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Older Adults with Ph Negative Acute Lymphoblastic Leukemia: A Monocentric Experience on 57 Patients Focusing on Treatment Intensity and Age-Related Prognosis

Keywords: Acute Lymphoblastic Leukemia; Elderly patients; Ph negative; Intensive treatment.

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To the editor.

Acute lymphoblastic leukemia (ALL) represents the most common malignant disease in the pediatric setting, while in adults, it is far less frequent. However, after the pediatric peak and adult slope down, its incidence increases with age, and nearly 20-30% of patients are older than 50 years,[1] an age limit in which the outcome of treatment is often compromised by comorbidities and enhanced susceptibility to treatment toxicities, obtaining a 5-year survival of about 20-30%.[2,3] Given the difficulties in balancing treatment intensity with the risk of toxicity, the identification of a standard treatment policy for these patients remains a challenge, particularly for those with Ph-negative ALL, a cohort who cannot take advantage of the use of tyrosine kinase inhibitors, which have a more favorable risk-benefit profile compared to cytotoxic agents.

In our study, we retrieved retrospectively a population of 229 unselected ALL patients consecutively diagnosed in our Unit from 2001 to 2022. We selected the cohort of 86 (37.6%) patients aged over 55 years (median age: 70, range: 55-88) at the time of diagnosis, focusing on Ph negative ALL **(Figure 1).** We evaluated their characteristics and outcomes according to age and treatment received at dose adjusted by age, including, whenever possible, high-dose consolidation with stem cell transplantation (SCT).

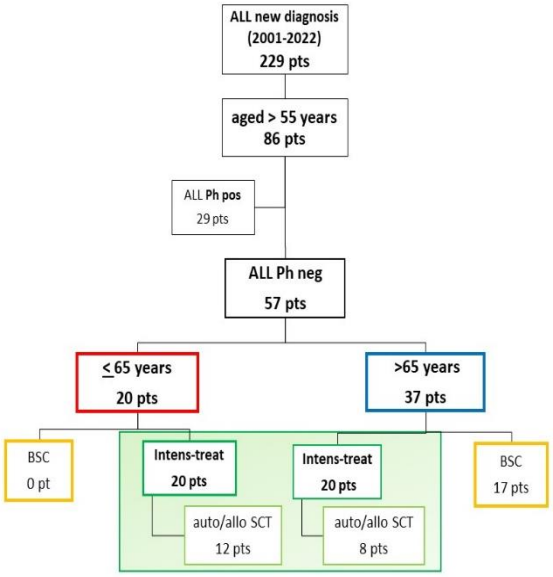
Among the 86 patients aged more than 55 years, 29 (33%) were *BCR::ABL1* positive, 16 (55%) were older than 65 years, and 57 were Ph-negative, 37 (65%) were older than 65 years.

According to physician choice, intensive treatment with chemotherapy was given to 40 patients (70%) according to paediatric-inspired protocols (NILG Protocols[4,5] or similar therapeutic program) with dose adjustment by age (in patients older than 65 years, reduction of idarubicin, cyclophosphamide, methotrexate, vincristine, and steroid doses and omission of L-asparaginase were applied) (**Appendix 1**). Written informed consent to treatment was obtained from patients in accordance with the Declaration of Helsinki. All patients under 65 years were intensively treated, while only 54% (20/37) of patients aged more than 65 years (*p*: 0.0002). Seventeen (30%) patients, aged more than 65 years, received only corticosteroids and best supportive care (BSC) (**Figure 1**).

The characteristics of the 57 Ph-negative patients are summarized in **Table 1**.

The median age of the 40 intensively treated patients was significantly lower than that of patients receiving

Figure 1. Flow diagram of all patients ≥ 55 years with ALL diagnosis and treatment really received



Abbreviations: ALL: Acute Lymphoblastic Leukemia; pts: patients; neg: negative; pos: positive; Intens-treat: intensive treatment; BSC: best supportive care; Allo: allogeneic; Auto: Autologous; SCT; stem cell transplantation

Table 1. Characteristics of older Ph negative ALL population.

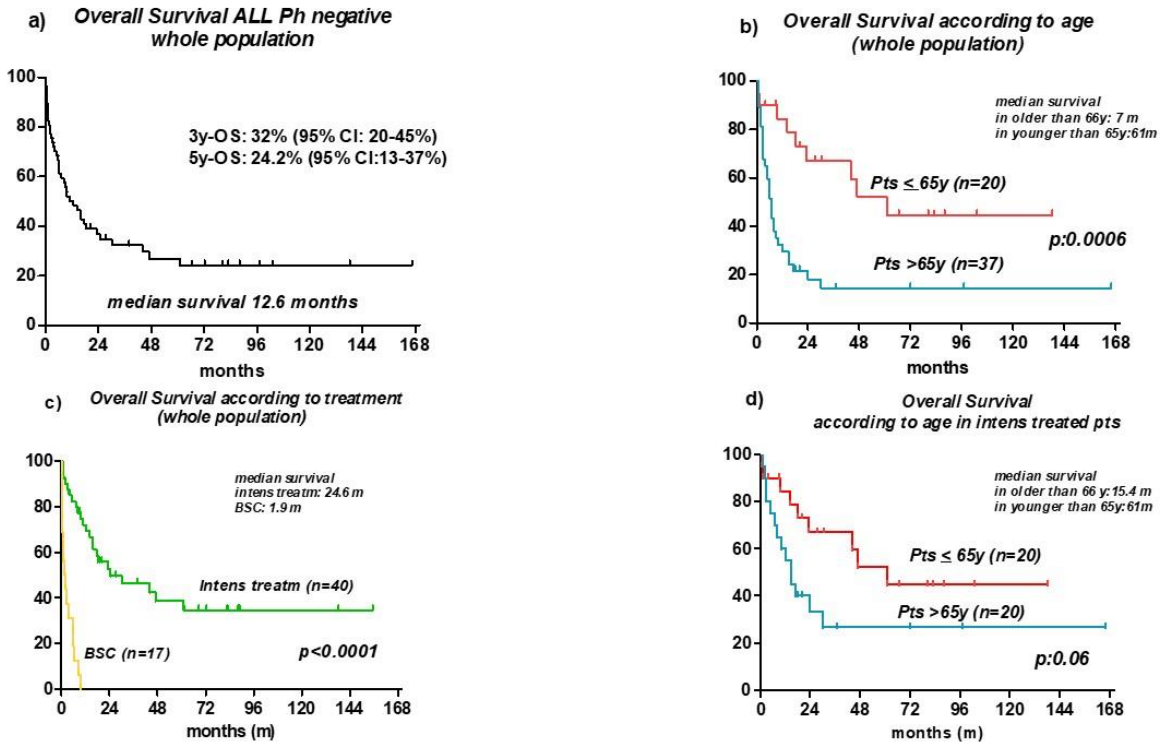
	ALL	BSC group	Intensively treated group		
			Total	</=65y	>65y
	57 pts	17 pts	40 pts	20 pts	20 pts
Parameter					
Median age (range)	70 (55-88)	78 (69-88)	65.5 (55-79)	62 (55-65)	72 (66-79)
Gender M/F	29/28	11/6	18/22	8/12	10/10
ECOG >/=2 n (%)	22 (39%)	10 (59%)	12 (30%)	4 (20%)	8 (40%)
CCI at diagnosis, n (%): 0-1 2 >/=3	 35 (61%) 13 (23%) 9 (16%)	 8 (47%) 4 (24%) 5 (29%)	 27 (67.5%) 9 (22.5%) 4 (10%)	 14 (70%) 5 (25%) 1 (5%)	 13 (65%) 4 (20%) 3 (15%)
Disease features					
WBC (1/nl), median (range)	9.9 (0.8-700)	5.2 (0.89-700)	10.1 (0.9-375)	12.9 (0.96-340)	10.4 (0.8-375)
Hepato/splenomegaly n	3 (5%)	0	3 (7.5%)	0	3 (15%)
Lymphadenopathy n	7 (12%)	1 (6%)	6 (15%)	3 (15%)	3 (15%)
EGIL immunophenotype					
BI-proB	14 (25%)	4 (24%)	10 (25%)	5 (25%)	5 (25%)
BII-common	24 (42%)	9 (53%)	15 (37.5%)	10 (50%)	5 (25%)
B-mature	1 (2%)	0	1 (2.5%)	1 (5%)	0
TII pre-TCD1a-	6 (11%)	0	6 (15%)	1 (5%)	5 (25%)
TIII/cortical CD1a+	11 (19%)	3 (18%)	8 (20%)	3 (15%)	5 (25%)
M-PAL	1 (2%)	1 (6%)	0	0	0
Cytogenetics/molecular genetics, n (%)	41 (82%)	6 (35%)	35 (87.5%)	17 (70%)	18 (90%)
Adverse n (%) t(9;22) and/or *BCR::ABL1* t(4;11)(q21;q23) and other *KMT2A* translocations Complex K Other (a)	14 (34%) 0 5 (36%) 6 (43%) 3 (21%)	2 (33%) 0 0 2 (100%) 0	12 (34%) 0 5 (42%) 4 (33%) 3 (25%)	7 (41%) 0 2 (12%) 3 (18%) 2 (12%)	5 (28%) 0 3 (16%) 1 (6%) 1 (6%)
Not adverse n (%) Normal K Other (b)	27 (65.8%) 15 (56%) 12 (44%)	4 (67%) 2 (50%) 2 (50%	23 (65.7%) 13 (57%) 10 (43%)	10 (59%) 5 (29%) 5 (29%)	13 (72%) 8 (44%) 5 (28%)
Not known (cytogenetics) (c)	16 (28%)	11 (65%)	5 (12.5%)	3 (15%)	2 (11%)
Clinical risk class, n (%)					
Standard Risk	19 (33%)	4 (24%)	15 (37.5%)	7 (35%)	8 (40%)
High Risk	30 (53%)	5 (29%)	25 (62.5%)	13 (65%)	12 (60%)
Undefined	8 (14%)	8 (47%)	0	0	0

Abbreviations. pts: patients, y: years, M: male, F: female, WBC: white blood count, CCI: Charlson Comorbidity Index, MPAL: mixed phenotype acute leukemia, K: karyotype, BSC: best supportive care. a) Other adverse abnormalities included low- hypodiploidy (n = 1), near triploidy (Ntr) (n=1) and del7 (n=1). b) Other not adverse abnormalities included deletion (n=3), i7q (n=1), Trisomy (n=1), numeric abn (n=3), tetraploidy Tt (n=1), High hyperdiploidy (HeH) (n=3). c) No metaphase or not done.

BSC (65.5 vs. 78 years, *p*:<0.0001), and ECOG performance status was ≥2 in 30% of the intensively treated patients compared to 59% of the BSC subgroup patients (*p*: 0.07). At diagnosis, fewer patients treated intensively (10%) had a CCI >2 compared to those receiving BSC (29%), although not significant (*p*: 0.1). The two subgroups did not differ in phenotype, karyotype, white blood cell count and clinical risk profile at diagnosis.

In the intensively treated subgroup, the complete remission (CR) after induction therapy was 77.5% (31/40), without significant differences according to age (85% in 55-65 years vs 75% in >65 years; *p:* 0.7). Three patients died during induction (7.5%) (fungal infection n=1, multiorgan failure n=2) and six patients (15%) were refractory. Immunophenotype, age, and karyotype did not impact CR achievement. Evaluation of measurable residual disease (MRD) with RQ-PCR technology was performed,[6,7] obtaining one or more patient-specific probe(s) with a sensitivity of at least 10e-3 in 26 patients (45.6%). After about 10 weeks from diagnosis, MRD was negative in 17 patients (65%) and positive but not quantifiable in two. Overall, severe adverse events (grade >2) occurred in 4.5% and did not

Figure 2. Overall Survival. a) in the whole population; b) in the whole population according to age; c) in the whole population according to treatment; d) in intensively treated patients, according to age.



Abbreviations: pts: patients; BSC: best supportive care; intens-treatm: intensive treatment, y: years.

impact on subsequent chemotherapy.

Overall, 20 patients (50% of the intensively treated group), considered at high risk of relapse (HR) (**Appendix 1**), underwent SCT, both autologous or allogeneic, as part of their treatment program; 8 (40%) of them were over 65 years. Considering patients older than 65 years, only 22% (8/37) underwent SCT, compared to 60% (12/20) of younger patients (*p*: 0.0078). Ten received an allogeneic SCT and eight (80%) in the first CR. The donor was haploidentical in four patients (40%), sibling in two, and matched unrelated in four. Ten patients not eligible for allo-SCT received autologous SCT. The median age at the time of transplant was 70 years (range: 63-76) in autologous and 60.5 years (range: 55-70) in allogeneic SCT (*p*: 0.0051).

Twenty patients (50%) classified as standard risk (SR) at diagnosis or as HR but achieving MDR negativity, received 2-year maintenance chemotherapy.

The relapse rate was 62.5% (20/32), without differences according to age (53% under 65 vs 73% over 65 years, *p*: 0.29). The median time to relapse was 8.7 months (range: 2.7-43), with relapse-free survival at 1 and 3 years of 57.3% (95% CI: 38.7-72) and 36.7% (95% CI: 20-53.2), respectively, without differences according to age (*p:* 0.4). Three patients (15%) had an isolated central nervous system relapse, despite the intrathecal prophylaxis, and were treated with radiotherapy and with intensified intrathecal chemotherapy. Only five patients (5/20; 25%) received Blinatumomab and/or Inotuzumab Ozogamicin, and four subsequently underwent allo-SCT, with MRD negativity in three cases.

With a median follow-up of 66.5 months, 3- and 5-year survival for the entire cohort, including patients receiving only BSC, was 32% (95% CI: 20-45%) and 24.2% (95% CI: 13-37%), respectively, with significant age-related differences for patients aged 55-65 years and over 65 years (median survival 61 vs 6 months; *p:* 0.0005) (**Figure 2a** and **2b**).

No significant differences in survival were observed between patients diagnosed during the first decade (2001-2011) and the second (2012-2022) (median survival 6 vs 14 months; *p:* 0.3).

The median survival in the BSC group was 1.9 months (range, 0.2-9.7), significantly lower than in the 40 patients treated intensively (24.6 months, $p<0.0001$) (**Figure 2c**).

In the intensively treated group, the 3- and 5-year survival was 46.3% (95% CI: 29.6-61.4%) and 34.7% (95% CI: 18.8-51%), respectively; 17 patients were alive (43%), 11 in first CR and 6 beyond first CR. Most patients died of progressive disease (65%); eight (35%) died while on CR (COVID-19 =1, secondary myelodysplastic syndrome =1, allo-transplant related mortality =3, death in aplasia =3), independently from age. According to age, 5-year survival was better in younger patients (<65 years) compared to their older counterparts, with a borderline statistically significant difference [47% (95% CI: 19.7-67%) vs 26.7% (95% CI: 9-48%); *p*: 0.06] (**Figure 2d**). Adverse karyotype,

ECOG, CCI (CCI 0-1 vs. CCI >/=2), risk at diagnosis, and phenotype had no impact on survival. In contrast, MRD positivity had a negative impact on outcome (median survival: 14.6 months vs. undefined in MRD negative, *p:* 0.046).

In patients undergoing allo-SCT, the 3-year survival was 54.8% (95% CI: 29-91%), and the median survival was not reached. Three patients relapsed (33%) after transplant, and one of them died. Survival at 3 years of patients receiving autologous SCT was 46.7% (95% CI: 9.5-73.7%), with a median of 30.2 months. The relapse rate was 50%; transplant-related mortality (TRM) was 0%.

At multivariable analyses for survival, only BSC remained significantly associated with reduced survival (*p:* 0.001). When achieving CR was added to the model, it proved to be independently associated with better survival.

In Ph negative ALL patients, chemotherapy with pediatric-inspired regimens still represents the standard treatment backbone, even if the rotating and long-term use of chemotherapeutic agents, even at high doses, and of corticosteroids can be particularly detrimental in older adults.

Therefore, we addressed our analysis of the feasibility and treatment outcomes in 57 Ph-negative ALL patients. We used a relatively low age cutoff (55 years) to identify older patients, lower than in Acute Myeloid Leukemia but similarly adopted in most clinical trials[8-10] and used in recent ELN recommendations.[2]

We treated most patients intensively, although with reduced doses of chemotherapy, particularly in patients older than 65 years, according to protocol guidelines (see **Appendix 1**), to allow them to tolerate therapy better. Only 29.8% received palliation with corticosteroids and/or BSC. Clinical judgment and chronological age itself represented the main criteria for excluding a patient from potentially curative treatment. Their proportion and their features are like those reported in other studies.[11,12] Their median survival was very poor, and in the multivariate analysis, BSC was the only variable that independently predicted an adverse outcome.

The first important management issue in older patients is the selection of frail patients who do not deserve intensive treatment, even at reduced doses. While in Acute Myeloid Leukemia and in hematological diseases, a comprehensive geriatric assessment, including the evaluation of daily life activities, cognitive and psychological functions, and other geriatric parameters, has proven useful for selecting the most appropriate treatment intensity in older patients,[13,14] in ALL, there are no validated criteria to define their fitness.

In our experience, more than 70% of patients have been treated intensively, obtaining a median survival of 24.6 months and a 3-year survival of 46.3%, without differences according to karyotype, ECOG PS or CCI. With the predefined dose adjustments of treatment protocols, chronological age did not represent a limitation to the use of an intensive treatment in selected fit patients, particularly in very old patients. Chemotherapy was given up to 79 years, and autologous transplants up to 76 years of age. Overall, 54% of patients aged more than 65 years were treated intensively, and 22% received a transplant procedure, respectively, obtaining an unsatisfactory but acceptable median survival of 15 months with a plateau, particularly compared to patients receiving only BSC. These results are in line with data reported by the PETHEMA group that showed a superiority of intensive treatment in event-free survival and overall survival. The intensity of treatment was the only variable with independent significance for event-free survival in multivariate analysis.[8]

The intensive chemotherapy used in this study proved feasible even if the treatment-related mortality was quite high (20%) and mortality in CR was 12.5%, like those reported by other studies.[8,9] Notably, the program was also well tolerated by 14 selected patients aged over 70 years included in the study, whose mortality in CR was 7.1% and whose survival was not significantly different compared to younger patients.

The use of SCT as consolidation treatment in an older population is also debatable. In our series, 17% of patients (median age: 60.5) received an allotransplant, and despite a TRM of 33%, they achieved a satisfactory 3 year-survival of 54.8%. An additional 17% of patients (median age: 70) received an autologous SCT with no TRM. The proportion of older ALL patients submitted to allo-SCT in other studies was lower than in the present study, 8% in the GMALL trial[10] and 9% in a real-life Canadian trial.[15] A recent study comparing patients >55 years, treated with reduced intensity-allo-SCT vs auto-SCT, showed no significant difference between the two options [5 year-survival: *p:* 0.23]. Non-relapse mortality was higher with allogeneic SCT (25% versus 10%: *p:* 0.001).[16]

The limitations of the present study include its retrospective nature, the relatively low number of patients, and the long duration of the study, which spanned periods when the new drugs were not yet available and supportive therapy progressively improved. In addition, patients treated intensively were selected by medical judgment without using objective criteria. Nevertheless, considering the rarity of this disease in older adults and the paucity of prospective studies in this patient's population, the study supports the concept that it is important to consider old ALL patients for curative treatment, which can be successful in a significant proportion of cases, without excluding them “a priori” based on age.

Overall, the present study's results showed that the

majority of older ALL patients can receive curative treatment with dose-adjusted chemotherapy, including transplantation. It was desirable to identify objective criteria for patient selection and incorporate novel, more efficient, and less toxic immunologic agents into the treatment algorithm.[17-20]

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