Acute Lymphoblastic Leukemia in Young Adults Treated with Intensive “Pediatric” Type Protocol

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Abstract Young adults with acute lymphoblastic leukemia do better when treated on “pediatric” protocols. Young adults (18–30 years) with Ph-negative ALL treated between 2000 and 2014 were retrospectively analyzed. Two-hundred and thirty-two patients were included [median age 21 years (18–30); 176 (76%) males; median WBC 16,000/cmm]. Protocols used were: BFM 95 (N = 147, 63%), MCP-841 (N = 51, 22%), GMALL (N = 21, 9%), INCTR (N = 9, 4%) and UKALL (N = 4, 2%). Complete remission was achieved in 194/232 (84%). Twenty patients (9%) died due to toxicity which was higher with BFM versus others (18/147 vs. 2/85; $p = 0.031$). After a median follow-up of 48 months, median RFS and OS were 35.5 months (25–46), and 25 months (18–31) and actuarial RFS and OS (5-years) were 45% (37–53) and 39% (32–46). BFM protocol improved RFS (51 vs. 35%, $p = 0.027$) but not OS (43 vs. 33%, $p = 0.2$). The survival outcomes reported are 15–20% lower than those reported from West. Better supportive care and risk-adapted therapy may improve outcomes.

Keywords Acute lymphoblastic leukemia · India · BFM protocol · Young adult

Introduction

Age is an important consideration in selecting treatment protocols for acute lymphoblastic leukemia (ALL). Young adults have better outcomes when treated with more intense “pediatric” type protocols. Compared to “adult” type protocols, “pediatric” protocols are characterized by use of high dose methotrexate, a higher dose of l-asparaginase, a re-intensification phase, prolonged maintenance (at least 2 years) and reduced inter-cycle duration. [1] Though standard adult protocols have not improved survival over the last few decades, outcomes $\geq 60\%$ have been demonstrated in “standard risk” adults treated with pediatric type protocols. [2] Though these results have been demonstrated in multiple studies which have shown the feasibility of delivering these protocols in adults, toxicity is expected to be more severe and there is little published data from non-trial settings.

Intense protocols demand a better supportive care infrastructure which can be a challenge in resource-constrained settings. Acute leukemia therapy in these situations is complicated by multiple factors like delay in diagnosis, higher risk disease at presentation, multi-drug resistant (MDR) bacterial infections, and inadequate social and economic support. [3] The latter 2 issues are particularly relevant in the young adult population and adds to the complexity of the problem. At our center, young adult patients have been treated with variable protocols (adult/pediatric) depending on the philosophy of the physician. Originally, the adult-type GMALL [4] and UKALL [5] protocols were used with a few younger

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patients receiving the MCP 841 [6] or INCTR [7] protocols. Even though the latter 2 were originally developed as pediatric protocols, they differ from the BFM (no high dose methotrexate, lesser dose intensity). In 2005, we started using more dose-intensive BFM 95 protocol [8] for all pediatric patients which was gradually extended to adult patients (initially 18–22 years, later extended to 25 and then 30 years). We present our experience in the treatment of young adult patients (18–30 years) treated at our center over a 15 year period and compare the outcomes between different protocols used. The results presented here are outcomes of patients treated in a ‘field’ setting where all patients were considered eligible for treatment without strict inclusion criteria.

Methods

The records of patients registered as ALL by the hospital tumor registry (age 18–30 years) between January 2000 and December 2014 were analyzed. Patients who had a diagnosis of ALL [MPO-negative blasts by cytochemistry and characteristic phenotype (pre B or T)] and received 7 days of steroids/1 dose of chemotherapy were included for analysis. Phenotyping was done by flow cytometry (2-color between 2000 and 2012 and 6-color flow cytometry after that). Cytogenetics and/or polymerase chain reaction (PCR) evaluation for the *BCR-ABL* transcript was performed when feasible (in a few patients between 2005 and 2011 and all patients diagnosed after 2012). Cerebrospinal fluid (CSF) was studied in all patients. Those with CNS involvement received extra doses of intrathecal methotrexate and a higher dose of cranial radiation (24 vs. 18 Gy). Post-Induction 1 marrow was studied after recovery of counts, usually 1 week after the last (4th) dose of daunorubicin. Complete remission was defined as recovery of counts (neutrophils > 1000/cmm and platelet counts > 100,000/cmm) with < 5% blasts in the marrow by morphology. No minimal residual disease studies were done during this period. No patient received allogeneic transplant in CR1.

Baseline characteristics were obtained from the records. For the purpose of this analysis, patients were grouped based on the immunophenotype as well as the presenting WBC counts as follows—pre B phenotype/mixed phenotype with WBC count > 30,000/cmm—high risk; T-cell and unknown phenotype with WBC count > 100,000—high risk and all others as standard risk. The BFM protocol was delivered with the following modifications: there was no stratification based on baseline risk status or on MRD studies, and all patients received the standard arm containing high-dose methotrexate of 5 g/m² during consolidation. The induction dose of L-asparaginase was reduced

from 10,000 units/m² to a uniform dose of 10,000 units per patient from 2013 (Supplementary Table I).

Relapse-free survival (RFS) was calculated (in patients achieving a complete response after induction) from documentation of remission till occurrence of relapse or death. Event-free survival (EFS) was calculated from the date of start of treatment till the date of the last follow-up in complete remission or an event. Event was defined as failure to achieve remission after induction, relapse, or death due to any cause. Overall survival (OS) was calculated from the start of treatment till death due to any cause. Follow-up data was censored on June 2015. Probabilities of survival were estimated using Kaplan–Meier method and compared by the log-rank test using SPSS (version 13).

Results

Baseline Characteristics and Treatment

In a 15-year period (2000–2014) we identified 232 evaluable patients with Ph-negative ALL (18–30 years). The median age was 21 years (18–30) and males constituted 76% (N = 176), (Table 1). The median WBC count was 16,000/cmm [Pre B cell median: 8800 (400–330,000); Pre-T cell median: 47,050 (500–500,000)]. Majority received BFM protocol (N = 147, 63%). The baseline risk grouping of those treated with BFM protocol was similar to those treated with other protocols. However, among those treated with BFM, 84% were in the 18–25 year group while only 74% among the other were in this group. However the mean ages were not different (BFM vs. other 21.8 years vs. 22.4 years, $p = 0.218$, t test). There was also lower representation of B cell phenotype among the BFM treated patients. The reason for this difference is not clear, though there were more “unknown” phenotypes in the “other” group. The median duration of I1 phase (from the start of the first phase of induction until the start of the second phase-I2) was 49 days (34–88). Complete remission was achieved in 194/232 (84%) and 148 of these (75%) went on to start maintenance.

Response to Treatment

Complete hematological remission (CR) was achieved in 194 (84%) patients (192 after I1 and 2 after I2). Phenotype, age and sex did not determine achievement of CR. High risk patients had lower CR rate (76 vs. 86%) and higher induction mortality (12 vs. 4%, $p = 0.053$, Chi square test) than the lower risk patients. The CR rate was similar between those who received BFM versus other protocols (84 vs. 82%). Among those patients treated with the BFM

Table 1 Baseline characteristics of Ph-ve ALL patients who were treated at Cancer Institute between 2000 and 2014 (N = 232)

Parameter	All patients N (%)	BFM ^b N (%)	Other ^c N (%)	<i>p</i> value ^d
Age group, 26–30 years				
18–25 years	190 (82)	126 (86)	63 (74)	0.023
26–30 years	42 (18)	21 (14)	22 (26)	
Male sex				
Males	176 (76)	115 (78)	61 (72)	0.171
Females	56 (24)	32 (22)	24 (28)	
WBC count				
WBC count ≥ 100,000/cmm	53 (23)	30 (20)	23 (27)	0.15
WBC count < 100,000/cmm	117 (77)	117 (80)	62 (73)	
WBC count ≥ 50,000/cmm	81 (35)	50 (34)	31 (36)	0.40
WBC count < 50,000/cmm	151 (65)	97 (66)	54 (64)	
WBC count ≥ 20,000/cmm	112 (48)	71 (48)	41 (48)	0.55
WBC count < 20,000/cmm	120 (52)	76 (52)	44 (52)	
CNS involvement				
Involved at diagnosis	15 (6)	13 (9)	2 (3)	0.04
Not involved	217 (94)	134 (91)	83 (97)	
Immunophenotype				
Pre B	89 (38)	69 (47)	20 (24)	<0.001
T cell	100 (43)	63 (43)	37 (44)	
Bi phenotype	8 (3)	3 (2)	5 (6)	
Not known	35 (15)	12 (8)	23 (27)	
Socioeconomic status				
General ward	184 (79)	114 (78)	70 (82)	0.24
Special ward	48 (21)	33 (22)	15 (18)	
Risk grouping				
Standard	152 (66)	97 (66)	55 (66)	0.49
High	78 (34)	49 (34)	29 (34)	

BFM Berlin-Frankfurt Munster 95 protocol, *MCP-841* Multicenter protocol-84, *GMALL* German Multicenter ALL protocol, *INCTR* International Network for Cancer treatment and research, *UKALL* United Kingdom ALL protocol

^aRisk grouping was based on WBC count at presentation—those with Pre B and biphenotypic with WBC count > 30,000—high risk; Pre T and unknown phenotype with WBC count > 100,000—high risk

^bTreated with the BFM protocol (N = 147, 63%)

^cTreated with other protocols (N = 85): MCP 841 (N = 51, 22%), GMALL (N = 21, 9%), INCTR (N = 9, 4%), UKALL (N = 4, 2%)

^dComparing the parameters between BFM and Other using the Chi square test

protocol (N = 147), 23 (16%) did not clear peripheral blood lymphoblasts on Day 8 and these patients had lower chance of achieving CR after I1 (61 vs. 90%, $p < 0.001$).

Death during induction occurred in 16 (7%) patients of whom 4 had documented residual disease in the bone marrow. The commonest cause of mortality during induction was sepsis (N = 12, fungal in 4 and other in 8) followed by cortical vein thrombosis (N = 3) and intracranial hemorrhage (N = 1). The mortality during induction was significantly increased with the BFM-95 versus other protocols (10 vs. 1%, $p = 0.001$). Conversely, residual disease

(defined as > 5% blasts in bone marrow at end of induction) was significantly increased with “other” protocols (18%) compared to 6% with BFM ($p = 0.001$).

Survival Outcomes

After a median follow-up of 21 months (all patients, range 0.3–165 months), and a median follow-up of 48 months among patients who are alive, 139 patients had an event. This included 38 who did not achieve remission and ninety-four (40%) of the 194 patients in CR, who relapsed

during follow-up. An additional 4 patients died due to treatment-related complications during the consolidation ($N = 3$) and maintenance phases ($N = 1$) of therapy. Overall treatment-related deaths were 20/232 (9%) and this was higher with the use of BFM protocol compared to others (18/147, 12% vs. 2/85, 2%; $p = 0.031$). Three patients died due to unrelated/unknown reasons without documented relapse.

Commonest site of relapse was the bone marrow ($N = 88$, including 4 patients who had simultaneous CNS relapse) followed by isolated CNS relapse ($N = 5$) and testis ($N = 1$). Among the 94 patients who relapsed, only 3 underwent subsequent allogeneic transplant and 1 is in remission at last follow up. The median EFS, RFS and OS were 21 months (13–29), 35.5 months (25–46), and 25 months (18–31) respectively. The actuarial EFS, RFS and OS at 5-years were 36% (29–43), 45% (37–53) and 39% (32–46) respectively (Fig. 1).

On univariate analysis, high risk disease predicted for poorer EFS, RFS and OS (Table 2). Patients who required a longer time to complete I1 had poorer EFS and OS (based on an arbitrary cut-off of 50 days), but this was not statistically significant. The use of BFM protocol improved relapse free survival (51 vs. 35%, $p = 0.027$) in comparison to other protocols, but there was no difference in the OS (43 vs. 33%, $p = 0.2$). Among patients treated with the BFM protocol, a duration of > 9 months from start of induction till maintenance predicted for worse RFS (69 vs. 43%, $p = 0.003$).

Discussion

Use of a BFM-based therapy improved the RFS among young adult patients with Ph-ve ALL when compared to less intense protocols (51 vs. 35%). However, this improvement came at the cost of increased incidence of treatment-associated deaths (12 vs. 2%) which negated any impact on the OS. High-risk disease, defined by elevated WBC counts at presentation strongly predicted outcomes. Prolonged duration of the intensive treatment increased relapses among those treated with BFM protocol.

The BFM protocol improved both the CR rate and the RFS. However, the higher treatment related mortality negated the impact on OS. Much of the TRM occurred in induction, but some patients died due to subsequent toxicity. The major causes of death in I1 were sepsis and L-asparaginase associated thrombotic complications. Sepsis is an important challenge during treatment of acute

leukemia in India, as reported previously from patients with AML. [9] Though treatment-related mortality is less in ALL compared to AML, it remains a significant problem, especially when using intense protocols. In comparison, the mortality during induction reported from centers in the West varies between 1 and 4% (Table 3). There was a slightly higher representation of younger age groups in the BFM protocol and whether this had any bearing on the outcomes is not clear. However, the mean ages, risk groups were similar between the groups. Also, age group did not emerge as a prognostic factor on analysis. The BFM protocol utilizes more intensive therapy when compared to the other protocols used (Supplementary Table I). Moreover, it had high dose methotrexate which is totally absent from other protocols, and may be an important component of therapy especially in the T cell subsets which constitute almost half our population.

The RFS (51%) in our study even among patients treated with BFM-95 protocol is lower by 15–20% when compared with other reports using pediatric type protocols in a comparable age group (Table 3). The proportion of patients with ‘high risk’ disease was more (median WBC 15,000/cmm compared to < 10,000 in other studies) in our patient population. Also, we had not delivered a risk-adapted treatment using the minimal residual disease assessment as this facility was not available during this period. The proportion of MRD positivity after standard 4-drug induction therapy is higher in AYAs compared to younger children (50 vs. 33%) and MRD-adapted therapy is a key factor in improving outcomes. [10, 11] None of our patients underwent MRD assessments or were treated with any form of “risk-adapted” therapy.

Another factor that emerged significant in predicting the outcome in patients treated with BFM protocol was the overall duration of the intensive phase of therapy which is expected to be 6–7 months as per the protocol. The median duration in our patients treated with BFM-95 was 9 months. Patients treated with BFM and with an intensive phase longer than 9 months had increased relapses (Table 2). The reasons for the delay could be multifactorial (due to infections, nutrition, noncompliance, employment issues and finances), which could not be determined in this retrospective study.

We illustrate the real-world issues encountered when attempting to deliver a high-intensity protocol therapy in a developing country. The proportion of patients at high risk partly explains the inferior outcomes despite using intense protocols. However, we have also identified modifiable factors which could be addressed to increase the survival of

Fig. 1 Event-free (EFS), overall (OS) and relapse free (RFS) survival of patients in months. **a** EFS, low risk (solid) versus high risk (dashed). **b** EFS, BFM (solid) versus other (dashed). **c** OS, low risk

(solid) versus high risk (dashed). **d** OS, BFM (solid) versus other (dashed). **e** RFS, low risk (solid) versus high risk (dashed). **f** RFS, BFM (solid) versus other (dashed)

Table 2 Factors affecting survival outcomes in Ph-ve ALL

Parameter	N	Median EFS (months)	EFS 5 years (%)	<i>p</i> value	Median OS (months)	OS 5 years (%)	<i>p</i> value	N	Median RFS ^b (months)	RFS 5 year (%)	<i>p</i> value
Age											
18–25 years	189	22	37	0.23	28	40	0.4	161	37	46	0.5
26–30 years	43	16	29		23	31		33	25	41	
Sex											
Male	176	22	39	0.21	27	40	0.2	150	37	48	0.5
Female	56	16	23		21	35		44	34	31	
Presenting WBC											
< 100,000/cmm	179	23	37	0.15	30	40	0.14	151	39	47	0.13
≥ 100,000/cmm	53	15	30		21	35		43	20	37	
Immunophenotype											
Pre B cell	89	22	33	0.15	33	37	0.26	72	13	52	0.023
T cell	100	21	41		26	43		87	23	42	
Unknown	35	16	27		22	35		29	35	34	
Biphenotype	8	5	16		12	15		7	NR	19	
Risk group											
Standard	152	31	41	0.011	33	43	0.03	134	42	50	0.04
High	78	13	27		21	32		60	22	36	
D 8 blast clearance ^a											
Absent	124	31	43	0.14	38	46	0.16	109	NR	52	0.9
Present	23	18	29		23	28		16	NR	45	
Induction duration ^d											
< 50 days	100	36	44	0.26	30	51	0.216	100	42	48	0.21
≥ 50 days	93	22	37		43	37		93	30	41	
Protocol used											
BFM 95	147	29	40	0.054	35	43	0.2	124	NR	51	0.027
Other	85	16	27		22	33		70	22	35	
General versus Special ward											
Special ward	48	30	35	0.36	38	41	0.19	40	37	45	0.25
General ward	184	19	35		23	38		155	35	44	
Intensive phase duration ^{a,c}											
≤ 9 months								36	NR	69	0.003 ^d
> 9 months								89	NR	43	

^aOnly for patients on BFM protocol (N = 147)^bFor those who achieved CR after induction (N = 194)^cTime from start of I1 till start of maintenance therapy- calculated only for those who received BFM 95 protocol *and* received maintenance therapy (N = 125)^dOnly for those patients who completed induction and achieved CR (n = 191)

these patients. These are: rate of mortality during induction, delays in treatment, patient compliance, evaluation of MRD and risk adapted treatment. All the above factors can be addressed with suitable modifications in the treatment protocol and improvements in patient education. Improvement in supportive care like increased doctor–patient ratio, better infection control practices, more intense monitoring would probably help reduce treatment related

mortality but may not be always feasible in resource-constrained settings.

Use of the more intense BFM protocol reduced relapses and ALL-related deaths in young adult patients at the cost of increased treatment related toxicity. Better supportive care and institution of risk-adapted therapy could potentially improve outcomes in the real-world setting.

Table 3 Comparison of various studies of young adult ALL treated with pediatric type protocols

Ref	N	Age	Median WBC	TC > 50,000(%)	Protocol	CR (%)	Induction mortality (%)	EFS (%)	OS (%)	RFS (%)
Ribera et al. [12]	87	20 (15–30)	7–8.9	NR	PETHEMA ALL-96	94–100	0	60 (6 years)	77 (6 years)	NR
Hough et al. [10]	229	16–24 ^a	NR	10	UKALL2003	NR	NR	72 (5 years)	76 (5 years)	NR
Usvasalo et al. [13]	97	18.9 (16–25)	7.9	NR	Finnish ^b	97	NR	60 (5 years)	NR	NR
Rijeneveld et al. [14]	54	26 (17–39)	5.3–12.7	NR	HOVON 70 ^c	91	4	66 (2 years)	72 (2 years)	NR
DeAngelo et al. [15]	92	28 (18–50)	15.5	NR ^d	DFCI 01-175	85	1	NR	67 (4 years)	66 (4 years)
Beck et al. [16]	887	15–35	NR	NR ^f	GMALL 07/03	91	4	NR	66 (5 years)	61 (5 years)
Hayakawa et al. [17]	139	15–24	10.5	25	ALL-202U, Japan	94	3	NR	73 (5 years)	67 (5 years)
Stock et al. [18]	318	25 (16–39)	NR	NR	US Intergroup C 10403	NR	2	NR	78 (2 years)	66 (2 years)
Current study	147	21 (18–29)	15.6	34	BFM	84	10	40 (4 years)	41 (4 years)	50 (5 years)
Current study	85	21 (18–30)	17.5	36	Non-BFM	81	1	27 (4 years)	27 (4 years)	34 (5 years)

PETHEMA Programa Español de Tratamiento en Hematología, UKALL United Kingdom Acute Lymphoblastic Leukemia, CCG Children's cancer group (various protocols), DFCI Dana Farber Protocols, GMALL GERMAN Multicenter study group for adult ALL, BFM Berlin Frankfurt Munster

^aOnly 41 patients were over 20 years of age

^bThis has been described as an adult type protocol though the doses of vincristine, asparaginase were higher than usual adult protocols

^cProtocol inspired by FRALLE-93 with the addition of allogeneic transplant whenever feasible (35%)

^dWBC > 20,000 in 38%

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Compliance with Ethical Standards

Conflict of interest None of the authors have any relevant conflicts of interests to declare.

Ethical Approval This study was a retrospective analysis of outcomes and doesn't require ethical committee approval as per our Institute policy.

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