Hyper-CVAD vs. BFM-Like Regimens in Adult Patients with Philadelphia-Negative Acute Lymphoblastic Leukemia: A Single-Center Experience

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Abstract

Background: ALL (Acute lymphoblastic leukemia) known as one of the diversity group of diseases associated with lymphoblasts proliferation. Innovations in ALL results do have unmet needs in adult patients.

Objective: This research was performed at Mansoura University Oncology Center to compare the effects of BFM-like chemotherapy versus hyperCVAD in adult ALL patients.

Material and methods: This research was conducted to 77 adult Philadelphia negative ALL patients: **49** males **(63.6%)** and **28** female**s (36.4%)**, mean age of **28** years (range: **16–60**). The results in both arms are compared; BFM-like versus hyper-CVAD.

Results: Of the 77 patients involved, there were 48 (62.3%) of B-cell ALL, 29 (37.7%) of T-cell ALL. 51 (66.2%) of those received BFM-like chemotherapy, 26 (33.8%) were treated with Hyper-CVAD. The rate of first complete remission (CR) was 90.2% in BFM-like chemotherapy arm versus **73.1%** in and hyper-CVAD arm, (**p=0.05**). Relapse rate was not statistically different in both treatment groups. In terms of the different toxicities, ICU admission rates, and therapy related deaths, both regimens were equivalent. In contrast to hyper-CVAD, patients with BFM- demonstrated significant advantage for overall survival (OS) (median; **28** vs. **12** month **p=0.008**). Furthermore; younger patients (**<30** years) showed significant more OS (median; **32** months p **0.01**) versus BFM-like regimen in subset analysis.

Conclusions: For young adult ALL patients, BFM-like regimen appears to be suitable. In adult patients ≥30 years, both BFM-like and the hyper-CVAD regimen seems equivalent, safe and effective.

KEY WORDS: ALL, BFM-like regimen, hyper-CVAD

Introduction:

Acute lymphoblastic leukemia (ALL) is a malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood and extra-medullary sites. Age was known to be the most significant prognostic factor in ALL, it affects the prognosis between childhood and adults, and there is a strong connection between age and prognosis for patients aged between 20 and 65 years [1]**.** Throughout the last decades, several efficient chemotherapeutic protocols were documented for the management of adult ALL, the majority of which mainly reliant on pediatric programs. There is no standard protocol for induction management in ALL [2]**.** Treating adults with pediatric protocols of high dose of non myelosuppressive medications, rather than the adult protocols, might improve their outcomes and increase the chance of continuous remission [3]**.** BFM-like chemotherapy regimen e.g. augmented BFM, and "hyper-CVAD" regimen [4] can be used in management of adult ALL. A number of studies showed better outcome in adolescent young adult (AYA) treated with pediatric protocols [5]. This study conducted to evaluate the efficacy of the two widely used regimens (Hyper-CVAD and BFM regimens) for treatment of adult Philadelphia negative ALL patients at Oncology Center Mansoura University (OCMU). Primary objectives were; rate of first CR of each regimen, and tolerability and toxicity of each regimen.

Patients and Methods:

This study is a prospective and retrospective study conducted to compare outcome of poly-chemotherapy regimens BFM–like (BFM/ABFM) [6] and Hyper-CVAD [7] in Philadelphia negative ALL patients, see appendix 1. ALL patients were diagnosed between 2013 and 2019 at Oncology Center Mansoura University (OCMU), Egypt.

Initial evaluation included; through history and physical examination. Complete blood count (CBC) and blood film. Baseline laboratory investigations including

serum creatinine, full liver function tests, uric acid, LDH and serum electrolytes. Virology; HIV, HBV and HCV. BMA and biopsy (BMA, BMB) and Imunophenotyping. Baseline radiological evaluation; chest x-ray, abdominal-pelvic US, CT scan, MRI brain when clinically indicated and ECHO. Lumbar puncture.

According to institutional guidelines; transfusion support, antibiotics, antiviral, antifungal agents and granulocyte colony-stimulating factor were provided when indicated. After the completion of the first induction chemotherapy, the bone marrow aspiration was carried out to test their treatment response.

The rate of first CR after induction was the primary objective of this work. CR was characterized by <5% marrow blasts, a normalization of peripheral counts (neutrophil count $\geq 1 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and no abnormal peripheral blasts), and without any extramedullary disease.

SPSS version 16 was performed for analysis of the data and the results. P value of < 0.05 will be considered statistically significant.

Results:

A total of 77 patients were included, 49 (63.6%) were males and 28 (36.4%) were female, with a mean age of 28 years (range 16-60). By Immunophenotyping 48 (62.3%) patients had B-ALL (pre B; 31.2%, common B; 37.6%, and not identified 31.2%), and 29 (37.7%) patients had T-ALL, see table 1.

Table (1) clinical and laboratory presentation in B- ALL and T – ALL

	B – ALL 48 patients	T- ALL 29 patients
Age (years)		
< 30	29(60.4%)	20(69%)
≥ 30	19(39.6%)	9(31%)
Gender		
Male	27(56.2%)	22(75.9%)
Female	21(43.8%)	7(24.1%)
Leukocytosis	22 (45.8%)	22 (75.9%)
Normal count	11 (22.9%)	3 (10.3%)
Leucopenia	15 (31.3%)	4 (13.8%)
Hyperleukocytois	4 (8.3%)	6 (20.7%)
Thrombocytopnia	43 (89.6%)	22 (75.9%)
Anemia	44 (91.7%)	19 (65.5%)
Pancytopenia	14 (29.2%)	2 (6.9%)
Need of prephase	16 (33.3%)	16 (55.2%)
TLS with treatment	4 (8.3%)	2 (6.9%)
Therapy protocol		
Hyper CVAD	18 (37.5%)	8 (27.6%)
BFM-like	30 (62.5%)	21 (72.4%)

Fifty-one (66.2%) patients received BFM –like protocol while 26 (33.8%) patients received Hyper CVAD regimen. There were 65 (84.4%) patients achieved CR at the end of induction. 34 (52.3%) patients developed disease relapse (either during or after finishing treatment) at different sites, 31 (91.2%) patients with bone marrow relapse, one patient (2.9%) with CNS and two (5.9%) patients in more than one site, table (2).

Table (2): Treatment characterization and toxicity in ALL patients

Treatment protocol	BFM–like protocol: 51 (66.2%) Hyper-CVAD: 26 (33.8%)
Response (1st CR)	
CR	65(84.4%)
Refractory disease	12(15.6%)
1ST Relapse	34 out of 65 patients (52.3%)
Site of relapse	
Bone marrow	31 (91.2%)
CNS	1 (2.9%)
More than 1 site	2 (5.9%)
Tumor lysis syndrome	6 (7.8%)
Nephrotoxicity	1 (1.3%)
Hepatotoxicity	26 (33.8%)
Neurotoxicity	3 (3.9%)
Neutropenic Fever	45 (58.4%)
Mucositis	10 (13%)
Cardiotoxicity	2 (2.6%)
Asparginase related toxicity	5 (6.5%)
Need of dose modification *	14 (18.2%)
ICU admission	12 (15.6%)
Therapy related deaths	9 (11.7%)
Transplant	6 (7.8/%)

There was marginal significance *P 0.05* regarding the response (1stCR) favoring BFM–like protocol, while There were no statistical significance differences in relapse rate in B cell / T cell leukemia among the both treatment protocols, see tables (3 & 4).

Table (3): Response regarding the treatment protocol

Treatment Response	Hyper CVAD (26)	BFM –like protocol (51)	P
CR (1st)	19 (73.1%)	46 (90.2%)	0.05
No CR	19 (73.1%)	46 (90.2%)	

Table (4): relapse regarding B/T cell leukemia among Hyper CVAD and BFM –like protocol

	Hyper CVAD	P	BFM –like	P

	Relapse (12)	Non-relapse (7)		Relapse (22)	Non-relapse (24)	
B cell leukemia	7 (58.3%)	5 (71.4%)	0.65	14 (63.6%)	13 (54.2%)	0.5
T cell leukemia	5 (41.7%)	2 (28.6%)		8 (36.4%)	11 (45.8%)	

Regarding toxicity profile; neutropenic fever, hepatoxicity, mucositis, including need of dose modification and ICU admission. Both treatment arms were equivalent without a significant difference (table 5).

Table (5): Treatment toxicity and need for dose modifications as regarding hyper-CVAD vs. BFM-like

Toxicity profile	Hyper CVAD 26 patients	BFM-like 51 patients	P
Tumor lysis syndrome	0 (0%)	6 (11.8%)	
Hepatotoxicity (any)	8 (30.8%)	18(35.3%)	0.69
Neutropenic fever	19 (73.1%)	26 (51%)	0.06
Mucositis	2 (7.7%)	8 (15.7%)	0.32
Need of dose modification	5 (19.2%)	9 (17.6%)	0.86
Patients needed ICU admission during treatment course	5 (19.2%)	7 (13.7%)	0.5
Therapy related deaths	3 (11.5%)	6 (11.8%)	0.97

Disease free survival (DFS) among both treatment arms were not significantly different (median 13 vs. 30 months; for Hyper CVAD, and BFM-like, respectively *P 0.07).* In subset analysis younger patients (<30 years) demonstrated a high median DFS (56 months) in BFM-like arms but with non-significant *P* value (0.2), see table (6,7) and figure (1,2).

Table (6): Disease free survival according to treatment regimens

	No.	Median	Log Rank	P
Hyper CVAD	19	13	3.3	0.07
BFM-like	46	30		

Table (7): Disease free survival according to age in both treatment regimens

Age	Treatment	No.	Median	Log Rank	P
Age <30	HyperCVAD	6	13	3.9	0.2
	BFM-like	38	56		
Age≥ 30	HyperCVAD	13	13		
	BFM-like	8	12		

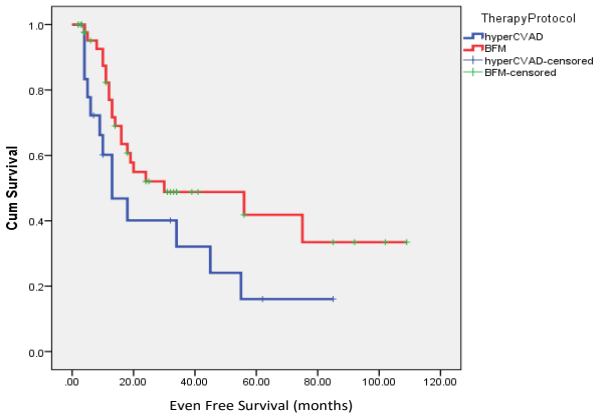

Figure (1): disease free survival according to treatment regimens

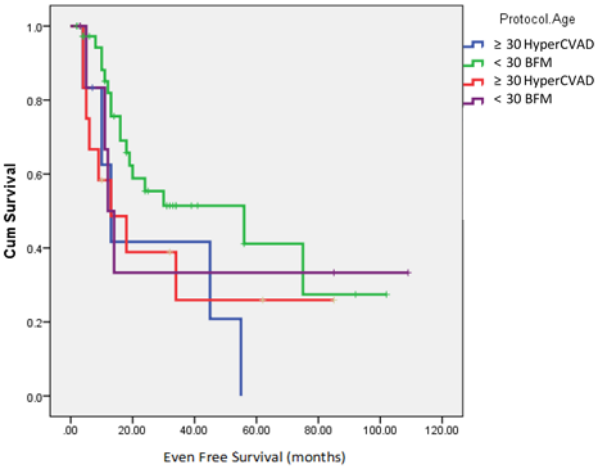

Figure (2): DFS as regard age in both treatment arms

OS was significantly improved in BFM-like treatment arm versus Hyper CVAD arm (median; 28 vs. 12 months *P .008).* Younger age group (<30 years) demonstrated a significant OS improvement in BFM-like arm versus Hyper CVAD arm (median 32 versus 11 months, respectively *P 0.01),* table (8,9) and figure (3,4).

Table (8*):* Overall Survival according to treatment regimens

	No.	Median	Log Rank	P
Hyper CVAD	26	12	7.1	0.008
BFM-like	51	28		

Table (9): Overall Survival according to age in both treatment regimens

Age	Protocol	No.	Median	Log Rank	P
Age <30	HyperCVAD	8	11	10.7	0.01
	BFM-like	41	32		
Age≥ 30	HyperCVAD	18	13		
	BFM-like	10	13		

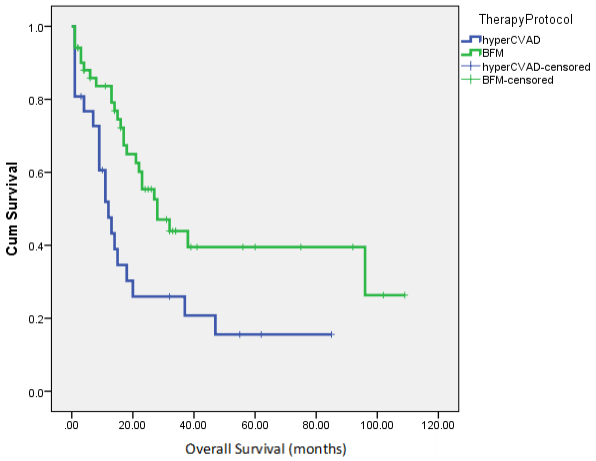

Figure (3): Overall Survival according to treatment regimens

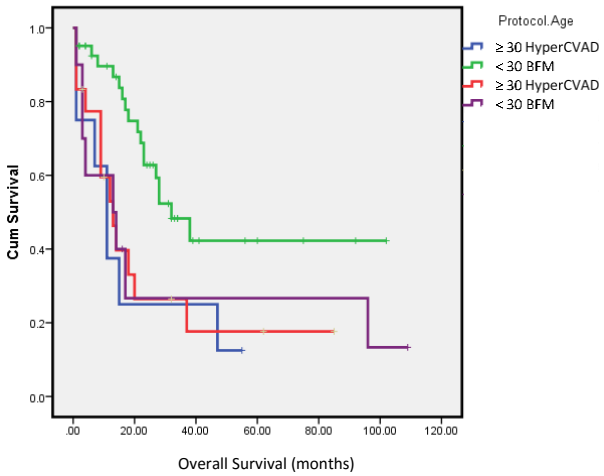

Figure (4): Overall Survival according to age in both treatment regimens

Discussion:

Throughout the last decades, several efficient chemotherapeutic protocols were documented for the management of ALL, the majority of which mainly reliant on pediatric programs. There is no standard successful protocol for induction management in ALL. Our study was conducted on newly diagnosed 77 Philadelphia negative ALL patients with age range 16 – 60 years (mean 28), 63.6% males and 36.4% females and this mean age and male predominance was similar to previous reports by Alacacioglu et al, 2014 [8]. Fifty-one patients (66.2%) received BFM-like while 26 patients (33.8%) received Hyper CVAD protocol.

In the current study there were 62.3% B ALL patients (15 patient; 31.2% with pre –ALL, 18 patients; 37.6% with common B-ALL and 15 patients; 31.2%patient were not identified. While 29 patients (37.7%) diagnosed with T ALL. B ALL was more common than T ALL as in previous study by Alacacioglu et al, 2014 [8].

Variable toxicity profiles were reported in both treatment arms but without any significant difference. 11.8% of patients received BFM developed tumor lysis syndrome while, tumor lysis not reported in Hyper CVAD arm. Hepatotoxicity was comparable in both treatment arms (35.3% and 30.8% in BFM and Hyper CVAD, respectively). Development of neutropenic fever was marginally significant with Hyper CVAD (73.1% vs. 51%; P 0.06). Mucositis grade III/IV was found in 15.7% vs. 7.7% in BFM and Hyper CVAD, respectively (P 0.32). These toxicity profiles were similar to many previous reports by Gaynon et al, 2010 and Huguet et al, 2009 [9,10].

ICU admission rate and number of therapy related deaths were comparable in both treatment arms (13.7% and 19.2% in BFM and Hyper CVAD for ICU admission, respectively, and 11.8% and 11.5% in BFM and Hyper CVAD for therapy related deaths, respectively) which come in consistence with series reported by Gaynon et al, 2001 [11].

Our result reported 84.4% first CR rate in both treatment arms which was similar to CR rate achieved in [12]. Report, that evaluated 92 eligible patients aged 18–50 years to receive the pediatric protocol (BFM), conducted at 13 centers. Frist complete remission reported in 85% (78 patients) after 1 month with induction intensifies chemotherapy. Slightly higher CR rate (90%) was reported with incorporating of rituximab in hyper CVAD treatment protocol [13].

Among 34 relapsed patients, 47.8% received BFM, and 63.2% received Hyper CVAD, without a significant relation which denoting the equivalent relapse rate among both treatment arms. Patients who received BFM have a trend of improvement in EFS (P 0.07). Our findings did not demonstrate any difference in EFS with both treatment arms within patient's age group (P 0.3). However, a similar study by Alacacioglu et al. [8] reported a significant relapse free survival times in BFM arm than Hyper CVAD arm.

In the current study OS was significantly favoring BFM versus Hyper CVAD (P 0.008) and this finding was explained by subset analysis regarding the age group of studied patients and cope with Alacacioglu et al. study which reported statistically greater OS in the BFM cases than hyper-CVAD. Similarly, a study done by Alabdulwahab et al. [14] on 73 patients less than 50 years of age in Saudi Arabia, showed a significant 3-year OS, 72.6% vs. 48.5%, P 0.04 in pediatric protocol and hyper-CVAD protocol respectively. However, in a similar study carried out in Lebanon, El-Cheikh and

colleagues [15] did not find a difference in survival outcome between Hyper-CVAD and BFM groups despite older age and a greater number of patients with high-risk category (including Philadelphia chromosome-positive) in the hyper-CVAD group. This could be explained by the high rate of allogeneic transplantation in first CR in patients with high risk features in the Lebanese report.

Patients with age < 30 years in BFM arm reported better OS than patients ≥ 30 years in BFM arm (P 0.01) while, patients with age < 30 years in hyper CVAD arm showed comparable OS to patients ≥ 30 years in same arm and this could be explained by the efficacy of BFM protocol in young adult cases.

Conclusion:

Philadelphia negative ALL can be treated with either BFM-like regimen or Hyper CVAD with acceptable and comparable response rate, toxicity profiles and DFS however, BFM-like regimen appears to be appropriate for young adult patients with ALL with significant better OS.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Conflict of interest: all authors declared that he/she had no conflict of interest.

Ethical approval: In line with the institutional and/or national research committee and the Helsinki declaration of 1964 and their later amendments or related ethical principles all procedures conducted in this study were subject to ethical standards.

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All Data Availability for this work are available upon request to corresponding author

Authors' contributions:

Rania Lasheen: Conceptualization, Methodology, Software

Fady Ghobrial: Project administration; Resources, Writing- Original draft preparation

Mohamed A. Ebrahim: Supervision, Project administration, Resources, Writing- Original draft preparation

ElBaiomy MA: Supervision, writing- Reviewing and Editing

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Appendix 1

Augmented BFM protocol (Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols, A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood. 2008;112:1646-54.)

Treatment	Dose
Induction phase (4 weeks)	
Vincristine,	1.5 mg/m 2 per week for 4 weeks;
Daunorubicin*,	25 mg/m 2 per week for 4 weeks;
Prednisone,	60 mg/m 2 per day for 28 days;
Asparaginase,	6000 units/m 2 IM 3 times a week for 9 doses;
Intrathecal cytarabine on day 0; and Intrathecal methotrexate on day 14	
Consolidation phase (9 weeks)	
Cyclophosphamide	1000 mg/m 2 IV, days 0, 28
Cytarabine	75 mg/m 2 SC or IV, days 1-4, 8-11, 29-32, 36-39
Mercaptopurine	60 mg/m 2 orally, days 0-13, 28-41
Vincristine	1.5 mg/m 2 IV, days 14, 21, 42, 49
Asparaginase	6000 units/m 2 IM, days 14,16, 18, 21, 23, 25, 42, 44, 46, 49, 51, 53
Intrathecal methotrexate	12 mg, days 1, 8, 15, 22
Radiotherapy	Cranial, 1800 cGy; cranial, 2400 cGy, and spinal, 600 cGy; testicular, 2400 cGy
Interim maintenance phase (8 weeks)	
Vincristine	1.5 mg/m 2 IV, days 0, 10, 20, 30, 40
Methotrexate	100 mg/mg 2 IV, days 0, 10, 20, 30, 40 (escalate by 50 mg/m 2 per dose)
Asparaginase	15,000 units/m 2 IM, days 1, 11, 21, 31, 41
Delayed intensification I phase (8 weeks)	
- **Reinduction phase (4 weeks)**	
Dexamethasone	10 mg/m 2 orally, days 0-20, then taper for 7 days
Vincristine	1.5 mg/m 2 IV, days 0, 14, 21
Doxorubicin	25 mg/m 2 IV, days 0, 7, 14
- **Reconsolidation phase (4 weeks)**	
Asparaginase	6000 units/m 2 IM, days 3, 5, 7, 10, 12, 14
Vincristine	1.5 mg/m 2 IV, days 42, 49
Cyclophosphamide	1000 mg/m 2 IV, day 28
Thioguanine**	60 mg/m 2 orally, days 28-41
Cytarabine	75 mg/m 2 per day SC or IV, days 29-32, 36-39
Intrathecal methotrexate	12 mg, days 29, 36
Asparaginase	6000 units/m 2 IV, days 42, 44, 46, 49, 51, 53
Interim maintenance II phase (8 weeks)	
Vincristine	1.5 mg/m 2 IV, days 0, 10, 20, 30, 40
Methotrexate	100 mg/m 2 IV, days 0, 10, 20, 30, 40 (escalate by 50 mg/m 2 per dose)
Asparaginase	15,000 units/m 2 IM, days 1, 11, 21, 31, 41
Intrathecal methotrexate	12 mg, days 0, 20, 40
Delayed intensification II phase (8 wk)	
Same as for delayed intensification I phase	
Long-term maintenance phase (12 weeks)	
Vincristine	1.5 mg/m 2 IV, days 0, 28, 56
Prednisone	60 mg/m 2 orally, days 0-14, 28-32, 56-60
Mercaptopurine	75 mg/m 2 orally, days 0-83
Methotrexate	20 mg/m 2 orally, days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77
Intrathecal methotrexate	12 g, day 0

*Doxorubicin 25 mg/m2 weekly/4weeks used instead of daunorubicin in induction phase.
**Thioguaninewas omitted in reconsolidation phase.

Hyper-CVAD regimen (Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia." J Clin Oncol.2010; 28(24): 3880-89)

Hyper-CVAD is used for courses 1, 3, 5, and 7			
Cyclophosphamide	IV	300 mg/m 2 over 2 to 3 hours every 12 hours for 6 doses	Days 1 to 3
Mesna	IV	600 mg/m 2 /day administered as a continuous infusion starting with cyclophosphamide and ending 6 hours after last dose of Cyclophosphamide	Days 1 to 3
Vincristine	IV	2 mg per day	Days 4 and 11
Doxorubicin	IV		Day 4
Dexamethasone	PO or IV	40 mg per day	Days 1 to 4 and days 11 to 14
High dose methotrexate plus cytarabine (courses 2, 4, 6, and 8)			
Methotrexate	IV	200 mg/m 2 administered over first 2 hours then 800 mg/m 2 administered over 24 hours (total dose per cycle of 1 gram/m 2)	Day 1
Leucovorin	IV	50 mg IV 12 hours after end of methotrexate; then 15 mg IV every 6 hours for 8 doses or until methotrexate level ≤0.1 micromol/L. Dose modifications made based upon methotrexate levels.	Day 2
Cytarabine	IV		Days 2 and 3
Methylprednisolone	IV	50 mg twice daily	Days 1 to 3
CNS prophylaxis			
Methotrexate	IT	12 mg (6 mg if through Ommaya)	Day 2 of each cycle
Cytarabine	IT	100 mg	Day 8 of

each cycle