

Age but not Philadelphia positivity impairs outcome in older/elderly patients with acute lymphoblastic leukemia in Sweden

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Abstract

Objectives: Older/elderly patients with acute lymphoblastic leukemia (ALL) are poorly represented in clinical trials.

Methods: Using Swedish national leukemia registries, we investigated disease/patient characteristics, treatment choices, outcome, and the impact of an age-adapted protocol (introduced in 2009) in this population-based study of patients aged 55-85 years, diagnosed with ALL 2005-2012.

Results: Of 174 patients, 82% had B-phenotype, 11% Burkitt leukemia (excluded), and 7% T-phenotype. Philadelphia chromosome positivity (Ph+) occurred in 35%. Of the 155 B- and T-ALL patients, 80% were treated with intensive protocols, and 20% with a palliative approach. Higher age and WHO performance status ≥ 2 influenced the choice of palliation. Intensive, palliative, and both approaches resulted in complete remission rate 83/16/70% and 3-year overall survival (OS) 32/3/26%. The age-adapted protocol did not improve outcome. With intensive treatment, platelet count $\leq 35 \times 10^9/L$ and age ≥ 75 years were adverse prognostic factors for OS, Ph+ was not. Male sex was an adverse prognostic factor in the 55-64 year age-group.

Conclusions: We report a high frequency of Ph+ in older/elderly patients, with no evidence of poorer outcome compared to Ph-negative disease. Overall prognosis for elderly patients with ALL remains dismal, despite the use of age-adapted treatment.

KEYWORDS

acute lymphoblastic leukemia, chemotherapy, elderly, epidemiology

1 | INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a highly proliferative blood malignancy, treated with complex and intensive chemotherapy protocols, which, over the last few decades, have markedly enhanced outcome for children and young adults. However, survival has not improved for patients >70 years of age, with modest improvements achieved for those aged 60-70 years.¹ Patients up to 55 or 65 years (older adults) are often included in clinical trials with intensive therapy

and considered for allogeneic hematopoietic stem cell transplantation (hSCT), in contrast to those >65 years (elderly). In studies of intensive chemotherapy, older patients exhibited an inferior complete remission (CR) rate, and disease-free and overall survival (OS), as compared with younger adults.²⁻⁵ This is partly explained by their comorbidities, poorer performance status at diagnosis, need for chemotherapy dose reductions, increased toxicity, and higher proportions of adverse risk cytogenetics, including Philadelphia chromosome positivity (Ph+).^{2,4-9} Ph+ has, historically, been recognized as a high-risk factor, but its

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impact on the outcome for older patients has declined since the introduction of tyrosine kinase inhibitors (TKI).^{5,6}

Due to poor outcome for patients >55 years (according to the Swedish ALL/Acute Leukemia Registries),¹⁰ and based on the promising results of the European Working Group on Adult ALL (EWALL) backbone,¹¹ this age-adapted protocol (adding TKI in Ph+ ALL) was introduced in Sweden for older/elderly ALL patients as of October 2009. Based on the Swedish ALL/Acute Leukemia Registries, we performed a population-based study to assess the efficacy of different therapeutic strategies for patients aged 55–85 years, treated for ALL between 2005 and 2012, in accordance with Swedish national guidelines. Our hypothesis was that outcome would have improved since October 2009, with the introduction of the age-adapted protocol. The aim was also, in this unselected population, to investigate disease and patient characteristics in relation to age, treatment choices, and outcome.

2 | PATIENTS AND METHODS

Every Swedish citizen has a unique social security number, enabling disease surveillance in population-based registries. Patients are reported to the Swedish ALL/Acute Leukemia Registries since 1997, and as previously described, coverage versus the compulsory Swedish Cancer Registry has been 98%.¹⁰ In this study, patients were identified through the Swedish ALL/Acute Leukemia Registries and additionally through the Swedish Cause of Death Registry. Vital status was obtained through 30th of June 2015. The study was conducted in accordance with the declaration of Helsinki, including informed consent from patients, and approved by the Regional Ethical Review Board in Uppsala/Sweden (2014/063).

Clinical and laboratory data, together with pathology and genetic reports, were verified from medical records by P.K and E.L. Registry data were supplemented in terms of comorbidities, treatment description, and toxicity. Diagnoses were verified by morphology reports, immunophenotyping, and genetics, according to the World Health Organization (WHO) Classification of 2005.¹² Performance status (PS) at diagnosis was reported according to Eastern Cooperative Oncology Group (ECOG) criteria.¹³ The comorbidity component (CC) from the adjusted Charlson Comorbidity Index¹⁴ was estimated retrospectively. The ALL diagnosis was not included in the score. Toxicity was assessed retrospectively according to Common Terminology Criteria for Adverse Events.¹⁵ National guidelines for the treatment of patients >55 years, and the main protocols, ABCDV¹⁶ and the EWALL-backbone-based protocol, are shown in the Tables S1 and S2 (the Online Supporting Information). Allogeneic hSCT in CR1 was recommended for fit patients up to 65 years fulfilling at least one of the following high-risk criteria: white blood cells (WBC) >30×10⁹/L in B-ALL or >100×10⁹/L in T-ALL, T-cell phenotype (from 2009), Ph+ disease, *MLL* rearrangement, CR achieved after more than one therapy course (two courses for hyper-CVAD¹⁷), minimal residual disease (MRD) >1% after remission induction, increasing MRD levels, or failure to attain MRD <0.1% after consolidation therapy. MRD analysis was not mandatory in the EWALL-backbone.

Genetics, other diagnostic evaluations, and toxicity assessments are further described in the Online Supporting Information.

2.1 | Statistical methods

For categorical data, differences in proportions were compared using the Chi-square or two-tailed Fischer's exact test, where appropriate. Continuous variables were compared using the Mann-Whitney U test. OS was calculated from diagnosis to death, or the date of last follow-up. Event-free survival (EFS) was estimated from diagnosis to relapse, death, or last follow-up in CR. Event was considered on day one for patients who died without a CR evaluation, or because of refractory disease. Distributions of OS and EFS were estimated by the Kaplan-Meier method, with differences analyzed using the log-rank test. In addition, univariate and multivariate Cox regression analyses were performed to assess the effects [hazard ratio (HR)] of relevant covariates on OS and EFS (included in the multivariate model if *P* value <0.1 in univariate analysis). The association of CR achievement with different variables was evaluated by logistic regression. Statistical tests were used with an alpha significance level of 5% and 95% confidence intervals (CI). Multiplicity adjustment was not performed, and *P* values should be interpreted as explorative. IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY, USA), was used.

3 | RESULTS

3.1 | Patients in the total population-based ALL cohort

3.1.1 | Patient characteristics

A total of 183 patients were identified via the Swedish ALL /Acute Leukemia Registries. Eleven patients were excluded (one with a blast crisis of chronic myeloid leukemia, two with leukemic phase of follicular lymphoma, two with T-lymphoblastic lymphoma, one with diffuse large B-cell lymphoma, one with T-cell prolymphocytic leukemia, three without a verified ALL diagnosis, and one because of withdrawn consent). Additionally, two patients with ALL were identified through the Swedish Cause of Death Registry. In our cohort of 174 patients B-ALL was the most common phenotype (82%), followed by Burkitt leukemia (11%), and T-ALL (7%). The median age for the respective ALL subtype was: 67, 73, and 70.5 years. Patients with Burkitt leukemia were excluded from further analyses (separate entity according to the WHO 2005 classification). The characteristics of the final study cohort of 155 patients are presented in Table 1. The male/female distribution was comparable, except that T-ALL was more common in males [10/72 (14%)] compared to females [2/83 (2%); *P*=.01]. Bulky disease was documented in one and mediastinal mass in two patients. Cytogenetic abnormalities are summarized in Table 1. G-band karyotyping, and/or fluorescence in situ hybridization (FISH), and/or reverse transcription polymerase chain reaction (RT-PCR) for *BCR-ABL* were performed and could be evaluated for 140/155 (90%) of the cohort.

3.1.2 | Treatment approaches

The majority of patients (80%) were treated with intensive (remission inducing) protocols (Table 1). Their median age was lower than in those treated with a palliative approach (*P*<.001). The most common

**TABLE 1** Patient characteristics and treatment approach

		Treatment	
		Intensive	Palliative
Number of patients (%)	155	124 (80)	31 (20)
Age, median (range) y	67 (55-85)	65 (55-82)	79 (55-85)
Age-group, n (%):			
55-64 y	60 (39)	59 (47)	1 (3)
65-74 y	60 (39)	53 (43)	7 (23)
75-85 y	35 (22)	12 (10)	23 (74)
Male: Female	72:83	57:67	15:16
Phenotype, n (%):			
B-cell	143 (92)	116 (93)	27 (87)
T-cell	12 (8)	8 (7)	4 (13)
Cytogenetics, n (%):			
<i>BCR-ABL/Ph</i> ^a	49/140 (35)	42/120 (35)	7/20 (35)
<i>MLL/t(4;11)</i> ^b	8/126 (6)	7/107 (7)	1/19 (5)
Normal ^c	10/118 (8)	10/101 (10)	0
CNS leukemia ^d , n (%):			
Yes	9/113 (9)	6/106 (6)	3/7 (43)
No	104/113 (91)	100/106 (94)	4/7 (57)
WBC ($\times 10^9/L$), median (range)	11.9 (0.6-420)	13.0 (0.6-420)	8.8 (1.7-105)
PLT ($\times 10^9/L$), median (range)	41 (6-654)	37 (6-654)	53 (9-200)
LDH ratio ^e , median (range)	2.7 (0.5-42.7)	2.7 (0.5-33.3)	2.8 (0.5-42.7)
Hb (g/L), median (range)	10.1 (4.0-15.0)	9.9 (4.0-15.0)	11.1 (6.0-13.9)
Creatinine (mg/dL), median (range)	8.5 (3.3-34.3)	8.5 (3.3-26.1)	8.6 (3.9-34.3)
Performance status, n (%):			
0	40 (26)	35 (28)	5 (17)
1	70 (46)	62 (50)	8 (28)
2	25 (16)	18 (15)	7 (24)
3	10 (7)	6 (5)	4 (14)
4	7 (5)	2 (2)	5 (17)
Number of comorbidities, n (%):			
0	52 (34)	49 (40)	3 (10)
1	48 (31)	40 (32)	8 (26)
≥ 2	54 (35)	34 (28)	20 (64)
Comorbidity component, n (%):			
0	85 (55)	75 (61)	10 (32)
1	31 (20)	24 (19)	7 (23)
2	19 (12)	12 (10)	7 (23)
3	12 (8)	10 (8)	2 (6)
≥ 4	7 (5)	2 (2)	5 (16)
Number of drugs, median (range)	2 (0-14)	1 (0-13)	6 (0-14)

^aOf those evaluable by G-banding/FISH/RT-PCR.^bOf those evaluable by G-banding/FISH 11q23 (regardless of fusion partner).^cOf those evaluable by G-banding.^dOf those performed/evaluable.^eA ratio of serum lactate dehydrogenase versus the upper limit for normal LDH.

comorbidities were diabetes: 23/154 (15%) [16/123 (13%) in intensively treated patients] and a history of myocardial infarction: 16/154 (10%) [12/123 (10%) in intensively treated patients]. The proportions

of patients with PS ≥ 2 , CC ≥ 1 , number of comorbidities ≥ 2 , and the median number of drugs (Table 1) were lower for those receiving intensive treatment (P : $<.001$, $=.005$, $<.001$, and $<.001$, respectively).



CC values were used in further analyses for comorbidity assessments. In multivariate analysis (PS, CC, age; logistic regression), only age (as a continuous variable), and proportion of patients with PS ≥ 2 , remained significantly different between the intensive treatment and palliative cohorts ($P < .001$ and $< .05$, respectively).

3.1.3 | Overall outcomes

CR was reached for 108/155 (70%) of the entire B- and T-ALL cohort, with 1- and 3-year OS of 50% (95% CI: 42, 58) and 26% (95% CI: 20, 33), respectively.

3.2 | Patients with B- and T-ALL treated with remission intention

3.2.1 | Treatment characteristics

Remission inducing therapy was given to 124 patients. The characteristics of these patients and their treatments, for three age-groups, are presented in Table 2. Patients receiving EWALL-backbone +/- TKI ($n=35$) were older than those treated with ABCDV +/- TKI ($n=79$) [median age of 69 years (range: 62-82) versus 63 years (range: 55-79), respectively; $P < .001$]. Both protocols were modified for an equivalent proportion of patients [12/35 (34%) and 27/79 (34%), respectively]. In total, 12/35 (34%) patients completed the EWALL-backbone therapy and 48/79 (61%) the ABCDV protocol. Of the 10 remaining patients, five received hyper-CVAD and four remission induction with daunorubicin/cytarabine (DA) due to initially erroneous diagnosis as acute myeloid leukemia (AML). One patient died after prephase treatment. All 42 patients with Ph+ disease (and one with Ph-) commenced with TKI at induction (41 imatinib and two dasatinib) in combination with the EWALL-backbone protocol ($n=12$), ABCDV ($n=29$), hyper-CVAD ($n=1$), and DA ($n=1$).

3.2.2 | Remission rate and survival

The proportion of patients achieving CR (83%) was not influenced by age as continuous variable (odds ratio 0.95, 95% CI: 0.89, 1.03; $P=.20$), but was lower in the oldest versus youngest age-group ($P=.03$, Table 2). CR frequency was slightly higher in Ph+ ALL (93% vs 80%; $P=.07$). No other factors were found to influence the probability of CR achievement (data not shown). Median survival was 16 months (range 0-126). OS was 59% (95% CI: 50, 67) after 1 year, and estimated to be 32% (95% CI: 24, 40) after 3 years. Corresponding EFS was 47% (95% CI: 38, 56) and 25% (95% CI: 17, 33), respectively. Median follow-up of survivors was 74 (33-126) months. During follow-up, 96 of 124 (77%) patients died of: early death (ED; within 60 days) in 18/124 (15%) patients (four in CR), relapse in 56 (45%), transplant-related mortality (TRM) in 9 (7%; eight after hSCT in CR1, and one in CR2), refractory disease in five (4%), secondary AML in two, and a late induction treatment complication in one. Five (4%) patients (one >75 years) died in remission more than 60 days from diagnosis from causes not directly related to the treatment. The only factor associated with ED was PS ≥ 2 at diagnosis [7 of 26 (27%) vs 11 of 97 patients (11%) with PS <2; $P=.046$].

TABLE 2 Patient and treatment characteristics according to age-group (intensive approach)

	n (%)	Age-group		
		55-64 y	65-74 y	75-82 y
Number of patients	124	59 (47)	53 (43)	12 (10)
Median age years	65	60	69	77
Male: Female	57:67	26:33	23:30	8:4
T-cell phenotype	8 (7)	3 (5)	4 (8)	1 (8)
Ph ⁺ ^a	42 (35)	21 (36)	16 (32)	5 (46)
Performance status ≥ 2	26 (21)	13 (22)	11 (21)	2 (17)
Comorbidity component ≥ 1	49 (40)	17 (29)	25 (47)*	7 (58)
Protocol used:				
ABCDV	79 (64)	49 (83)	24 (45)*	6 (50)*
EWALL	35 (28)	5 (8.5)	25 (47)*	5 (42)*
Other	10 (8)	5 (8.5)	4 (8)	1 (8)
Protocol adherence	86 (70)	44 (76)	37 (70)	5 (42)*
CR	103 (83)	53 (90)	43 (81)	7 (59)*
Early death	18 (15)	6 (10)	10 (19)	2 (17)
Infectious toxicity	97 (79)	46 (79)	40 (76)	11 (92)
Septicemia	80 (65)	39 (67)	34 (64)	7 (58)
Pneumonia	28 (23)	12 (21)	12 (23)	4 (33)
Pneumocystis pneumonia	4 (3)	2 (4)	2 (4)	0
Invasive fungal infection	22 (18)	15 (26)	6 (11)	1 (8)
Non-infectious toxicity	52 (42)	19 (33)	27 (51)	6 (50)
Enterocolitis	14 (11)	7 (12)	6 (11)	1 (8)
Mucositis	4 (3)	0	3 (6)	1 (8)
Heart failure	13 (11)	3 (5)	8 (15)	2 (17)
Renal failure	9 (7)	0	7 (13)*	2 (17)*
Liver failure	6 (5)	1 (2)	4 (8)	1 (8)
Thrombosis	6 (5)	3 (5)	3 (6)	0
Neuropathy	8 (7)	4 (7)	4 (8)	0
Diabetes at discharge	3 (2)	1 (2)	2 (4)	0
Bleeding	3 (2)	1 (2)	2 (4)	0
ICU ^b admission	21 (17)	11 (19)	10 (19)	0
hSCT in CR1	20 (16)	18 (31)	2 (4)*	0*

^aFour missing values.

^bIntensive care unit.

*Significant difference as compared with the 55-64 y age-group.

3.3 | Outcome according to treatment protocol (EWALL/ABCDV+/-TKI)

3.3.1 | The whole cohort

Induction with the EWALL-backbone protocol resulted in CR for 25 of 35 (71%) patients. CR was achieved for 70 of 79 (89%; in seven patients after ≥ 2 courses) patients with ABCDV. ED occurred in 20% and 13% of the patients, respectively. One- and three-year OS in the



cohort treated with EWALL-backbone was 49% (95% CI: 32, 65) and 20% (95% CI: 7, 33), respectively. These data for the ABCDV protocol were 63% (95% CI: 53, 74) and 39% (95% CI: 28, 50).

3.3.2 | Patients aged 65-74 years

As a consequence of the new guidelines, a shift from ABCDV before October 2009 (22/31, 71%), to the EWALL-backbone in the later period (19/22, 86%), occurred for the 65-74 year age-group ($P < .001$), with approximately equal proportions of patients having received either treatment by the end of the study (Table 2). The median age was 69 years for either protocol. The proportions of patients with a PS ≥ 2 (16 vs 25%) and CC ≥ 1 (44 vs 50%) did not differ significantly for EWALL-backbone and ABCDV. CR was achieved in 18/25 (72%) after EWALL induction and 21/24 after ABCDV (88%; $P = .18$). Neither ED rate (20% vs 21%), nor OS, differed between protocols in this age-group (Figure 1).

3.4 | Toxicity

3.4.1 | The whole cohort

The proportion of patients affected by toxicity (recorded retrospectively), especially serious infections, was high (Table 2). However, it did not differ significantly among the three age-groups, except for renal failure, which was more common in patients aged ≥ 65 years. The frequency of probable or proven invasive fungal infection was higher in patients with diabetes, compared to those without [7/16 (44%) vs 15/106 (14%), $P = .004$]. Invasive candidiasis (with positive blood

cultures) was diagnosed in four patients, aspergillosis in four, with the etiologic agent unknown in a further 14. No case of pancreatitis was recorded. Median time to neutrophil recovery was 23 days from the start of chemotherapy in patients achieving CR.

3.4.2 | According to protocol (EWALL/ABCDV+/-TKI)

Serious infections (mainly septicemia) during induction/consolidation were less common in EWALL-backbone as compared to ABCDV-treated patients [23/35 (66%) vs 69/79 (87%); $P = .007$], with *pneumocystis jiroveci* pneumonia occurring exclusively in the latter cohort. Median time to neutrophil recovery was equivalent for both protocols (EWALL-24 vs ABCDV-23 days; $P = .3$), despite the greater use of granulocyte colony stimulating factor in the former [31/32 (97%) vs 34/73 (47%); $P < .001$]. Serious TKI toxicity (leading to substitution with another TKI or long-lasting intermissions) was less frequent in EWALL-backbone compared to ABCDV-treated patients [1/12 (8%) vs 13/29 (45%), $P = .03$], but did not differ among the three age-groups ($P = .64$).

3.5 | Allogeneic hSCT in CR1

Allogeneic hSCT was performed in 20 of 103 (19%) patients in first CR (10 males and 10 females) after ABCDV ($n = 17$) and hyper-CVAD ($n = 3$) treatment. Their median age was 60 years (range

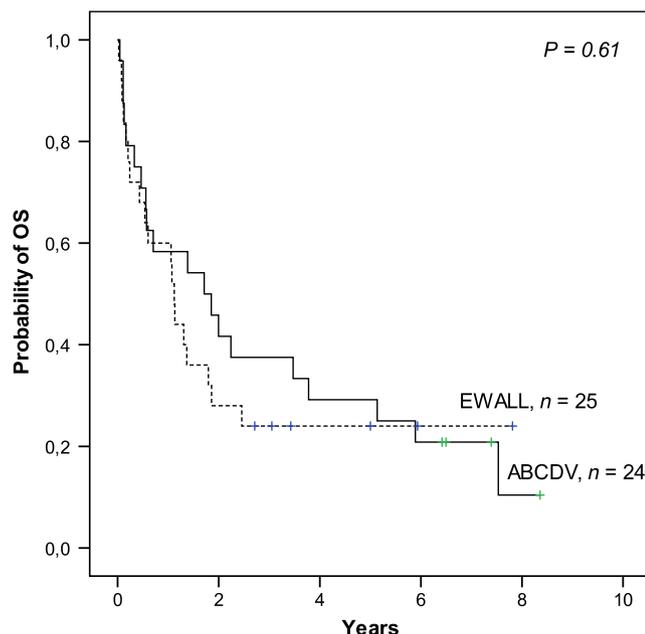


FIGURE 1 Overall survival in patients with ALL aged 65-74 according to protocol (EWALL-backbone-based vs ABCDV). Patient characteristics were similar in both groups [Colour figure can be viewed at wileyonlinelibrary.com]

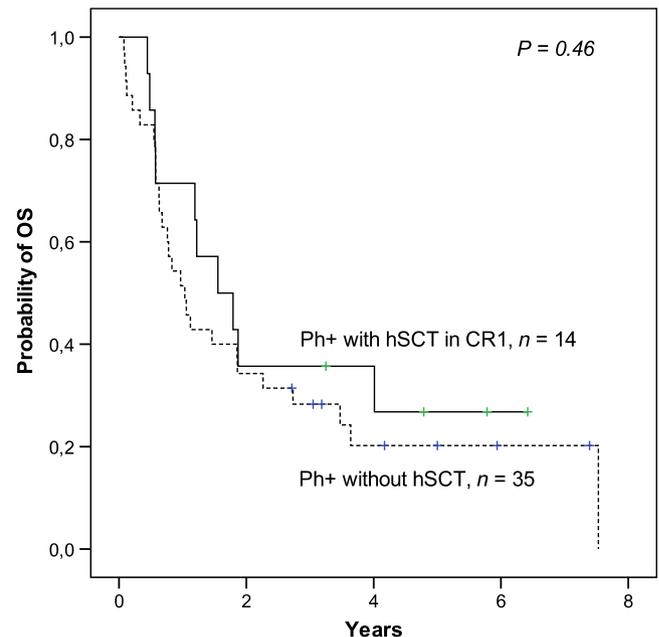


FIGURE 2 Philadelphia positive (Ph+) ALL: Overall survival in 14 patients receiving intensive therapy [including tyrosine kinase inhibitors (TKI)] with subsequent allogeneic hematopoietic stem cell transplantation (hSCT) vs 35 patients receiving intensive therapy (including TKI) without hSCT, or palliative treatment (with TKI in 5/7). Transplant-related mortality was 43% (6/14). Median age was lower in the transplanted group [59.5 y (range: 55-65) vs 69 (range: 58-84); $P < .001$] [Colour figure can be viewed at wileyonlinelibrary.com]



55-66). High-risk disease was present in 19 patients due to: Ph+ (n=14), T-ALL (n=1), high WBC at diagnosis (n=3, as the only high-risk criterion), late remission (n=1), and MRD (n=1). Stem cells were obtained from peripheral blood (n=19) or bone marrow (n=1) of HLA-identical siblings (n=10), or matched, unrelated donors (n=10). Reduced-intensity conditioning [fludarabine-based, including total body irradiation (TBI) in five patients] was given to 13 patients and myeloablative to the remaining seven (mainly cyclophosphamide and TBI). Three-year OS and EFS were 40% (95% CI: 18, 62) and 25% (95% CI: 6, 44), respectively. Transplanted patients died mainly because of TRM (8/20) and relapse (6/20). OS in 14 transplanted Ph+ patients was not different from all the non-transplanted Ph+ patients, including those receiving palliative treatment (Figure 2; Table S3).

3.6 | Prognostic factors

Univariate and multivariate analyses of prognostic factors for OS are shown in Table 3. The multivariate model revealed that age ≥ 75 years (Figure 3A) and a platelet count (PLT) of $\leq 35 \times 10^9/L$ were negative prognostic factors for OS (Table 3) and EFS (data not shown). No impact on survival was observed for: Ph+, PS ≥ 2 , and CC ≥ 1 . When analyzing the three age-groups versus Ph status, age negatively influenced OS for the Ph- group, with this effect less apparent for the Ph+ ALL group (Figure 3B,C). For the youngest age-group, EFS (not shown) and OS were significantly reduced for males (Figure S1), even when adjusted for WBC $> 100 \times 10^9/L$, phenotype, creatinine > 0.9 mg/dL, and PLT $\leq 35 \times 10^9/L$ ($P = .001$). MRD analyses after remission induction (MRD1) were performed in only 55 of 94 patients achieving CR (13

TABLE 3 Univariate and multivariate analyses of pretreatment prognostic factors for overall survival (OS) in intensively treated patients with B- or T-ALL

	n	3 y OS% (95% CI)	Univariate analyses: HR (95% CI); P value	Multivariate analyses ^a : HR (95% CI); P value
Age-group:				
55-64 y	59	39 (26, 51)		
65-74 y	53	30 (18, 43)	1.30 (0.85, 1.99); .23 ^b	1.20 (0.77, 1.85); .42 ^b
75-82 y	12	8 (0, 24)	2.71 (1.40, 5.22); .003 ^b	2.60 (1.30, 5.19); .007 ^b
			2.08 (1.08, 4.00); .028 ^c	2.17 (1.10, 4.31); .026 ^c
Female	67	40 (28, 52)		
Male	57	23 (12, 34)	1.52 (1.02, 2.27); .04	1.37 (0.82, 2.29); .22
B-cell phenotype	116	34 (26, 43)		
T-cell phenotype	8	0	2.04 (0.98, 4.27); .06	1.49 (0.68, 3.28); .32
Ph-	78	31 (21, 41)		
Ph+	42	33 (19, 48)	0.96 (0.62, 1.47); .84	
No MLL rearrangement	100	31 (22,40)		
MLL rearrangement	7	13 (0, 40)	1.06 (0.92, 1.21); .45	
No CNS leukemia	100	37 (27,46)		
CNS leukemia	6	17 (0, 46)	1.36 (0.55, 3.38); .50	
WBC $\leq 100 \times 10^9/L$	108	35 (26, 44)		
WBC $> 100 \times 10^9/L$	16	13 (0, 29)	1.64 (0.94, 2.87); .08	1.63 (0.92, 2.87); .09
PLT $> 35 \times 10^9/L$	65	39 (27, 50)		
PLT $\leq 35 \times 10^9/L$	59	25 (15, 36)	1.53 (1.02, 2.29); .04	1.81 (1.16, 2.79); .008
LDH ratio $< 3^d$	61	41 (29, 53)		
LDH ratio ≥ 3	49	25 (15, 36)	1.41 (0.92, 2.17); .11	
Creatinine ≤ 0.9 mg/dL	74	40 (29, 52)		
Creatinine > 0.9 mg/dL	48	19 (8, 30)	1.73 (1.15, 2.61); .009	1.26 (0.76, 2.09); .37
Performance status < 2	97	34 (24,43)		
Performance status ≥ 2	26	27 (10, 44)	1.34 (0.82, 2.18); .24	
Comorbidity component < 1	75	32 (21, 42)		
Comorbidity component ≥ 1	49	33 (20, 46)	1.01 (0.67, 1.53); .95	

^aTwo patients excluded due to missing values.

^bAs compared with the 55-64 y age-group.

^cAs compared with the 65-74 y age-group.

^dA ratio of serum lactate dehydrogenase versus the upper limit for normal LDH.

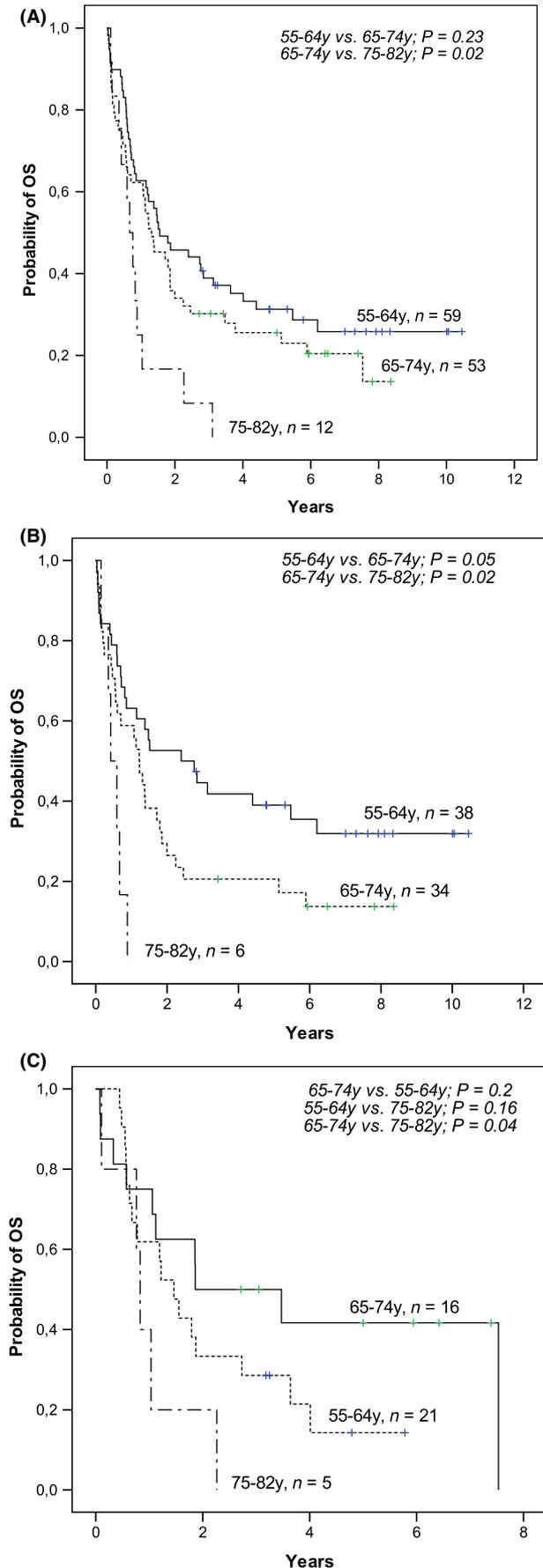


FIGURE 3 Overall survival in intensively treated patients according to age: for the whole ALL cohort (A), Philadelphia negative ALL (B), and Philadelphia positive ALL (C), respectively [Colour figure can be viewed at wileyonlinelibrary.com]

after EWALL induction, 39 after ABCDV, and three after other protocols). Detectable MRD1 ($>0.1\%$) had no significant impact on OS or EFS.

3.7 | Outcome before and after the introduction of new guidelines

In total, 92 of 155 (59%) patients with B- and T-ALL were diagnosed before and 63 of 155 (41%) after October 2009. The proportion of patients treated with remission intention was equivalent in both periods [74/92 (80%) vs 50/63 (79%)]. There was no significant difference in the distribution of: age-groups, sex, ALL-phenotype, Ph+/*MLL* status, $WBC >100 \times 10^9/L$, $PS \geq 2$, $CC \geq 1$, and allogeneic hSCT frequency between the two periods (not shown). Of 124 intensively treated patients, 115 (93%) started treatment according to the contemporary guidelines. Neither OS nor EFS differed between periods for the whole cohort or for the three age-groups (not shown).

3.8 | Palliation

The characteristics of 31 patients are shown in Table 1. Of these, 17 (55%) received more intensive palliative treatment: modified (heavily reduced) induction according to ABCDV ($n=2$), or EWALL ($n=1$), COP/CHOP [$n=9$: with rituximab ($n=1$) or with TKI ($n=2$)], VAD [$n=2$ (with TKI $n=1$)], vincristine/thioguanine/corticosteroid combination ($n=1$), or corticosteroid/TKI combination ($n=2$). Five of 17 (29%) achieved CR. “Non-intensive” palliation (14/31) consisted of oral cyclophosphamide/corticosteroid ($n=1$), thioguanine/corticosteroid ($n=1$), corticosteroid alone ($n=2$), hydroxyurea ($n=1$), or no specific antileukemic therapy ($n=9$). OS after one and 3 years in all palliatively treated patients was 13% (95% CI: 1, 25) and 3% (95% CI: 0, 9), respectively. OS was not significantly impaired in the oldest age-group (75-85 years) given palliation ($n=23$), as compared with the 12 patients (75-82 years) receiving remission induction therapy ($P=.12$).

4 | DISCUSSION

We present a truly population-based study of older and elderly ALL patients which, to our knowledge, is the only publication in the last 20 years¹⁸ describing an unselected cohort including information of cytogenetics and treatments. Low T-ALL and bulky disease but high Ph+ incidences agree with findings from other studies.^{2,4,6-9} As regards therapy, the national guidelines were followed to a large extent. The decision to refrain from intensive treatment appeared to be based primarily on age and PS, with a minority of patients aged ≥ 75 years receiving remission induction compared to over 90% of those younger than 75 years.



Complete remission rate (83%) after intensive induction was as high as that achieved by other protocols (34%-87%),^{2,3,6-9,19,20} considering the population-based character of our study. The drawback was high early mortality (15%), even if comparable with other studies (11%-34%).^{2,4,6-9,20} The 3-year OS was similar to that reported in other ALL studies of older/elderly patients,^{4,6} as was the high toxicity rate, especially concerning infections.^{2,4,19} A new finding was the increased frequency of invasive fungal infections in patients with diabetes. This could indicate the need for broad-spectrum antimycotic prophylaxis in this group. In common with other studies, ALL recurrence was the main cause of death,^{2,4,6,8} suggesting the need for intensified/more effective consolidation therapy.

Introduction of the age-adapted EWALL-backbone-based protocol, which was used mainly for patients aged ≥ 65 years, did not improve overall outcome. Despite a satisfactory CR rate of 71% for patients aged 65-74 years, this did not translate into prolonged survival, and a high ED rate (20%) was observed. The CR rates previously reported for EWALL-backbone,¹¹ EWALL-backbone (with deescalated induction)+nilotinib,²¹ or +dasatinib²² were 85, 97, and 96%, respectively, and no¹¹/very low^{21,22} early mortality was observed in contrast to our study. However, a recently presented Spanish study showed CR and ED rates of 74% and 13%, respectively, for an EWALL-derived protocol in Ph- ALL.²⁰ One-year OS in our Ph- EWALL cohort was 46%, compared to 61% in the previously cited abstract.¹¹ A straightforward comparison of ABCDV and the EWALL-backbone-based protocol in terms of efficacy and toxicity is not justified given that they were used in different (but overlapping) age cohorts. However, when looking at the 65-74 year age-group, where comparable numbers of patients with similar baseline characteristics received each treatment option, we could not see any significant difference in outcome.

An adverse prognostic impact of age in older/elderly patients was demonstrated by us and other authors,^{7,8,19} but is not universally reported.^{6,9} In epidemiological studies, outcome according to age is striking.^{1,23} Clinical trials often include patients up to 55 or 65 years. Our results suggest that also the 65-74 year group can benefit from intensive chemotherapy. Intensive treatment beyond the 75-year age-limit resulted in low CR rate and low protocol adherence, with almost no possibility of cure. Less intensive chemotherapy ("intensive palliation") in this age-group, inclusive of the use of TKIs for Ph+ disease, seems to be an option, especially as age had a limited impact on outcome in Ph+ ALL. Ph+ disease is classically regarded as a high-risk factor in ALL,²⁴ inclusive of our national guidelines. However, the introduction of TKIs has challenged this paradigm.²⁵ We identified a similar OS in Ph- and Ph+ ALL, and a trend toward favorable outcome (compared to Ph- disease) was previously reported in a small Ph+ cohort of elderly patients.⁶ In the previously cited Spanish study, older/elderly patients with Ph+ ALL treated with imatinib and a low-intensity protocol had better outcome than those with Ph- ALL receiving EWALL-derived protocol.²⁰

The hSCT frequency in patients <65 years was high. According to some authors,^{4,26} hSCT in CR1 should be considered for eligible older patients with high-risk features (particularly Ph+).²⁴ In our study, OS was similar in Ph+ patients treated with chemotherapy+TKI

(regardless of treatment intention) and patients receiving hSCT. Even if the number of patients was low, one can speculate whether intensive treatment including hSCT is too toxic for this age-group, as reflected by the high TRM. Low-intensity protocols+TKIs have generated promising results in elderly,^{27,28} and our study indicate that a more restrictive use of hSCT should be considered for older patients with Ph+ ALL.

Thrombocytopenia was associated with impaired OS and EFS. This finding was not reported previously in elderly ALL, but has been noted in a population-based study from Denmark,²³ and in patients treated with hyper-CVAD.¹⁷ In our study, the impaired outcome was not an effect of major hemorrhage, as this affected very few patients. Instead, we interpreted the thrombocytopenia as a pseudo-marker for more aggressive disease.

Notably, survival was impaired for males compared to females in the youngest age-group. Previously reported data on the prognostic significance of sex are conflicting. Historically, male sex was regarded as a negative prognostic factor, mainly in children. In Poland, OS and probability of CR achievement in elderly were found to be superior in females.⁷ To speculate, the differences in outcome may be protocol specific, as survival impairment reported for males has disappeared during population-based study periods,²⁹ as in modern pediatric protocols.³⁰

Our study has some potential limitations. Toxicity and comorbidity data were collected retrospectively and the prognostic impact of MRD could not be accurately assessed due to lack of measurement in a high proportion of patients achieving CR.

We conclude that the prognosis remains dismal for most older and elderly ALL patients, despite intensive therapy. The use of an age-adapted protocol did not improve outcome in Sweden. Risk factors based on disease and patient characteristics, including age, can probably predict response to intensive treatment. However, Philadelphia positivity is, in the TKI-era, no longer a negative prognostic factor in older/elderly ALL patients. Our finding of an adverse prognostic impact of male sex in patients aged 55-65 years warrants further investigation. Intensive treatment should primarily be reserved for patients aged <75 years. The challenge remains to decrease early mortality and the frequency of relapse. Novel treatment modalities are urgently needed for elderly ALL patients.

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