic stem cell transplantation and improved supportive therapies. Allogeneic stem cell transplants have been performed in our patients from 30% of BFM-95 group, 19% of Hyper-CVAD group and 43% of CALGB group. However, the patients with transplantation have been censored from the transplant date in order to more accurately compare the induction protocols. Therefore, allogeneic stem cell transplant prognosis has not been evaluated in our study.

The retrospective nature of our study and the low number of patients are the limitations of this study. The relatively short duration of follow-up may have led to shorter OS and DFS durations. The possibility of biased induction protocols could have affected the results. For patients receiving the BFM-95 protocol, exclusion of prior chemotherapy regimens may also have resulted in better outcomes of the BFM-95 protocol. In our study, pediatric protocols were more effective, but steroids and L-asparaginase-related adverse effects were more frequent. When the patients are closely followed in terms of these side effects; pediatric regimens are acceptable and tolerable for young adults. Adult protocols are less effective than pediatric protocols due to the higher relapse rates and slightly lower survival rates.

In conclusion, a pediatric regimen, BFM-95, can be used, especially in young adults, with more frequent adverse effects due to L-asparaginase and steroids in adult patients. Elucidating the prognosis of pediatric protocols in adults is vital for long-term studies of where T-ALL and Ph + ALL patients. There is also a need for studies in which pediatric protocols are given to elderly patients. There is a need for future studies that focuses on the development of new induction protocols which have less toxicity for adult ALL patients but as effective as pediatric regimens.

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