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RESEARCH

Pegaspargase administration and tolerability in patients aged 55 years or older with acute lymphoblastic leukemia treated with the LAL1913 program. A subanalysis of the Campus ALL group

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Abstract

The adoption of pediatric-inspired regimens for the treatment of Ph-negative acute lymphoblastic leukemia (ALL) in adults has improved prognosis. However, the feasibility of these intensive regimens in older patients is limited, due to the increased incidence of therapy-related side effects, including those related to asparaginase. In this sub-analysis carried out by the Campus ALL network, 90 ALL patients aged 55 or more (median age 59 years) homogeneously treated in real-life according to the GIMEMA LAL1913 program, were analyzed to evaluate the feasibility and tolerability of pegaspargase (PEG-ASP) treatment. Among the 90 patients analyzed, 86 (96%) received PEG-ASP at least in one of the first two courses (C1-C2) of chemotherapy and were evaluated for toxicity and outcome. In detail, 51 patients received PEG-ASP in both courses and 35 in either C1 or C2. The most common adverse event was hepatic toxicity (HT), with 38% of patients experiencing any grade of HT at C1 (HT grade≥3, 19%) and 23% at C2 (HT grade≥3, 9%). Additionally, HT at C1 was the primary reason for withholding PEG-ASP at C2. Coagulopathy was the second most frequent toxicity (any grade of toxicity in 26% of patients at C1 and in 20% at C2). No deaths directly related to PEG-ASP therapy were reported. The CR rate after C1 and C3 was 94% and 93%, respectively. MRD negativity rate was 40% and 68%, respectively. The OS and DFS probability at 3 years was 54% and 47%, respectively. PEG-ASP administration in older ALL patients is feasible, but HT is a concern, being the major cause of PEG-ASP interruption. Therefore, a dose adjustment, according to age and concomitant comorbidities, is advisable to balance PEG-ASP efficacy with its toxicity.

Keywords Acute lymphoblastic leukemia · Older patients · Pegaspargase · Real-life study

Introduction

Asparaginase is a key drug in treating pediatric patients with Ph-negative acute lymphoblastic leukemia (ALL), but has long been considered too toxic for adults. However, several studies [1–7] have shown how incorporating multiple doses of asparaginase (native or pegylated) in pediatric-inspired therapy regimens for adults has led to excellent long-term outcomes, suggesting that prolonged asparagine depletion plays a key role in achieving better response rates in adults just as in the pediatric ALL population [8]. However, as the age of patients increases, an increasing incidence of asparaginase-related adverse events is also observed. These events are correlated with a higher burden of specific comorbidities,

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such as obesity and hepatic disease, in this adult population. Therefore, the application of pediatric-inspired therapy regimens in older adults is harder than in young adults, even with a reduced asparaginase dosage [9, 10].

Unlike L-Asparaginase which is a short-acting form, polyethylene glycolated-Asparaginase (PEG-ASP), thanks to the pegylation mechanism which protects the native compound from inactivation, yields a prolonged half-life, ensuring a therapeutic activity of asparaginase depletion lasting up to 2–3 weeks, whilst being associated with a reduced toxicity profile [11, 12]. The recently published GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) LAL1913 study [1] added PEG-ASP at the dose of 2000 IU/m^2 to courses (C) 1, 2, 5, and 6 of an 8-course pediatric-inspired protocol, applying a dose reduction (1000 IU/m^2) to patients aged more than 55 years, demonstrating the feasibility of this therapeutic program.

Following the publication of this trial, we recently published data gathered within the Italian Campus ALL consortium [13] and reported the high feasibility of the LAL1913 program in real-life settings, with similar outcomes to those published in the trial [1].

Considering that there is very limited information on the feasibility and tolerability of pediatric-inspired regimen in older adults with ALL and, more specifically, on the tolerability of PEG-ASP in a real-life setting, we conducted a sub-analysis of our recently published study [13] to evaluate the feasibility and the toxicity profile of PEG-ASP treatment in ALL patients included and aged 55 or more.

Methods

Characteristics and aims of the study

This is a sub-analysis of the recently published Campus ALL multicenter study, which included 421 patients [13]. This study aimed to analyze and describe the behavior of 90 patients aged over 55 (out of the 97 originally included in the study) for whom detailed information on PEG-ASP administration and toxicity was available. All patients had newly diagnosed Philadelphia-negative (Ph-) ALL or lymphoblastic lymphoma (LL, with < 20% bone marrow blasts) and were treated according to the GIMEMA LAL1913 protocol outside the previous clinical trial [1], between September 2016 and December 2022, with specific drug dose reductions according to age. Follow-up was last updated in June 2023. Baseline characteristics of the 90 patients are reported in Supplementary Table 1.

The main objectives of this analysis were to describe the feasibility and tolerability, in a real-life setting, of PEG-ASP treatment in a population of older adults treated homogeneously according to the GIMEMA LAL1913 program, with particular attention to PEG-ASP dose modulation and PEG-ASP related toxicities in the first two courses of chemotherapy (respectively named C1 and C2). In these patients, aged 55 or more, the PEG-ASP dose was generally reduced to 1000 IU/m^2, as suggested by the GIMEMA LAL1913 protocol. The detail of the drugs included in each cycle (C1-C8) of the LAL1913 protocol is reported in the Supplementary Table 2.

Treatment-related toxicity was assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Toxicities were defined as follows:

- Hepatic toxicity (HT): an increase in bilirubin and/or liver function tests.
- Coagulopathy: abnormalities in the levels of fibrinogen, antithrombin III, prothrombin time or activated partial thromboplastin time, without thrombotic or hemorrhagic events.
- Pancreatic toxicity: clinical pancreatitis with signs and symptoms, excluding chemical pancreatitis (i.e., high amylase/lipase levels without clinical or imaging manifestations of pancreatitis)
- Metabolic toxicity: the presence of hypertriglyceridemia or hyperglycemia.
- Hypersensitivity: any clinical manifestation of an allergic reaction (e.g. erythema, urticaria, angioedema, anaphylactic shock). Silent inactivation was not routinely tested.
- Thrombotic events: venous thrombosis with or without thromboembolism, arterial thrombosis or embolism.
- Hemorrhagic events: venous or arterial bleeding.

The grade of relationship of an adverse event to PEG-ASP was graded as follows:

- Unrelated causality: no evidence of any causal relationship.
- Unlikely causal relationship: little evidence to suggest a causal relationship or another reasonable explanation for the event.
- Possible causal relationship: some evidence to suggest a causal relationship, but other factors may have contributed to the event.
- Probable causal relationship: evidence to suggest a causal relationship; the influence of other factors is unlikely.

We also described patient outcomes in terms of complete remission (CR) rate, measurable residual disease (MRD) negativity rate, overall survival (OS), disease-free survival (DFS), and allogeneic stem cell transplantation (HSCT)

rate in the subgroup of patients with very high risk (VHR) ALL, and/or MRD positivity. Time point 2 (TP2) for MRD assessment after the third course of chemotherapy (C3) was chosen as the endpoint for MRD response assessment in this analysis.

ALL diagnostic evaluation, risk stratification, and MRD analysis were performed as previously described [1, 13]. Antibiotic, antifungal and antiviral prophylaxis, and PEG-ASP toxicity management were administered according to each center's policy.

This sub-analysis was approved by the Ethics Committee of Friuli Venezia Giulia, Italy (ethical approval number CEUR-2022-Os-03) and conducted in accordance with the 2008 revision of the Declaration of Helsinki. Patients provided written informed consent before participation.

Statistical analysis

Descriptive statistics was used to assess the general characteristics of the study population, the PEG-ASP dosage administered, and the PEG-ASP related toxicity rate.

Logistic regression was used to identify variables associated with the development of PEG-ASP related toxicity and the achievement of MRD negativity.

OS was calculated from the date of diagnosis to the date of last follow-up or to the date of death from any cause. DFS was calculated from the date of first CR to the date of last follow-up, relapse or death from any cause. OS and DFS were estimated using the Kaplan–Meier method, and differences between subgroups were compared using the log-rank test. Multivariate analysis for DFS was carried out by Cox regression.

In all cases, statistical significance was considered when the P value was less than 0.05.

Results

Patients' characteristics

Among the 90 patients included in this sub-analysis, 86 (96%) received PEG-ASP at least in one of the first two courses (C1-C2) and were therefore analyzed for toxicity and outcome. In detail, 51 patients received PEG-ASP in both courses and 35 in either C1 or C2. The baseline characteristics of the 86 patients treated with PEG-ASP are reported in Table 1. The median age was 59 years (range 55–71), 12% ($n=10$) of the patients were older than 65 years, and 44% ($n=38$) were male. Fifty-nine (69%) patients had B-ALL, while 27 (31%) had T-ALL. According to risk stratification at diagnosis, 42% ($n=36$) were standard risk (SR), 12% ($n=10$) were high risk (HR), and 46% ($n=40$) VHR.

Table 1 Baseline characteristics of the 86 patients older than 55 years who received PEG-ASP in at least one of the first two courses

Characteristic	$N=86$ patients
Age, median (range)	59 (55–71)
• Age > 65, *n* (%)	10 (12)
Sex	
• Male, *n* (%)	38 (44)
• Female, *n* (%)	48 (56)
ECOG, *n* (%), available in 85 patients	
• 0–1	75 (88)
• 2 or more	10 (12)
Comorbidities, *n* (%)	
• None	32 (37)
• Obesity	4 (5)
• Hepatic steatosis and other liver diseases	9 (10)
• Cardiac	5 (6)
• Metabolic (diabetes or dyslipidemia)	9 (10)
Lineage	
• B, *n* (%)	59 (69)
• T, *n* (%)	27 (31)
Baseline risk	
• SR, *n* (%)	36 (42)
• HR, *n* (%)	10 (12)
• VHR, *n* (%)	40 (46)

PEG-ASP pegaspargase, *ECOG* Eastern Cooperative Group, *SR* standard risk, *HR* high risk, *VHR* very high risk

The ECOG score was 0–1 in 88% ($n=75$) of patients. All cases were deemed suitable for an intensive chemotherapy regimen. Hepatic steatosis or other liver disease were found in 10% ($n=9$) of patients, while 5% ($n=4$) were obese.

Pegaspargase administration

As reported in the flowchart (Fig. 1), at C1 81/90 (90%) patients received PEG-ASP; 54/81 (67%) patients at the dose of 1000 IU/m^2 (as per protocol according to patient's age), 11/81 (13%) at a higher dose (median 1500 IU/m^2, range 1200–2000 IU/m^2), while 16/81 (20%) received PEG-ASP at a lower dose (median 500 IU/m^2, range 500–800 IU/m^2), based on medical decision. PEG-ASP was not given to 9 patients at C1 due to advanced age or comorbidities in 3 cases (33%) and complications or infections during C1 in 6 cases (67%). Considering only the 13 patients aged over 65 years at C1, 4/13 received PEG-ASP at a reduced dose and 4/13 did not receive it.

C2 was administered to 77/90 (86%) patients (6 died in induction, 5 showed disease progression and 2 changed therapy) and 56/77 (73%) received PEG-ASP; 39/56 (70%) patients received the scheduled dose of 1000 IU/m^2, 4/56 (7%) received PEG-ASP at a higher dose (median 2000 IU/m^2, range 1500–2000 IU/m^2) based on a medical decision, and 13/56 (23%) received PEG-ASP at a reduced dose (median 500 IU/m2, range 500–800 IU/m^2). PEG-ASP was

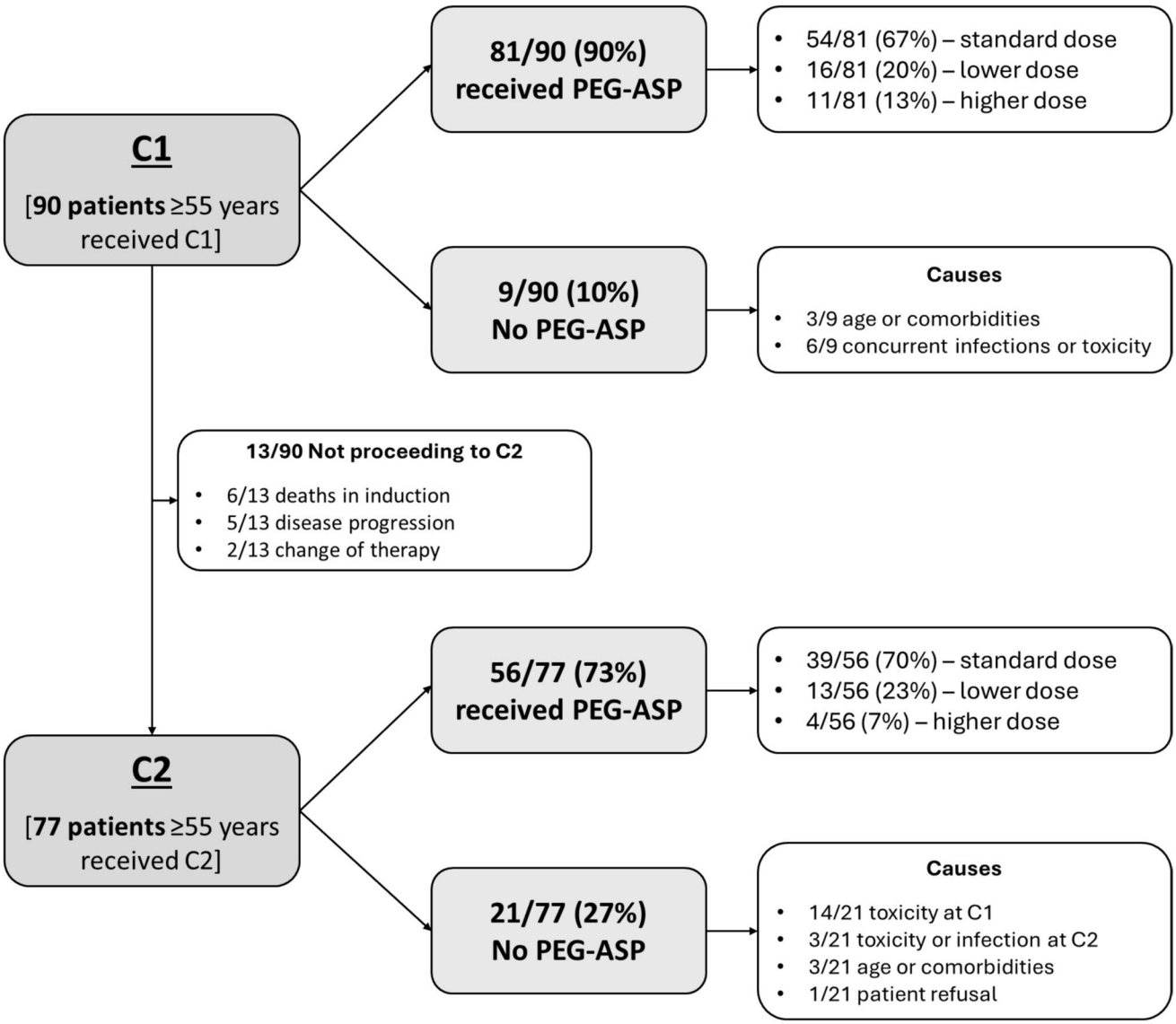

Fig. 1 PEG-ASP administration in course 1 (C1) and/or in course 2 (C2) (5 patients received PEG-ASP only in C2)

not given to 21 patients at C2 due to toxicity in the previous course in 67% (14/21) of cases (hepatic toxicity in 8/14 cases, possibly or probably related to PEG-ASP), age or comorbidities in 14% of cases (3/21), and infections or other occurred toxicities at C2 (not related to PEG-ASP) in 14% of cases (3/21), Fig. 1-C2. Considering only the 11 patients aged over 65 years at C2, 3/11 received PEG-ASP at a reduced dose, 3/11 did not receive it and 5/11 received it at the scheduled dose.

Pegaspargase-related toxicity

This section describes the observed toxicities that are possibly or probably related to PEG-ASP, in the treated population (Tables 2 and 3). Hepatic toxicity (HT) was the most common adverse event, with 38% ($n=31$) of patients experiencing any grade of HT at C1 and 23% ($n=13$) at C2. Coagulopathy was the second most frequent toxicity (any grade of toxicity in 26% of patients at C1 and 20% at C2); however, this did not translate into a high number of thrombotic events, that occurred in 5% of patients at C1 and in 7% of patients at C2. Hemorrhagic events were rare (2% only at C1). Tables 2 and 3 detail the toxicities observed at C1 and C2, respectively.

As reported in Table 2, among the 81 patients who received PEG-ASP at C1, HT (of any grade) occurred in 41% of patients who received a dose of 1000 UI/m^2, in 45% of those who received 1500 UI/m^2, and in 25% of

Table 2 Summary of PEG-ASP-related toxicities at course 1 (C1) according to the PEG-ASP dose

Toxicity at C1	All cases	PEG-ASP standard dose (median 1000 IU/m^2)	PEG-ASP higher dose (median 1500 IU/m^2)	PEG-ASP low dose (median 500 IU/m^2)
Number of patients (%)	81 (100)	54 (67)	11 (13)	16 (20)
Median age (range)	59 (55–71)	60 (55–71)	57 (55–62)	60 (55–67)
Hepatic toxicity, *n* (%)				
• All grades	31 (38)	22 (41)	5 (45)	4 (25)
• Grade≥3	19 (23)	15 (28)	2 (18)	2 (13)
Coagulopathy, *n* (%)				
• All grades	21 (26)	15 (28)	3 (27)	3 (19)
• Grade≥3	5 (6)	2 (4)	1 (9)	2 (13)
Thrombotic events, *n* (%)				
• All grades	4 (5)	2 (4)	1 (9)	1 (6)
• Grade≥3	2 (2)	0 (0)	1 (9)	1 (6)
Hemorrhagic events, *n* (%)				
• All grades	2 (2)	2 (4)	0 (0)	0 (0)
• Grade≥3	1 (1)	1 (2)	0 (0)	0 (0)
Pancreatic toxicity, *n* (%)				
• All grades	1 (1)	1 (2)	0 (0)	0 (0)
• Grade≥3	1 (1)	1 (2)	0 (0)	0 (0)
Metabolic toxicity, *n* (%)				
• All grades	9 (11)	5 (9)	(0)	4 (7)
• Grade≥3	4 (5)	2 (4)	(0)	2 (4)
Hypersensitivity reactions, *n* (%)				
• All grades	1 (1)	0 (0)	0 (0)	1 (6)
• Grade≥3	1 (1)	0 (0)	0 (0)	1 (6)

Table 3 Summary of PEG-ASP-related toxicities at course 2 (C2) according to the PEG-ASP dose

Toxicity at C2	All cases	PEG-ASP standard dose (median 1000 IU/m^2)	PEG-ASP higher dose (median 1500 IU/m^2)	PEG-ASP low dose (median 500 IU/m^2)
Number of patients (%)	56 (100)	39 (70)	4 (7)	13 (23)
Median age (range)	60 (55–70)	61 (55–70)	56 (56–59)	59 (55–70)
Hepatic toxicity, *n* (%)				
• All grades	13 (23)	11 (28)	0 (0)	2 (15)
• Grade≥3	5 (9)	5 (13)	0 (0)	0 (0)
Coagulopathy, *n* (%)				
• All grades	11 (20)	9 (23)	1 (25)	1 (8)
• Grade≥3	2 (4)	2 (5)	(0)	(0)
Thrombotic events, *n* (%)				
• All grades	4 (7)	3 (8)	1 (25)	0 (0)
• Grade≥3	3 (5)	2 (5)	1 (25)	0 (0)
Hemorrhagic events, *n* (%)				
• All grades	0	0 (0)	0 (0)	0 (0)
• Grade≥3	0	0 (0)	0 (0)	0 (0)
Pancreatic toxicity, *n* (%)				
• All grades	0	0 (0)	0 (0)	0 (0)
• Grade≥3	0	0 (0)	0 (0)	0 (0)
Metabolic toxicity, *n* (%)				
• All grades	1 (2)	1 (3)	0 (0)	0 (0)
• Grade≥3	1 (2)	1 (3)	0 (0)	0 (0)
Hypersensitivity reactions, *n* (%)				
• All grades	1 (2)	1 (3)	0 (0)	0 (0)
• Grade≥3	1 (2)	1 (3)	0 (0)	0 (0)

those who received 500 UI/m^2; however, no significant differences in grade≥3 HT across the different dose groups were found. The percentage of patients who experienced any grade of coagulopathy across the three different PEG-ASP dose groups (1000 IU/m^2, 1500 IU/m^2, and 500 IU/m^2) were, respectively, 28%, 27%, and 19%. No significant differences were observed in grade 3 or higher coagulopathy between these subgroups.

At C1, other PEG-ASP-related toxicities were rare, with thrombotic events of any grade occurring in 4–9% of patients, hemorrhagic events of any grade in 0–4% of patients, metabolic toxicity of any grade in 7–9% of patients, and pancreatic toxicity of any grade in 0–2% of cases (not significant difference between the 3 dose subgroups). We recorded only one hypersensitivity event at C1 (Table 2).

As reported in Table 3, At C2, most toxic events occurred in patients (n=39) who received PEG-ASP at the standard dose of 1000 IU/m^2. In this subgroup, 28% of patients experienced HT of any grade (13% grade 3 or higher), 23% developed a coagulopathy of any grade (5% grade 3 or higher), and 8% experienced thrombotic events of any grade. Other toxicities were rare, and only one hypersensitivity event was recorded at C2 (Table 3). There were no significant differences between the subgroups.

Among patients that received PEG-ASP in both courses (n=51), we observed HT in 31% of cases at C1 (16% grade 3 or higher) and in 24% of cases at C2 (8% grade 3 or higher).

According to medical judgement and LAL1913 protocol recommendations, PEG-ASP was administered at a significantly reduced dose (<1000 IU/m^2 per course) in older patients (OR 0.902, 95% CI 0.814–0.998, P=0.0458) and in patients with baseline hepatic comorbidity (OR 0.0816, 95% CI 0.0156–0.428, P=0.003). Taking into account this dose modulation, in univariate and multivariate analysis, no significant correlation between the occurrence of HT at C1 and obesity, prior hepatic disease or patient age (OR for obesity: 0.578, 95% CI 0.0575–5.810, P=0.6410, OR for antecedent hepatic disease: 1.48, 95% CI 0.367–5.980, P=0.5810, and OR for age: 0.735, 95% CI 0.176–3.070, P=0.6730) was found.

Infectious morbidity was high at C1, with 21% (n=19) of patients experiencing at least one episode of bacteremia/sepsis and 11% (n=10) developing pneumonia. However, these events were not directly related to PEG-ASP administration.

Six of the 86 treated patients (7%) died during induction, 3 due to infectious complications, 1 to hemorrhagic complications, 1 due to neurologic complications (all unrelated to PEG-ASP), and 1 died of hepatic encephalopathy (occurring during severe infectious complication), with unlikely causal relationship to PEG-ASP. Among the 3 patients who died after C2, 1 died due to infectious complications, one for disease progression and one for vascular complications (all unrelated to PEG-ASP). Overall, no deaths directly related to PEG-ASP therapy were reported.

Patients' outcome

The CR rate after C1 (TP1) was 94% (73/77 evaluable patients) and the rate of MRD negativity at the same time point was 40% (29/73). Patients not evaluable for MRD were those with LL without bone marrow involvement and those in whom the bone marrow examination could not be performed. After C2, 65 patients proceeded to C3 (3 died, 8 showed a disease progression or recurrence, 1 switched therapy). The CR rate after C3 (TP2) was 93% (53/57 evaluable patients), and the MRD negativity rate at the same TP was 68% (36/53 evaluable patients).

Patients who received the planned dose of PEG-ASP or higher (1000 UI/m^2 or 1500 UI/m^2) had in univariate analysis a significantly higher MRD negativity rate at TP1 (42% vs 21% of the patients that received a reduced dose, OR 3.31, 95% CI 0.996–11.00, P=0.05), and at TP2 (78% vs 39% of the patients that received a reduced dose, OR 4.55, 95% CI 1.44–14.40, P=0.01). In a multivariate analysis for the obtainment of MRD negativity rate at TP2, including the variables age≥65 years, antecedent hepatic disease, obesity, the presence of two or more comorbidities, ECOG≥2 and PEG-ASP dose, only PEG-ASP dose retained statistical significance (OR 5.290, 95% CI 1.32–21.20, P=0.02).

Of the 65 patients who proceeded to C3 and beyond, 27 underwent first-line HSCT (30% of the whole group and 46% of those with indication for HSCT, i.e., those with VHR at diagnosis or MRD positivity at TP2). Regarding the patients who did not proceed to HSCT, PEG-ASP was administered to 26 out of 31 patients (84%) who reached C5 and 18 out of 25 patients (64%) who reached C6.

The OS and DFS probability at 3 years for patients who received at least 1 PEG-ASP dose (86 patients) were 54% and 47%, respectively (Fig. 2). In multivariate analysis for DFS including PEG-ASP dose, age≥65 years, ALL risk category, MRD negativity at TP2, antecedent hepatic disease, obesity, presence of two or more comorbidities and ECOG≥2, only MRD negativity at TP2 predicted an improved DFS (HR 0.181, 95% CI 0.057–0.568, P=0.003).

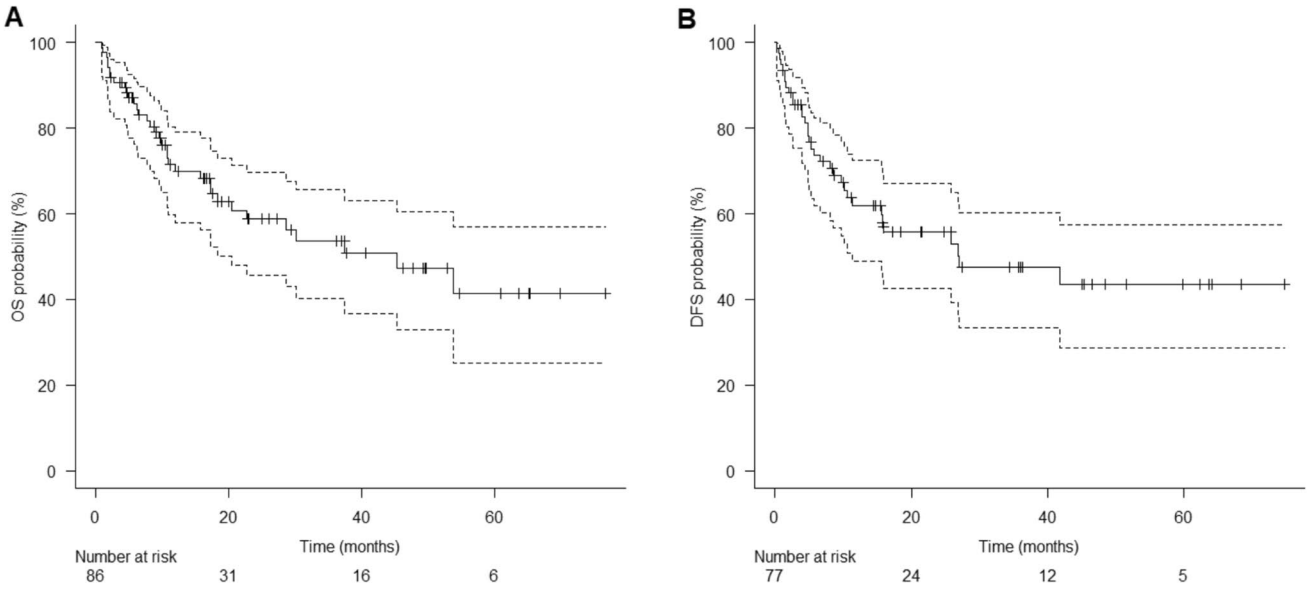

Fig. 2 Survival curves. A. OS of the treated population (median OS 45 months). B. DFS of the treated population (median DFS 27 months)

Discussion

Applying and adapting pediatric-inspired regimens in the treatment of older adults with Ph- ALL is challenging, and the efficacy of the treatment has to be balanced against its toxicity. Few clinical trials have enrolled older adults in pediatric-inspired therapy programs [1–5, 14]; in these trials, older age was found to carry a worse prognosis and a higher induction mortality, even if the results were better than in previous experiences [9]. Chemotherapy dose reductions and asparaginase reduction or omission have been implemented in various trials to reduce overall treatment toxicity [2, 5, 9]. In the GIMEMA LAL1913 clinical trial [1], that enrolled patients up to 65 years of age, specific chemotherapy and PEG-ASP dose reductions were established for patients older than 55 years, as detailed in Supplemental Table . However, in the published results there is no specific detailed analysis on asparaginase-toxicity in the older patient population. In addition, real-life studies investigating the use of asparaginase plus pediatric-inspired regimens in older adults are scarce, with a small sample size and often include patients heterogeneously treated [15–17].

Our report is a sub-analysis of the previously published Campus ALL study [13] and includes only patients aged 55 or more (12% older than 65 years) homogeneously treated with the GIMEMA LAL1913 program. To our knowledge, this is the largest real-life study that evaluated the feasibility and tolerability of PEG-ASP in a population of this age. We focused the analysis on the first two PEG-ASP containing courses (C1 and C2), because after C3 (PEG-ASP free) patients with given indications (VHR at onset and/or MRD positive after C3) could receive an allogeneic HSCT, and therefore we selected the response at TP2 (after C3) as the endpoint for the outcome. Accordingly, 96% (86/90) of patients received PEG-ASP in at least one of the first two courses (C1-C2) and 59% of them (51/86) in both. This rate of older patients able to receive PEG-ASP is similar to the rate reported in another recent study [18]. The majority of treated patients received PEG-ASP (according to the LAL1913 protocol) at an age-adjusted dose of 1000 IU/m^2 (67% at C1 and 70% at C2). In addition, 20% of patients at C1 and 23% at C2 received a reduced dose of PEG-ASP (less than 1000 IU/m^2) based on medical decision due to more advanced age and/or hepatic comorbidities. Taking into account this preventive dose reduction, we did not find, in univariate and multivariate analysis, a significant correlation between the occurrence of PEG-ASP-related toxicity and concomitant obesity, hepatic comorbidities or advanced age. These observations suggest that it is advisable to reduce the dose of PEG-ASP in patients with more advanced age and hepatic comorbidities to mitigate this drug toxicity. Recently, the importance of a thorough patient evaluation before PEG-ASP administration to find risk factors for toxicity was underlined in an Italian consensus [19] and in the recent GIMEMA LAL2317 trial [20] that also provided specific indications for PEG-ASP dose reduction based on age, previous comorbidities, and toxicities. However, the impact of comorbidities on PEG-ASP-related

toxicity was not reported in the LAL2317 trial related published paper.

Regarding the characteristics of toxic events, HT was the major issue in our elderly patient population, particularly in C1, where 23% of treated patients developed a grade ≥ 3 HT (possibly or probably PEG-ASP-related), and this was the main reason to avoid PEG-ASP at subsequent C2. However, our study found a lower rate of all grade HT compared to other published experiences [8, 10, 12, 15, 17, 21, 22], but this can be explained by the different protocols and PEG-ASP doses that were used. Pancreatic and metabolic toxicities, as well as thrombotic or hemorrhagic events, were rare and did not affect treatment continuation.

In our analysis, we did not find differences in the incidence of any kind of toxicity related to PEG-ASP in patients treated with different doses of this drug. However, we can suppose that this result can be explained by the preventive dose reduction in our patient population.

Regarding patients' outcomes, the 3-year OS was 54% and the 3-year DFS was 47%, that is in line with other real-life studies [16]. In addition, 46% of patients with indication could receive an allogeneic HSCT.

The patients who received the standard (or higher dose) of PEG-ASP obtained higher rates of MRD negativity at both TP1 and TP2 compared to those who received a cumulative reduced dose for any reason but, as reported, the dose of PEG-ASP did not significantly affect DFS. In fact, in multivariate analysis for DFS (including PEG-ASP dose, age ≥ 65 years, ALL risk category, MRD negativity at TP2, antecedent hepatic disease, obesity, presence of two or more comorbidities and ECOG ≥ 2), only MRD negativity at TP2 predicted an improved DFS (HR 0.181, 95% CI 0.057–0.568, $P = 0.003$). We can suppose that PEG-ASP has a concurrent role in obtaining MRD negativity, but it is MRD negativity the variable that remains the strongest determinant of DFS.

Obviously, this study has clear limitations due to its retrospective nature and as a sub-analysis of the large previously published report on Ph-negative ALL adults aged 18–80 years treated with a pediatric-inspired regimen (LAL1913) in real-life setting outside a clinical trial [13]. It cannot provide data on toxicity follow-up or treatment, and it lacks sufficient power to detect differences between OS/DFS results based on PEG-ASP dosing. Despite that, we underline that real-life information in older adults with Ph- ALL would be useful in broadening the age range of PEG-ASP treatment.

In conclusion, PEG-ASP administration in the real-life of older adults with Ph- ALL was feasible, and the adapted pediatric-inspired regimen could achieve good results (even if inferior to those observed in younger patients) allowing a significant proportion of patients with indication to undergo a HSCT. In this patient population it is of paramount importance to reduce the toxicity of the treatment while maintaining its efficacy, and a thorough evaluation of the patients is needed to identify potential causes of increased PEG-ASP toxicity. In this regard, specific guidelines or recommendations regarding risk factor monitoring and appropriate PEG-ASP dose adjustments could optimize treatment [19, 23]. Prospectively, therapeutic regimens that incorporate frontline immunotherapy [24, 25] could help to mitigate the toxicity and further improve outcomes.

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Declarations

Competing interests The authors declare no competing interests.

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