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Treatment Outcome of Berlin-Frankfurt-Münster Chemotherapy Induction: Protocol for Adults with Philadelphia Negative Acute Lymphoblastic Leukemia in Oncology Centre, Mansoura University

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ABSTRACT

Background: Acute Lymphoblastic Leukemia (ALL) is a blood cancer involving the overproduction of immature lymphoid cells. Risk factors include advanced age, prior chemotherapy or radiation exposure, and certain genetic disorders. **Aim:** To evaluate adult patients with Philadelphia, negative ALL received Berlin-Frankfurt-Münster (BFM) Chemotherapy induction protocol.

Methods: This study included 98 patients diagnosed with Philadelphia negative ALL by morphology, bone marrow examination, and flowcytometry without prior malignancy with age ranging from 18 to 60 years old. After completion of the BFM induction chemotherapy protocol, patients should be verified to undergo Bone Marrow Aspiration and Trephine Biopsy examination, and morphologic response was assessed along with performing measurable residual disease (MRD) using flowcytometry.

Results: B-cell lineage ALL was predominant (77.6%), while T-ALL was present in 22.4% of the cases. All patients began the BFM protocol, but only 52% completed the full course; 36.7% discontinued due to relapse or refractory disease. Prophylactic cranial irradiation was administered to 63.3% of patients. Overall, 58.2% of patients were alive at follow-up. The median overall survival (OS) was 20.1 months, and the median event-free survival (EFS) was 15.15 months.

Conclusion: Patients who achieved complete remission had significantly better EFS and OS compared to those who did not. Furthermore, bleeding, cerebrospinal fluid (CSF) infiltration, relapse, and COVID-19 infection were found to significantly impact OS. The study underscored the importance of achieving complete remission (CR) for improved survival outcomes.

Keyword: Berlin-Frankfurt-Münster, Philadelphia, Acute Lymphoblastic Leukemia.

INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is a type of blood cancer marked by the excessive growth of immature lymphoid cells within the bone marrow, bloodstream, and various body tissues. The age-adjusted incidence rate of ALL in the United States is 1.8 per 100,000 individuals per year, with around 5,690 new cases and 1,580 deaths estimated in 2021 [(1)].

The median age at diagnosis for ALL is 17 years with 53.5% of patients diagnosed at younger than 20 years of age. In contrast, 29.6% of cases are diagnosed at 45 years or older and only approximately 13.7% of patients are diagnosed at 65 years or older [(2)].

ALL is the most common form of childhood leukemia accounting for 75% to 80% of childhood acute leukemias. On the other hand, ALL represents 20% of all Adulthood leukemias [(3)]. Several factors are associated with an increased risk of developing ALL, including advanced age (particularly over 70 years), prior exposure to chemotherapy or radiation, and specific genetic disorders—most notably Down syndrome. Though uncommon, additional inherited conditions linked to a higher risk of ALL include Li–Fraumeni syndrome, neurofibromatosis, Klinefelter syndrome, Fanconi anaemia, Shwachman-Diamond syndrome, Bloom syndrome, and ataxia-telangiectasia [(4)]. The clinical manifestations of ALL are often vague and nonspecific, commonly presenting with symptoms such as fatigue, lethargy, general constitutional complaints (including fever, night sweats, and unintended weight loss), shortness of breath, dizziness, frequent infections, and a tendency for easy bruising or bleeding [(5)].

In pediatric patients, limb or joint pain can sometimes be the sole initial symptom of ALL. Physical examinations may reveal lymphadenopathy, splenomegaly, or hepatomegaly in around 20% of cases. In mature B-cell variants, the abdomen is the most affected site, particularly in cases linked to sporadic occurrence or immunodeficiency-related ALL, where extranodal involvement is also frequently observed [(6)].

A hallmark of ALL in laboratory diagnosis is leucocytosis, predominantly lymphocytosis, alongside bicytopenia, with ≥20% lymphoblasts found in peripheral blood smears or bone marrow specimens. Immunophenotyping allows classification of ALL into three major subtypes: precursor B-ALL, mature B-ALL, and T-ALL. In adults, B-cell lineage ALL accounts for approximately 75% of cases, with mature B-ALL representing 5% of these, while the remaining 25% are T-ALL [(7)].

Treatment of ALL involves a combination of supportive care, cytoreductive therapies, and management of tumour lysis syndrome (TLS). Initial chemotherapy may include prephase regimens such as Hyper-CVAD (HCVAD) and pediatric-inspired protocols like Augmented BFM or GRAALL. Targeted therapies are also integral to treatment, including

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tyrosine kinase inhibitors (TKIs) and anti-CD20 monoclonal antibodies. One of the earlier approaches for treating advanced ALL involved adoptive cell therapy through allogeneic hematopoietic cell transplantation (HCT) or donor lymphocyte infusion (DLI) to promote a graft-versus-leukemia effect, though this carried a high risk of graft-versus-host disease (GVHD). To reduce such risks, recent advances focus on using the patient's own T cells. The development of chimeric antigen receptor (CAR) T-cell therapy represents a major breakthrough in ALL treatment [(8)].

Allogeneic hematopoietic cell transplantation (HCT) is commonly incorporated into post-consolidation therapy for adolescent and young adult (AYA) as well as adult patients with high-risk features, such as Philadelphia chromosome (Ph)-positive ALL, Ph-like subtypes, or persistent measurable residual disease (MRD)[(9)].

AIM OF WORK

This study aims to evaluate adult patients with Philadelphia negative ALL received Berlin-Frankfurt-Münster (BFM) Chemotherapy induction protocol regarding the response rate, overall survival, relapse rates and adverse events developed during treatment.

PATIENTS AND METHODS

PATIENTS

This current work was a retrospective study. The study recruited adult patients with Philadelphia negative ALL between 18 to 60 years of age attended Oncology Centre, Mansoura University in period between 2017 to 2022. This study included patients who are diagnosed with Philadelphia negative ALL by morphology, bone marrow examination and flowcytometry without prior malignancy. We excluded patients who refused to sign the informed consent or withdraw their written informed consent, patients who have history of previous hematologic malignancy, patients with inadequate baseline BM evaluation presentation, patients with minimal leukemic BM involvement (defined as baseline BM blasts <20%), patient who received chemotherapy before enrolment with the exclusion of hydroxyurea as cytoreductive therapy, patients who couldn't complete their induction protocol for whatever reasons and patient who didn't have response assessment at end of induction.

Methods

All patients recruited in the study should ensure were subjected to full history taking with attention to the presence or absence of systemic symptoms, and history suggestive of other medical disease or organ failure. Thorough physical examination, emphasizing on lymph node chains, size of the liver and spleen, cardiac, chest, neurologic examinations were done.

The enrolled patients had full investigations included complete blood count (CBC), blood film and differential leucocyte count (DLC), immunophenotyping, bone marrow aspiration and Trephine Biopsy (BMA & BMB), cancer cytogenetic analysis either conventional karyotyping or FISH (Fluorescence Institute Hybridization) analysis, liver function test, kidney function tests, coagulation profile: prothrombin time (PT) and Activated Partial Thromboplastin Time (APTT), and virology Markers: HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus.

Also, every patient had fundus examination, cerebrospinal fluid analysis by lumbar puncture, chest X-Ray, Pelvi-abdominal ultrasound, computerized Topography (CT) for assessment of mediastinal lymphadenopathy and screening for COVID-19 Infection with doing polymerase chain reaction (PCR) swab in suspicious cases, echocardiogram (ECHO), magnetic resonance imaging (MRI) of the brain in case of positive neurologic symptoms, fundus examination or CSF sample. After completion of the BFM induction chemotherapy protocol, patients should be verified to undergo BMA & BMB examination and morphologic response were assessed along with performing MRD using flowcytometry.

Ethical Consideration

The whole study design was approved by the institutional review Board, Faculty of Medicine, Mansoura University. Confidentiality and personal privacy were respected in all levels of the study. Patients feel free to withdraw from study at any time without any consequences. Collected data was not and will not be used for any other purpose. The study was conducted in accordance with Declaration of Helsinki.

Statistical Analysis

The collected data was revised, coded, and tabulated using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Mean, standard deviation (± SD), median, and range were used for numerical data. Frequency and percentage were used for non-numerical data. Shapiro-Wilk and Kolmogorov-Smirnov tests were done to test the normality of data distribution. Chi-Square (χ^2) test was used to examine the relationship between two qualitative variables. Fisher Exact (FE) or Monte Carlo test: were used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells. Marginal homogeneity test was used to determine if there are differences on a dichotomous dependent variable between two related groups. A dichotomous variable is a categorical variables with more than two categories. Student t-test was used to assess the statistical significance of the difference of parametric variable between two study group means. Mann Whitney Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups. Wilcoxon Test (Z test) was used to assess the statistical significance of the difference of a non-parametric

variable between two periods. The Log Rank **test** was used to test the null hypothesis that there is no difference between the populations in the probability of an event (here relapse/death) at any time point . Cox regression analysis: was used for prediction of survival times. Regression analysis is Logistic regression analysis was used for the prediction of risk factors when the dependent variable is categorical. An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure.OR=1 Exposure does not affect odds of outcome,OR>1 Exposure associated with higher odds (risk) of outcome,OR<1 Exposure associated with lower odds of outcome (protective).

The 95 % confidence interval (CI) is used to estimate the precision of the OR. A large CI indicates a low level of precision of the OR, whereas a small CI indicates a higher precision of the OR.

A p value is considered significant if <0.05 at confidence interval 95% measurable.

RESULTS

Table **(1)** shows that 64.3% of this study were males and 35.7% being females, with wan average age of 29, and the age range of 18 to 69 years old. The treatment BFM protocol was employed, with 43.9% of patients received the augmented form of BFM, whereas 56.1% of patients received the standard regimen. While 14.3% of patients with Philadelphia-negative ALL have concomitant illnesses, the vast majority of patients (85.7%) do not. Hypertension was the most common comorbidity (10.2%), followed by DM (4.1%) and gall stone (1%). Regarding clinical data, the most prevalent symptoms reported by patients with Philadelphia-negative ALL, with 78.6% of patients reported weight loss, and a comparable number, 77.6%, reported night sweats. Night fever and bone pains also occurred frequently, affecting 71.4% and 75.5% of patients, respectively. Lymphadenopathy was seen in a variety of locations, the most prevalent being cervical and generalized lymphadenopathy, which affected 34.7% and 18.4% of patients, respectively. The results also suggest that 76.5% of patients had enlarged spleens. History of bleeding was found in 41.8%. The mean WBC count was 55.28 k/uL, with a median of 26.60 k/uL. Mean hemoglobin level was low, with an average of 8.86 g/dL, and mean platelet count was also low, averaging 73.78 k/uL. Mean ESR was 45.24 in the first hour and 83.85 in the second hour. Mean INR was 1.1, and mean APTT was 36.88 seconds. Regarding the distribution of different forms of Philadelphia-negative ALL among the patients, there were 77.6% had B-ALL, 17.3% had pre-B and 60.2% had B. T-cell were found in 22.4% of the cases. Regarding virology data, indicating that a small fraction of patients tested positive for hepatitis B and C, with no instances of HIV found.

Table (1): Demographic data, Berlin-Frankfurt-Münster, Comorbidity, Clinical data, Laboratory data, treatment and types among adult patients with Philadelphia negative ALL

	Variables	ALL patients (n = 98)	
		No.	%
Sex	Male	63	64.3
	Female	35	35.7
Age (years)	Mean ± SD.	29.0 ± 13.21	
	Median (Min. – Max.)	24.0 (18.0 – 69.0)	
Berlin-Frankfurt-Münster (BFM)	Standard	55	56.1
	Augmented	43	43.9
Comorbidity	Negative	84	85.7
	Positive	14	14.3
	Gall stone	1	1.0
	DM	4	4.1
	Hypertension	10	10.2
Clinical data	Weight loss	77	78.6
	Night sweat	76	77.6
	Night fever	70	71.4
	Bone aches	74	75.5
Lymphadenopathy	Free	35	35.7
	Abdominal	3	3.1
	Axillary	2	2.0
	Cervical	34	34.7
	Generalized	18	18.4
	Iliac	3	3.1
	Inguinal	1	1.0
	Mediastinal	1	1.0
	Para aortic	1	1.0

	Variables	ALL patients (n = 98)	
		No.	%
Spleen	Normal	21	21.4
	Enlarged	75	76.5
	Splenectomy	2	2.0
Bleeding	Mean ± SD.	55.28 ± 78.09	
WBC (k/uL)	Median (Min. – Max.)	26.60 (1.23 – 410.0)	
Hb (g/dL)	Mean ± SD.	8.86 ± 2.48	
Platelets (k/uL)	Mean ± SD.	73.78 ± 8.95	
ESR 1st hour (mm/h)	Mean ± SD.	45.26 ± 8.17	
ESR 2nd hour (mm/h)	Mean ± SD.	83.85 ± 4.83	
INR	Mean ± SD.	1.10 ± 0.16	
APTT (sec)	Mean ± SD.	36.88 ± 9.34	
Types	B-ALL	76	77.6
	Pre-B	17	17.3
	Mature B	59	60.2
	T-ALL	22	22.4
ALT (U/L)	Mean ± SD.	46.88 ± 7.75	
AST (U/L)	Mean ± SD.	51.84 ± 6.16	
Albumin (g/dL)	Mean ± SD.	3.77 ± 0.52	
Uric acid (mg/dL)	Mean ± SD.	7.62 ± 1.01	
Creatinine (mg/dL)	Mean ± SD.	1.22 ± 0.32	
Bilirubin (mg/dL)	Mean ± SD.	0.86 ± 0.16	
LDH (IU/L)	Mean ± SD.	1057.2 ± 134.7	
Virology	HBV	1	1.0
	HCV	5	5.1
	HIV	0	0.0
Treatment	Chemo (BFM)	98	100.0
	Prophylactic cranial irradiation	62	63.3
	Therapeutic cranial irradiation	7	7.1
Treatment tolerability	Completed full course BFM	51	52.0
	Discontinued BFM (Without relapse)	0	0.0
	Discontinued BFM (dt relapse or refractory)	36	36.7
	Treatment related mortality	12	12.2

BFM, Berlin-Frankfurt-Münster; DM, Diabetes Mellitus; WBC, White Blood Cell count; Hb, Hemoglobin; ESR, Erythrocyte Sedimentation Rate; INR, International Normalized Ratio; APTT, Activated Partial Thromboplastin Time; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; LDH, Lactate Dehydrogenase; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus.

Table **(2)** shows that most patients (84.7%) had free mediastinal space, with only a few showings lymphadenopathy (3.1%) or mass (12.2%); 11.2% of patients had pleural effusion. CSF examination reveals that 93.9% of patients had negative findings. However, 6.1% of patients tested positive infiltration. Testicular involvement was uncommon, with only one patient reporting positive infiltration. Regarding the patients' risk classification, with 56.1% falling into the standard risk group and 43.9% classed as high risk. Regarding the incidence of COVID-19 infection among patients with Philadelphia-negative ALL. The great majority of patients, 98%, tested negative for COVID-19, with only 2% positive.

The treatment regimens for patients with Philadelphia-negative ALL showed that all patients underwent chemotherapy according to the BFM protocol. Furthermore, 63.3% received prophylactic cranial irradiation. However, only 7.1% required therapeutic cranial irradiation. The tolerability of treatment was also noted, with 52% completing the whole course of BFM and 36.7% discontinuing treatment owing to recurrence or refractory illness. The treatment-related death rate of 12.2%, 38.8% of the patients suffered of relapse, with 25.5% having isolated bone marrow relapses. Notably, the findings show that a considerable number of relapses occurred during the BFM therapy (68%). The prevalence of isolated BM relapses was (25.5%), isolated CNS relapses was (4.1%), and combined CNS and BM relapses was (9.2%).

Table (2): Systemic examination, Risk stratification, treatment, and relapse among adult patients with Philadelphia negative ALL

Variables	ALL patients (n = 98)	
	No.	**%**
Mediastinal		
Free	83	84.7
LN	3	3.1
Mass	12	12.2
Pleural effusion		
Free	87	88.8
Yes	11	11.2
CSF		
Negative	92	93.9
Positive	6	6.1
Testicular		
Negative	97	99.0
Positive	1	1.0
Risk stratification		
Standard	55	56.1
High risk	43	43.9
COVID infection		
Negative	96	98.0
Positive	2	2.0
Response		
Non-CR	12	12.2
CR	86	87.8
Relapse		
No	60	61.2
Yes	38	38.8
Isolated BM relapse	**25**	**25.5**
During BFM	17	68.0
After BFM	8	32.0
Isolated CNS relapse	**4**	**4.1**
During BFM	3	75.0
After BFM	1	25.0
Combined CNS and BM relapse	**9**	**9.2**
During BFM	7	77.8
After BFM	2	22.2

ALL, Acute Lymphoblastic Leukemia; LN**,** Lymph Node; CSF, Cerebrospinal Fluid; CR, Complete Remission; BM, Bone Marrow; **BFM**, Berlin-Frankfurt-Münster chemotherapy protocol; CNS, Central Nervous System; COVID, Coronavirus Disease 2019.

Among all studied cases, table **(3)** shows that 62.2% had infections with neutropenia. Blood cultures revealed growth in 49% of all cases, out of them, Klebsiella was found in 2.1%, pseudomonas in 10.4%, E coli in 14.6%, S. aureus in 58.3% and S. epidermidis in 14.6%. Urine cultures were positive in 10.2%.

They revealed Klebsiella in 20%, pseudomonas in 50%, E coli in 20% and S. aureus in 10%. Sputum culture showed pathogenic growth in 9.2%, out of them 88.9% were Klebsiella and 11.1% were pseudomonas. The neurological complications were recorded in 11.2% of patients, with sensory neuropathy being the most frequent, accounting for 63.6% of those with neurological disorders. Other neurological problems included convulsions and encephalopathy, but at a lesser frequency. Hepatic and gastrointestinal complications were less prevalent, occurring in 5.1% of patients and presenting with a variety of symptoms including bloody diarrhea and intestinal perforation. Pulmonary complications were particularly common, involving 33.7% of patients, with infections accounting for 90.9% of pulmonary cases. Furthermore, renal problems were reported in 2% of patients, with AKI and hyperuricemia nephropathy being the most common. Thrombosis was recorded in 3.1% of the cohort. Regarding the overall outcomes for the patients, there were 58.2% alive, while 41.8% died. The median OS was 20.1 months. The median EFS was 15.15 months.

Table (3): Toxicity events, complications and outcomes among adult patients with Philadelphia negative ALL.

Variables	ALL patients n = 98	
	No.	**%**
Infectious course		
Infection with neutropenia	61	62.2
Blood cultures	**48**	**49.0**
Klebsiella	1	2.1
Pseudomonas	5	10.4
E coli	7	14.6
Staphylococcus aureus	28	58.3
Staphylococcus epidermidis	7	14.6
Urine culture	**10**	**10.2**
Klebsiella	2	20.0
Pseudomonas	5	50.0
E coli	2	20.0
Staphylococcus aureus	1	10.0
Sputum culture	**9**	**9.2**
Klebsiella	8	88.9
Pseudomonas	1	11.1
Neurological complications	**11**	**11.2**
Sensory neuropathy	7	63.6
Convulsion	1	9.1
Encephalopathy /confusion	1	9.1
Sensory and motor neuropathy	2	18.2
Hepatic / GIT complications	**5**	**5.1**
Bloody diarrhea	1	20.0
Diarrhea	1	20.0
Hematemesis and melena	1	20.0
Intestinal perforation	1	20.0
Vomiting and diarrhea	1	20.0
Pulmonary complications	**33**	**33.7**
Infection	30	90.9
Effusion	2	6.1
ARDS	1	3.0
Renal complications	**2**	**2.0**
AKI	1	1.0
Hyperuricemia nephropathy (TLS)	1	1.0
Thrombosis	**3**	**3.1**
Outcomes		
Alive	57	58.2
Died	41	41.8
OS (months)		
Mean ± SD.	30.04 ± 25.79	
Median (Min. – Max.)	20.10 (0.70 – 107.8)	
EFS (months)		
Mean ± SD.	27.48 ± 26.39	
Median (Min. – Max.)	15.15 (0.10 – 102.7)	

ALL, Acute Lymphoblastic Leukemia; AKI**,** Acute Kidney Injury; TLS, Tumor Lysis Syndrome; ARDS, Acute Respiratory Distress Syndrome; OS, Overall Survival; EFS, Event-Free Survival.

Table **(4)** shows the bone marrow aspirate (BMA) results before and after induction treatment for patients with Philadelphia-negative ALL. The results show a significant improvement in cellularity, with the proportion of normocellular samples rising from 72.4% before induction to 93.9% after, demonstrating the efficacy of the induction therapy ($p<0.001$). The mean proportion of blast cells decreased substantially from 84.16% to just 10.31% ($p<0.001$).

Table (4): BMA before and after induction among adult patients with Philadelphia negative ALL

Variables	Before induction n = 98		After induction n = 98		Test	p
	No.	%	No.	%		
Cellularity						
Normocellular	71	72.4	92	93.9	U 13.50*	<0.001*
Hypercellular	25	25.5	6	6.1		
Hypocellular	2	2.0	0	0.0		
Blast cells (%)						
Median (Min-Max.)	90.0 (40.0 – 98.0)		2.0 (1.0 – 90.0)			

SD. Standard deviation, Min.: Minimum, Max.: Maximum, MH: Marginal Homogeneity Test, Z: Wilcoxon Test, p: Comparing before and after induction. *: Significant when p value <0.05.
BMA, Bone Marrow Aspirate; SD, Standard Deviation; Min, Minimum; Max**,** Maximum**;** MH**,** Marginal Homogeneity Test; **Z**, Wilcoxon Test.

Table **(5)** demonstrates the BMA results between the standard and augmented BFM groups. The results show that the two groups are similar in terms of cellularity and blast cells after treatment. However, there is a significant difference in cellularity before treatment, with the augmented BFM group having a higher proportion of patients with hypercellular marrow. The results show that the two groups are similar in terms of complete remission (CR), relapse, and mortality rates.

Table (5): Comparison between standard and augmented BFM regarding BMA before and after treatment, regarding outcomes

Variables	Standard BFM N=55		Augmented BFM N=43		Test	p
	No.	%	No.	%		
Cellularity						
Before						
Normocellular	45	81.8	26	60.5	χ^2= 8.990	MC 0.006*
Hypercellular	8	14.5	17	39.5		
Hypocellular	2	3.6	0	0		
After						
Normocellular	52	94.5	40	93.0	χ^2= 0.097	FE 1.0
Hypercellular	3	5.5	3	7.0		
Blast cells (%)						
Before						
Mean ± SD.	83.04±14.45		85.6±10.2		U= 1146.0	0.774
Median (Min.-Max.)	90(40-98)		90(48-95)			
After						
Mean ± SD.	10.89±24.81		9.56±23.88		U= 1090.0	0.484
Median (Min.-Max.)	2(1-90)		2(1-90)			
CR						
No	7	12.7	5	11.6	χ^2=0.027	0.869
Yes	48	87.3	38	88.4		
Relapse						
No	35	63.6	25	58.1	χ^2=0.307	0.579
Yes	20	36.4	18	41.9		
Outcome						
Alive	35	63.6	22	51.2	χ^2=1.543	0.214
Died	20	36.4	21	48.8		

SD. Standard deviation, Min.: Minimum, Max.: Maximum, U: Mann-Whitney test, χ^2: Chi-Square test, FE: Fisher Exact, MC: Monte Carlo. BFM, Berlin-Frankfurt-Münster protocol; BMA, Bone Marrow Aspirate**;** CR, Complete Remission.

Table (**6**) compares B-ALL and T-ALL based-on risk stratification. The difference between groups was not statistically significant (p>0.05). Regarding comparing B-ALL with T-ALL in terms of complications, the findings showed that T-ALL was associated with renal complications (p=0.049). The other complications, such as hepatic/GIT, pulmonary, and thrombosis, did not differ significantly across the groups. Regarding comparing the results of B-ALL with T-ALL patients, with emphasis on CR, relapse, and overall outcome, the findings showed no significant differences in CR rates, relapse rates, or overall outcomes between the two groups.

Table (6): Comparison between B-ALL and T-ALL regarding risk stratification and complications

	Variables	B-ALL (n = 76)		T-ALL (n = 22)		Test	p
		No.	%	No.	%		
Risk stratification	Standard	40	52.6	15	68.2	χ^2=1.675	0.196
	High risk	36	47.4	7	31.8		
Neurological	Negative	66	86.8	21	95.5	χ^2= 1.270	FE 0.447
	Positive	10	13.2	1	4.5		
Hepatic / GIT	Negative	73	96.1	20	90.9	χ^2= 0.932	FE 0.312
	Positive	3	3.9	2	9.1		
Pulmonary	Negative	50	65.8	15	68.2	χ^2= 0.044	0.834
	Positive	26	34.2	7	31.8		
Renal	Negative	76	100.0	20	90.9	χ^2= 7.053*	FE 0.049*
	Positive	0	0.0	2	9.1		
Thrombosis	Negative	74	97.4	21	95.5	χ^2= 0.211	FE 0.538
	Positive	2	2.6	1	4.5		
CR	No	9	11.8	3	13.6	χ^2= 0.051	FE 0.729
	Yes	67	88.2	19	86.4		
Relapse	No	45	59.2	15	68.2	χ^2= 0.578	0.447
	Yes	31	40.8	7	31.8		
Outcome	Alive	42	55.3	15	68.2	χ^2= 1.170	0.279
	Died	34	44.7	7	31.8		

χ^2: Chi-Square test, FE: Fisher Exact. B-ALL, B-cell Acute Lymphoblastic Leukemia; T-ALL, T-cell Acute Lymphoblastic Leukemia; CR, Complete Remission.

Table **(7)** shows the connection between treatment response and bone marrow aspiration results before and after therapy. The results revealed a substantial reduction in blast cell percentages after therapy associated with CR. The findings show that there is no significant difference in treatment response based on WBC counts in both the B-ALL and T-ALL subgroups (p-values of 0.725 and 1.0, respectively).

Table (7): Association between response to treatment and BMA before and after and between CR and WBC in each subgroup.

Variables	Complete remission (CR)				Test	p
	No (n = 12)		Yes (n = 86)			
	No.	%	No.	%		
Cellularity						
Before						
Normocellular	10	83.3	61	70.9	χ^2= 0.734	MC 0.789
Hypercellular	2	16.7	23	26.7		
Hypocellular	0	0.0	2	2.3		
After						
Normocellular	10	83.3	82	95.3	χ^2= 2.645	FE 0.156
Hypercellular	2	16.7	4	4.7		
Blast cells (%)						
Before						
Mean ± SD.	84.0 ± 14.52		84.19 ± 12.60		U= 461.0	0.513
Median	90.0		90.0			
Min. – Max.	48.0 – 95.0		40.0 – 98.0			
After						
Mean ± SD.	71.42 ± 23.52		1.78 ± 0.96		U= 0.0*	<0.001*
Median	80.0		1.0			
Min. – Max.	17.0 – 90.0		1.0 – 5.0			
WBC in B-ALL <30	4	44.4	37	55.2	χ^2= 0.371	FE 0.725
>30	5	55.6	30	44.8		
WBC in T-ALL <100	2	66.7	13	68.4	χ^2= 0.004	FE 1.0
>100	1	33.3	6	31.6		

SD. Standard deviation, Min.: Minimum, Max.: Maximum, U: Mann-Whitney test, χ^2: Chi-Square test, FE: Fisher Exact, MC: Monte Carlo. *: Significant when p value <0.05. BMA, Bone Marrow Aspirate; CR, Complete Remission; WBC, White Blood Cell count.

Table **(8)** shows that the results demonstrated no significant variation in treatment response based on age (p-value = 0.163).

Table (8): Association between CR that received standard BFM and age

Variables	CR that received standard BFM				Test	p
	No (n = 7)		Yes (n = 48)			
	No.	%	No.	%		
Age						
<60 years	5	71.4%	44	91.7%	χ^2= 2.575	FE 0.163
>60 years	2	28.6%	4	8.3%		

χ^2: Chi-Square test, FE: Fisher Exact.

Table **(9)** shows that a logistic regression analysis was conducted to predict the occurrence of CR based on a variety of parameters. The findings show that being female is substantially related with a greater susceptibility of achieving CR, with a p-value of 0.040 and an odds ratio of 2.628. Other parameters, including age, comorbidities, laboratory data, type of ALL, treatment protocol, did not exhibit significant relationships. Table **(10)** shows the factors affecting EFS. The data indicates that patients with negative CSF have a significantly higher mean EFS of 58.16 months compared to those with positive CSF, who have a mean EFS of only 10.53 months, with a p-value of 0.001. The response to treatment shows that the patients achieving CR having a mean EFS of 58.52 months compared to those with Non-CR, who have a mean EFS of only 6.50 months, with a highly significant p-value of <0.001. Better EFS was significantly associated with free CSF and achieved CR. Otherwise, no significant association was found between EFS and other parameters studied.

Table (9): Logistic regression analysis for prediction CR

Variables	P	OR	95% CI
Females versus males	0.040*	2.628	1.047–6.593
Age <60 versus >60 years	0.150	2.232	0.749–6.651
Augmented versus standard BFM	0.869	1.056	0.553–2.016
Comorbidity	0.804	0.894	0.369–2.163
Lymphadenopathy	0.404	0.741	0.366–1.500
WBC	0.146	0.997	0.994–1.001
Blast cells at diagnosis	0.963	1.001	0.976–1.026
LDH	0.772	1.153	0.4403.021
ESR 1st hour	0.124	0.992	0.981–1.002
B-ALL versus T-ALL	0.822	1.090	0.514–2.311
CSF infiltration	0.150	0.448	0.150–1.335

CR, Complete Remission**;** OR, Odds Ratio; CI, Confidence Interval; WBC**,** White Blood Cell count; LDH**,** Lactate Dehydrogenase**;** ESR**,** Erythrocyte Sedimentation Rate; **CSF**, Cerebrospinal Fluid; BFM**,** Berlin-Frankfurt-Münster protocol; ALL, Acute Lymphoblastic Leukemia.

Table (10): Factors affecting EFS

Variables	EFS (months)						
	N	No. of events	Mean	SE.	EFS at 3 years (36m)	EFS at 5 years (60m)	p for Log Rank
Sex							
Male	**63**	**28**	54.84	6.56	48.9	46.0	0.979
Female	**35**	**16**	47.69	6.71	49.2	49.2	
Age							
<60 years	**92**	**43**	54.31	5.25	47.9	46.1	0.398
>60 years	**6**	**1**	41.97	12.03	66.7	66.7	
BFM							
Standard	**55**	**22**	61.96	6.83	57.1	54.1	0.130
Augmented	**43**	**22**	39.95	6.27	37.5	37.5	
Comorbidity							
Negative	**84**	**38**	55.21	5.55	48.7	46.8	0.912
Positive	**14**	**6**	31.13	6.31	50.6	50.6	
Weight loss							
No	**21**	**12**	53.78	10.47	50.6	44.3	0.899

Variables	EFS (months)						
	N	No. of events	Mean	SE.	EFS at 3 years (36m)	EFS at 5 years (60m)	p for Log Rank
Yes	**77**	**32**	47.84	4.83	48.1	48.1	
Night sweat							
No	**22**	**9**	65.85	10.71	59.6	59.6	0.254
Yes	**76**	**35**	44.71	4.77	45.4	42.9	
Night fever							
No	**28**	**13**	57.20	9.90	51.1	0.0	0.917
Yes	**70**	**31**	46.54	4.93	47.7	44.7	
Bone aches							
No	**24**	**15**	43.54	9.68	38.3	33.5	0.158
Yes	**74**	**29**	51.06	4.84	52.6	52.6	
Lymphadenopathy							
No	**35**	**17**	42.08	7.11	45.8	40.7	0.218
Yes	**63**	**27**	58.40	6.40	50.1	50.1	
Spleen							
Normal	**21**	**10**	60.79	11.02	59.9	53.2	0.835
Enlarged	**75**	**33**	46.09	4.80	45.2	45.2	
Splenectomy	**2**	**1**	12.80	8.77	-	-	
Bleeding							
No	**57**	**22**	63.43	6.73	56.9	56.9	0.067
Yes	**41**	**22**	37.03	5.92	37.3	33.2	
WBC							
<30 k/uL	**49**	**24**	53.76	7.13	48.1	44.7	0.814
>30 k/uL	**49**	**20**	48.67	6.07	49.8	49.8	
Type							
B-ALL	**76**	**36**	44.68	4.69	45.6	43.2	0.204
T-ALL	**22**	**8**	67.48	11.27	61.0	61.0	
US (Spleen Size)							
Normal or Splenectomy	**24**	**11**	61.81	10.28	60.9	54.8	0.587
Splenomegaly	**74**	**33**	45.39	4.83	44.2	44.2	
US (Liver)							
Normal	**39**	**17**	46.48	5.93	53.8	49.4	0.724
Hepatomegaly	**59**	**27**	53.40	6.76	45.3	45.3	
Effusion							
Free	**87**	**39**	55.54	5.46	49.4	47.4	0.868
Yes	**11**	**5**	45.05	12.52	43.8	43.8	
CSF							
Negative	**92**	**39**	58.16	5.30	52.1	50.2	0.001*
Positive	**6**	**5**	10.53	4.86	0	0	
Risk stratification							
Standard	**55**	**22**	61.96	6.83	57.1	54.1	0.130
High risk	**43**	**22**	39.95	6.27	37.5	37.5	
COVID infection							
Negative	**96**	**43**	55.79	5.17	49.4	47.6	0.060
Positive	**2**	**1**	5.90	0.0	0	0	
Response							
Non-CR	**12**	**6**	6.50	1.30	28.6	28.6	<0.001*
CR	**86**	**38**	58.52	5.31	52.0	50.1	
LDH							
Low	**2**	**1**	27.60	2.09	50	50	0.979
High	**96**	**43**	55.25	5.21	77.1	53.4	

EFS, Event-Free Survival; SE, Standard Error; CR, Complete Remission**;** CSF, Cerebrospinal Fluid; LDH**,** Lactate Dehydrogenase; BFM**,** Berlin-Frankfurt-Münster protocol; ALL, Acute Lymphoblastic Leukemia.

Table **(11)** examines the OS in ALL patients. A notable finding is the significant association between bleeding and OS (p-value = 0.030), indicating that patients without bleeding had a higher survival rate. Furthermore, positive infiltration of CSF was substantially related with poor survival outcomes, as evidenced by a p-value of <0.001. Also, the results underscore the critical importance of achieving CR in improving OS rates, as patients who did not achieve CR had significantly lower OS time and OS rates compared to those who did achieve CR, with a p-value also less than 0.001. Moreover, those who relapsed had lower OS p<0.001). In addition, those who had COVID-19 infection showed significantly lower OS (p=0.007). While other studied factors had non-significant impact on OS.

Table (11): Factors affecting OS

Variables	OS (months)						
	N	**No. of events**	**Mean**	**SE.**	**OS at 3 years (36m)**	**OS at 5 years (60m)**	**p for Log Rank**
Sex Male	**63**	**25**	60.98	6.69	53.8	47.6	0.884
Female	**35**	**16**	49.59	6.50	47.8	47.8	
Age							
<60 years	**92**	**40**	59.64	5.36	50.7	46.9	0.400
>60 years	**6**	**1**	45.93	9.61	66.7	66.7	
BFM							
Standard	**55**	**20**	67.47	6.80	60.3	54.2	0.092
Augmented	**43**	**21**	43.34	6.22	39.5	39.5	
Comorbidity							
Negative	**84**	**35**	60.80	5.64	51.8	47.9	0.865
Positive	**14**	**6**	33.92	5.86	50.6	-	
Weight loss							
No	**21**	**11**	58.96	9.95	50.3	43.1	0.981
Yes	**77**	**30**	51.26	4.76	52.2	50.0	
Night sweat							
No	**22**	**8**	70.79	10.11	58.7	58.7	0.265
Yes	**76**	**33**	48.11	4.70	49.3	44.2	
Night fever							
No	**28**	**11**	65.50	9.53	54.1	54.1	0.611
Yes	**70**	**30**	48.88	4.85	50.4	44.6	
Bone aches							
No	**24**	**14**	47.92	9.34	38.1	31.7	0.155
Yes	**74**	**27**	54.53	4.74	56.9	54.6	
Lymphadenopathy							
No	**35**	**16**	46.31	6.87	47.4	41.5	0.385
Yes	**63**	**25**	63.07	6.51	53.1	50.6	
Spleen Normal	**21**	**9**	63.85	10.77	58.7	51.4	0.883
Enlarged	**75**	**31**	50.03	4.68	49.0	46.9	
Splenectomy	**2**	**1**	17.0	6.51	-	-	
Bleeding							
No	**57**	**19**	70.45	6.72	59.6	59.6	0.030*
Yes	**41**	**22**	39.16	5.70	39.9	31.1	
WBC							
<30 k/uL	**49**	**22**	59.27	7.17	52.1	45.2	0.895
>30 k/uL	**49**	**19**	51.61	5.96	50.7	50.7	
Type B-ALL	**76**	**34**	48.51	4.58	49.1	44.5	0.317
T-ALL	**22**	**7**	70.68	10.94	59.7	59.7	
US (Spleen Size)							
Normal or Splenectomy	**24**	**10**	65.31	10.05	60.0	53.4	0.711
Splenomegaly	**74**	**31**	49.36	4.72	48.1	45.9	
US (Liver)							
Normal	**39**	**17**	48.12	5.74	52.4	47.6	0.983
Hepatomegaly	**59**	**24**	60.33	6.84	50.6	48.0	
Effusion Free	**87**	**36**	61.14	5.54	52.1	48.1	0.575
Yes	**11**	**5**	45.67	12.46	45.0	45.0	
CSF Negative	**92**	**36**	63.64	5.38	54.6	50.8	<0.001*

Variables		OS (months)						
		N	No. of events	Mean	SE.	OS at 3 years (36m)	OS at 5 years (60m)	p for Log Rank
Positive		**6**	**5**	10.93	2.63	0	0	
Risk stratification								
Standard		**55**	**20**	67.47	6.80	60.3	54.2	0.092
High risk		**43**	**21**	43.34	6.22	39.5	39.5	
COVID infection								
Negative		**96**	**40**	61.10	5.26	52.0	48.3	0.007*
Positive		**2**	**1**	6.90	0.0	0	0	
Response	Non-CR	**12**	**6**	7.50	1.30	28.6	28.6	<0.001*
	CR	**86**	**35**	64.28	5.37	54.9	51.0	
Relapse	No	**60**	**6**	77.82	3.62	88.6	88.6	<0.001*
	Yes	**38**	**35**	21.74	3.27	10.3	3.4	
LDH	Low	**2**	**1**	31.25	1.22	50	50	0.942
	High	**96**	**40**	60.50	5.31	49.8	47.7	

OR: Odd Ratio; CI, confidence interval. *: Significant when p value <0.05, CR, OS**,** Overall Survival; Complete Remission **,**WBC**,** White Blood Cell count; LDH**,** Lactate Dehydrogenase; ESR**,** Erythrocyte Sedimentation Rate; CSF**,** Cerebrospinal Fluid; BFM, Berlin-Frankfurt-Münster protocol; ALL, Acute Lymphoblastic Leukemia.

Table **(12)** shows that Cox regression analysis was conducted for factors affecting EFS. In univariate analysis, positive CSF results were associated with significantly unfavorable EFS (p=0.003, OR>1), while CR was associated with better EFS (p<0.001, OR<1).

Bleeding was associated with poor EFS, however, it did not reach significant level. Variables which had p<0.1 in univariate analysis were included in multivariate analysis, bleeding, positive CSF results and non-remission were associated with poor EFS.

Table **(13)** shows that Cox regression analysis was conducted for factors affecting OS. In univariate analysis, presence of bleeding, positive CSF results were associated with significantly unfavorable OS (p=0.033, <0.001), while CR was associated with better OS (p<0.001, OR<1). Augmented BFM was associated with poor OS, however, it did not reach a significant level. Variables which had p<0.1 in univariate analysis were included in multivariate analysis. In multivariate analysis, augmented BFM, bleeding, positive CSF results and non-remission were associated with poor OS.

Table (12): Cox regression analysis for factors affecting EFS

Variables	Univariate			Multivariate		
	p	HR	95% CI	p	HR	95% CI
Sex	0.98**0**	0.992	0.534 - 1.841			
Age	0.294	1.012	0.99 - 1.034			
Augmented vs standard BFM	0.134	1.582	0.869 - 2.879			
Comorbidity	0.912	1.05	0.443 - 2.489			
Weight loss	0.899	0.957	0.482 - 1.9			
Night sweat	0.258	1.559	0.722 - 3.364			
Night fever	0.917	1.036	0.531 - 2.023			
Bone aches	0.163	0.634	0.335 - 1.202			
Lymphadenopathy	0.562	0.953	0.811 - 1.121			
Bleeding	0.071	1.738	0.954 - 3.164	0.043*	1.883	1.019 - 3.479
WBC	0.684	1.001	0.997 - 1.005			
T-ALL vs B-ALL	0.209	0.595	0.265 - 1.338			
Splenomegaly	0.588	1.217	0.599 - 2.471			
Hepatomegaly	0.724	1.116	0.606 - 2.058			
Effusion	0.868	1.082	0.426 - 2.751			
CSF	0.003*	4.183	1.626 - 10.764	0.002*	4.619	1.729 - 12.334
CR	<0.001*	0.149	0.056 - 0.394	<0.001*	0.162	0.06 - 0.437
LDH	0.457	1.475	0.53 - 4.101			

HR, hazard ratio; CI, confidence interval; factors included in multivariate analysis which had p<0.1 in univariate analysis; p<0.05 is considered significant. EFS**,** Event-Free Survival; **CSF**, Cerebrospinal Fluid; **CR**, Complete Remission; BFM, Berlin-Frankfurt-Münster protocol; ALL**,** Acute Lymphoblastic Leukemia; LDH, Lactate Dehydrogenase.

Table (13): Cox regression analysis for factors affecting OS

Variables	Univariate			Multivariate		
	p	HR	95% CI	p	HR	95% CI
Sex	0.884	1.048	0.559 - 1.964			
Age	0.346	1.011	0.989 - 1.033			
Augmented vs standard BFM	0.096	1.687	0.912 - 3.12	0.032*	2.092	1.066 - 4.105
Comorbidity	0.865	1.078	0.453 - 2.568			-
Weight loss	0.981	0.991	0.497 - 1.98			-
Night sweat	0.269	1.547	0.713 - 3.355			-
Night fever	0.612	1.197	0.598 - 2.397			-
Bone aches	0.159	0.629	0.33 - 1.2			-
Lymphadenopathy	0.352	0.74	0.393 - 1.395			-
Bleeding	0.033*	1.954	1.056 - 3.616	0.007*	2.444	1.275 - 4.683
WBC	0.47	1.001	0.997 - 1.006			-
T-ALL vs B-ALL	0.321	0.662	0.293 - 1.494			-
Splenomegaly	0.711	1.144	0.561 - 2.337			-
Hepatomegaly	0.984	1.007	0.541 - 1.874			-
Effusion	0.576	1.306	0.512 - 3.331			-
CSF	<0.001*	5.949	2.241 - 15.791	0.001*	5.695	1.997 - 16.242
CR	<0.001*	0.067	0.023 - 0.196	<0.001*	0.054	0.017 - 0.167
LDH	0.288	1.757	0.621 - 4.969			

HR, hazard ratio; CI, confidence interval; factors included in multivariate analysis which had p<0.1 in univariate analysis; p<0.05 is considered significant**.** OS, Overall Survival; CSF, Cerebrospinal Fluid; CR, Complete Remission; BFM, Berlin-Frankfurt-Münster protocol; ALL, Acute Lymphoblastic Leukemia; LDH, Lactate Dehydrogenase.

DISCUSSION

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy and accounts for around 30-35% of all types of malignancies. The incidence of leukemia among all cancer cases in Türkiye has been reported to be 31.3% [(10)]. ALL in adolescents and young adults (AYAs) accounts for less than one-fourth of the total ALL cases but leads to 80% of ALL-related deaths. The AYA cohort has inferior outcomes compared with the younger children, who achieve cure rates of .90%. They fall at the transition between pediatric and adult populations because a uniform treatment strategy has never been followed and they are underrepresented in clinical trials [(11)].

The genetic landscape of ALL is heterogeneous and varies with age. Philadelphia-chromosome is the most common cytogenetic abnormality among adult ALL patients, accounting for 25% of cases with incidence increasing to more than 40% in the elderly [(12)]. Diagnosis of ALL was made by bone marrow morphological examination showing blast cells >20% and flow-cytometry criteria were used for confirmation. Cerebrospinal fluid (CSF) analysis for cytology, cell type and cell count were used for CNS involvement [(13)].

Our study aimed to evaluate adult patients with Philadelphia negative ALL received Berlin-Frankfurt-Münster (BFM) Chemotherapy induction protocol regarding the response rate, overall survival, relapse rates and adverse events developed during treatment between 2017 to 2022. The current study conducted at oncology center, Mansoura University, conducted on 98 patients. This study reported that 64.3% of the cohort was males and 35.7% was females, with an average age of 29, and the age range of 18 to 69 years. The treatment BFM protocol was employed, with 43.9% of patients received the augmented form of BFM, whereas 56.1% of patients received the standard regimen. While 14.3% of patients with Philadelphia-negative ALL had concomitant illnesses, most patients (85.7%) did not. Hypertension was the most common comorbidity (10.2%), followed by Diabetes Mellitus (DM) (4.1%) and gall stone (1%) with one patient having both HTN & DM.

This study was consistent with **Ghobrial *et al.*** [(14)], who compared the outcome of polychemotherapy regimens, augmented Berlin-Frankfurt-Munster (ABFM) regimen and GRAALL-2003, in Philadelphia-negative, B-cell ALL in AYA patients. They reported that the mean age of patients was 22.35±5.72 years, 27 (73%) patients were males and 10 (27%) were females.

Our results showed that the most prevalent symptoms reported by patients with Philadelphia-negative ALL were weight loss 78.6% and night sweats 77.6%. Night fever and bone pains also occurred frequently, affecting 71.4% and 75.5% of patients, respectively. Lymphadenopathy was seen in a variety of locations, the most prevalent being cervical and generalized lymphadenopathy, which affected 34.7% and 18.4% of patients, respectively. The results also suggest that 76.5% of patients had enlarged spleens. History of bleeding was found in 41.8%. Also, **Chang *et al.*** [(15)], revealed that none of the patients presented

with bulky mediastinal masses (>10 cm), and only 4 (13.8%) patients presented with significant lymphadenopathy (>2 cm). Six (20.7%) patients had splenomegaly with or without concurrent hepatomegaly at diagnosis.

This study revealed that the mean WBC count was 55.28 k/uL, with a median of 26.60 k/uL. Mean hemoglobin level was low, with an average of 8.86 g/dL, and mean platelet count was also low, averaging 73.78 k/uL. Mean ESR was 45.24 in the first hour and 83.85 in the second hour. Mean INR was 1.1, and mean APTT was 36.88 seconds. Also, **Rytting *et al.*** [16], reported their results with ABFM and compared outcomes with hyper-CVAD in a similar historical adolescents and young adults (AYA) population. They demonstrated that median WBC at diagnosis (range) in Augmented BFM was 14 (0.4-494.2). Also, **Ghobrial *et al.*** [14], demonstrated that WBC ×109 /l (mean±SD, range) was 38.8±73.67 (0.3–420), HB (g/dl) was 8.17±2.15 (3.8–13), Platelet ×109 /l was 63.32±91.43 (3–526).

As regards the distribution of different forms of Philadelphia-negative ALL among the patients, demonstrating that the majority, 77.6%, had B-ALL, with 17.3% classed as pre-B and 60.2% as mature B. **Lazzarotto *et al.***, reported that 33.0% of patients in the Campus ALL study and 68.5% in the GIMEMA LAL1913 trial had B-ALL/T-ALL [17].

Our results showed that the patients' risk classification, with 56.1% falling into the standard risk group and 43.9% classed as high risk. **Lazzarotto *et al.***, aimed to report the efficacy and safety data of a chemotherapy program performed according to the GIMEMA LAL1913 protocol in adult patients with Ph-ALL treated outside the clinical trial, in a real-life setting. They found that 207 (49%) patients in standard risk group, 42 (10%) patients classed as high risk, and 171 (41%) falling into very high risk [17].

Our results described the treatment regimens for patients with Philadelphia-negative ALL, indicating that all patients underwent chemotherapy according to the BFM protocol. Furthermore, 63.3% received prophylactic cranial irradiation. However, only 7.1% required therapeutic cranial irradiation. The tolerability of treatment is also noted, with 51.2% completing the whole course of BFM and 36.6% discontinuing treatment owing to recurrence or refractory illness with no other reasons to discontinue treatment. The treatment-related death rate of 12.2%.

Chang *et al.*, found that 4 (14%) patients received prophylactic cranial irradiation. As regard treatment tolerability they found that 15 (52%) patients completed the full course of BFM, 6 (21%) discontinued BFM early without relapse, and 7 (24%) discontinued BFM early treatment owing to relapsed or refractory disease. Treatment-related mortality was 7% [15].

Our results showed that the patients' treatment response rates, with 87.8% achieving CR and 12.2% failing to reach CR. **Ghobrial *et al.***, demonstrated that out of 17 patients as regard ABFM, they found that 16 (94.1%) patients achieving CR [14].

Regarding complications experienced by adult patients with Philadelphia-negative ALL. The neurological complications were recorded in 11.2% of patients, with sensory neuropathy being the most frequent, accounting for 63.6% of those with neurological disorders. Other neurological problems included convulsions and encephalopathy, but at a lesser frequency. Hepatic and gastrointestinal complications were less prevalent, occurring in 5.1% of patients and presenting with a variety of symptoms including bloody diarrhea and intestinal perforation. Pulmonary complications were particularly common, involving 33.7% of patients, with infections accounting for 90.9% of pulmonary cases. Furthermore, renal problems were reported in 2% of patients, with AKI and hyperuricemia nephropathy being the most common. Thrombosis was recorded in 3.1% of the cohort. Our study supported by **Lazzarotto *et al.*** who reported that 9% of patients had CNS involvement.

Our findings the overall outcomes for the patients, revealing that 58.2% are alive, while 41.8% have died. The median OS was 20.1 months. The median EFS was 15.15 months. **Gong *et al.***, reported that the median OS of the cohort has not yet been reached. The median EFS of all patients were 25.6 months. The 5-year OS, EFS, rates were 53.8%, and 45.0% respectively [18].

Regarding to the BMA results of the standard and augmented BFM groups. The results showed that the two groups were similar in terms of cellularity and blast cells after treatment. However, there was a significant difference in cellularity before treatment, with the augmented BFM group having a higher proportion of patients with hyper cellular marrow. **Ghobrial *et al.***, 2022 found that, pre-B was (13.5%), common B was (70.3%) and B typing not identified was (16.2%)[14].

According to virology of the standard and augmented BFM groups. The results showed that the standard and augmented BFM groups were similar in terms of HBV, HCV, and HIV.

Ghobrial *et al.*, reported that, non-hepatitis C/B patient was (86.5%), hepatitis C patient was (5.4%) and not available was (8.1)[14].

Regarding the toxicity events between the standard and augmented BFM groups, our results showed that there was a significant difference in sputum culture, with the augmented BFM group having a higher proportion of patients with growth. Also, the two groups are similar in terms of neurological, hepatic/Gastrointestinal Tract (GIT), pulmonary, renal, and thrombosis complications. **Ghobrial *et al.***, reported that there was no significant difference between the studied groups regarding neurological complications and thrombocytopenia [14].

Regarding the outcome between the standard and augmented BFM groups. Our results showed that the two groups are similar in terms of CR, relapse, and mortality rates. **Ghobrial *et al.***, reported that there was

no significant difference between the studied groups regarding relapse [14].

This study revealed that there is no significant difference in CR rates between patients who received the standard BFM regimen and those who received the augmented type, with a p-value of 0.869, there was no significant link between response to therapy and comorbidity status. **Chang *et al.***, reported that complete remission after induction therapy was higher in patients treated with standard BFM (94%) than who's treated with Augmented BFM (92%)[15]. Also, **Rytting *et al.***, who reported that CR rate of 94% in adult patients with ALL treated with Augmented BFM (ABFM) [16].

The current study showed that the relationship between treatment response with risk stratification. The statistics reveal that there was no significant difference in response to therapy between the standard and high-risk groups, as indicated by the p-value of 0.869. In contrast, **Biondi *et al.***, who concluded that revealed that there was a significant difference in response to therapy between the standard and high-risk groups. This study reported that there was no significant variation in treatment response based on age. There was no significant difference in treatment response based on WBC counts in both the B-ALL and T-ALL subgroups [19].

Our findings showed that being female was substantially related with a greater susceptibility of achieving CR, with a p-value of 0.040 and an odds ratio of 2.628. Other parameters, including as age, comorbidities, laboratory data, type of ALL, treatment protocol, did not exhibit significant relationships. As regards factors affecting EFS, the data indicated that patients with negative CSF had a significantly higher mean EFS of 58.16 months compared to those with positive CSF, who have a mean EFS of only 10.53 months, with a p-value of 0.001.

The response to treatment showed that the patients achieving CR had a mean EFS of 58.52 months compared to those with non-CR, who have a mean EFS of only 6.50 months, with a highly significant p-value of <0.001. Better EFS was significantly associated with free CSF and achieved CR. Otherwise, no significant association was found between EFS and other studied parameters.

Also, **Radhakrishnan *et al.***, reported that on univariate analysis NCI risk stratification, sex, WBC count, day 8 blast clearance, and income were significantly associated with EFS. However, on multivariate analysis only sex (P = 0.01) and day 8 blast clearance (P = 0.006) were significantly associated with EFS. NCI risk stratification (P = 0.2), income (P = 0.3), and WBC count (P = 0.3) were not significantly associated with EFS on multivariate analysis [20].

Our results showed that there was significant association between bleeding and OS (p = 0.030), indicating that patients without bleeding had higher survival rates. Furthermore, positive infiltration of CSF was substantially related with poor survival outcomes. Also, the results underscore the critical importance of achieving CR in improving OS rates, as patients who did not achieve CR had significantly lower OS time and OS rates compared to those who did achieve CR. Moreover, those who relapsed had lower OS p<0.001). In addition, those who had COVID-19 infection showed significantly lower OS (p=0.007). While other studied factors had non-significant impact on OS.

Also, **Chang *et al.***, revealed that the overall and event-free survival at 3 and 5 years did not differ between the groups stratified by risk to receive either aBFM or sBFM, suggesting that use of a more dose-intensive chemotherapy approach with aBFM may improve outcomes in the setting of adverse prognostic indicators in adult ALL [15]. However, our results disagreed with **Rytting *et al.***, who revealed that initial white blood cell count was an independent predictive factor of OS and CR [16].

CONCLUSION

The treatment achieved a high complete remission rate (87.8%), but relapse rates remained significant, with many relapses occurring during therapy. Neurological and pulmonary complications were common. The study showed good treatment tolerability, although 12.2% of patients died due to treatment-related causes. The findings highlighted the need for better relapse prevention strategies and management of complications. The study found no significant differences between the standard and augmented BFM groups in terms of clinical features, treatment response, or survival outcomes. Both groups had similar rates of CR, relapse, and mortality. No significant relationship was found between treatment response and age, WBC count, or risk stratification. However, factors such as female sex and negative CSF were associated with better EFS. Patients who achieved CR had significantly better EFS and OS compared to those who did not. Furthermore, bleeding, CSF infiltration, relapse, and COVID-19 infection were found to significantly impact OS. The study underscored the importance of achieving CR for improved survival outcomes.

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