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ORIGINAL REPORT

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ABSTRACT

Purpose
To evaluate randomly the role of hyperfractionated cyclophosphamide (hyper-C) dose intensification in adults with newly diagnosed Philadelphia chromosome–negative acute lymphoblastic leukemia treated with a pediatric-inspired protocol and to determine the upper age limit for treatment tolerability in this context.

Patients and Methods
A total of 787 evaluable patients (B/T lineage, 525 and 262, respectively; median age, 36.1 years) were randomly assigned to receive a standard dose of cyclophosphamide or hyper-C during first induction and late intensification. Compliance with chemotherapy was assessed by median doses actually received during each treatment phase by patients potentially exposed to the full planned doses.

Results
Overall complete remission (CR) rate was 91.9%. With a median follow-up of 5.2 years, the 5-year rate of event-free survival (EFS) and overall survival (OS) was 52.2% (95% CI, 48.5% to 55.7%) and 58.5% (95% CI, 54.8% to 61.9%), respectively. Randomization to the hyper-C arm did not increase the CR rate or prolong EFS or OS. As a result of worse treatment tolerance, advanced age continuously affected CR rate, EFS, and OS, with 55 years as the best age cutoff. At 5 years, EFS was 55.7% (95% CI, 51.8% to 59.4%) for patients younger than 55 years of age versus 25.8% (95% CI, 19.9% to 35.6%) in older patients (hazard ratio, 2.16; $P < .001$). Patients ≥ 55 years of age, in whom a lower compliance to the whole planned chemotherapy was observed, benefited significantly from hyper-C, whereas younger patients did not.

Conclusion
No significant benefit was associated with the introduction of a hyper-C sequence into a frontline pediatric-like adult acute lymphoblastic leukemia therapy. Overall, tolerability of an intensive pediatric-derived treatment was poor in patients ≥ 55 years of age.

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INTRODUCTION

The treatment of adult Philadelphia chromosome (Ph)–negative acute lymphoblastic leukemia (ALL) has recently evolved. New insights into ALL genetics have contributed to a better comprehension and prognostic stratification of the disease.[1] In addition, despite the lack of major new drugs until recently, important therapeutic improvements have occurred. After several reports showing a better outcome of adolescents treated with pediatric rather than adult protocols, intensified pediatric-inspired regimens with continuous dose-intense exposure to chemotherapy and higher cumulative doses of nonmyelotoxic drugs such as L-asparaginase and glucocorticoids have been proposed for adult patients.[2] The Group of Research on Adult ALL (GRAALL) Intergroup contributed to the validation of the feasibility and superiority of such an intensified approach in its first GRAALL-2003 trial, which

ASSOCIATED CONTENT

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Data Supplement
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demonstrated significant increases in complete remission (CR) rate, event-free survival (EFS), and overall survival (OS) compared with a conventional historical protocol.[3] The present GRAALL-2005 trial aimed to confirm these results on a larger scale and included a randomized evaluation of sequential administration of hyperfractionated cyclophosphamide (hyper-C), a cornerstone of the adult hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimen.[4] Another important issue studied was the role of age on outcome to define more precisely the population of adults likely to benefit from a pediatric-like approach, an issue that remains controversial.

PATIENTS AND METHODS

Study Design

The multicenter GRAALL-2005 protocol was relatively similar to that of GRAALL-2003 but with the addition of two randomized evaluations: a hyper-C sequence during induction and late intensification in all patients and rituximab in the subset of patients with $CD20^+$ B-cell precursor (BCP) ALL. The whole study design assumed that no interaction would be observed between these two evaluations, as actually reported in the GRAALL-2005/R substudy that showed a significant benefit in EFS for patients who received rituximab.[5]

Study Population

Patients 18 to 59 years of age with newly diagnosed Ph-negative BCP- or T-lineage ALL were eligible in the absence of other evolving malignancy, pregnancy, HIV infection or active viral hepatitis, or organ damage that contraindicated intensive chemotherapy. Patients with Burkitt mature B-cell lymphoma/leukemia or lymphoblastic lymphoma were not eligible. Between May 2006 and April 2014, 813 patients were randomly assigned. Eleven patients had noneligibility criteria (seven with Ph-positive ALL, one with lymphoblastic lymphoma, one with acute myeloid leukemia, one with concomitant malignancy, and one with HIV infection), 12 received a different therapy from the beginning for various reasons, and three withdrew consent. These 26 patients were excluded from the primary intention-to-treat analysis presented here, which thus included 787 patients (Fig 1).

Study Overview

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the Institutional Ethics Committee of Ile-de-France VI. Signed informed consent was obtained from all patients at trial entry. The GRAALL scientific board designed the study. The GRAALL investigators and their research teams collected data. A list of centers and investigators is provided in the Data Supplement.

Treatments

The full GRAALL-2005 protocol is detailed in the Data Supplement. Treatment phases comprised a prephase, a first induction, an optional second induction if no CR after the first induction, consolidation 1, consolidation 2, late intensification, consolidation 3, prophylactic CNS irradiation, and 2-year maintenance. During the first induction phase, cyclophosphamide was given at the standard dosage of 750 mg/m^2 on day 1 for all groups. According to the randomization arm, cyclophosphamide was then given at the same 750 mg/m^2 standard dose on day 15, which was termed standard-C group, or at the intensified dose of 300 mg/m^2 every 12 hours on days 15, 16, and 17 (six total infusions), which was termed hyper-C group. For patients who had reached CR after the first induction, standard-C or hyper-C also was used during the late intensification phase according to randomization arm. No chemotherapy dose adaptations were planned according to patients' age.

Risk Groups and Allogeneic Hematopoietic Stem-Cell Transplantation

High-risk ALL was defined by at least one of the following criteria: CNS involvement; low hypodiploidy/near triploidy as previously described[6]; complex karyotype[6,7]; poor early peripheral blood blast clearance, defined by a peripheral blood blast count $> 1.0 \times 10^9$/L at the end of the prephase; poor early bone marrow (BM) blast clearance, defined by > 5% blasts in the BM at day 8 of first induction; and late CR, defined by the need for a second induction course to reach CR. Additional factors were used in patients with BCP-ALL, including WBC $\geq 30 \times 10^9$/L; immature $CD10^-$ immunophenotype; *KMT2A* gene rearrangement, defined as t(4;11) chromosomal translocation and/or *KMT2A-AFF1* gene fusion, or another *KMT2A* rearrangement; and t(1;19) chromosomal translocation and/or *TCF3-PBX1* gene fusion. Patients who did not present with any criteria were classified as having standard-risk ALL. Molecular minimal residual disease (MRD) monitoring was neither mandatory nor used as a treatment-stratifying factor. MRD levels were evaluated on immunoglobulin/T-cell receptor gene rearrangements on BM samples from a subset of 339 patients as previously described.[8] Allogeneic hematopoietic stem-cell transplantation (HSCT) was indicated in the first CR for all patients ≤ 55 years of age with high- or undetermined-risk ALL and a matched related or 10/10 allelic-matched unrelated donor.[9]

Statistical Methods

The primary study end point was EFS. A sample size of 810 patients was estimated to be required to detect a 10% gain in 5-year EFS from 35% in the standard-C to 45% in the hyper-C arm (hazard ratio [HR], 0.76; two-sided log-rank test power, 85%; type I error, 5%). Analyses were performed according to the intention-to-treat principle. OS and EFS were calculated from the date of randomization. Events that accounted for EFS were failure of CR induction, relapse, and death. Secondary end points were OS, cumulative incidence of relapse (CIR), cumulative incidence of death in first remission (CID), and safety. Failure time data, except for cumulative incidences, were estimated by Kaplan-Meier method[10] then compared by log-rank test, with HRs estimated by the Cox proportional hazards regression model.[11] Proportional hazards assumptions were graphically checked. For estimating CIR and CID, deaths in first remission and relapses were taken into account as competing risks using cumulative incidence curves. For CIR and CID comparisons, Cox proportional hazards regression models were used to estimate cause-specific HR (SHR). Because most patients who received allogeneic HSCT did not eventually receive the second hyper-C sequence, we also performed sensitivity analyses after censoring those who underwent transplantation during first CR at the time of HSCT. Medians with interquartile ranges were compared using the Mann-Whitney *U* test. All analyses were performed with SAS 9.3 (SAS Institute, Cary, NC) or R version 2.14.0 (R packages survival, cmprsk; www.r-project.org) statistical software.

RESULTS

Patients

Patient characteristics are listed in Table 1. The median age was 36.1 years. No imbalances existed between both randomization groups except for a larger number of patients with BCP-ALL with poor early BM blast clearance in the standard-C group. A patient flowchart is shown in Figure 1.

Hyper-C Versus Standard-C Randomization

A total of 723 patients (91.9%) achieved CR. The CR rate was not significantly higher in the hyper-C than in the standard-C arm (93.6% *v* 90.2%; $P = .091$; Table 1). More patients, however, achieved CR in one course in the hyper-C arm ($P = .048$). In patients who achieved CR after the first induction, the proportion

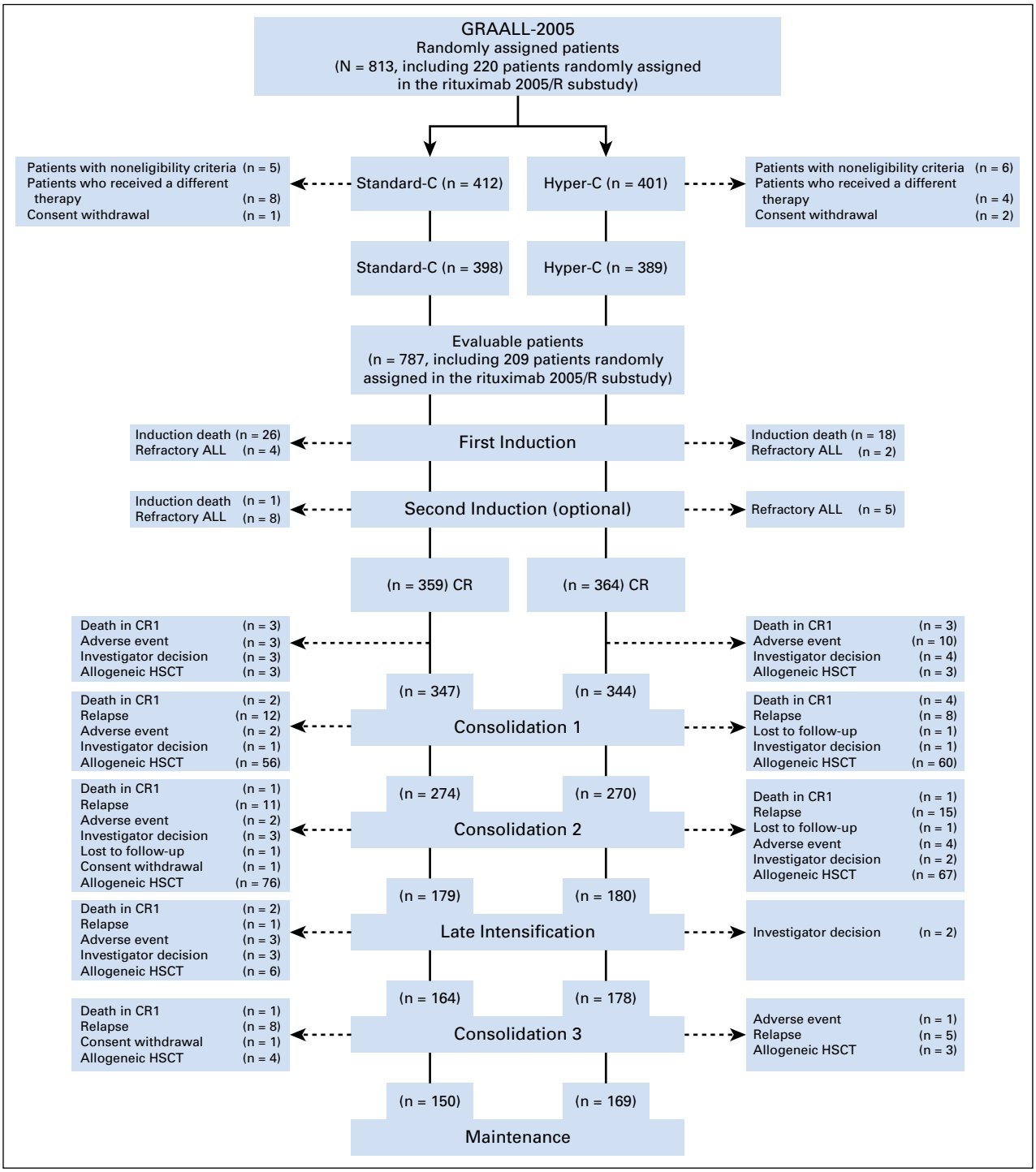

Fig 1. CONSORT diagram. ALL, acute lymphoblastic leukemia; CR, complete remission; CR1, first complete remission; HSCT, hematopoietic stem-cell transplantation; hyper-C, hyperfractionated cyclophosphamide; standard-C, standard cyclophosphamide.

of patients with a postinduction MRD level $< 10^{-4}$ was similar in both arms (108 of 164 and 105 of 175 evaluable patients in the standard-C and hyper-C arms, respectively; $P = .31$). Incidences of induction death and resistant disease after induction were similar in both arms, as was day 60 mortality (Table 1).

With a median follow-up of 5.25 years, 216 of 723 patients with CR experienced relapse (relapse sites: 163 BM, 18 BM + CNS, 19 isolated CNS, five BM + other extramedullary sites, 11 isolated other extramedullary sites). Overall, 322 patients died, including 90 deaths in first CR (causes of death: 20 infections, 50 transplant-related deaths, six secondary neoplasms, four fatal bleedings, two myocardial infarctions, two suicides, and six unknown). Globally, EFS and OS rates were estimated at 52.2% (95% CI, 48.5% to 55.7%) and 58.5% (95% CI, 54.8% to 61.9%), respectively, at

Table 1. Patient Characteristics and Outcomes According to Randomization Arm

Characteristic	Patients, No. (%)			*P*
	All	Standard-C Arm	Hyper-C Arm	
No. of patients	787	398	389	
Median age, years (IQR)	36.1 (24.8-48.4)	36.4 (24.3-47.6)	35.7 (25.3-49.3)	—
Age, years				
18-24	200 (25.4)	106 (26.6)	94 (24.2)	—
25-34	172 (21.9)	82 (20.6)	90 (23.1)	—
35-44	171 (21.7)	94 (23.6)	77 (19.8)	—
45-54	151 (19.2)	73 (18.4)	78 (20.1)	—
≥ 55	93 (11.8)	43 (10.8)	50 (12.8)	—
BCP-ALL	525 (67)	266 (67)	259 (67)	—
WBC ≥ 30×10^9/L	118 (22.5)	51 (19.2)	67 (25.9)	—
CNS involvement	27 (5.1)	15 (5.6)	12 (4.6)	—
t(4;11)/*KMT2A-AFF1*, No. evaluable	55 of 508 (10.8)	21 of 260 (8.1)	34 of 248 (13.7)	—
t(9;11)/*TCF3-PBX1*, No. evaluable	21 of 486 (4.3)	9 of 252 (3.6)	12 of 234 (5.1)	—
Poor early PB blast clearance, No. evaluable	79 of 523 (15.1)	42 of 266 (15.8)	37 of 257 (14.4)	—
Poor early BM blast clearance, No. evaluable	189 of 515 (36.7)	111 of 261 (42.5)	78 of 254 (30.7)	—
T-ALL	262 (33)	132 (33)	130 (33)	—
CNS involvement	28 (10.7)	15 (11.4)	13 (10.0)	—
Poor early PB blast clearance	104 of 262 (39.7)	57 of 132 (43.2)	47 of 130 (36.1)	—
Poor early BM blast clearance	118 of 260 (45.4)	67 of 130 (51.5)	51 of 130 (39.2)	—
High-risk ALL, No. evaluable	467 of 677 (69)	244 of 338 (72)	223 of 339 (66)	—
Outcome				
CR	723 (91.9)	359 (90.2)	364 (93.6)	.09
CR in one course	705 (89.6)	348 (87.5)	357 (91.8)	.05
Induction death	44 (5.6)	26 (6.5)	18 (4.6)	.28
Resistant disease	20 (2.5)	13 (3.3)	7 (1.8)	.26
60-day mortality	52 (6.6)	31 (7.8)	21 (5.4)	.20
Allogeneic HSCT in first CR	278 (35)	145 (36)	133 (34)	.55
Time from CR to HSCT in first CR, days (IQR)	111 (84-142)	112 (86-143)	110 (84-139)	.69
5-year CIR, % (95% CI)	30.5 (27.2 to 34.1)	31.6 (26.9 to 36.8)	29.4 (25.0 to 34.5)	.62
5-year CID, % (95% CI)	12.3 (10.1 to 15.0)	12.3 (9.2 to 16.2)	12.4 (9.3 to 16.4)	.63
5-year EFS, % (95% CI)	52.2 (48.5 to 55.7)	50.1 (44.9 to 55.1)	54.2 (49.0 to 59.2)	.25
5-year OS, % (95% CI)	58.5 (54.8 to 61.9)	57.4 (52.2 to 62.3)	59.5 (54.2 to 64.3)	.45

Abbreviations: ALL, acute lymphoblastic leukemia; BCP, B-cell precursor; BM, bone marrow; CID, cumulative incidence of death in first complete remission; CIR, cumulative incidence of relapse; CR, complete remission; EFS, event-free survival; HSCT, hematopoietic stem-cell transplantation; hyper-C, hyperfractionated cyclophosphamide; IQR, interquartile range; OS, overall survival; PB, peripheral blood; standard-C, standard cyclophosphamide.

5 years. As depicted in Figure 2A, EFS was not longer in the hyper-C than in the standard-C arm (54.2% [95% CI, 49.0% to 59.2%] *v* 50.1% [95% CI, 44.9% to 55.1%] at 5 years; HR, 0.89; 95% CI, 0.72 to 1.09; $P = .25$). Similarly, OS (HR, 0.92; 95% CI, 0.74 to 1.14; $P = .45$), CIR (SHR, 0.94; 95% CI, 0.72 to 1.22]; $P = .62$), and CID (SHR, 1.04; 95% CI, 0.82 to 1.33; $P = .63$) were not longer or higher in the hyper-C arm (Table 1). Similar results were observed when the 278 patients who received HSCT in first CR (259 of 513 eligible patients + 19 patients with standard-risk ALL) were censored at the time of HSCT (Data Supplement).

To investigate further the effects of hyper-C, we evaluated treatment arm effects among various patient subgroups. Results of this post hoc analysis (Fig 3) revealed a lower HR for EFS in favor of the hyper-C arm in patients ≥ 55 years of age (HR, 0.51; 95% CI, 0.32 to 0.84), with a significant interaction test ($P = .029$). No interaction with rituximab administration was found in the 209 patients also randomly assigned in the GRAALL-2005/R study.

Effect of Age

Given this unexpected interaction between age and the efficacy of hyper-C, we analyzed the overall effect of increasing age on outcome and compliance to the planned therapy. Table 2 lists patient outcomes according to the five age subsets listed in Table 1. As indicated, increasing age continuously worsened EFS and OS, with 55 years appearing to be the most relevant age cutoff. At younger than 55 years of age, 5-year EFS and OS rates remained > 50% (55.7% [95% CI, 51.8% to 59.4%] and 62.7% [95% CI, 58.8% to 66.3%], respectively), whereas in older patients, 5-year EFS and OS rates were estimated at 25.8% (95% CI, 19.9% to 35.6%) and 27.4% (95% CI, 18.3% to 37.4%) only (Fig 2B for EFS; Data Supplement for OS). As listed in Table 2, this worse outcome was associated with higher incidences of induction death and death in first CR, even in patients without transplants, rather than with higher incidences of relapsed/refractory disease. Analysis of compliance to the planned protocol revealed that patients ≥ 55 years of age received significantly lower doses of most chemotherapy drugs than younger patients during each treatment phase (Table 3).

Figure 2C illustrates this interaction between age ≥ 55 years and the hyper-C effect. A similar interaction was found when patients who received HSCT in first CR were censored at the time of HSCT (Data Supplement). Despite that they retained lower EFS than younger patients, patients ≥ 55 years of age significantly benefited from the hyper-C regimen, whereas younger patients did not. Of note, this benefit was only observed in the subset of patients with chemotherapy-sensitive ALL, defined as good early BM blast

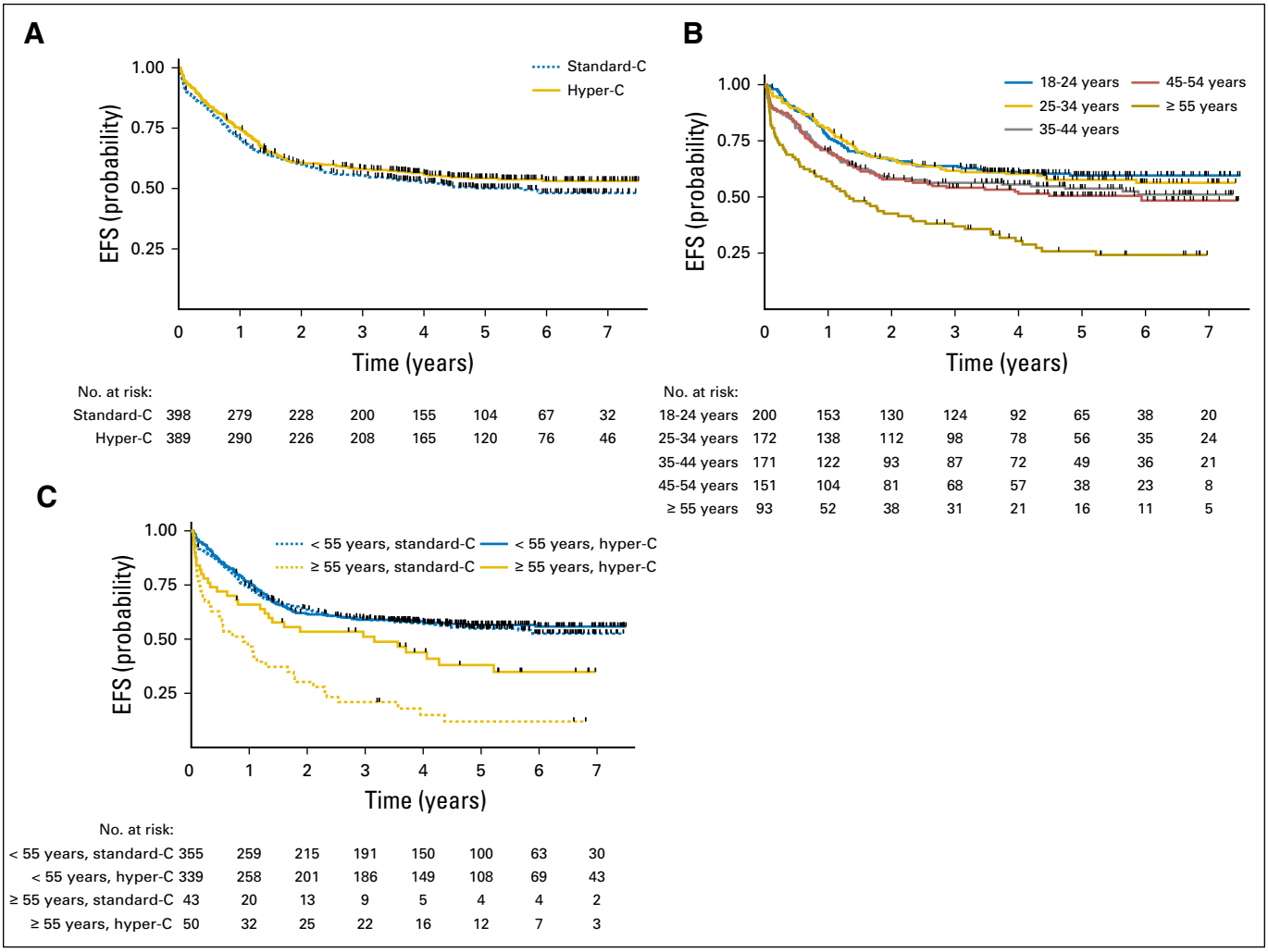

Fig 2. Event-free survival (EFS). (A) EFS according to hyperfractionated cyclophosphamide (hyper-C) versus standard cyclophosphamide (standard-C) randomization. EFS was not significantly higher in the hyper-C arm than in the standard-C arm (hazard ratio [HR], 0.89; 95% CI, 0.72 to 1.09; $P = .25$). Five-year EFS estimates are listed in Table 1. (B) EFS according to age subsets. Five-year EFS estimates are listed in Table 2. Patients ≥ 55 years of age had significantly shorter EFS than those younger than 55 years (HR, 2.16; 95% CI, 1.66 to 2.82; $P < .001$); at 5 years, EFS rate estimates were 25.8% (95% CI, 16.9% to 35.6%) and 55.7% (95% CI, 51.8% to 59.4%), respectively. Within the latter group, patients age 35 to 54 years had a shorter EFS than those age 18 to 34 years (HR, 1.31; 95% CI, 1.05 to 1.64; $P = .019$); at 5 years, EFS rate estimates were 52.2% (95% CI, 46.5% to 57.7%) and 58.7% (95% CI, 53.4% to 63.6%), respectively. (C) EFS according to age (< 55 or ≥ 55 years) and hyper-C versus standard-C randomization. In the 18 to 54 age range, 5-year EFS rate estimates were 56.5% (95% CI, 51.0% to 61.7%) in the hyper-C versus 54.8% (95% CI, 49.3% to 60.0%) in the standard-C arm (HR, 0.95; 95% CI, 0.76 to 1.19; $P = .66$). In patients ≥ 55 years of age, 5-year EFS rate estimates were 38.0% (95% CI, 23.8% to 52.1%) in the hyper-C versus 12.0% (95% CI, 4.1% to 24.3%) in the standard-C arm (HR, 0.51; 95% CI, 0.32 to 0.84]; $P = .007$). With respect to each type of EFS event in this older age subset, the complete remission rate was 82.0% versus 76.7% ($P = .61$), induction mortality was 18.0% versus 18.6% ($P = .99$), 5-year cumulative incidence of relapse was 33.3% (95% CI, 20.8% to 50.5%) versus 45.8% (95% CI, 30.6% to 64.2%; HR, 0.66; 95% CI, 0.31 to 1.38; $P = .27$), and 5-year cumulative incidence of death in first remission was 18.9% (95% CI, 9.4% to 35.8%) versus 36.9% (95% CI, 22.9% to 55.9%; HR, 0.48; 95% CI, 0.20 to 1.18; $P = .11$) in the hyper-C versus the standard-C arm, respectively.

clearance at day 8 (Data Supplement). Conversely, patients younger than age 55 years drew no benefit from the hyper-C treatment, whatever their BM blast clearance was at day 8.

DISCUSSION

We report the results of the GRAALL-2005 trial, which enrolled a large cohort of 787 adults age18 to 59 years with Ph-negative ALL. These results are very close to those observed in an updated analysis of our previous GRAALL-2003 study.[3] In these two consecutive trials, rates of CR were 93.5% and 91.9%; 5-year EFS, 53.0% and 52.2% (Data Supplement); and 5-year OS, 58.6% and 58.5%, respectively. Such achievements compare favorably to previous adult-type protocols. For instance, in 1,418 adults with Ph-negative ALL enrolled in the largest Medical Research Council UKALL XII/ECOG E2993 trial, the OS rate was estimated at 43% at 5 years.[12,13]

Better outcomes have been reported repeatedly when using intensified protocols in younger adults, with 5-year OS rate estimates approaching or even surpassing 60%. The first trials to use unmodified pediatric protocols included relatively low numbers of patients and often were limited to selected adolescents and young adults (AYAs) younger than 40 years of age.[2] The largest C10403 trial from the US Intergroup evaluated the pediatric Children's Oncology Group regimen in AYAs 16 to 39 years of age.[14] With

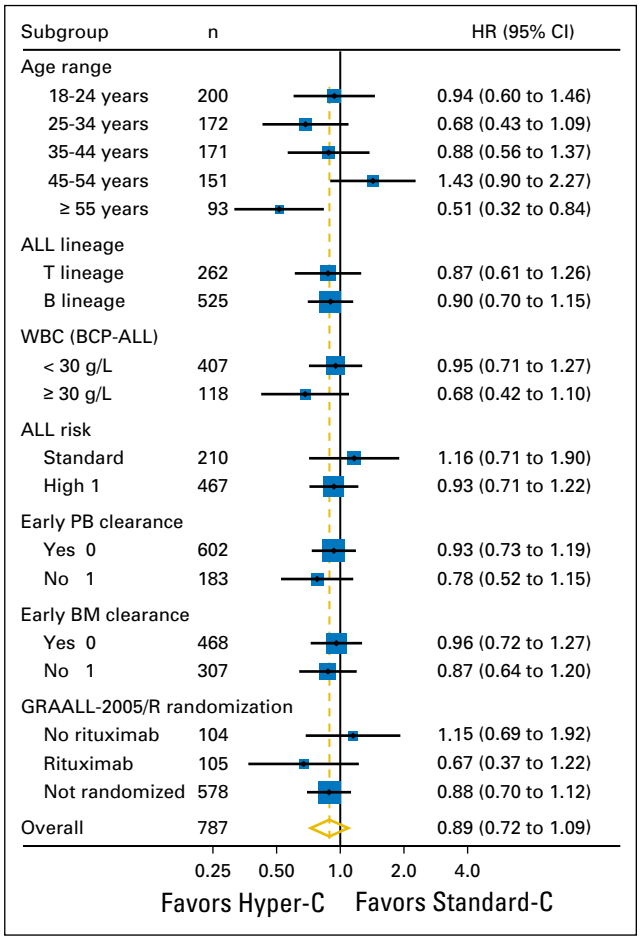

Fig 3. Effects of hyperfractionated cyclophosphamide (hyper-C) versus standard cyclophosphamide (standard-C) randomization on event-free survival in patient subgroups. ALL, acute lymphoblastic leukemia; BCP, B-cell precursor; BM, bone marrow; HR, hazard ratio; PB, peripheral blood.

a relatively short median follow-up of 28 months, EFS and OS rates were estimated at 66% (95% CI, 60% to 72%) and 78% (95% CI, 72% to 83%), respectively, at 2 years.[14] Conversely, some European study groups, including the Northern Italy Leukemia Group,[15] the German Multicenter Study Group for Adult ALL,[16,17] and the GRAALL, have developed pediatric-inspired protocols adapted to be tolerated by adults up to 55 to 65 years of age. These groups progressively and cautiously have incorporated most pediatric treatment elements, even if allogeneic HSCT was still proposed for a majority of patients defined by high-risk features or unsatisfactory MRD response. Of note, early MRD response was not used to stratify therapy in the GRAALL-2005 trial. Because the predictive value of MRD for allogeneic HSCT superiority over chemotherapy was later demonstrated,[8,9] MRD levels currently are used to guide additional therapy in the ongoing GRAALL-2014 study. To date, no randomized study has prospectively compared an unmodified pediatric with a pediatric-derived protocol in younger adults. Thus, no upper age limit has been recommended for using a pediatric protocol in AYAs. Nevertheless, with an estimated 2-year EFS rate of 65.1% (95% CI, 60.5% to 69.3%) and 2-year OS rate of 74.3% (95% CI, 70.0% to 78.1%), the outcome of the 456 patients ≤ 39 years of age treated in the current GRAALL-2005 trial seem to be very close to those observed with the pediatric Children's Oncology Group regimen in the C10403 trial.

The GRAALL-2005 trial enrolled patients up to 59 years of age, whereas the upper age limit was 65 years in the Northern Italy Leukemia Group ALL 09/00 study and remains at 55 years in the German Multicenter Study Group for Adult ALL studies,[15-17] which underscores a similar uncertainty with respect to the upper limit for using a pediatric-derived protocol in adults. This issue was addressed retrospectively in the current report. Of note, increasing age was already an unfavorable prognostic factor in the previous GRAALL-2003 trial, with a best prognostic cutoff at 45 years at that time.[3] In the current trial, this best cutoff increased to 55 years, which might be due to statistical issues related to different sample sizes but might also suggest that a learning phase has been necessary to allow physicians to administer an intensified protocol appropriately to adult patients. For instance, in patients 45 to 54 years of age, the CR rate increased from 86.0% to 89.4% and the 5-year OS rate from 46.2% (95% CI, 30.8% to 60.2%) to 56.7% (95% CI, 48.0% to 64.5%) between the GRAALL-2003 and GRAALL-2005 trials.

The poorer results obtained in older patients mostly were related to worse tolerance of the planned therapy, with higher treatment-related mortality, rather than to a higher incidence of chemotherapy-resistant, refractory, or relapsed ALL. The poor tolerability of pediatric-like ALL therapy is an important concern in patients ≥ 55 years of age, with an induction death rate of 18.5%, a 25.5% incidence of death in first CR in patients without transplants, and a worse compliance with planned chemotherapy doses. Even if it was planned to treat patients up to 59 years of age, the GRAALL protocol cannot be administered easily to patients age ≥ 55 years. Poor tolerance to L-asparaginase has been reported in patients older than 50 years, with major hepatic, pancreatic, metabolic, and thromboembolic toxicities.[18-23] Such patients also present a poorer tolerance to glucocorticoid therapy, which exposes them to metabolic, vascular, and infectious complications. In the GRAALL experience, the median age of patients who developed invasive fungal infections before HSCT was 47 years.[24] This poor treatment tolerance, which led to a dismal 27.4% 5-year OS in the older age population, suggests that 55 years is a reasonable upper age limit to treat adult patients with ALL with a pediatric-derived protocol. One might argue that an age limit is arbitrary and does not reflect the real health status of patients. However, because eligibility also specified a lack of organ dysfunction, the trial population likely was more homogeneous than a general population of the same age, and age, nevertheless, retained its prognostic value in patients selected for the trial.

Another important protocol used to treat adults with ALL is the hyper-CVAD regimen. The concept of hyper-C was first developed in childhood Burkitt mature B-cell lymphoma/leukemia, which relies on the specific kinetics of this tumor,[25] and was then widely applied to adults and other lymphoid malignancies, including BCP- and T-ALL. In 229 adults 15 to 59 years of age, including patients with Ph-positive ALL, the CR rate was 94.8% and estimated 5-year OS rate 51% in patients younger than 40 years versus 30% in those age 40 to 59 years.[4] With necessary caution in interpreting results of single-center nonrandomized studies, the hyper-CVAD regimen has been shown to be as effective as

Table 2. Patient Outcomes According to Age Subsets

Outcome	Age Subset (years), No. (%)						Comparison of ≥ 55 *v* < 55 years
	All	18-24	25-34	35-44	45-54	≥ 55	
No. of patients	787	200	172	171	151	93	—
High-risk patients with ALL, No. evaluable	467 of 677 (69.0)	124 of 188 (66)	108 of 149 (72.5)	99 of 147 (67.3)	88 of 127 (69.3)	48 of 66 (72.7)	
No. of patients with allogeneic HSCT in first CR	278	71	77	58	54	18	—
Postinduction status							
Poor early BM blast clearance, No. evaluable	307 of 775 (39.6)	72 of 199 (36.2)	65 of 169 (38.5)	78 of 168 (46.4)	59 of 147 (40.1)	33 of 92 (35.9)	.50
CR	723 (91.9)	197 (98.5)	164 (95.3)	153 (89.5)	135 (89.4)	74 (79.6)	$P < .001$
Induction deaths	44 (5.6)	1 (0.5)	3 (1.7)	13 (7.6)	10 (6.6)	17 (18.3)	$P < .001$ *
Resistant disease	20 (2.5)	2 (1)	5 (3)	5 (2.9)	6 (4)	2 (2.1)	$P = .57$
Postinduction MRD level $< 10^{-4}$, No. evaluable	213 of 339 (62.8)	60 of 96 (62.5)	61 of 89 (68.5)	45 of 82 (54.9)	34 of 49 (69.4)	13 of 23 (56.5)	.51
Relapse							
No. of relapses	216	62	44	49	33	28	—
5-year CIR, % (95% CI)	30.5 (27.2 to 34.1)	32.2 (26.1 to 39.4)	27.7 (21.4 to 35.4)	31.4 (24.6 to 39.6)	25.5 (18.8 to 34.0)	39.1 (28.8 to 51.4)	SHR, 1.32 (0.89 to 1.97; $P = .17$)
Death in first CR							
No. of deaths in first CR	90	14	19	12	25	20	—
No. of post-HSCT deaths in first CR	50	12	13	8	13	4	—
5-year CID, % (95% CI)	12.3 (10.1 to 15.0)	7.2 (4.3 to 11.9)	11.5 (7.4 to 17.6)	8.2 (4.7 to 14.1)	17.6 (12.1 to 25.4)	26.9 (18.0 to 39.0)	SHR, 2.74 (1.66 to 4.50; $P < .001$)
5-year CID after HSCT censoring, % (95% CI)	7.4 (5.4 to 10.2)	1.3 (0.3 to 5.4)	5.0 (2.2 to 11.2)	4.3 (1.6 to 11.3)	11.6 (6.3 to 21.0)	25.5 (16.0 to 39.2)	SHR, 5.56 (2.95 to 10.5; $P < .001$)
EFS							
No. of events	370	79	71	79	74	67	—
5-year EFS, % (95% CI)	52.2 (48.5 to 55.7)	59.5 (52.2 to 66.1)	57.6 (49.6 to 64.9)	53.7 (45.7 to 61.1)	50.5 (41.9 to 58.4)	25.8 (16.9 to 35.6)	HR, 2.16 (1.66 to 2.82; $P < .001$)
5-year EFS after HSCT censoring, % (95% CI)	52.2 (47.5 to 56.6)	59.7 (50.5 to 67.7)	56.9 (46.0 to 66.3)	56.5 (46.4 to 65.4)	51.1 (40.0 to 61.1)	24.8 (14.7 to 36.3)	HR, 2.42 (1.68 to 3.01; $P < .001$)
OS							
No. of deaths	322	63	61	67	66	65	—
5-year OS, % (95% CI)	58.5 (54.8 to 61.9)	68.1 (60.9 to 74.2)	64.8 (56.8 to 71.6)	59.5 (51.5 to 66.6)	56.7 (48.0 to 64.5)	27.4 (18.3 to 37.4)	HR, 2.51 (1.91 to 3.30) $P < .001$
5-year OS after HSCT censoring, % (95% CI)	57.3 (52.6 to 61.6)	68.1 (59.1 to 75.5)	60.8 (49.9 to 70.1)	60.3 (50.3 to 68.9)	58.0 (46.8 to 67.2)	25.1 (15.0 to 36.6)	HR, 2.66 (1.97 to 3.59) $P < .001$

Abbreviations: ALL, acute lymphoblastic leukemia; BM, bone marrow; CID, cumulative incidence of death in first remission; CR, complete remission; EFS, event-free survival; HR, hazard ratio; HSCT, hematopoietic stem-cell transplantation; OS, overall survival; MRD, minimal residual disease; SHR, cause-specific hazard ratio.

*Induction death rate was already higher in the 322 patients 35 to 54 years of age compared with the 372 younger patients (7.1% *v* 1.1%; $P < .001$).

Table 3. Compliance With the Planned Therapy According to Age (< 55 or ≥ 55 Years) by Treatment Phase

Treatment Phase	Cumulative Planned Dose	Patients, No.		Patients 18 to 54 Years of Age		Patients ≥ 55 Years of Age		
		Treatment Initiated	Evaluable	No.	Cumulative Dose Actually Received, Median (IQR)	No.	Cumulative Dose Actually Received, Median (IQR)	P*
First induction		787	738	662	—	76	—	—
VCR, mg	8	—	738	662	8 (8-8)	76	8 (8-8)	.190
DNR, mg/m^2	210	—	738	662	210 (207-210)	76	210 (206-210)	.580
L-aspa†, IU/m^2	48,000 (30,000)	—	737	661	48,000 (36,000-48,000)	76	36,000 (24,000-48,000)	< .001
PDN, mg/m^2	840	—	736	660	819 (700-840)	76	837 (721-840)	.072
Standard-C arm, mg/m^2	1,500	398	370	335	1,500 (1,486-1,500)	35	1,497 (1,477-1,500)	.170
Hyper-C arm, mg/m^2	2,550	389	368	327	2,545 (2,488-2,550)	41	2,550 (2,466-2,550)	.600
Consolidation 1		691	681	614	—	67	—	—
Ara-C, mg/m^2	8,000	—	679	613	7,860 (7,600-8,000)	66	7,728 (7,306-8,000)	.010
MTX, mg/m^2	3,000	—	678	612	2,955 (2,865-3,000)	66	2,874 (2,730-3,000)	< .001
CPM, mg/m^2	1,000	—	681	614	986 (954-1,000)	67	958 (940-1,000)	.005
Consolidation 2		544	474	423	—	51	—	—
Ara-C, mg/m^2	8,000	—	474	423	7,907 (7,596-8,000)	51	7,643 (7,215-8,000)	< .001
MTX, mg/m^2	3,000	—	474	423	2,973 (2,856-3,000)	51	2,871 (2,768-3,000)	.011
CPM, mg/m^2	1,000	—	474	423	995 (956-1,000)	51	970 (938-1,000)	.037
Late intensification		359	357	315	—	42	—	—
VCR, mg	8	—	357	315	8 (8-8)	42	8 (4-8)	.051
DNR, mg/m^2	150	—	357	315	150 (143-150)	42	147 (140-150)	.039
L-aspa, IU/m^2	48,000	—	357	315	48,000 (0-48,000)	42	36,000 (0-48,000)	.150
PDN, mg/m^2	840	—	357	315	809 (688-840)	42	770 (614-826)	.028
Standard-C arm, mg/m^2	1,500	179	178	161	1,500 (1,432-1,500)	17	1,470 (1,402-1,500)	.092
Hyper-C arm, mg/m^2	2,550	180	179	154	2,507 (2,300-2,550)	25	2,429 (1,620-2,512)	.028
Consolidation 3		342	337	297	—	40	—	—
Ara-C, mg/m^2	8,000	—	337	297	8,000 (7,614-8,000)	40	7,670 (7,403-8,000)	.011
MTX, mg/m^2	3,000	—	333	295	3,000 (2,880-3,000)	38	2,835 (2,703-3,000)	< .001
CPM, mg/m^2	1,000	—	334	295	1,000 (964-1,000)	39	958 (940-1,000)	.002

NOTE. Compliance with the most important drugs was evaluated at the end of each treatment phase in patients with available data and potentially exposed to the full planned doses during the treatment phase of interest; patients who died received allogeneic stem-cell transplants in first complete remission or experienced relapse during the treatment phase were not considered in these comparisons.

Abbreviations: Ara-C, cytarabine; CPM, cyclophosphamide; DNR, daunorubicin; hyper-C, hyperfractionated cyclophosphamide; IQR, interquartile range; L-aspa, L-asparaginase; MTX, methotrexate; PDN, prednisone; standard-C, standard cyclophosphamide; VCR, vincristine.

*Median doses actually received by patients 18 to 54 and ≥ 55 years of age were compared using the Mann-Whitney *U* test.

†L-aspa was planned to be administered for a total of eight injections at 6,000 IU/m^2 per injection during both first induction and late intensification phases. In patients with CNS involvement at diagnosis, the planned number of L-aspa injections was reduced to five during the first induction phase to prevent cumulative toxicities with early intrathecal therapy; 55 patients had initial CNS involvement, including 51 of the 738 patients evaluable for the first induction phase (48 who were 18 to 54 years of age, three who were ≥ 55 years of age; *P* = .35).

a pediatric-derived protocol.[26] In the GRAALL-2005 study, the role of this hyper-C component was evaluated during induction and late intensification. In the context of a totally different protocol, hyper-C failed to prolong EFS overall. Nevertheless, post hoc analyses suggested that hyper-C might benefit the group of patients with ALL ≥ 55 years of age with good early sensitivity to chemotherapy (ie, good early BM blast clearance before standard-C *v* hyper-C initiation). Even if possibly a result of chance with respect to the number of unplanned subgroup analyses, this observation suggests that older patients who cannot optimally tolerate the planned GRAALL protocol might benefit from early intensification of a tolerable drug, at least if they do not have chemotherapy-resistant ALL. Novel, more immediately tolerable strategies thus could be designed for older patients as has been proposed with the antibody drug conjugate inotuzumab ozogamicin.[27]

In conclusion, the results of the GRAALL-2005 study confirm the value of a pediatric-derived approach to treating adults with Ph-negative ALL, at least those between 18 and 54 years of age, because treatment compliance and tolerability worsen in those age ≥ 55 years. Although the ongoing GRAALL-2014 trial also was designed for patients in the 18 to 59 age range, we planned dose reductions for all patients age ≥ 45 years. On the other hand, the lower age limit to enter GRAALL trials specifically designed for elderly patients is now 55 years, with overlap for patients 55 to 59 years of age.

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Disclosures provided by the authors are available with this article at jco.org.

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Intensified Therapy of Acute Lymphoblastic Leukemia in Adults: Report of the Randomized GRAALL-2005 Clinical Trial

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