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ORIGINAL ARTICLE

Evaluating the efficacy and toxicity of dose adjusted pegylated L-asparaginase in combination with therapeutic drug monitoring

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Abstract

The incorporation of pediatric-inspired regimens in the adolescent-young-adult (AYA) and adult populations have resulted improved survival outcomes (Stock et al. Blood 133(14):1548–1559 2019; Dunsmore et al. J Clin Oncol 38(28):3282–3293 2020; DeAngelo et al. Leukemia 29(3):526-534 2015). Nonetheless incorporation of such regimens is limited by increased toxicity to asparaginase. Dosing strategies that reduce the weight-based dose of pegylated-L-asparaginase (PEG-asparaginase) utilizing activity monitoring have been shown to result in better tolerability of these regimens. The purpose of this study was to analyze the efficacy and safety of treating adults with Philadelphia chromosome negative (Ph−) ALL with pediatric-inspired regimens that incorporate PEG-asparaginase dose adjustments and asparaginase activity level monitoring. Patients aged 18–65 years initiated on pediatric-inspired regimens utilizing dose-reduced PEG-asparaginase with therapeutic drug monitoring-guided adjustments were included. The screening of 122 patients treated between 2015 and 2021 resulted in the inclusion of 54 patients. The median age of the cohort was 35 years (16–65 years), and median body mass index (BMI) was 30 kg/m^2 (18.3–53.4 kg/m^2). The 36-month survival estimate was 62.1% (95% CI 48.1–77.7%), and the median overall survival (OS) was 62.2 months (95% CI 35.1–89.3 months). In the AYA cohort, the 36-month survival was 71.2% (95% CI 55.8–91%) and the median overall survival was not reached. Survival was not significantly affected by immunophenotype or BMI. Discontinuation due to toxicity or hypersensitivity reactions was low at 11% and 9% respectively. The encouraging survival outcomes and favorable tolerability of this older population in the real-world setting support the use of individualized PEG-asparaginase dosing with PharmD-guided therapeutic drug monitoring.

Keywords Acute lymphoblastic leukemia · Pediatric-inspired therapy · Asparaginase · Pegasparaginase · Therapeutic drug monitoring

Introduction

Acute lymphoblastic leukemia (ALL) represents 0.3% of new cancer diagnoses in the USA, and over half of these diagnoses are in patients less than 20 years old [1]. However, patients over the age of 20 years account for over 85% of deaths from this disease. The Cancer and Leukemia Group B (CALGB) 10403 trial assessed outcomes associated with using a pediatric ALL regimen with an asparaginase backbone for patients up to the age of 40 years and found a significant increase in survival compared to a historical cohort utilizing adult regimens [2]. Pediatric ALL regimens such as CALGB 10403 place an emphasis on the use of asparaginase and multiple blocks of multi-agent chemotherapy over a period of years. As such, tolerability of this type of regimen in the adult population can be problematic. Although asparaginase has been shown to improve survival outcomes for adolescents and young adults (AYAs), as patients increase in age, the risk of more severe asparaginase-related toxicities increases as well. In adults treated with PEG-asparaginase in the C10403 trial, grade 3 or higher hyperbilirubinemia occurred in 26% of patients, pancreatitis in 6%, and thrombosis in 11% [2, 3].

In the CALGB 10403 trial, patients received 2500 international units/m^2 (IU/m^2) with no dose cap [2]. A

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subsequently published exploratory retrospective review compared reduced-dose PEG-asparaginase (less than 1000 IU/m^2) to standard dose PEG-asparaginase (greater than or equal to 1000 IU/m^2). Investigators found no difference in relapse-free survival between the two dosing cohorts and a significantly decreased rate of grade 3 or 4 toxicities in the reduced dose group [4]. In a follow-up study, this group evaluated a reduced dose PEG-asparaginase regimen and found it to be feasible in older adults up to the age of 76 or patients with metabolic and/or hepatic comorbidities [5]. Asparaginase activity levels were measured in both studies revealing that approximately 15% of patients had subtherapeutic levels with the reduced-dose PEG-asparaginase. However, the doses were not increased to ensure at least 14 days of asparagine depletion. Both studies indicate that patients with significant risk factors for toxicity can receive PEG-asparaginase at a lower dose without unacceptable intolerance. They also highlight the need for therapeutic drug monitoring (TDM)-guided dose adjustment to ensure adequate asparagine depletion in patients, as a significant proportion of patients in their studies did not achieve complete asparagine depletion with empiric dose reductions. Further research is needed to determine whether TDM-guided dosing can result in a higher proportion of patients achieving complete asparagine depletion than empiric dose reductions and whether this method can reduce toxicity in adults.

At Michigan Medicine, patients treated by the adult leukemia program are initiated on individualized dosing of PEG-asparaginase at 1000 to 2500 IU/m^2 with a dose cap of 3750 IU with therapeutic drug monitoring (TDM). An algorithm was developed for monitoring activity levels and was previously published in a review of its utility in stewarding the use of erwinia asparaginase in cases when patients have hypersensitivity reactions [6]. The purpose of this study was to analyze the efficacy and safety of treating adults with Philadelphia chromosome negative (Ph−) ALL with pediatric-inspired regimens that incorporate PEG-asparaginase dose adjustments and asparaginase activity level monitoring.

Patients and methods

This was a retrospective, single-center cohort study evaluating the use of PEG-asparaginase with dose adjustments and TDM for pediatric-inspired regimens in patients 18–65 years old. The electronic medical record was used to identify patients with newly diagnosed ALL initiated on a PEG-asparaginase containing induction regimens by the adult program at Michigan Medicine, a public and academic tertiary care center, between January 2015 and June 2021. Patients were included if they received at least 1 dose of PEG-asparaginase, and subsequent asparaginase activity levels were obtained. Patients were excluded if they had Philadelphia chromosome-positive ALL, as these patients receive non-PEG-asparaginase-based regimens at our institution, if they received care under the pediatric program (as this program does not follow the dosing and TDM monitoring the adult program has established), or if they did not have follow-up at Michigan Medicine after induction as this would limit the ability to evaluate both efficacy and safety outcomes of interest.

Initial PEG-asparaginase dosing in induction was determined according to patient-specific characteristics based on previously published data to suggest improved tolerability with individualized dosing (Table 1) [4, 7]. Patients initiated PEG-asparaginase at a maximum dosage of 3750 IU or a decreased dose of 500–1000 IU/m^2 dependent on the clinical criteria. TDM of asparaginase activity levels was subsequently utilized to inform further dosing per the previously published algorithm and further described in Supplementary Table 1 [6]. All asparaginase activity levels were obtained by performing phlebotomy from patients and preparing samples on drawn on-site which were then shipped to Granger Genetics for processing and analysis [8]. All patients receiving PEG-asparaginase received laboratory monitoring at least weekly for tolerability including complete blood cell count with differential, complete metabolic panel including liver function tests (aspartate transaminase, alanine transaminase, total bilirubin and direct bilirubin if indicated), amylase, lipase, triglycerides, prothrombin time and partial thromboplastin time, and fibrinogen. Workup

Table 1 PEG-asparaginase initial dosing strategy

BSA	PEG-asparaginase dose
Less than or equal to 2 m^2	2500 IU/m^2 (capped at 3750 IU)
Greater than 2 m^2	1000 IU/m^2 (capped at 3750 IU)
Additional criteria for adjustments by provider/ PharmD	500–1000 IU/m^2 (capped at 3750 IU) - Age > 55 yrs - Additional comorbidities (e.g., baseline liver dysfunction, new significant VTE, poor performance status)

PEG pegylated, *BSA* body surface area, *IU* international units, *yrs* years, *VTE* venous thromboembolism

for venous thromboembolism was initiated when clinically indicated.

This was an IRB exempt study due to the retrospective nature of evaluation (HUM00205082). Data were collected using REDCAP™. Demographic information included patient's age, measured weight and height, body surface area (BSA), and body mass index (BMI) at start of induction therapy. Body surface area (BMI) was calculated based on weight and height, and body surface area (BSA) was calculated using the Mosteller method. Disease characteristics collected included immunophenotype, CD-20 status, cytogenetics, and molecular data. Treatment-related data included number of PEG-asparaginase doses, asparaginase activity levels, receipt of rituximab, receipt of blinatumomab for minimal residual disease positivity (if B-cell ALL), and receipt of allogeneic hematopoietic cell transplant (alloHCT). The primary outcome was the estimated 36-month overall survival (OS) [2]. Secondary outcomes included overall survival (OS), rates of complete response (CR), complete response with incomplete count recovery (CRi), and measurable residual disease (MRD) negativity at end of induction and at the 8–12-week mark. Toxicity outcomes of interest included those that are well-established adverse of PEG-asparaginase therapy and those that could be evaluated based on objective criteria that was well-documented in the electronic medical record for all patients. These included hepatotoxicity, defined as bilirubin ≥ 3 times the upper limit of normal (ULN) within 30 days of receiving PEG-asparaginase, grade II or higher pancreatitis (defined as amylase and lipase > 2 times the ULN and imaging and symptoms consistent with pancreatitis within 30 days of receiving PEG-asparaginase), grade III or higher venous thromboembolism (VTE), clinically relevant major bleeding defined as a decrease in hemoglobin > 5 g/dL, intracranial hemorrhage, or fatal bleeding event, as well as discontinuation of PEG-asparaginase from the regimen due to toxicity or hypersensitivity [7, 9–12]. A detailed description of how hypersensitivity reactions were evaluated and what severity warranted a discontinuation is beyond the scope of this review and can be found in previously published work [6]. Grading for adverse events was based on CTCAE Version 5 [10].

Statistics

Baseline demographic, disease, and treatment characteristics were evaluated using descriptive statistics. Continuous data were described using medians and ranges or means and interquartile ranges based on normality, while dichotomous data were expressed as counts and percentages. Dichotomous data were analyzed using chi-squared tests or Fisher's exact tests as indicated. Continuous data were analyzed using either the Student's unpaired *t* test or Wilcoxon rank sum test based on normality. Kaplan-Meier analysis with log-rank test was performed to estimate event-free survival (EFS) and overall survival (OS). Statistical analyses were performed using SPSS statistical software (version 26.0; IBM Corporation, Armonk, NY), and the 36-month estimate was performed using R software and corroborated on SPSS [13]. Asparaginase activity levels obtained throughout therapy were collected and sectioned into three clinically relevant time points to generate median data for reporting. Peak levels were defined as day 0–3, a second time point was defined as day 7–10, and the trough was defined as day 13–16 with day 0 being the day PEG-asparaginase was administered.

Results

Baseline disease characteristics and treatment regimens

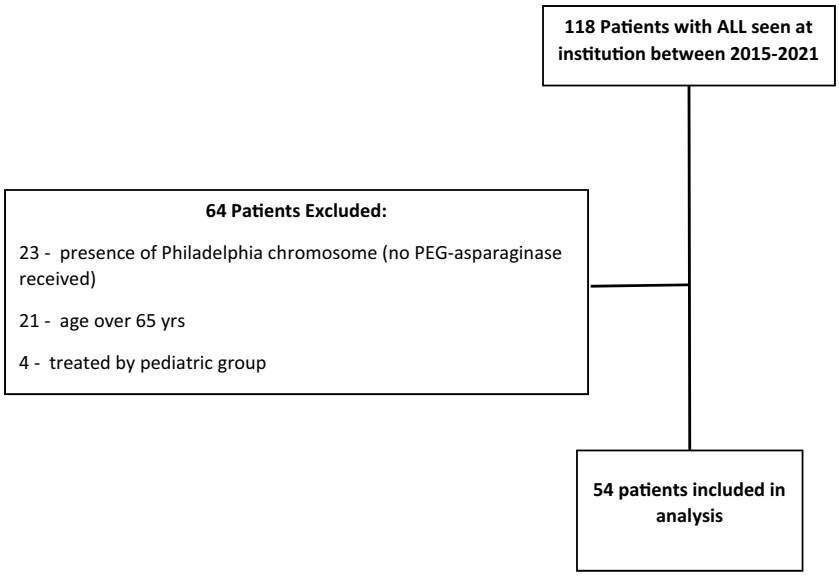
One hundred twenty-one patients were screened for eligibility, of which 188 were identified at newly diagnosed adults with ALL, and 54 patients were included for analysis. Twenty-three were excluded due to the presence of the Philadelphia chromosome, 22 were excluded due to age greater than 65 years, 9 were excluded due to not receiving a PEG-asparaginase containing regimen due to contraindications for asparaginase therapy, 7 were excluded due to not having PEG-asparaginase levels drawn after administration (all treated in 2015 when the practice of obtaining levels had just been formalized), and finally, 4 were excluded due to being treated by the pediatric group under a clinical trial protocol (Fig. 1).

Baseline demographic and disease characteristics are described in Table 2. The median age of the cohort was 34 years (range 21–65 years). Twenty-eight patients (52%) had a BMI greater than 30 kg/m^2. As for baseline disease characteristics, most patients had B-cell ALL (72%). Fifty percent of patients were CD20(+) of whom all received rituximab as part of their induction regimen. All patients received pediatric-inspired protocols, including Michigan medicine–modified 10403 (MM-10403) (79.6%), traditional CALGB10403 (14.8%), CALGB 8811 (9.2%), and the USC regimen (5.6%) [14, 15].

Efficacy

After a median follow up of 25 months, 22 deaths occurred. For the entire cohort, the estimated 36-month overall survival was 62.1% (95% CI 48.1–77.7%) (Table 3; Fig. 2A). The median event–free survival was 33.6 months (95% CI 10–57.2 months), and the median overall survival was 62.2 months (95% CI 35.1–89.3 months). The survival of various

Fig. 1 CONSORT diagram



subgroups was evaluated. Median OS was not reached for AYAs, and the 36-month estimated OS was 71.2% (95% CI 55.8–91%) for this subgroup. For those 40 years and older (adults), the 36-month estimated OS was 45.2% (95% CI 21–69%), and a median OS of 32.4 months (95% CI 2.9–61.8 months) (Fig. 2B). Patients' overall survival was comparable regardless of BMI or immunophenotype (Fig. 2C and D).

After induction, 65% of patients achieved a CR ($n = 36$), and 83% achieved either a CR or CRi ($n = 45$) (Table 2). Fifty-five percent (26/47) of patients tested for MRD in the marrow were MRD negative after induction. MRD negativity was confirmed at the 8th–12th week mark for 21/28 patients (75%) including 6 patients who converted from MRD(+) to MRD(−) with receipt of additional traditional chemotherapy via early-intensification per their respective protocols. Five patients (9.3%) received blinatumomab for MRD positivity; 2 patients received this agent after induction, and 3 patients received it due to persistent MRD after early-intensification with pediatric-inspired therapy. Twenty-four patients (44%) proceeded to alloHCT due to high-risk disease characteristics at baseline and/or suboptimal response to therapy.

Safety

Overall, 20% of the cohort had to discontinue PEG-asparaginase due to toxicities or hypersensitivity (Table 4). Six of these patients (11%) discontinued due to toxicities, and five (9%) discontinued due to hypersensitivity reactions. Two patients died within the first 30 days of diagnosis, one due to MRSA bacteremia, and one due to *Escherichia coli* bacteremia. Hepatotoxicity and VTE were the two most frequent toxicities, affecting 13 (23.6%) and 7 (12.7%) patients, respectively. Of the 7 VTE events, 3 (43%) were associated with presence of a peripherally inserted central catheter. Three patients had pancreatitis, and 1 patient died of a fatal bleed.

Asparaginase activity levels and dose adjustments

Asparaginase activity levels were characterized by PEG-asparaginase dose given and grouped into two dosing cohorts: doses $\leq$ 1000 IU/m^2 and doses $>$ 1000 IU/m^2 which is as described in Table 5 and visualized in Fig. 3. The median peak asparaginase activity level was 0.45 IU/mL and 0.241 IU/mL for the $>$ 1000 IU/m^2 doses and $\leq$ 1000 IU/m^2 doses respectively. The median activity levels were appropriate for depletion ($>$ 0.1 IU/mL) over a 14-day period across both dosing cohorts.

Asparaginase activity levels during the second week (days 12–14) were undetectable for 5 patients (Supplementary table 2). All but one of these patients had a hypersensitivity reaction upon administration of a subsequent PEG-asparaginase dose, which would suggest silent inactivation due to PEG-asparaginase antibodies was the reason for the low second week levels. Two patients had undetectable peak levels which correlated with anaphylactic reactions to the dose.

There were 25 total dose adjustments in the cohort. Seven adjustments were due to toxicities, 8 adjustments due to subtherapeutic day 14 asparaginase activity levels ($<$ 0.1), and 10 adjustments were for other reasons including weight rounding adjustments and provider preference to increase dosing closer to the cap (3750 IU) in patients who were initially dose-adjusted per the institutional protocol and tolerated the initial dose without toxicities. No subtherapeutic asparaginase activity levels occurred after dose modifications.

Table 2 Baseline demographic and disease characteristics

	Entire cohort ($N = 54$)
Age, yrs[a]	34 (21–65)
Age < 40[b]	32 (58.2)
Gender, female[2]	18 (33.3)
BMI, kg/m^2[a]	30.3 (18.3–53.4)
BMI > 30[2]	28 (52)
Charlson Comorbidity Index Score ≥ 4	16 (29.6)
Immunophenotype[bc]	
B-cell	39 (72)
T-cell	13 (24)
ETP− ALL	2 (4)
CD20(+)[b]	27 (50)
Disease risk[b]	
Favorable	1 (2)
Standard	27(50)
Adverse	26 (48)
Cytogenetic findings[b]	
Normal karyotype	16 (30)
Hypodiploidy	5 (9)
Hyperdiploidy	2 (4)
MLL rearranged	3 (6)
Complex karyotype	2 (4)
TCF3-PBX1	1 (2)
Other	21 (39)
No karyotype available	4 (7)
Molecular findings[b]	
Ph-like	6 (11.1)
IKZF1 mutated	2 (4)
IKZF1 plus	8 (15)
Other	6 (11)
None identified	30 (56)
Not tested	2 (4)
Chemotherapy regimen[b]	
MM-10403[d]	38 (70.4)
CALGB 10403	8 (14.8)
CALGB 8811	5 (9.2)
Douer/USC	3 (5.6)
Receipt of AlloHCT	24 (44.4)
Number of PEG-asparaginase doses[a]	3 (1-8)
Starting dose (IU/m^2)[a]	1623 (434–2180)
Dose adjusted to 1000 IU/m^2[b]	21 (38.9)
Dose capped at 3750 IU[b]	28 (52%)

Yrs years, *BMI* body mass index, *ETP* early T-cell precursor, *MLL* mixed lineage leukemia, *IKZF1* ikaros, *alloHCT* allogeneic hematopoietic cell transplant, *PEG* pegylated, *IU* international units

[a]Median (range)

[b]*n* (%)

[c]Risk classification per National Comprehensive Cancer Network Acute Lymphoblastic Leukemia guidelines. Version 2.2021

[d]5-drug induction including cyclophosphamide, daunorubicin, vincristine, prednisone, and PEG-asparaginase followed by traditional CALGB10403 beyond induction

Table 3 Efficacy

	Entire cohort ($N = 54$)
Response after induction[b]	
CR	36 (65.5)
CRi	9 (16.7)
MRD negativity[b]	
After induction	26/47 (55)
8–12 weeks after induction	21/28 (75)
Follow up (months)[a]	23.7 (0.7–76.0)
Median event–free survival (months)[c]	33.6 (10–57.2)
Median overall survival	Months (95%CI)
Entire cohort ($n = 54$)	62.2 mo (35.1–89.3)
AYA population ($n = 32$)	Not reached
Adults ≥ 40 years ($n = 22$)	32.4 mo (2.9–61.8)
36-month survival estimates[d]	% surviving (95% CI)
Entire cohort ($n = 54$)	62.1 (48.1–77.7)
AYA population ($n = 32$)	71.2 (55.8–91)
Adults ≥ 40 years ($n = 22$)	45.2 (21–69)

CR complete response, *CRi* CR with incomplete count recovery, *MRD* measurable-residual disease, *AYA* adolescent young adult

[a]Median (range)

[b]*n* (%)

[c]Median (95% CI)

[d]36-month survival estimates were utilized given that they would be best representative of a survival estimate given the median follow-up period for all patients was 25 months

Discussion

The used pediatric-inspired regimens that emphasize the use of PEG-asparaginase represent the best standard of care for the adolescent young adult population (AYA), but prior publications have focused on younger patients in this age range [16, 17]. Historically, increased toxicity in the AYA and adult populations has led to decreased tolerability of these regimens; for example, in C10403, the completion rate of therapy was < 40% [3]. This study demonstrates that older AYAs, adults up to the age of 65 years, and obese individuals can tolerate pediatric-inspired PEG-asparaginase-based regimens without compromising efficacy when TDM-guided dose adjustments are implemented. The efficacy outcomes achieved with this dosing strategy compare favorably to those reported in C10403. Despite an older population included, the 3-year predicted OS for our AYA population was 71.2%, while in CALGB 10403, it was 73% [2]. Additionally, our discontinuation rate of 20% is lower than previously reported for a pediatric-inspired regimen.

Asparaginase-related toxicities may be mitigated by capping the PEG-asparaginase dose to 3750 units, administering lower doses, and adjusting the dose based on the asparaginase activity level guidance. In our study, patients

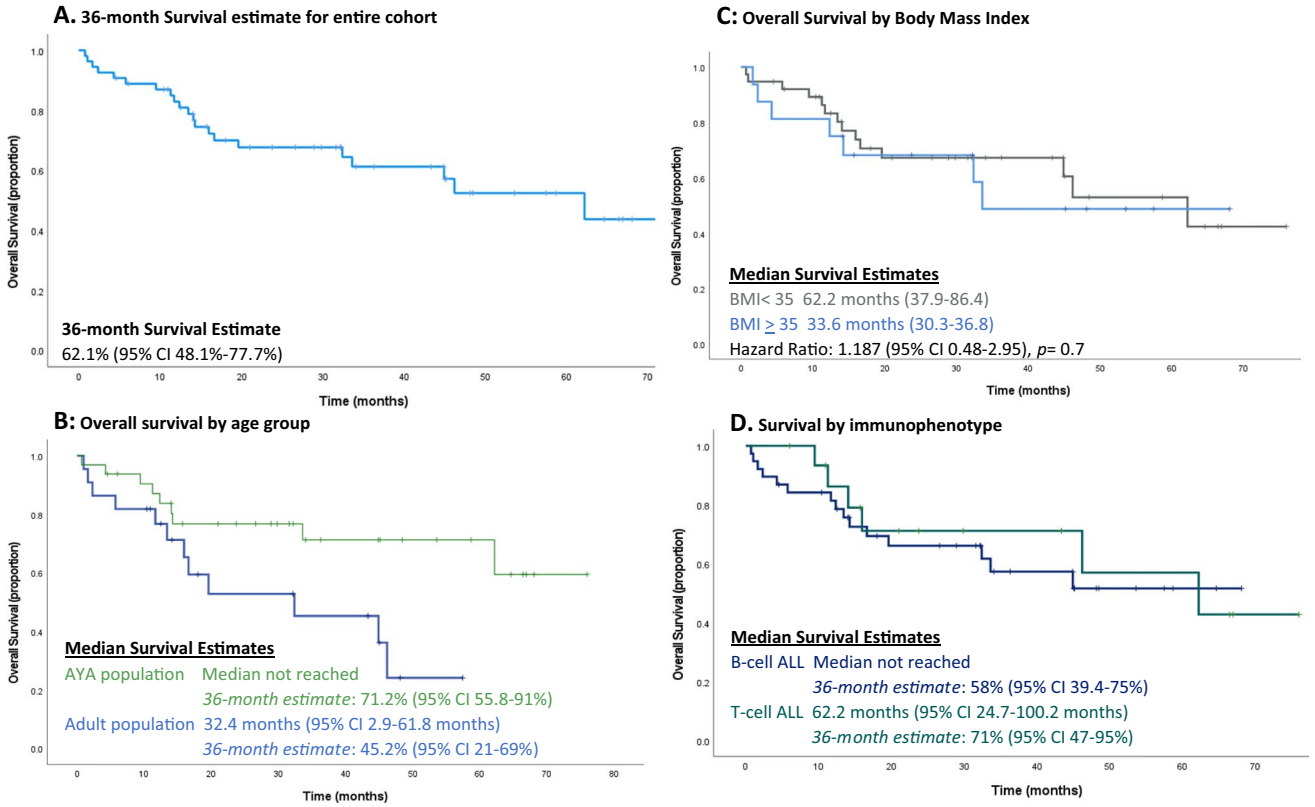


Fig. 2 Survival analyses. At a median follow-up of 25 months for all patients, 32 (59%) of patients remained alive and 22 (41%) deaths had occurred. The median OS for the entire cohort was 62 months (95% CI 35.1–89.3) with a 36-month survival estimate of 62.1% (**A**). The adolescent young adult (AYA) population has a 36-month survival estimate of 71.2%, and the median survival could not be estimated as more than 50% of the patients remained alive throughout the study period. For adults, the median OS was reached at 32.4 months (95% CI 2.9–61.8 months) and the 36-month estimated survival was 45.2% (**B**). Patient survival was similar regardless of body mass index (p = 0.7) (**C**). Patients with B-cell immunophenotype had a 36-month survival estimate of 58%, and the median could not be estimated as more than 50% of the patients remained alive throughout the study period. Patients with T-cell immunophenotype, the median OS was reached at 62.2 months (95% CI 24.7–100.2 months) and a 36-month survival estimate of 71% (**D**).

received a median of three doses of PEG-asparaginase, 52% received a dose that was capped at 3750 units, and 38% of patients received a dose of less than 1000 units/m^2. This approach permitted the treatment of older adults (up to 65-years) and obese patients (up to BMI of 53.4 kg/m^2) without excessive toxicity. Grade 3+ hepatotoxicity occurred in 24% of the patients, grade 2+ pancreatitis in 5.4%, and grade 3+ VTE in 12.7% which is comparable to the rates of these toxicities in CALGB 10403, which were 26%, 5%, and 11%, respectively [3]. It is critical to note that our population and CALGB 10403 have significant differences. First, our median age was 34, and 42% of patients were over the age of 40, whereas the median age in CALGB 10403 was 24, and no patients over 39 were included. Furthermore, the incidence of obesity was significantly greater in our study; 51% of patients had a BMI ≥ 30, compared to only 32% in CALGB 10403 [2]. Because age and obesity are strong predictors of asparaginase-associated toxicity, it is reassuring that, despite our cohort's higher age and obesity rate, toxicities were comparable to those observed in the CALGB 10403 study [7].

Some data suggest that in addition to poorer tolerability of ALL therapies, obese patients also have shorter EFS and OS [3, 18]. We were unable to recapitulate this observation. The fundamental causes for the correlation between obesity and poor outcomes in some studies have yet to be fully elucidated. Initially, it was believed that alterations in the pharmacokinetics and pharmacodynamics of chemotherapy could contribute to the inferior results of obese ALL patients compared to non-obese patients [19]. Additionally, comorbidities and intolerance may also play a role. Other data suggests that adipose tissue itself may have a protective effect on ALL cells [20]. In our cohort, there was no difference in OS between patients with a BMI less than 30 and those with a BMI more than 30. It is possible that reduced PEG-asparaginase doses led to decreased toxicity, and as a result, fewer treatment delays and discontinuations.

Table 4 Safety outcomes

	Entire cohort ($N = 54$)
Toxicity[a]	
30-day mortality	2 (3.6)
Hepatotoxicity[b]	13 (23.6)
Grade 2 or higher pancreatitis	3 (5.5)
Grade 3 or higher VTE	7 (12.7)
Bleeding[c]	1 (1.8)
PEG-asparaginase discontinuation[a]	
Due to toxicity	6 (10.9)
Due to hypersensitivity	5 (9)
Dose adjusted[a]	
Toxicity	7/25 (28)
Subtherapeutic	8/25 (32)
Other	10/25 (40)

VTE venous thromboembolism, *PEG* pegylated

[a]*n* (%)

[b]Bilirubin ≥ 3 times the upper limit of normal

[c]Clinically relevant major bleeding defined as a decrease in hemoglobin > 5 g/dL, intracranial hemorrhage, or fatal bleeding event

Table 5 Median asparaginase activity levels (IU/mL) at ≤ 1000 IU/m^2 vs > 1000 IU/m^2

Dose	Peak (day 0-3)	Day 7–10	Day 13–16
≤ 1000 IU/m^2	0.241	0.177	0.1
> 1000 IU/m^2	0.45	0.394	0.286

IU international units

Analyzing the cohort that received asparaginase doses of ≤ 1000 IU/m^2 compared to those that received > 1000 IU/m^2, patients in the ≤ 1000 IU/m^2 cohort had an expectedly lower median peak asparaginase activity level. There are some data to suggest that higher asparaginase activity level peaks are associated with higher rates of glutamine depletion, which may contribute to hepatotoxicity from PEG-asparaginase [21, 22]. However, despite the use of dose adjustments in patients at high risk for PEG-asparaginase toxicity, the median of patients maintained an asparaginase activity level of > 0.1 IU/mL by day 14. While our institutional strategy for dose adjustments for patients at high risk for toxicities was successful in limiting toxicities and maintaining adequate asparagine depletion for optimal long-term outcomes, it is important to note that TDM-directed dose-adjustments were also a core aspect of the treatment program for this cohort of patients. Approximately 15% of patients initially had trough activity levels below 0.1 IU/mL and were administered an increased dose of PEG-asparaginase to successfully achieve this goal during their next scheduled cycle. Expert consensus recommend a trough asparaginase activity level at day 14 that is > 0.1; however, some studies suggest patients may even maintain asparagine depletion at levels as low as 0.05 IU/mL. When this lower threshold is applied, our dosing strategy would enable 100% of patients to maintain asparagine depletion for a full 2-week period with their initial dose [5, 23–25].

Other studies have corroborated the safety of reduced doses of PEG-asparaginase in adults. A recent descriptive analysis was published describing the use of PEG-asparaginase in patients older than 40 years older in which 23% of patients discontinued PEG-asparaginase due to toxicity [26]. Similar to the strategy employed at our institution, 17/20 patients in this study above the age of 60 received a reduced dose of PEG-asparaginase (< 1000 IU/m^2). Seven patients out of 60 discontinued due to hypersensitivity (12%), and 5 patients discontinued due to hepatotoxicity (8%) [26]. Comparatively, in our study, 5 patients discontinued due to hypersensitivity (9%) and 4 patients discontinued due to hepatotoxicity (7%). However, despite similar toxicity rates in our cohort of patients, all patients

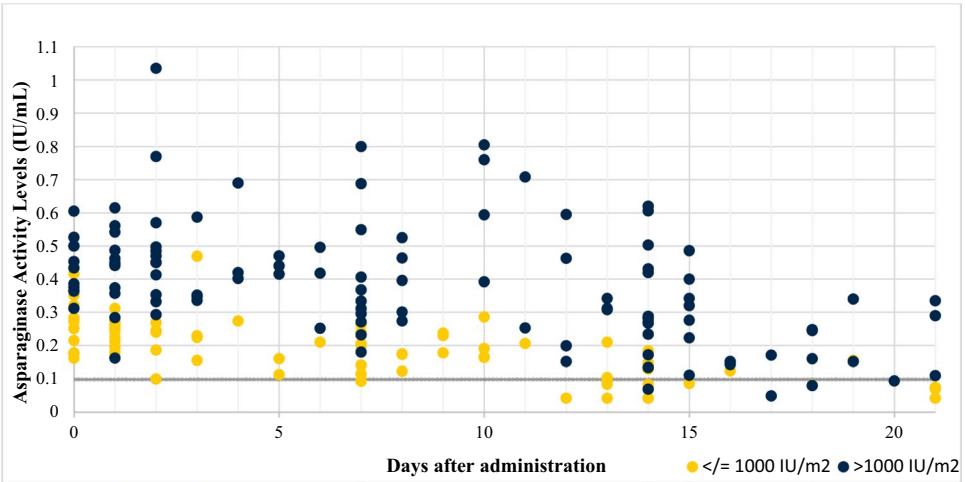


Fig. 3 Asparaginase activity levels

in our study received intensive pediatric-inspired therapy, and our data demonstrates the long-term efficacy of such a strategy and confirms adequate asparaginase activity levels can be achieved when utilizing dose-adjusted PEG-asparaginase. Another study to employ reduced doses of PEG-asparaginase for their older adult cohort was the ECOG-ACRIN 1910 study. Although not the focus of this study, their strategy proved to be successful in treating adults with a PEG-asparaginase-based chemotherapy backbone [27].

Some limitations in this study are the retrospective nature of the study which inherently limits the ability to collect all variables that would be of interest and relate to both efficacy and toxicity, as well as the relatively small study cohort. Specifically with regard to overall survival, there are well-established disease characteristics such as adverse cytogenetic and molecular findings that due to sample size limitations were unable to be explored as risk factors for worse outcomes with this treatment approach. While initial dose selection was driven by our protocol, incorporating risk factors for toxicity, including age, obesity, and performance status, the choice of subsequent PEG-asparaginase dosing is dynamic and difficult to protocolize, as it depends on TDM, patient tolerability, and response to therapy. Thus, a multidisciplinary approach to PEG-asparaginase dose modification involving clinical pharmacists and hematologists is paramount. Furthermore, expert consensus guidelines (and our study) support achieving a minimum of 14 days of depletion for each PEG-asparaginase dose. However, the optimal duration of asparagine depletion has not fully been elucidated, and the approval of even longer-acting asparaginase products (i.e., calaspargase pegol) will require further study of the appropriate dose reductions to avoid severe toxicity in adults and older AYA patients with newer agents. Finally, the MRD negativity rates in our study can be difficult to interpret due to the retrospective nature of the study. To avoid patient discomfort from additional bone marrow biopsies, if patients were MRD negative after induction, providers often will forego the bone marrow MRD measurement at consolidation, thus limiting the MRD sample size at this time point.

Going forward, further research focusing on whether this dosing strategy and use of TDM prevents unplanned hospitalizations and delays in treatment would be beneficial support for this treatment approach. Additionally, a multicenter trial comparing the toxicity, efficacy, and quality of life of pediatric-inspired regimens in adults that utilize PEG-asparaginase and TDM compared to traditional adult regimens that minimize PEG-asparaginase, such as Hyper-CVAD, is desperately needed. Lastly, with the release of the ECOG-ACRIN 1910 trial results, the incorporation of blinatumomab consolidation is anticipated to further enhance the safety and efficacy of our PEG-asparaginase dose-adjusted BFM-backbone [27].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00277-023-05373-5.

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Author contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Taylor Coe-Eisenberg, PharmD, and Lydia Benitez, PharmD, with collaboration from Vince Marshall, statistician with University of Michigan College of Pharmacy. The first draft of the manuscript was written by Taylor Coe-Eisenberg, Lydia Benitez, PharmD, and Anthony Perissinotti, PharmD. All authors contributed to all versions of the manuscript. All authors read and approved the final manuscript.

Data availability Not needed.

Declarations

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest Taylor Coe-Eisenberg, PharmD, declares no conflict of interest. Anthony J. Perissinotti, PharmD, has consulted or Servier, Amgen, and Pfizer pharmaceuticals. Bernard L. Marini, PharmD, has consulted for Servier. Kristen M. Pettit, MD, provides advising for the following companies: Kura Oncology, PharmaEssentia, CTI Biopharma. Dale L. Bixby, MD, Ph.D., declares no conflict of interest. Patrick W. Burke, MD, declares no conflict of interest. Lydia L. Benitez, PharmD, declares no conflict of interest.

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