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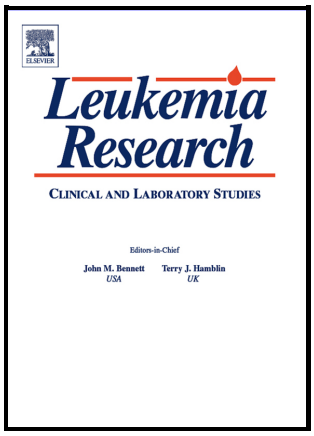

Comparison of a Modified Pediatric Protocol versus a Hyper-CVAD Protocol in Adolescents and Young Adults with Philadelphia-negative Acute Lymphoblastic Leukemia: A Multicenter Retrospective Analysis

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Comparison of a Modified Pediatric Protocol versus a Hyper-CVAD Protocol in Adolescents and Young Adults with Philadelphia-negative Acute Lymphoblastic Leukemia: A Multicenter Retrospective Analysis

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Abstract

Background

The outcomes of Pediatric acute lymphoblastic leukemia (ALL) have improved dramatically whereas outcomes for ALL amongst adolescents and young adults (AYA) have lagged behind. The introduction of pediatric-like regimens to manage adult ALL has shown promising outcomes across several analyses.

Materials and Methods

In this analysis, we aimed to retrospectively compare the differences in outcomes among patients aged 14-40 years with Philadelphia-negative ALL treated with a Hyper-CVAD protocol versus a modified pediatric protocol.

Results

A total of 103 patients were identified with 58 (56.3%) in the modified ABFM group and 45 (43.7%) in the hyper-CVAD group. The median duration of follow-up for the cohort was 39 months (range 1-93). There were significantly lower rates of MRD persistence after consolidation (10.3% vs. 26.7%, P=0.031) and transplantation (15.5% vs. 46.6%, P<0.001) in the modified ABFM group. 5-year OS rates (83.9% vs. 65.3%, P=0.036) and DFS rates

(67.4% vs. 44%, P=0.014) were higher in the modified ABFM groups. The incidence of grade 3 and 4 hepatotoxicity (24.1% vs. 13.3%, P<0.001) and osteonecrosis (20.6% vs. 2.2%, P=0.005) were higher in the modified ABFM group.

Conclusion

Our analysis demonstrates that the use of a pediatric modified ABFM protocol demonstrated superior outcomes compared to the hyper-CVAD regimen in the treatment of Philadelphia-negative ALL amongst AYA patients. However, the modified ABFM protocol was associated with an increased risk of certain toxicities including high grade liver toxicity and osteonecrosis.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common hematological malignancy in children with survival rates approaching 90% [1]. However, ALL amongst adolescents and young adults (AYA) portrays inferior survival outcomes with a more aggressive disease course [2].Several factors are thought to contribute to the observed inferior outcomes amongst AYA patients, including the increased incidence of high-risk clinical and molecular phenotypes [3]. Moreover, the AYA population resides at a critical transition point between the Pediatric and older adult population. Therefore, there has not been a uniformly established treatment protocol for patients within the AYA population. Consequently, patients within the AYA population are often underrepresented within larger multicenter clinical trials [4].

There has been an evolving paradigm shift in the treatment of AYAs with ALL. The results of several retrospective analyses as well as prospective trials have demonstrated that treating AYAs with pediatric inspired regimens proves to be an efficacious strategy [5-8]. Pediatric regimens incorporate higher doses of non-myelosuppressive agents such as asparaginase and corticosteroids. On the other hand, adult protocols employ myelosuppressive agents such as cyclophosphamide, higher doses of cytarabine, and anthracycline. As a result, the use of pediatric-inspired regimens amongst AYAs may increase the risk of certain complications such as hepatitis, avascular necrosis, and pancreatitis [9]. Additionally, adult protocols rely more heavily on the use of hematopoietic stem cell transplantation (HSCT) for dose

intensification [10]. This increased use of HSCT within adult regimens may incur higher economic costs and may increase the risk of treatment related morbidity and mortality.

One of the most widely used regimens in the treatment of adults with ALL encompasses the hyper-CVAD regimen which was pioneered by the MD Anderson Cancer Center Group. The hyper-CVAD regimen was shown to be an efficacious regimen with initial complete remission rates of 92% [11]. The hyper-CVAD protocol has also shown to be highly efficacious within the AYA age group with complete remission rates of 97% [12]. Regarding Pediatric-inspired regimens, the ABFM (Augmented Berlin-Frankfurt-Münster) is one of the most widely tested regimens amongst AYA patients [13]. Within our institutions, patients with ALL over the age of 14 years were previously treated with the hyper-CVAD regimen. However, with the emergence of new studies suggesting superior prognostic outcomes amongst AYA patients treated with pediatric-inspired regimens [5-8], consequently began implementing a modified-ABFM protocol among patients with Philadelphia-negative ALL who are between 14 to 40 years of age.

Herein, we report the findings of a retrospective analysis which compares the prognostic outcomes of adolescents and young adults between the ages of 14-40 years with Philadelphia-negative ALL treated with the hyper-CVAD protocol versus those who were treated with a modified ABFM protocol. We aim to highlight the modifications which were made to the initial ABFM protocol. In addition, we aim to compare the impact of both protocols on prognostic outcomes whilst comparing the rates of observed treatment-related toxicities between both regimens.

1. Materials and Methods

2.1 Patients

In this retrospective analysis we included patients aged 14-40 years who are newly diagnosed with ALL. Patients with Down syndrome, Philadelphia-positive ALL, and pre-existing organ dysfunction were excluded from the analysis. Patients treated at the King Abdulaziz Medical City and Princess Noura Oncology Center between the years of 2010 and 2021 were included in this analysis. This study was approved by the King Abdullah International Medical

Research Center (KAIMRC) institutional review board. All clinical data was obtained from electronic medical records available at our institution.

2.2 Diagnosis and Assessment of MRD

The diagnosis of ALL was established through morphological assessment of bone marrow specimens and the use of flow cytometry. Cytogenetic analysis through fluorescent in situ hybridization (FISH) was undertaken. Moreover, central nervous system involvement was investigated through morphological and flow cytometry assessment of the cerebrospinal fluid.

Flow cytometry minimal residual disease (Fc-MRD) was performed on bone marrow specimens for all patients. Flow cytometry test was performed using FACSCanto II Becton Dickinson (BD) cytometer and 2 tubes of 8 color antibody panels for B-ALL: (CD20-V450, CD45-V500, CD81-FITC, CD66c/CD123-PE,CD34- PerCPCy5.5, CD19-PECy7,CD10-APC,CD38-APCH7), (CD20-V450, CD45-V500, CD81-FITC,CD73/CD304-PE,CD34-PerCPCy5.5, CD19- PECy7,CD10-APC,CD38-APCH7). The following were used for T-ALL: (CytoCD3-V450, CD45-V500, MPO-FITC, CD79a-PE,CD34- PerCPCy5.5, CD19-PECy7, CD7-APC, CD3-APCH7),(CytoCD3-V450, CD45-V500, TdT-FITC, CD99-PE,CD5-PerCPCy5.5, CD10- PECy7,CD1a-APC,CD3-APCH7),(CytoCD3-V450, CD45-V500, CD2-FITC, CD117-PE,CD4- PerCPCy5.5, CD8- PECy7,CD7-APC,CD3-APCH7). BM specimens were processed and stained following Euroflow instrument setting and staining protocols as previously described [14]. Data analysis was performed using FACSDiva software version 8.1. A minimum of 20 clustered events is required to consider a sample as MRD positive (lower limit of detection, LOD) and a minimum of 50 clustered events for accurate quantification of the MRD level (lower limit of quantitation, LLOQ) for a cut off of 0.01%. The test sensitivity is 0.01%.

2.3 Risk Stratification

Patients were stratified into standard-risk and high-risk groups based on certain clinical and cytogenetic parameters in accordance with pre-established guidelines [15, 16]. Patients were stratified as high-risk based if the presenting white blood cell (WBC) count was >30 × 109/L for B-ALL and >100 × 109/L for T-ALL. Moreover, patients with high-risk cytogenetics including t(4,11), t(1,19), hypodiploidy, and complex cytogenetics were classified as high-risk. All other patients were classified as having standard-risk disease.

2.4 Chemotherapy Protocols

Patients in the hyper-CVAD group received a protocol which is identical to the previously published protocol with the incorporation of rituximab for CD20 positive individuals [11]. Moreover, patients with the modified ABFM protocol received a protocol which is similar to the established ABFM protocol with a few specific modifications which are highlighted in the section below [13]. Regarding treatment intensity within the modified-ABFM protocol, patients received 5 cycles of chemotherapy followed by 30 months of maintenance. On the other hand, patients receiving the Hyper-CVAD protocol received 8 cycles of chemotherapy followed by 24 months of maintenance.

2.4.1 *The use of a pre-phase period and dexamethasone in induction/pre-phase stages*

In our modified protocol, we have included a 3–5-day pre-phase of dexamethasone and intrathecal cytarabine prior to induction. The reason for this modification was to allow time for the availability of cytogenetic and molecular analysis findings as we aimed to exclude Philadelphia-positive patients from the Modified-ABFM. Several Pediatric protocols including the GRAALL-2003 have utilized pre-phase steroids [17]. In addition, we have decided to use dexamethasone as the corticosteroid of choice during the induction and pre-phase periods. dexamethasone, despite being associated with a higher-risk of infections and toxicities, has better CNS penetration and has been associated with a lower risk of relapse [18]. To accommodate the increased toxicity with dexamethasone use, antimicrobial prophylaxis and Granulocyte colony-stimulating factor (GCSF) were utilized.

2.4.2 *The use of Asparaginase*

Several studies which investigated the role of asparaginase in adult ALL treatment have outlined four risk-factors which correlate with an increased incidence of liver toxicity. The aforementioned risk factors include: age, body mass index, dose of asparaginase, and the presence of hepatic steatosis [19]. As a result, we have decided to incorporate an age-dependent dosing scheme. The scheme limits the total dose to 5000 units, and patients aged 25 years and above will be dosed at 2000 IU/m2. When considering the route of administration for PEG-asparaginase, both the pharmacokinetics and toxicity profiles are similar for intramuscular and intravenous administration [20]. Moreover, there is no evidence that intravenous administration of PEG-asparaginase is more toxic than intramuscular administration [20]. Intramuscular administration may also be affected during periods of thrombocytopenia. Therefore, we have decided to switch the administration of PEG-asparaginase to the intravenous route. Erwinia asparaginase was used as a second-line alternative to PEG-asparaginase in patients who develop allergic reactions [21]. It is worth noting that we did not perform antibody screening to assess for the development of asparaginase hypersensitivity within our cohort.

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2.4.3 ***The use of high-dose methotrexate in interim maintenance***

In the original ABFM protocol high-dose methotrexate was reserved only for T-ALL.

The COG ALL0232 study randomized all patients with Pre-B ALL to receive either high-dose methotrexate or escalating doses of IV methotrexate during the interim maintenance phase and high-dose methotrexate was associated with a superior OS and EFS in high risk ALL [22].

As a result, we decided to include high-dose methotrexate for all ALL patients during interim maintenance-1. The dose of methotrexate used was 5g/m2 for patients less than 25 years and 3.5g/m2 for older patients.

2.4.4 ***Incorporation of Rituximab for B-ALL***

Retrospective studies have demonstrated more favorable outcomes in patients treated with Rituximab plus hyper-CVAD when compared to hyper-CVAD alone [23]. Moreover, CD20

up-regulation has been described amongst patients with CD20-positive B-ALL after exposure of the leukemic blasts to corticosteroid therapy. Dworzak et al. described that CD20-positivity significantly increased from 45% in the pre-induction phase to 81% post-induction therapy [24]. Based on the aforementioned findings, we have decided to include rituximab in B-ALL, regardless of CD20 status.

2.4.5 *The Incorporation of MRD into decision making and the use of blinatumomab and nelarabine to eradicate MRD*

We have also incorporated the (MRD) into the decision-making process within the protocol. Moreover, we used a persistent MRD (≥ 10-4) at the end of the consolidation period as an indication to proceed to HSCT. Patients with MRD below the required cut-off will continue on the chemotherapy protocol regardless of their initial risk stratification. The persistence of MRD at the time of transplantation carries a higher risk of relapse [25]. Therefore, every effort should be made to eradicate MRD before transplantation. In accordance with findings from the BLAST trial, blinatumomab was approved for the eradication of MRD in B-Cell ALL and as a bridging therapy prior to transplantation [26]. Thus in 2017, we decided to incorporate one or two cycles of blinatumomab after consolidation for B-ALL patients with MRD persistence prior to HCST. There is no approved medication to eradicate MRD in T-ALL. However, based on studies highlighting the efficacy of nelarabine in T-ALL, we decided to incorporate it as a single agent for MRD persistence prior to transplantation [27,28].

2.4.6 *Optimal duration and components of maintenance*

The most widely used maintenance protocol is the POMP (6-MP, methotrexate, Prednisolone and Vincristine), usually administered for two years. Some protocols prolong the maintenance duration beyond conventional two years of total treatment duration. In children, a meta-analysis of 42 trials showed that both prolonged maintenance therapy (3 years versus 2 years), resulted in increased rates of death in remission but also in lower relapse rates [25]. Consequently, we have decided to use a POMP maintenance for 2.5 years with prednisolone given only in the first 2 years of treatment.

2.4.7 *Prophylaxis*

Trimethoprim / Sulfamethoxazole prophylaxis will continue to be used as in the ABFM protocol for PJP prophylaxis. Moreover, the protocol was amended to include antiviral HSV prophylaxis during periods of neutropenia and potential mucositis. Antifungal prophylaxis has also been added to phases of prolonged neutropenia and mucositis. However, due to potential pharmacological interactions, azoles were not used during the induction phase. Micafungin or Anidulafungin were used for antifungal prophylaxis during induction. Moreover, fluconazole was used for short periods during consolidation and delayed intensification. Due to the profound neutropenia and risk of infections associated with myelosuppressive therapy and dexamethasone usage, GCSF support was also used.

2.5 Toxicities

Toxicities recorded included the incidence of prolonged neutropenia and thrombocytopenia, pancreatitis, liver toxicity, neuropathy, osteoporosis, avascular necrosis, and ICU admission. Prolonged neutropenia was defined as a white blood cell count less than 1.0 x109/L for a consecutive period of 10 days. Prolonged thrombocytopenia was defined as a platelet count less than 50.0 x109/L for a consecutive period of 10 days. The degree of liver toxicity was graded from 0-5 in accordance with guidelines from the national cancer institute [29]. Moreover, neuropathy was graded in accordance with the WHO grading scale from 0-4 [30]. Patients in the modified ABFM group underwent DEXA scans to assess bone mineral density and determine the degree of osteoporosis/osteopenia. However, patients receiving the hyper-CVAD protocol were not subject to DEXA scanning, hence the degree of osteoporosis/osteopenia was not compared between groups.

2.6 Statistical Analysis

Numerical variables were described according to their medians and ranges whereas categorical variables were described according to their relative frequencies and percentages. Numerical variables were compared using the Man-Whitney U test whereas categorical variables were compared using the chi-square test. Overall-survival (OS) was defined as the occurrence of death (from any cause) during the follow-up period. Disease-free survival (DFS) was calculated from the time of diagnosis until the incidence of a documented relapse, refractory disease, or death. The Kaplan-Meier method was used to estimate the 3-year and 5-year overall-survival and disease-free survival. Differences between individual protocols were compared using the log-rank test. The cox-proportional hazard model was used for univariate and multivariate analysis to determine the impact of certain prognostic factors on overall-survival and disease-free survival. Prognostic factors which had a statistically significant impact on overall survival or disease-free survival at univariate analysis were entered into the multivariate model. P-values <0.05 were considered statistically significant. All statistical analyses were carried out using version 27.0.1.0 of SPSS statistics.

2. Results

3.1 Baseline Characteristics

The median length of follow-up for the hyper-CVAD group was 39 months (range 1-93) versus 41 months (range 5-81) for the modified ABFM group. A total of 103 patients were identified with 45 (43.7%) in the hyper-CVAD group and 58 (56.3%) in the modified ABFM group. The comparison of baseline characteristics between both groups is shown in Table 1.

Characteristic	Hyper-CVAD	Modified ABFM	Total	*P*
Patient Numbers (%)	45.0 (43.7)	58.0 (56.3)	103.0 (100)	
Age, years				NS
Median (range)	20.0 (14.0-40.0)	17.0 (14.0-40.0)	18.0 (14.0-40.0)	

Sex				NS
Male (%)	31.0 (68.9)	40.0 (69.0)	71.0 (68.9)	
Female (%)	14.0 (31.1)	18.0 (31.0)	32.0 (31.1)	
BMI				NS
Median (range)	22.0 (15.2-46.7)	23.0 (13.3-24.1)	22.5 (13.3-48.3)	
Number of patients with Obesity (BMI >30)	10.0 (22.2)	15.0 (25.9)	25.0 (24.3)	
Subtype of ALL				NS
B-Cell (%)	28.0 (62.2)	45.0 (77.6)	73.0 (70.9)	
T-cell (%)	17.0 (37.8)	13.0 (22.4)	30.0 (29.1)	
WBC at Presentation, $x10^9/L$				NS
Median (range)	8.3 (0.8-693.0)	5.7 (0.3-296.0)	6.6 (0.3-693.0)	
LDH at Presentation, Units per liter				NS
Median (range)	404.0 (117.0-4048.0)	511.0 (169.0-11441.0)	431.0 (117.0-11441.0)	
Cytogenetics				**0.022**
Normal (%)	20.0 (44.4)	24.0 (41.4)	44.0 (42.7)	
Complex (%)	3.0 (6.7)	18.0 (31.0)	21.0 (20.4)	

Hyperdiploidy (%)	7.0 (15.6)	12.0 (20.7)	19.0 (18.4)	
t (4; 11) (%)	3.0(6.7)	1.0 (1.7)	4.0 (3.9)	
Deletion 9p (%)	7.0(15.6)	2 (3.4)	9.0 (8.7)	
Other (%)	5.0 (11.0)	1 (1.8)	6.0 (5.9)	
ALL Risk Category				NS
Standard risk (%)	26.0 (57.8)	40.0 (69.0)	66.0 (64.1)	
High risk (%)	19.0 (42.2)	18.0 (31.0)	37.0 (35.6)	
CD20 Positivity				NS
Yes (%)	20.0 (44.4)	28.0 (48.3)	48.0 (46.6)	
No (%)	25.0 (55.6)	30.0 (51.7)	55.0 (53.4)	
Rituximab Used				**0.012**
Yes (%)	20.0 (44.4)	40.0 (69.0)	60.0 (58.3)	
No (%)	25.0 (55.6)	18.0 (31.0)	43.0 (41.7)	
Blinatumomab Used				**0.003**
Yes (%)	0.0 (0.0)	10.0 (17.2)	10.0 (9.7)	
No (%)	45.0 (100.0)	48.0 (82.8)	93.0 (90.3)	

Table 1: Baseline Characteristics amongst patients in the Hyper-CVAD and Modified ABFM groups

There was no statistically significant difference in the age range, gender distribution, ALL risk-stratification category, BMI, and presenting WBC and LDH counts. There was a statistically significant difference in the distribution of cytogenetic parameters between the two groups (P=0.022). Notably, the incidence of complex cytogenetics was higher in the modified ABFM group (31.0%) when compared to the hyper-CVAD group (6.7%). Moreover, the use of rituximab was significantly higher in the modified ABFM group compared to the hyper-CVAD group [69.0% vs 44.4% (P=0.012)]. This difference was likely a result of the modification we employed in the modified ABFM protocol as all patients with B-ALL received rituximab. On the other hand, only patients with CD20 positivity received rituximab in the hyper-CVAD group. Similarly, none of the patients in the hyper-CVAD group received blinatumomab whereas 17.2% of patients received blinatumomab in the modified ABFM group (P=0.003).

3.2 Comparison of survival outcomes and treatment response rates

Table 2 shows the treatment outcomes and response rates between the modified ABFM protocol and the hyper-CVAD protocol. The difference in MRD persistence after induction was not statistically significant between the two groups. However, there was a statistically significant difference in MRD persistence after consolidation between the two groups [10.3% modified ABFM versus 26.7% hyper-CVAD (P=0.031)]. Moreover, patients in the hyper-CVAD group demonstrated statistically significant higher rates of relapse when compared to the modified ABFM group [46.6% versus 15.5% (P<0.001)]. The incidence of death of any cause between the two groups was also significantly higher in the hyper-CVAD group versus the modified ABFM group [37.8% versus 12.8% (P=0.005)]. Notably, the rates of hematopoietic stem cell transplantation in CR1 were significantly lower in the modified ABFM group (12.1%) when compared to the hyper-CVAD group (40.0%) (P<0.001).

Variable	**Hyper-CVAD** (%)	**Modified ABFM** (%)	**Total** (%)	***P***
MRD positivity after induction				NS

MRD positive	23.0 (51.1)	22.0 (37.9)	45.0 (43.7)	
MRD negative	22.0 (48.9)	36.0 (62.1)	58.0 (56.3)	
MRD positivity after consolidation				**0.031**
MRD positive	12.0 (26.7)	6.0(10.3)	18.0 (17.5)	
MRD negative	33.0 (73.3)	52.0 (89.7)	85.0 (82.5)	
Relapse Rate				**<0.001**
Patients with a documented relapse	21.0 (46.7)	9.0 (15.5)	30.0 (29.1)	
Patients without a documented relapse	24.0 (53.3)	49.0 (84.5)	73.0 (70.9)	
Death Rate				**0.005**
Dead	17.0 (37.8)	8.0 (12.8)	25.0 (24.3)	
Alive	28.0 (62.2)	50.0 (86.2)	78.0 (75.7)	
Transplant Rate				**<0.001**
Transplanted	27.0 (40.0)	7.0 (12.1)	34.0 (33.0)	

Table 2: Comparison of outcomes and treatment response rates between Hyper-CVAD and modified ABFM protocols

Figure 1 shows the Kaplan-Meier plot comparing overall-survival rates and disease-free survival rates between the modified ABFM group and the hyper-CVAD group. The difference in overall-survival rates compared between the two groups was statistically significant (P=0.036) as per the log-rank test. However, the estimated 3-year OS rates were comparable between the two groups (86.9% [95% CI 77.9- 95.9] in the modified ABFM group versus 84.9% [95% CI 73.7%-96.0%] in the hyper-CVAD group). The difference in estimated overall-survival becomes more noticeable at 5-years where the 5-year OS for the modified ABFM group is 83.9% (95% CI 73.3%-94.5%) versus 65.3% (95% CI 46.3%-84.3%) for the

hyper-CVAD group. The difference in DFS between the two protocols was statistically significant as per the log rank test (P=0.014). The 3-year DFS was 84.7% (95% CI 74.9-94.5%) for the modified ABFM group versus 70.9% (95% CI 57.0%-84.8%) for the hyper-CVAD group. Furthermore, the 5-year DFS was 67.4% (95% CI 49.8%-85.0%) for the modified ABFM group versus 44.0% (95% CI 26.8%-61.2%) for the hyper-CVAD group.

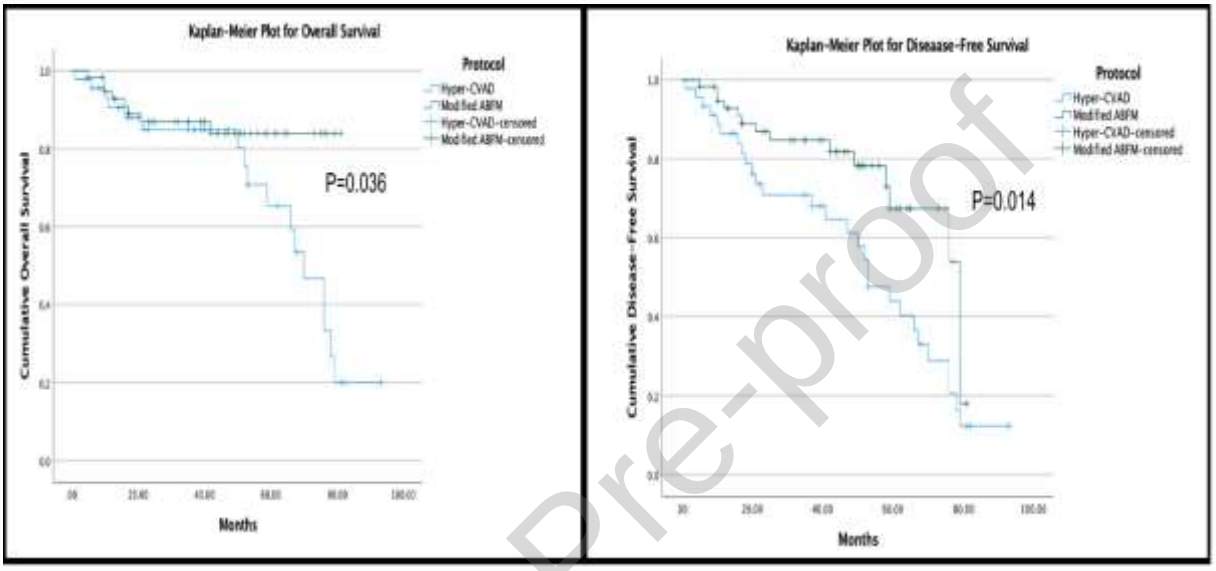

Figure 1: Kaplan-Meier plot comparing overall survival and disease-free survival between Hyper-CVAD and modified ABFM protocols

3.3 Univariate and Multivariate analyses for the effect of certain prognostic factors on overall-survival

A cox-proportional hazards model univariate and multivariate analysis was conducted to determine the effect of certain prognostic co-variates on overall-survival and disease-free survival. The co-variates incorporated into the analysis included: gender, age, subtype of ALL, the protocol of chemotherapy used (hyper-CVAD versus modified ABFM), risk-stratification category, MRD status at induction and consolidation, the occurrence of a documented relapse, transplantation status, rituximab usage, blinatumomab usage, and admission to the intensive care unit (ICU). All co-variates which had a statistically significant impact on overall survival or disease-free survival at univariate analysis were entered into the multivariate model. Table 3 and 4 show the results of the univariate and multivariate analyses,

respectively. At univariate analysis, MRD clearance after consolidation was significantly associated with superior overall-survival and disease-free survival with hazard ratios of 0.406 [95% CI 0.166-0.992, P=0.048] and 0.348 [95% CI 0.178-0.680, P=0.002], respectively. Moreover, the use of the hyper-CVAD protocol was significantly associated with an inferior OS and DFS with hazard ratios of 2.399 [95% CI 1.028-5.602, P=0.043] and 2.139 [95% CI 1.137-4.027, P=0.018], respectively. Additionally, the absence of admission to the ICU was significantly associated with a superior OS and DFS with hazard ratios of 0.138 [95% CI 0.057-0.336, P<0.001] and 0.291 [95% CI 0.146-0.580, P<0.001]. Male gender was associated with a superior DFS with a hazard ratio of 0.397 [95%CI 0.206-0.762, P=0.006]. The absence of a documented relapse was associated with superior DFS with a hazard ratio of 0.218 [95% CI 0.113-0.420, P<0.001]. Using the multivariate model, the absence of ICU admission displayed a statistically significant superior OS and DFS with hazard ratios of 0.144 [95% CI 0.057-0.364, P<0.001] and 0.330 [95% CI 0.160-0.680, P=0.003] . Furthermore, at multivariate analysis, the absence of a documented relapse demonstrated a statistically significant superior DFS with a hazard ratio of 0.256 [95% CI 0.127-0.517, P<0.001].

Variable	**Univariate Analysis P Value for overall survival**	**HR**	**95% CI**	**Univariate Analysis P value for disease-free survival**	**HR**	**95% CI**
Male Gender	0.220	0.576	0.238-1.392	**0.006**	0.397	0.206-0.762
Age	0.148	1.042	0.986-1.102	0.203	1.029	0.984-1.076
B Cell Subtype	0.196	0.589	0.264-1.313	0.980	1.009	0.518-1.965

Standard Risk	0.211	0.605	0.275-1.329	0.911	1.036	0.553-1.943
Negative MRD after induction	0.968	0.984	0.444-2.182	0.555	0.833	0.455-1.526
Negative MRD after consolidation	**0.048**	0.406	0.166-0.992	**0.002**	0.348	0.178-0.680
Absence of Relapse	0.071	0.481	0.218-1.065	**<0.001**	0.218	0.113-0.420
Absence of Transplant	0.797	1.114	0.489-2.534	0.303	0.729	0399.332
Hyper-CVAD protocol	**0.043**	2.399	1.028-5.602	**0.018**	2.139	1.137-4.027
No ICU admission	**<0.001**	0.138	0.057-0.336	**<0.001**	0.291	0.146-0.580
No Rituximab used	**0.216**	1.677	0.740-3.801	**0.620**	1.167	0.634-2.147
No blinatumomab used	**0.987**	1.010	0.301-3.391	**0.639**	0.813	0.342-1.932

Table 3: Univariate analysis of prognostic factors for overall survival and disease-free survival

Variable	Multivariate Analysis P Value for overall survival	HR	95% CI	Multivariate Analysis P value for disease-free survival	HR	95% CI
Male Gender	0.510	1.395	0.519-3.753	0.603	0.816	0.378-1.760
Negative MRD after consolidation	0.317	0.573	0.193-1.706	0.570	0.783	0.337-1.821

Absence of Relapse	0.339	0.644	0.261-1.588	**<0.001**	0.256	0.127-0.517
Hyper-CVAD protocol	0.262	1.682	0.678-4.176	0.356	1.382	0.696-2.744
No ICU admission	**<0.001**	0.144	0.057-0.364	**0.003**	0.330	0.160-0.680

Table 4: Multivariate analysis of prognostic factors for overall survival and disease-free survival

3.4 Comparison of the incidence of certain toxicities between the modified ABFM and hyper-CVAD protocols

Table 5 shows the differences in the rates of certain toxicities between the hyper-CVAD and modified ABFM protocols. Interestingly, there was no statistically significant difference in the incidence of prolonged neutropenia and thrombocytopenia between both groups. There was a statistically significant difference in the incidence and distribution of liver toxicities between both groups. 56.9% of patients in the modified ABFM group had no incidence of liver-toxicity during the treatment period versus only 6.7% in the hyper-CVAD group (P<0.001). However, the incidence of higher grades of hepatotoxicity (grades 3 and 4) were higher in the modified ABFM group (24.1%) when compared to the hyper-CVAD group (13.3%) (P<0.001). There were no patients with documented pancreatitis in the hyper-CVAD group whereas 5.2% of patients in the modified ABFM group had a documented episode of pancreatitis; however, this difference was not statistically significant. Additionally, there was no statistically significant difference in the incidence of neuropathy and ICU admission. The incidence of osteoporosis was not compared between both groups as patients in the hyper-CVAD group did not receive a DEXA scan to assess bone mineral density. The rates of osteoporosis and osteopenia in the modified ABFM group were 12.1% and 17.2% respectively. Lastly, the incidence of avascular necrosis was significantly higher in the modified ABFM group (20.7%) when compared to the hyper-CVAD group (2.2%) (P=0.005). Moreover, the causes of death during the follow-up period were stratified as either being related to disease progression or the onset of infections and sepsis, In the hyper-CVAD group 24.4% of all patients died due to disease progression compared to 3.4% in the modified ABFM group [P=0.004]. On the other hand, the rates of death due to infection were

comparable between the groups with 13,3% in the hyper-CVAD group versus 10.3% in the modified ABFM group [P=0.004].

Toxicity	Hyper-CVAD (%)	Modified ABFM (%)	Total (%)	*P*
Prolonged neutropenia				NS
Yes	10.0 (22.2)	21.0 (36.2)	31.0 (30.1)	
No	35.0 (77.8)	37.0 (63.8)	72.0 (69.9)	
Prolonged thrombocytopenia				NS
Yes	12.0 (26.7)	8.0(13.8)	20.0 (19.4)	
No	33.0 (73.3)	50.0 (86.2)	83.0 (80.6)	
Liver Toxicity Grade				**<0.001**
Grade 0	3.0 (6.7)	33.0 (56.9)	36.0 (35.0)	
Grade 1	16.0 (35.6)	6.0 (10.3)	22.0 (21.4)	
Grade 2	20.0 (44.4)	5.0 (8.6)	25.0 (24.3)	
Grade 3	5.0 (11.1)	13.0 (22.4)	18.0 (17.5)	
Grade 4	1.0 (2.2)	1.0 (1.7)	2.0 (1.9)	
Incidence of Pancreatitis				NS
Yes	0.0 (0.0)	3.0 (5.2)	3.0 (2.9)	
No	45.0 (100.0)	55.0 (94.8)	100.0 (97.1)	
Neuropathy Grade				NS
Grade 0	41.0 (91.1)	44.0 (75.9)	85.0 (82.5)	
Grade 1	2.0 (4.4)	8.0 (13.8)	10.0 (9.7)	
Grade 2	2.0 (4.4)	5.0 (8.6)	7.0 (6.8)	

Grade 3	0.0 (0.0)	1 (1.7)	1.0 (1.0)	
Grade 4	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
Incidence of Osteoporosis/Osteopenia				**<0.001** (NA)
Not assessed	45.0 (100.0)	15.0 (25.9)	60.0 (58.3)	
Normal bone mineral density	NA	26.0 (44.8)	26.0 (25.2)	
Osteopenia	NA	10.0 (17.2)	10.0 (9.7)	
Osteoporosis	NA	7.0 (12.1)	7.0 (6.8)	
Incidence of Avascular Necrosis				**0.005**
Yes	1.0 (2.2)	12.0 (20.7)	13.0 (12.6)	
No	44.0 (97.8)	46.0 (79.3)	90.0 (87.4)	
ICU admission				NS
Yes	8.0 (17.8)	9.0 (15.5)	17.0 (16.5)	
No	37.0 (82.2)	49.0 (84.5)	86.0 (83.5)	
Cause of Death				**0.004**
Alive	28.0 (62.2)	50.0 (86.2)	78.0 (75.7)	
Disease Progression	11.0 (24.4)	2.0 (3.4)	13.0 (12.6)	
Infection/Sepsis	6.0 (13.3)	6 .0 (10.3)	12.0 (11.7)	

Table 5: Comparison of toxicities between the Hyper-CVAD and modified ABFM protocol

3. Discussion

The outcomes of pediatric ALL have improved dramatically whereas outcomes for ALL amongst the AYA group have lagged behind [2].The introduction of pediatric regimens to manage adult ALL has shown promising outcomes across several studies [31]. In this analysis, we aimed to compare the differences in response rates and prognostic outcomes amongst patients aged 14-40 years with philadelphia-negative ALL treated with a Hyper-CVAD protocol and a modified ABFM protocol. Moreover, we aimed to compare the toxicity profiles across both regimens. There have yet to be any randomized prospective comparisons between both the hyper-CVAD and BFM-like regimens. However, certain studies have retrospectively compared the efficacy of both protocols [32,33]. We aimed to contribute to this existing body of literature whilst highlighting and justifying the adjustments we have made to the augmented-BFM protocol

Within our cohort the incidence of B-ALL was 70.9% versus 29.1% for T-ALL. Moreover, the incidence of complex cytogenetics was observed in 21.0% of patients. 37.0% of patients had their disease stratified as high risk whereas 63.0% of patients had been classified as standard risk. These findings are in keeping with the other studies conducted across the AYA age group and highlight that with increasing age the incidence of high-risk clinical and molecular phenotypes is often observed [3,34]. Our findings also reinforce the concept that MRD clearance is a critical prognostic indicator [35]. At univariate analysis, MRD clearance after consolidation was significantly associated with superior overall-survival and disease-free survival. Over the past years, the importance of MRD clearance has been shown to be of crucial prognostic significance and is of greater significance than clinical risk-stratification models and other molecular prognostic models [35,36]. A meta-analysis of 39 studies by Berry et al. demonstrated that Measurable residual disease (MRD) clearance after therapy was found to have a significant impact on disease-free survival and overall-survival in both adults and children [37]. However, the timing of MRD assessment is critical, as assessing MRD too early may compromise its prognostic significance, whilst over-delaying the assessment of MRD may allow patients who should have been salvaged earlier to relapse. Different protocols have used different cut-off times to manage MRD persistence. The GMALL group illustrated that MRD negativity after consolidation was significantly associated with higher rates of disease-free survival [36, 38-39] . Moreover, researchers at the MD Anderson cancer center published their recommendations for the assessment and management of MRD, which entailed the use of MRD persistence three months after the initiation of a hyper-CVAD protocol as a cut-off point to decide upon further management [40].

The 3 and 5-year OS for the hyper-CVAD group within our cohort was 84.9% and 65.3% respectively. Comparatively [P=0.036], the 3 and 5-year OS for the modified ABFM regimens were 86.9% and 83.9% respectively. Additionally, 3-year DFS was 84.7% for the modified ABFM group versus 70.9%for the hyper-CVAD group. 5-year DFS was 67.4% for the modified ABFM group versus 44.0% %) for the hyper-CVAD group. The difference in DFS between the two protocols was statistically significant as per the log rank test (P=0.014). A single-center retrospective analysis at the MD Anderson Cancer Centre compared the efficacy of the hyper-CVAD regimen and modified ABFM regimen in patients aged 15-40 with Philadelphia-negative ALL [32]. The findings of this study did not show a statistically significant difference in survival between both regimens with a 5-year OS of 60% observed amongst both protocols [32]. The 5-year OS survival for the hyper-CVAD group (60.0%) was comparable to the 5-year survival observed within our group (65.3%) whereas the 5-year OS

survival for the ABFM group was lower than that observed within our cohort (60.0% vs 83.9%). However, other trials have demonstrated statistically significant differences in survival with pediatric-like regimens when compared to adult regimens. For instance, a group from Saudi Arabia compared the Dana-Farber protocol to the hyper-CVAD protocol amongst 73 patients who were under 50 years of age [41]. The results of this analysis demonstrated statistically significant superior OS for the pediatric-like regimen when compared to the hyper-CVAD protocol (72.6% versus 48.5%, P=0.04) [41]. The 3-year OS rates for both groups reported in this trial are lower than those reported in our study; however, it is worth noting that this study did not exclude Philadelphia-positive ALL patients. Additionally, several trials have demonstrated promising results relating to the treatment of AYA patients with pediatric inspired regimens. For instance, the NOPHO ALL trial was conducted in 221 patients aged 18-45 demonstrating 5-year OS and event-free survival rates of 78% and 74% respectively [7]. Additionally, a trial of 85 Philadelphia-negative ALL patients aged 18-35 years treated with a modified pediatric regimen demonstrated a 3-year OS and DFS of 83% and 77% respectively [42].

Our findings demonstrate that the modified ABFM protocol demonstrated a statistically significant difference in OS and DFS when compared to the hyper-CVAD protocol; however, it is interesting to note that the differences in survival become more prominent after the 3-year mark. This may be explained by the higher rates of relapses and subsequent transplantation observed in the hyper-CVAD group when compared to the modified ABFM group. 46.7% of patients had a documented relapse in the hyper-CVAD group versus only 15.5% in the modified ABFM group (P<0.001). 26.7% of patients in the hyper-CVAD group had a persistent MRD after consolidation versus 10.3% in the modified ABFM group (P=0.031). Additionally, 40.0% of patients underwent transplantation in the hyper-CVAD group versus 12.1% in the modified ABFM group. The rate of HCST with the hyper-CVAD protocol at one of our centers was also reported to be 50% in a previous analysis [43]. Notably, patients undertaking the hyper-CVAD regimen at our institution were offered HCST if their disease has been stratified as high-risk or if they had MRD persistence at three months. Comparatively, patients in the modified ABFM group only underwent transplantation if they had MRD persistence after consolidation irrespective of their risk-stratification category. A meta-analysis comprising 11 trials and 2849 patients compared adult and Pediatric-inspired ALL regimens in the AYA group [44]. The findings of this analysis were in keeping with the findings observed within our cohort. For instance, the analysis demonstrated that patients treated with pediatric-inspired regimens had higher initial complete remission rates and lower relapse rates [45]. In regard to rates of HSCT transplantation, pediatric-inspired regimens have been shown to reduce the need for transplantation [45]. The use of pediatric-inspired regimens has also been shown to produce better outcomes than HCST transplantation after an initial remission [46]. It is also worth noting that individuals within the AYA group have been shown to have a higher incidence of toxicities with HCST including their susceptibility to the onset of severe acute graft-versus-host disease [47]

Adult protocols utilized for the treatment of ALL often utilize myelosuppressive agents whereas pediatric protocols employ non-myelosuppressive agents such as corticosteroids and asparaginase [9]. Consequently, the complications of adult protocols often encompass periods of prolonged bone marrow suppression and susceptibility to infection. Comparatively, pediatric protocols are often complicated by side effects such as pancreatitis, osteonecrosis, and hepatitis [9]. Interestingly, there was no statistically significant difference in the incidence of prolonged neutropenia and thrombocytopenia between the modified ABFM groups and the

hyper-CVAD group. Additionally, despite pancreatitis occurring in none of patients in the hyper-CVAD group vs. 5.2% in the modified ABFM group, this difference was not statistically significant. The incidence of higher grade (grades 3-4) liver toxicity was significantly higher in the modified ABFM group (24.1%) when compared to the hyper-CVAD group (13.3%) (P<0.001). The MD Anderson trial compared the toxicities in the ABFM group with those observed in the hyper-CVAD group. The trial noted grade 3-4 liver toxicity in 41% of patients and the incidence of pancreatitis in 11% of patients [32]. Comparatively, patients within the hyper-CVAD group had significantly higher rates of infections during the induction and consolidation phases [32]. The authors of this study concluded that the hyper-CVAD and modified ABFM regimens were associated with different toxicity profiles [32]. Within our cohort, the incidence of osteonecrosis was significantly higher in the modified ABFM group (20.7%) versus the hyper-CVAD group (2.2%). Analysis of toxicity profiles from the NOPHO and UKALL trials have shown that the incidence of osteonecrosis significantly increases in AYA when compared to the Pediatric population [7,48]. However, it is worth noting that within our cohort patients receiving the modified ABFM protocols underwent routine MRIs to assess for osteonecrosis whereas those undertaking the hyper-CVAD protocol only underwent assessment of osteonecrosis if symptomatic. Hence, this could account for the disparity in the incidence of osteonecrosis. Due to the high rates of obesity observed within our region and as evidenced by 24.3% of our cohort having a BMI over 30 kg/m^2, we have decided to implement specific modifications to the modified-ABFM protocol in order to attenuate the risk of certain toxicities. All patients receiving the modified ABFM protocol underwent a baseline liver ultrasound scan at diagnosis to assess for hepatic steatosis. Additionally, the dose of PEG-asparaginase was capped at 1500 IU/m^2 for all patients with evidence of hepatic steatosis or those with a BMI 30 kg/m^2.

However, there are several limitations to this study. One of the major limitations of this study lies in its retrospective nature. The hyper-CVAD regimen was utilized prior to 2016 which was prior to the utilization of blinatumomab for refractory B-ALL within our center. Additionally, patients with refractory T-ALL received nelarabine prior to HCST in the modified ABFM group due to clinical data supporting its efficacy [27,28]. Patients in the hyper-CVAD group did not receive blinatumomab due to it is efficacy being shown after 2016 [26]. Additionally, all patients with B-ALL in the modified ABFM group received rituximab due to potential CD20 up-regulation whereas only patients with CD20 positivity at diagnosis received rituximab in the hyper-CVAD group [24]. Consequently, HCST was the only intensification strategy utilized amongst hyper-CVAD patients. Therefore, the differences in therapeutics utilized amongst the modified ABFM and hyper-CVAD group may influence the prognostic differences reported in this study.

4. Conclusion

Our analysis demonstrates that the use of a Pediatric modified ABFM protocol displays superior DFS and OS when compared to the hyper-CVAD regimen in the treatment of Philadelphia-negative ALL among adolescents and young adults. However, the modified ABFM protocol was associated with an increased risk of certain toxicities including high grade liver toxicity and osteonecrosis. Larger multicenter randomized control trials and

prospective studies are required to accurately compare adult protocols and pediatric-inspired regimens.

Statements

6.1 Statement of Ethics

This study protocol was reviewed and approved by the institutional review board at King Abdullah International Medical Research Center (KAIMRC) in Riyadh and Jeddah, under the approval numbers [RYD-22-419812-124560] and [RYD-22-419813-132781], respectively. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. No potentially identifiable human images or data is presented in this study.

6.2 Conflict of Interest Statement

The authors have no conflicts of interest to declare.

6.3 Funding Sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

6.4 Author Contributions

Conceptualization, HS, SE, AH, AhA. Writing—original draft preparation, HS, SE, MO, AhA. Formal analysis, MO. Writing—review and editing, HS, SE, MO, AH, MD, MB, BA, MA, IE, MA, SA, WR, MK, SK, ASA, AAR, AI, AhA. Data Curation, LD, AyA, RK, MS. Methodology, ArA, AhA. Supervision, HS, SE, AH, AhA.

6.5 Data Availability Statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

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Figure and Table Legends

Figures:

Figure 1: Kaplan-Meier plot comparing overall survival and disease-free survival between Hyper-CVAD and modified ABFM protocols

Tables:

Table 1: Baseline Characteristics amongst patients in the Hyper-CVAD and Modified ABFM groups

Table 2: Comparison of outcomes and treatment response rates between Hyper-CVAD and modified ABFM protocols

Table 3: Univariate analysis of prognostic factors for overall survival and disease-free survival

Table 4: Multivariate analysis of prognostic factors for overall survival and disease-free survival

Table 5: Comparison of toxicities between the Hyper-CVAD and modified ABFM protocol

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Highlights

- Both Hyper-CVAD and pediatric inspired regimens have been used internationally in the treatment of adult acute lymphoblastic leukemia
- Our analysis demonstrates that the use of a modified pediatric-inspired regimen has resulted in superior prognostic outcomes, however; this superior prognosis comes at the expense of an increased incidence of certain toxicities including hepatotoxicity and osteonecrosis.

- Nonetheless, there remains conflicting evidence regarding the prognostic benefits of utilizing adult and pediatric protocols. Hence, larger multicenter randomized control trials are required to accurately compare adult protocols and pediatric-inspired regimens