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

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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. 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. 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
demonstrated significant increases in complete remission (CR) rate, event-free survival (EFS), and overall survival (OS) compared with a conventional historical protocol. 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. 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.

**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 no eligibility 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 Ille-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/m² on day 1 for all groups. According to the randomization arm, cyclophosphamide was then given at the same 750 mg/m² standard dose on day 15, which was termed standard-C group, or at the intensified dose of 300 mg/m² 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; complex karyotype; poor early peripheral blood blast clearance, defined by a peripheral blood blast count > 1.0 × 10⁹/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 ≥ 30 × 10⁹/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. 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.

**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 (CIRD), and safety. Failure time data, except for cumulative incidences, were estimated by Kaplan-Meier method then compared by log-rank test, with HRs estimated by the Cox proportional hazards regression model. Proportional hazards assumptions were graphically checked. For estimating CIR and CIRD, deaths in first remission and relapses were taken into account as competing risks using cumulative incidence curves. For CIR and CIRD 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 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.

**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% vs 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...
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
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* = .62), and CID (HR, 0.94; 95% CI, 0.72 to 1.22; *P* = .62), and CIR (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, 0.74 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).

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 response.
We report the results of the GRAALL-2005 trial, which enrolled a large cohort of 787 adults age 18 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. 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 53.0% and 52.2% (Data Supplement); and 5-year OS, 58.6% and 52.2% (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 (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**

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. The largest C10403 trial from the US Intergroup evaluated the pediatric Children's Oncology Group regimen in AYAs 16 to 39 years of age. With
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. Conversely, some European study groups, including the Northern Italy Leukemia Group, the German Multicenter Study Group for Adult ALL, 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 patients up to 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. 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. 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, 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. With necessary caution in interpreting results of single-center nonrandomized studies, the hyper-CVAD regimen has been shown to be as effective as the 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, 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. 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. 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. 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.

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### Table 3

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24 years</td>
<td>200</td>
<td>0.94 (0.60 to 1.46)</td>
</tr>
<tr>
<td>25-34 years</td>
<td>172</td>
<td>0.68 (0.43 to 1.09)</td>
</tr>
<tr>
<td>35-44 years</td>
<td>171</td>
<td>0.88 (0.56 to 1.37)</td>
</tr>
<tr>
<td>45-54 years</td>
<td>151</td>
<td>1.43 (0.90 to 2.27)</td>
</tr>
<tr>
<td>≥ 55 years</td>
<td>93</td>
<td>0.51 (0.32 to 0.84)</td>
</tr>
<tr>
<td>ALL lineage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T lineage</td>
<td>262</td>
<td>0.87 (0.61 to 1.26)</td>
</tr>
<tr>
<td>B lineage</td>
<td>525</td>
<td>0.90 (0.70 to 1.15)</td>
</tr>
<tr>
<td>WBC (BCP-ALL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 g/L</td>
<td>407</td>
<td>0.95 (0.71 to 1.27)</td>
</tr>
<tr>
<td>≥ 30 g/L</td>
<td>118</td>
<td>0.68 (0.42 to 1.10)</td>
</tr>
<tr>
<td>ALL risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>210</td>
<td>1.16 (0.71 to 1.90)</td>
</tr>
<tr>
<td>High 1</td>
<td>467</td>
<td>0.93 (0.71 to 1.22)</td>
</tr>
<tr>
<td>Early PB clearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes 0</td>
<td>602</td>
<td>0.93 (0.73 to 1.19)</td>
</tr>
<tr>
<td>No 1</td>
<td>183</td>
<td>0.78 (0.52 to 1.15)</td>
</tr>
<tr>
<td>Early BM clearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes 0</td>
<td>468</td>
<td>0.96 (0.72 to 1.27)</td>
</tr>
<tr>
<td>No 1</td>
<td>307</td>
<td>0.87 (0.64 to 1.20)</td>
</tr>
<tr>
<td>GRAALL-2005/R randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No rituximab</td>
<td>104</td>
<td>1.15 (0.69 to 1.92)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>105</td>
<td>0.67 (0.37 to 1.22)</td>
</tr>
<tr>
<td>Not randomized</td>
<td>578</td>
<td>0.88 (0.70 to 1.12)</td>
</tr>
<tr>
<td>Overall</td>
<td>787</td>
<td>0.89 (0.72 to 1.09)</td>
</tr>
</tbody>
</table>

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.
Table 2. Patient Outcomes According to Age Subsets

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

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).
a pediatric-derived protocol. 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 or 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.

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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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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