



Improved survival in adolescents and young adults (AYA) patients aged 14–55 years with acute lymphoblastic leukemia using pediatric-inspired protocol – a retrospective analysis of a real-world experience in 79 of patients treated at a national tertiary care referral center

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ABSTRACT

Background: Treating adolescents and young adults (AYA) patients with acute lymphoblastic leukemia (ALL) using pediatric-inspired protocols have shown improvement in outcomes. Most data available in the literature of such protocols is derived from well-controlled clinical trials. This report aims to provide a real-world experience from using a pediatric-inspired protocol in ALL-AYA population in larger number of patients treated at a national tertiary care referral center.

Methods: Newly diagnosed Philadelphia negative ALL-AYA patients ages between 14 and 55 years of age were treated on an institutional protocol (AYA-15 protocol) adopted from a modified version of Children's Cancer Group (CCG) 1900 protocol. At the time of this publication, a total of 79 patients were treated using the AYA-15 protocol between 2015 and 2020). Event-free survival (EFS), disease-free survival (DFS), and overall survival (OS) were analyzed using cumulative incidence and Kaplan-Meier methods.

Results: The median age at diagnosis was 18 years (14–51 years) with 63% male patients. Complete remission (CR) at day 28 of induction was achieved in 88.6% of which 73.4% were minimal residual disease (MRD) negative. At a median follow up of 5 years, EFS, DFS and OS were 57.5%, 69.2% and 75.8% respectively. Toxicities were within the expected range with infections and transaminitis being the most common adverse events.

Conclusion: Our single-center experience real-world data in treating AYA-ALL patients with pediatric-inspired protocol demonstrates encouraging results of high survival rate and excellent tolerability for patients aged 18–55 years.

1. Introduction

Treatment of acute lymphoblastic leukemia (ALL) in adults is challenging with poor outcomes in patients treated with adult-oriented chemotherapy regimens [1]. In the recent years, the increasing use of pediatrics-inspired chemotherapy protocols in adolescents and young adults showed significant improvement in outcomes [2].

Most published data regarding the efficacy and toxicity of pediatrics-inspired chemotherapy protocols in adult patients with ALL are mainly generated from clinical trials [3–5]. It is well known that the best evidence in the medical literature comes from randomized controlled trials (RCTs). Most phase III RCTs use very strict inclusion and exclusion criteria prior to randomization aiming to eliminate the influence of confounders. Additionally, follow up and monitoring of subjects are

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highly controlled. The results generated from trials represent a highly selected population and may not represent the real-world, daily practice, heterogeneous population, where patients can have various comorbidities and variable logistical aspects [6].

In 2015, we adopted a modified version of Children's Cancer Group (CCG) 1900 protocol [7] to treat our AYA ALL patients (modifications summarized in Table 1 in supplementary material). We called this modified version "AYA-15" protocol. The results of the first 40 patients were published in 2019 showing improvement in 5-years disease-free survival (DFS) of 72% and 5-years overall survival (OS) of 75% [8].

We herein, report an update of our results using the AYA-15 protocol on 79 consecutive patients treated at our institution.

2. Methods

Seventy-nine patients with B or T cell type ALL/LBL who were between 14 and 55 years of age at the time of therapy initiation with AYA-15 chemotherapy protocol were enrolled in this study. This study was approved by the institutional review board. Patients with Philadelphia chromosome, BCR-ABL positive ALL or biphenotypic leukemia/mixed phenotype leukemia were excluded from this protocol. We used electronic medical records to extract data on each patient including demographics, disease characteristics, treatment details and clinical outcomes data. The studied outcomes included disease-free survival (DFS), event-free survival (EFS), overall survival (OS), and toxicities. Minimal residual disease (MRD) was assessed at our lab using multicolor flow cytometry with a cutoff of 0.01%. MRD was checked at the end of induction and the end of consolidation. Complete remission (CR) was defined as 5% or less bone marrow blasts at the end of the induction phase. EFS is defined as survival from time of diagnosis till the occurrence of one of defined events including: induction failure, undergoing allo-SCT, relapsed disease, death, or taken off the protocol for any reason.

Patients were risk stratified into high-risk disease or very high-risk disease according to the criteria shown in Table 2 (in supplementary material). All patients with B-cell ALL were considered high risk (HRB) unless they had CNS disease at presentation or >5% blasts on induction day 14 bone marrow biopsy, such cases were classified as very high risk (VHRB). Patients with T-cell ALL were classified as very high risk (VHRT) disease if their presenting WBC was >50,000/ul or had CNS disease at presentation, otherwise, they were classified as high risk (HRT). None of the enrolled patients in this protocol were classified as low risk since all our patients are >10 years of age and according to pediatric risk classification, such patients are classified as either high or very high risk.

3. Chemotherapy protocol

AYA-15 chemotherapy protocol is a pediatric-inspired protocol with the same intensification as used in pediatrics ALL patients aiming to produce deep remissions with limited use of allogeneic stem cell transplantation (allo-SCT) (See Table 3 for details of chemotherapy phases). Indications to proceed with allo-SCT included induction failure and positive MRD after the consolidation phase. The presence of KMT2A (myeloid/lymphoid or mixed lineage leukemia (MLL)) gene was a controversial reason to proceed with allo-SCT in CR1 especially if MRD is negative at the end of consolidation.

Pre-phase with prednisone 40 mg/m² for 4 days was given to all patients before initiation of induction to reduce the risk of tumor lysis syndrome. Fig. 1 shows the choice of chemotherapy protocol according to risk stratification. The induction phase was the same regardless of risk stratification. We used pegylated-asparaginase (peg-asp) as our preferred asparaginase formula for all patients, starting from induction phase. For patients who could not tolerate or developed allergic reaction to peg-asp, we used Erwinia asparaginase. Prophylactic anticoagulation (enoxaparin 40 mg subcutaneous once a day) was used to prevent

Table 3
Chemotherapy protocol AYA 15.

Treatment	Dose	Days
Pre-phase (4 days)		
Prednisone	40 mg/m ²	For 4 days
Induction (28 days)		
Daunorubicin	25 mg/m ² IV	0,7,14,21
Vincristine	1.5 mg/m ² IV push	0,7,14,21
Peg-asparaginase	2500 IU/m ² IV (with prophylactic enoxaparin)	3
Prednisone	20 mg/m ² PO TID	0–28 then tapering
Rituximab (CD20 +ve)	375 mg/m ²	11,22
IT AraC	70 mg	7
IT MTX	12 mg	14,28
Consolidation (53 days)		
Cyclophosphamide	1000 mg/m ² IV	0 and 28
AraC	75 mg/m ² /d IV or SC	1–4, 7–10, 29–32, and 35–38
6-MP	60 mg/m ² /day PO	0–13 and 28–41
Vincristine	1.5 mg/m ² IV push	14, 21, 42, 49
Peg-asparaginase	2500 IU/m ² IV (with prophylactic enoxaparin)	14,42
Rituximab (CD20 +ve)	375 mg/m ²	1,21
IT MTX	12 mg	0, 7, 14, 21
Interim Maintenance (40 days)		
MTX (capizzi)	100 mg/m ² IV Escalate each subsequent dose by 50 mg/m ² /dose from previous dose	0, 10, 20, 30 and 40
Vincristine	1.5 mg/m ² IV push	0, 10, 20, 30 and 40
Peg-asparaginase	2500 IU/m ² IV (with prophylactic enoxaparin)	1
Rituximab (CD20 +ve)	375 mg/m ²	0,20
IT MTX	12 mg	0, 30
Delayed intensification (57 days)		
Re-induction		
Daunorubicin	25 mg/m ² IV	0,7,14
Vincristine	1.5 mg/m ² IV push	0,7,14
Peg-asparaginase	2500 IU/m ² IV (with prophylactic enoxaparin)	3
Dexamethasone	10 mg/m ² /day PO on	0–6 and 14–20. No taper
Re-consolidation		
Cyclophosphamide	1000 mg/m ² IV	28
AraC	75 mg/m ² /d IV or SC	29–32, and 35–38
Thioguanine	60 mg/m ² /day PO	28–41
Vincristine	1.5 mg/m ² IV push	42, 49
Peg-asparaginase	2500 IU/m ² IV (with prophylactic enoxaparin)	42
Rituximab (CD20 +ve)	375 mg/m ²	0,14
IT MTX	12 mg	28,35
Maintenance (83 days per cycle) (2 years for females and 3 years for males)		
Vincristine	1.5 mg/m ² IV push	0,28,56
Prednisone	40 mg/m ² /day	0–4, 28–32, 56–60
6-MP	75 mg/m ² /day PO	0–83
MTX	20 mg/m ² /dose PO	7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77
IT Methotrexate	12 mg	0 & 28 (cycles 1–4) 0 only (cycles 5 and after)

Notes:

Patients with T-ALL will receive HDMTX during interim maintenance instead of escalating dose MTX (Capizzi).

Patients with Very High Risk disease will receive double interim maintenance phases and double delayed intensification phases (Very High risk T-ALL will receive HDMTX during first interim maintenance phase. During the second interim maintenance, patient will receive Capizzi MTX).

Patient with Very High Risk disease received cranial radiotherapy.

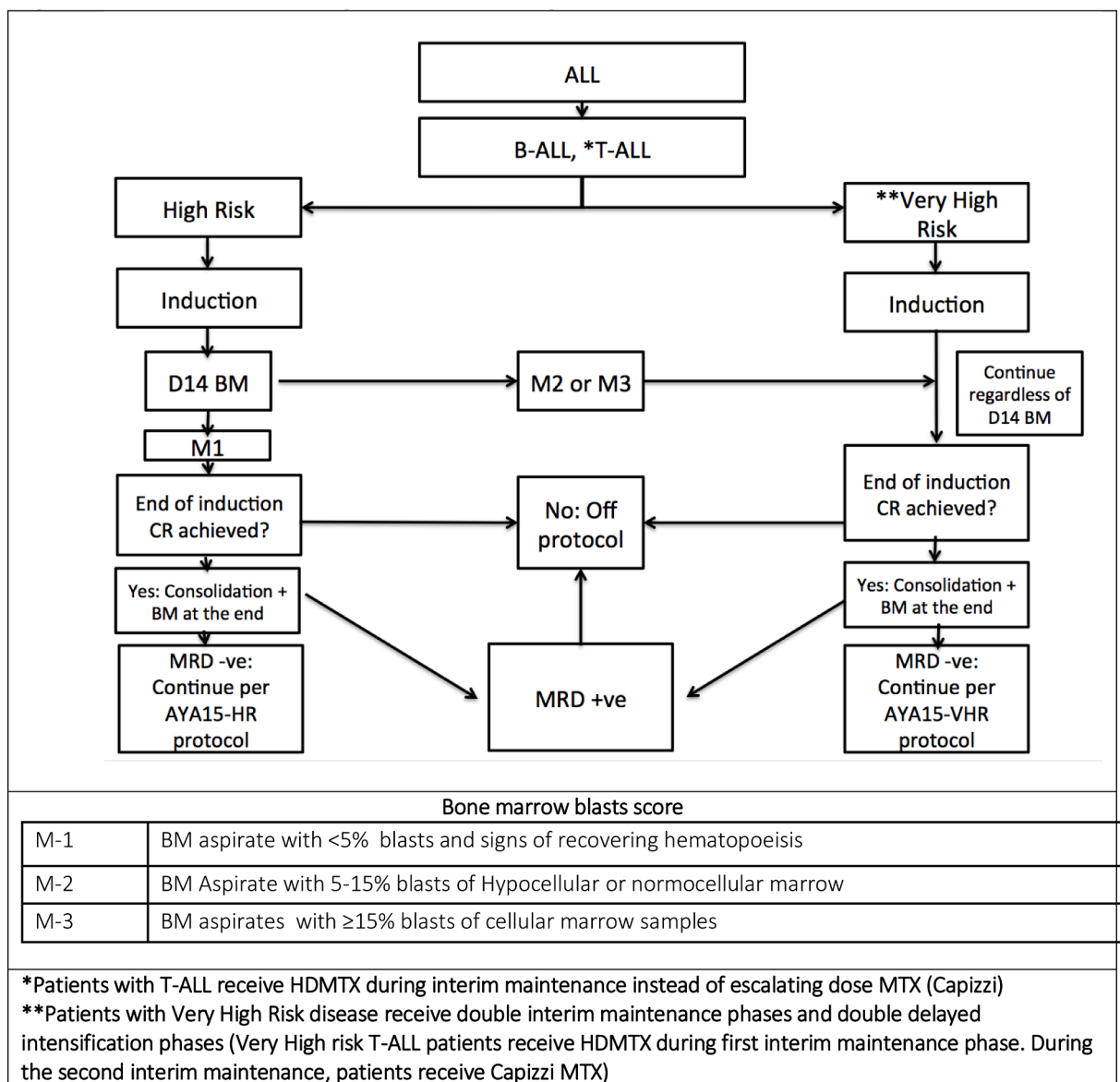


Fig. 1. For treatment assignment according to risk stratification.

thrombosis (schedule shown in Table 4 in supplementary material). Bone marrow biopsy was carried out on day 14 induction and the results were used for risk stratification as shown in Fig. 1. Remission status was based on day 28 of induction bone marrow biopsy results. The MRD result on day 28 bone marrow was used for prognostication purposes without affecting the schema of the protocol. All patients proceeded with consolidation phase thereafter unless they had induction failure (defined as bone marrow of >5% blasts at day 28 bone marrow evaluation), for which one of the standard salvage chemotherapy regimens was given followed by early allo-SCT. Evaluation of MRD was also done on bone marrow aspirate samples after finishing consolidation phase for assessment of sensitivity to chemotherapy. Patients with positive MRD after consolidation are considered allo-SCT candidates.

One of the distinguishing features of protocol is the use of methotrexate (MTX) in the interim maintenance phase. We used escalating dose intravenous MTX according to Capizzi strategy in patients with B-cell ALL (see Table 3), while we used high dose MTX (5 gm/m²) in patients with T-cell ALL.

Patients with high-risk disease, received a single delayed intensification (DI) and a single interim maintenance (IM) phases while patients with very high-risk disease received double DI and double IM phases.

Another feature of this protocol is the usage of intensified intrathecal therapy for all patients even without CNS 3 disease (definitions in Table 2) with an average of 24–29 intrathecal therapies during the entire phases of the protocol.

Prednisone was the steroid used during the induction phase while Dexamethasone was used during the other phases. For B-ALL patients with CD20 positivity (defined as expression of CD20 to be more than or equal to 20% in the blast population), we added Rituximab to the protocol according to the schedule seen in Table 3.

Cranial radiation (XRT) was only given to patients with CNS3 disease at a dose of 2400 cGy in 12 divided fractions.

All efforts were made to administer chemotherapy in a timely-fashion without interruptions unless needed. Reasons for interruption included febrile illnesses or grade III or IV liver toxicity. Myelosuppression alone was not a reason to delay chemotherapy except when moving from one phase to another then blood counts recovery was mandated.

4. Statistical analysis

Descriptive statistics were used to summarize demographics and

disease characteristics. Comparison between the study group was done using Wilcoxon rank-sum test for continuous and χ^2 tests for categorical outcomes. Kaplan-Meier curves were used to estimate survival using log-rank test to examine the different groups. DFS was estimated among patients achieving a CR after initiation of AYA-15 protocol from the time of CR to progression.

5. Results

5.1. Baseline characteristics

From July 2015 to January 2021, 79 patients with ALL/LBL were identified. Fifty-two (65.8%) patients had B-cell ALL and 27 (34.2%) patients had T-cell ALL. Baseline characteristics are summarized in Table 5. The median age of patients at diagnosis was 18 years (range, 14–51), and 50 (63.2%) patients were males. The most common risk stratification subtype was HRB; 43 patients (54%). Less common were HRT; 12 patients (15.2%), VHRB; 7 patients (8.9%), and VHRT; 17 patients (21%). For B-cell subtype, CD20 was positive in 26 patients (32.9%). CNS involvement at presentation was present in 4 patients (5.1%). Karyotype/FISH genetic analysis showed high-risk cytogenetics (hypodiploid, MLL gene rearrangement or complex cytogenetics) in 8 patients (10.1%).

Table 5
Patient characteristics.

Variable	Patient number 79 (%)
Age median (range)	18 (14–51) years old
Presenting WBC Median (range)	7.5 (0.44–1161) X10 ⁹ /L
Gender male no. (%)	50 (63.2)
Immunophenotyping classification	B-cell: 52 (65.8%) T-cell: 27 (34.2%)
Risk stratification	HRB: 43 (54%) VHRB: 7 (8.9%) HRT: 12(15.2%) VHRT: 17(21%)
CD 20 of B-cell ALL	CD20 +ve: 26 (50% of B-cell patients)
CD1a of T-cell ALL	CD1a +ve 12 (44.4% of T-cell patients) CD1a –ve 9 (33.3% of T-cell patients) Unknown: 6 (22.3%)
CNS involvement	CNS -ve: 75 (94.9%) CNS +ve: 4 (5.1%)
Cytogenetic by karyotyping	Standard: 65 (82%) Complex or hypodiploid or MLL: 4 (5.1%) None: 10 (12.7%)
Cytogenetic by FISH	Standard: 65 (82%) Complex or hypodiploid or MLL: 8 (10.1%) None: 6 (7.6%)
Bone marrow day 14(induction)	Negative: 65 (75.9%) Positive: 8 (10%) NA: 11 (13.9%)
Bone marrow day 28 (induction)	Negative: 73 (92.4%) Positive: 5 (6.3%) NA: 1 (1.3%)
PET in day 28 (for extramedullary)	Negative: 8 (66.7%) Positive: 4 (33.3%)
CR in day 28	Yes: 70 (88.6%) No: 8 (10.1%)
Day 28 MRD	Negative: 58 (73.4%) Positive: 15 (19%)
BM post consolidation MRD	Negative: 60 (75.9%) Positive: 7 (8.9%) NA: 12 (15%)
Relapse	Yes: 11 (13.9%) No: 62 (78.5%) NRM: 6 (7.6%)
Patient went for Allo SCT	Yes: 11 (13.9%) No: 68 (86.1%)
Death	Yes: 12 (15.2%) No: 67 (84.8%)

5.2. Outcomes

Complete remission (CR) rate after induction was achieved in 70 patients (88.6%). Day 28 post induction MRD negativity was confirmed in 58 patients (73.4%). Post consolidation MRD negativity increased to 75.9% (60 patients). Eleven patients (13.9%) underwent allo-SCT. The relapse rate (RR) was 13.9%. Non-relapse mortality (NRM) was 7.6% while all-cause mortality was 15.2%.

With a median follow-up of 5 years, the 5-year OS, DFS and EFS were 75.8%, 69.2% and 57.5%, respectively (Fig. 2).

Subgroup-analysis showed better DFS and OS in B-cell type as compared to T-cell type although the difference was not statistically significant. The 5-years OS of B-ALL and T-ALL was 80.1% and 69.6% respectively, (P -value = 0.1). 5-years DFS of B-ALL and T-ALL was 72.7% and 62.2% respectively, (P -value = 0.3). (Table 8 (in supplementary material) and Fig. 3).

The OS and DFS per risk groups were not statistically different, however, were dismal for the VHRT-ALL group. 5-year OS for HRB, VHRB, HRT and VHRT was 75.1%, 100%, 88.9% and 64.9%, respectively, (P -value = 0.2). 5-year DFS for HRB, VHRB, HRT and VHRT was 66.6%, 100%, 88.9% and 54.9%, respectively, (P -value = 0.2) (Table 9 and Figure 4 in supplementary material)

5.3. Adverse events

Adverse events are summarized in Tables 6.

During induction, febrile illness happened in 25 patients (31.6%). The rate of febrile illnesses was slightly higher during consolidation phase which was observed in 29 patients (36.7%). Hyperglycemia was much higher during induction because of prolonged steroid use (34 patients (43%)). During consolidation, hyperglycemia was reported in 6 patients (7.6%).

Thrombosis in different sites was seen in 14 patients (7.7%) during induction and in 3 patients (3.8%) during consolidation. Bleeding was reported in 9 patients (11.4%) during induction and 1 patient (1.3%) during consolidation. Allergic reaction from Peg-Asp-was reported in 24 patients (30.4%) during induction and in 24 patients (30.4%) during consolidation. Acute pancreatitis was observed in 10 patients (12.6%) during induction and in 2 patients (2.5%) during consolidation. All cases resolved without complications.

During induction, transaminitis (grade 1–4) was seen in 69 patients (87.3%). Grade 1 was the most common (44.3%). Almost similar results were seen during consolidation with transaminitis (grade 1–4) reported in 72 patients (91.1%) and similarly, grade 1 was the most common (44.3%). Grade 1 – 4 hyperbilirubinemia was seen in 52 patients (65.8%) during induction and in 46 patients (58.2%) during consolidation. No grade 5 hepatotoxicity was seen

6. Discussion

Treating adult ALL patients continues to be challenging with inferior outcomes when compared to pediatric patients [9]. Adult-oriented chemotherapy protocols which relies mainly on excessive use of upfront allogeneic stem cell transplant, showed consistently low DFS and OS results with average OS of 40–50% [9]. Multiple retrospective trials compared adult-based protocols with pediatric-inspired protocols in treating AYA patients with ALL and showed outcomes superiority of pediatric protocols in such population [10–11]. Improvement in outcome is mainly related to use of pediatric-inspired protocol in AYA patients rather than the differences between AYA and adult patients regarding high-risk features [12–14].

Definition of AYA continues to be variable between studies with most protocols using ages between 15 and 39 [15]. In our protocol we used ages between 14 and 55. There are published data on tolerance and good outcome of pediatric-inspired protocols in ages up to 55 averaging 5y-OS of 65–70% [16–17]. The main concern in older patients comes

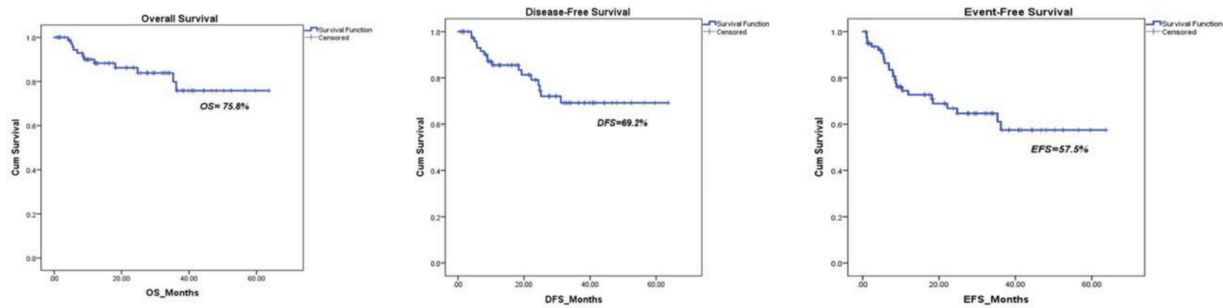


Fig. 2. OS, DFS and EFS of the whole patients.

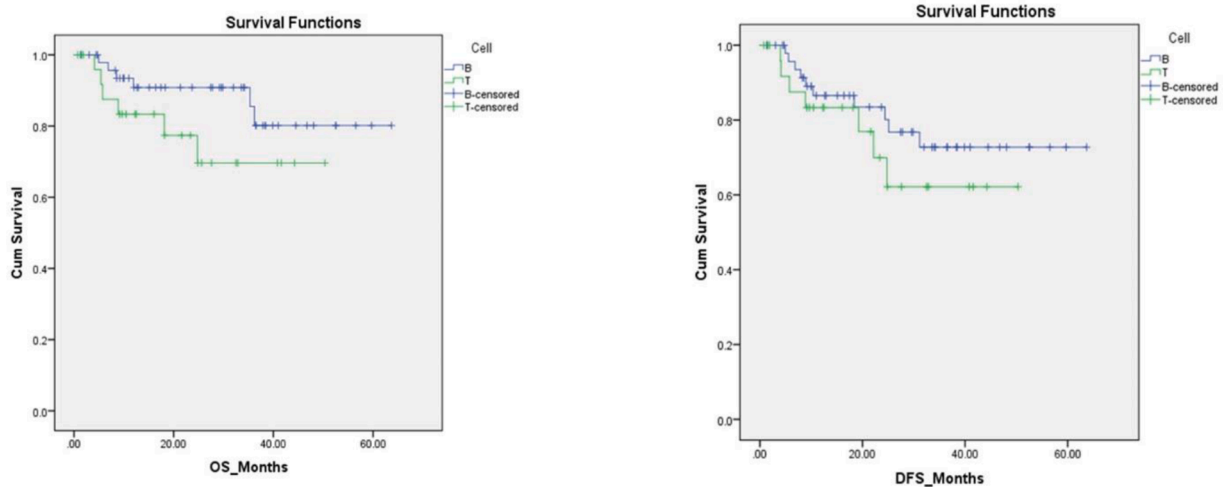


Fig. 3. OS and DFS according to cell type.

Table 6

Common adverse events in induction and consolidation phase including hepatotoxicity according to CTCAE grading.

Adverse Event N(%)	Induction phase		Consolidation phase	
Fever	25 (31.6%)		33 (41.8%)	
Infection	24 (30.4%)		29 (36.7)	
Thrombosis	14 (17.7%)		3 (3.8%)	
Bleeding	9 (11.4%)		1 (1.3%)	
Hyperglycemia	34 (43%)		6 (7.6%)	
Allergic reaction	24 (30.4%)		24 (30.4%)	
Pancreatitis	10 (12.6%)		2 (2.5%)	
Adverse event	Grade1	Grade2	Grade3	Grade4
Induction				
Transaminases N(%)	35 (44.3%)	12 (15%)	18(22.8%)	4(5.1%)
Bilirubin N(%)	20 (25%)	21 (26%)	9(11.4%)	2(2.5%)
Consolidation				
Transaminases N(%)	35(44.3%)	20 (25.3%)	17 (21.5%)	0
Bilirubin N(%)	21(26.6%)	20(25.3%)	4 (5.1%)	1 (1.3%)

from the peg-asparaginase toxicities which can be severe in such patients. In our protocol, we adjusted peg-asparaginase dose in patients who are older than 40 to be capped at 1 vial dose (3750 IU). Sub-analysis of patients above 40 could not be done at this time because of small sample size ($n = 4$).

The main differences between pediatric and adult chemotherapy regimens include: intensification of chemotherapy using non-myelosuppressive agents like vincristine, asparaginase and corticosteroids, intensive use of CNS prophylaxis, and relying mainly on MRD as an indicator to chemo-sensitivity as a reason to continue on chemotherapy vs moving to Allo-SCT. Pediatric protocols are characterized also by their focus on attaining maximal dose intensification and ensuring timely delivery of chemotherapy [18–20].

This real-world data from a single-center experience in treating AYA-ALL patients with an in-house designed pediatric-inspired protocol demonstrates high survival rate and excellent tolerability for patients ages 18–55 years, with results comparable to similar published controlled trials (DFS 75%, EFS 59%, OS 75). Subgroup-analysis showed worse outcomes of T-cell ALL as compared to B-cell ALL, although the difference was not statistically significant. Analysis according to risk stratification showed that VHRB-ALL carries the worst outcomes. VHRB-ALL had the best outcomes but this is likely related to the small sample number of patients in this subgroup ($n = 7$). Also difference between all subgroups was not statistically different. We could not correlate any other factors (ex. CR, MRD, FISH results, CNS status, etc.) with outcomes because of the small comparative numbers.

The backbone of AYA-15 protocol is the CCG 1900 protocol schema which is characterized by the use of peg-asparaginase starting as early as day 3 of induction, and the utilization of escalating dose IV methotrexate according to the Capizzi strategy in patients with B-cell ALL, while using high dose methotrexate (5 gm/m²) in patient with T-cell ALL. Different studies showed toxicity is higher in children with B-cell ALL treated with HDMTX which indicates that HDMTX is more suitable for T-cell ALL patients [21–22].

Additionally, the CNS prophylaxis is intensified with frequent IT chemotherapy given between 24 and 29 times during the whole protocol.

We used prednisone as the steroid of choice during the induction phase while we used Dexamethasone during the other phases of the protocol. This approach was used based on the results of a meta-analysis showing that dexamethasone is associated with higher mortality during induction with more neuropsychiatric events and more myopathy, while using dexamethasone in general was associated with less risk of relapse

including CNS relapse and less death from any cause [23].

Patients who had blasts more than 5% on day 14 of induction were considered late responders and their risk stratification was changed to very high risk for which they received double interim maintenance phase and double delayed intensification phase.

Currently, we only use cranial XRT (2400 cGy in 12 divided fractions) for patients with CNS3 disease and we administer it before initiation of the final maintenance phase.

We consider MRD as the most powerful prognostic tool. We use 8 multi-color flow cytometry to measure MRD with sensitivity of 10^{-4} (threshold of 0.01%). We checked MRD on 2 separate occasions for every patient, once after induction which we use primarily for prognostication and once after consolidation to decide about allo-SCT (Patients with +ve MRD after consolidation are considered chemo-resistant and we offer them allo-SCT). Patients with CD19 +ve B-ALL and +ve MRD after consolidation were treated with 1–2 cycles of Blinatumomab to eradicate MRD prior to allo-SCT. This approach is reported to improve outcomes after allo-SCT [24]. For patients with KMT2A (myeloid/lymphoid or mixed lineage leukemia (MLL)) gene, we applied the same criteria regarding proceed with allo-SCT in CR1 using MRD status as the sole reason in such cases.

One advantage of our protocol is the administration of chemotherapy in the outpatient setting in most of the phases of the treatment except for the induction phase and interim maintenance phase (for T-cell ALL in which HDMTX is administered). This approach is cost effective and has a better psychological impact on the patients (in a separate unpublished analysis, we showed around 1 million dollars savings per year as compared to previous cohort treated on adult protocols in our institution).

The toxicities reported on this protocol are manageable and the treatment in general is well tolerated. The toxicity profile is similar to what is published in other international protocols. The 2 most common toxicities as expected are myelosuppression and hepatotoxicity. Toxicity from asparaginase was a concern but our data showed acceptable rates and manageable side effects with no treatment-related mortality from the asparaginase. Regarding the incidence of asparaginase-related allergic reaction during induction (30.4%) which is much higher than what is published in the literature, this is likely related to inability to differentiate between infusion reaction and true allergic reaction.

We faced a number of issues while using this protocol, including limitation of our MRD sensitivity, lack of asparaginase level detection in our lab, suffering from global shortage of Erwinia asparaginase for patients who were allergic to peg-asp and the unavailability of pharmacogenomics in our center. Despite these issues, our outcomes are excellent with high CR rate, improvement in OS and DFS along a low treatment-related morbidity and mortality.

7. Conclusion

In this report, we report our real-world outcomes of AYA-15 protocol which is a pediatric-inspired protocol for patients 14–55 years of age. Our results showed significant improvement in 5-years OS, EFS and DFS compared to our previous adult-oriented protocol with excellent tolerance and low treatment-related morbidity and mortality. The main reasons for this improvement are related to the treatment protocol itself and the use of MRD as a prognostic factor. The advantages of this protocol included dose intensification, drug delivery in a timely fashion, use of Peg-asparaginase and early use of intensive CNS prophylaxis.

We will continue enrolling patients on this protocol with some strategies to improve our outcomes by increasing MRD sensitivity, incorporating pharmacogenomics, testing for asparaginase levels and possibly by increasing the use of immunotherapies

Declaration of Competing Interest

We declare that this manuscript has not been published elsewhere

and it has not been submitted simultaneously for publication elsewhere. All authors don't have financial disclosure or conflict of interest

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.lrr.2021.100270](https://doi.org/10.1016/j.lrr.2021.100270).

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