

Hematopoietic cell transplantation for older acute myeloid leukemia patients in first complete remission: results of a randomized phase III study

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Abstract

Given the selection of elderly patients with AML in first complete remission (CR1) the advantage of consolidation with allogeneic hematopoietic cell transplantation (HCT) over chemotherapy is still unclear. Newly diagnosed AML patients in CR1 aged 60–75 years were registered and a donor search initiated. After one consolidation cycle, patients with a matched donor were randomized to HCT with fludarabine/low-dose total body irradiation and cyclosporine/mycophenolate mofetil immunosuppression or conventional non-HCT. Primary outcome was restricted mean leukemia-free survival (RM-LFS) up to 5

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years. Between 2010 and 2017, 245 patients (median age 67 years) were registered at CR1. After one consolidation, 26.9% of patients failed inclusion criteria. Of the 179 (73%) patients still on study, 75.4% had an HLA identical donor. Ten ineligible patients were excluded, and 125 randomized to HCT (N=83) or non-HCT (N=42). The primary outcome RM-LFS up to 5 years was 24.5 months (95% confidence interval [CI]: 18.9-30.1) in the HCT and 15.6 months (95% CI: 10.4-20.8) in the non-HCT arm ($P=0.022$) due to a decrease in cumulative relapse incidence from 91.1% (95% CI: 80.7-100.0) after non-HCT to 37.8% (95% CI: 27.2-48.4) after HCT ($P<0.0001$). The secondary endpoints RM-OS up to 5 years was 27.8 months (95% CI: 22.3-33.2) in the HCT as compared to 28.6 months (95% CI: 22.2-35.0) in the non-HCT arm; non-relapse mortality at 5 years was 33.4% (95% CI: 23.0-43.9) with HCT and 0% without. In older patients with AML in CR1 5-year RM-LFS is better with HCT than with non-HCT consolidation treatment. The long-term RM-LFS benefit did not translate into a better RM-OS during the study period.

Introduction

Acute myeloid leukemia (AML) has a dismal prognosis in the continuously growing population of patients of greater age. Advances in supportive therapy have improved the proportion of patients who might benefit from a potentially curative treatment.¹⁻⁴ However, attempts to improve leukemia-free survival (LFS) by increasing therapy intensity have largely been unsuccessful, mostly because of very high relapse rates (>80%), resulting in average long-term survival rates of 20% or less.^{2,5} For the time being long-term outcome perspectives have not been significantly improved by more recent treatment approaches.⁶⁻¹¹

Hematopoietic cell transplantation (HCT) has been shown to be the treatment modality with a high anti-leukemic potential, combining immunological anti-leukemia effects with preparative regimens of variable intensities.¹² For decades, HCT was restricted to younger and fit patients up to the age of 60 years. Since the beginning of the century, the use of HCT has been extended to adults of greater age (generally up to the age of 75 years) by employing reduced-intensity conditioning (RIC) or non-myeloablative (NMA) preparative regimens.¹³⁻¹⁶ Retrospective analyses and prospective studies in elderly patients have confirmed the potential of HCT to induce durable long term remissions.¹⁶⁻¹⁹ On the basis of these clinical trials, the application of HCT at older age patients has risen substantially. Randomized studies have yet to be done so a critical assessment of the comparative therapeutic value of HCT has not yet become available. This is relevant especially in patients of greater age since various selection factors (e.g., leukemia prognostic risk, comorbidities) in the older age segment may significantly influence the access to HCT. As a consequence, the selection of more favorable risk patients for HCT may profoundly impact on therapeutic outcome.

Here, we report the results of a prospective randomized study in patients with AML aged 60-75 years eligible for an intensive and low-intensity induction treatment approach that were enrolled directly after achievement of first CR (CR1). The design enabled the assessment of the dropout rate of patients on consolidation and prior to HCT, the

chance of identifying a matched donor, the logistics of performing HCT within a predetermined maximal interval from diagnosis, and the kinetics of relapse.

Methods

Trial design

This is an international, prospective, open, randomized, controlled trial to compare allogeneic HCT *versus* conventional consolidation therapy in elderly patients with AML in CR1. The study design is detailed in the *Online Supplementary Figure S1*.

Patients, 60-75 years of age, with newly diagnosed AML were treated with one or two induction therapies (*Online Supplementary Table S4A*). After reaching CR1, patients were registered and subsequently HLA typed. A related/unrelated donor search was initiated and consolidation therapy started. After consolidation, patients were evaluated for comorbidity and hematological response. Eligible patients (see *Online Supplementary Table S1*) with an HLA-identical related or 10/10 matched unrelated donor were randomized (2:1 ratio) to receive HCT within 4 weeks or non-HCT consolidation according to institutional treatment protocols (*Online Supplementary Table S4B*) within 2 weeks after randomization. No additional chemotherapy was applied between randomization and HCT or non-HCT treatment. Randomization used Pocock minimization with center, type of donor (unrelated vs. HLA-identical sibling donors) and risk group at diagnosis (high-risk vs. intermediate- to low-risk according to Grimwalde *et al.*²⁰) as strata. Patients randomized to non-HCT treatment maintained the fallback option of using their stem cell donor in the event of relapse. The trial was approved by the ethics committees of the participating institutions, registered (EudraCT number: 2007-003514-34) and informed consent obtained from each participant.

Trial procedures

HCT was performed after conditioning with fludarabine/200 cGy total body irradiation and cyclosporine /mycophenolate mofetil immunosuppression as previously described.^{14,15} No ATG was used. Non-HCT consolidation was administered according to local protocols.

Outcomes

The primary endpoint was restricted mean (RM)-LFS, defined as time from randomization to the first of the following three events: hematological relapse, initiation of additional anti-leukemic therapy, or death from any cause. Secondary endpoints included cumulative incidence of relapse (RI), non-relapse mortality (NRM), overall survival (OS) and complications including graft-versus-host disease (GVHD).

Statistical analysis

In the initial protocol, the analysis relied on the proportional hazard assumption by specifying a Cox regression adjusting for randomization strata. At the planned first interim analysis in 2014 based on data from 78 patients, the proportional hazard assumption was not applicable because of crossing curves. In addition, both the accrual rate and the overall LFS was markedly lower than expected. After extensive discussion with the Data Monitoring Committee (DMC), the measure of difference in LFS was switched from the conceptually inadequate hazard ratio to the difference in 5-year restricted mean LFS (RM-LFS) recommended for situations with crossing curves.²¹⁻²⁶ It estimates the mean expectancy of time alive and in remission up to a specified time horizon; this corresponds to the area under the LFS curve up to the time horizon. Accrual was stopped in 2017 at 125 randomized patients, the end of the trial was on August 31, 2020 and the latest follow-up information was available on December 10, 2020.

RM-LFS estimation and regression analyses for LFS and OS were performed using the R-package “pseudo”.²¹⁻²⁶ RI and NRM were analyzed using competing risk methods. The primary analyses follow the intention to treat (ITT) principle. Additional information is given in the *Online Supplementary Appendix*.

Results

From 2010 to 2017, 245 patients in CR1 (median age 67 years) were registered in 25 trial sites in Germany, the Netherlands, Switzerland, France, and Australia (Figure 1; *Online Supplementary Table S2*).

There were 66 (27%) screening failures after first consolidation (Figure 1), six (9%) patients died, 26 (40%) were no longer in CR1 (relapse, non CR1, no hematological recovery), and 34 (51%) patients exited the study due to morbidity, withdrawal of informed consent, no donor available, or for unknown reasons. Of 179 patients still in CR1 after consolidation, 135 (75%) had an HLA-identical (related or 10/10 unrelated) donor. Ten patients with a suitable donor were not randomized and therefore allocated to the observation group: seven patients declined transplant; one patient was deemed unfit for transplant, and two patients were transplanted without randomization. The other 125 patients were randomized to HCT (N=83) or non-HCT (N=42), and 54 were assigned to observation (Figure 1). Mean time from diagnosis to randomization was 15 weeks, with 121 of 125 (97%) randomized within 5 months as per protocol (*Online Supplementary Figure S3A*).

Patient characteristics at randomization were balanced in both groups with respect to age, sex, diagnosis of AML and RAEB, cytogenetic risk, major molecular characteristics, comorbidity indices, and donor type (Table 1). The integrated NRM risk score²⁸ showed an imbalance in the distribution with more frequent lower beneficial scores (0-3) in the non-HCT and higher risk scores (4+) in the HCT arm ($P=0.01$). Determination of detailed molecular markers revealed no significant imbalance between the two groups (*Online Supplementary Table S3*).

The proportion of patients not receiving treatment according to randomization was 20.5% in the HCT (relapse N=7;

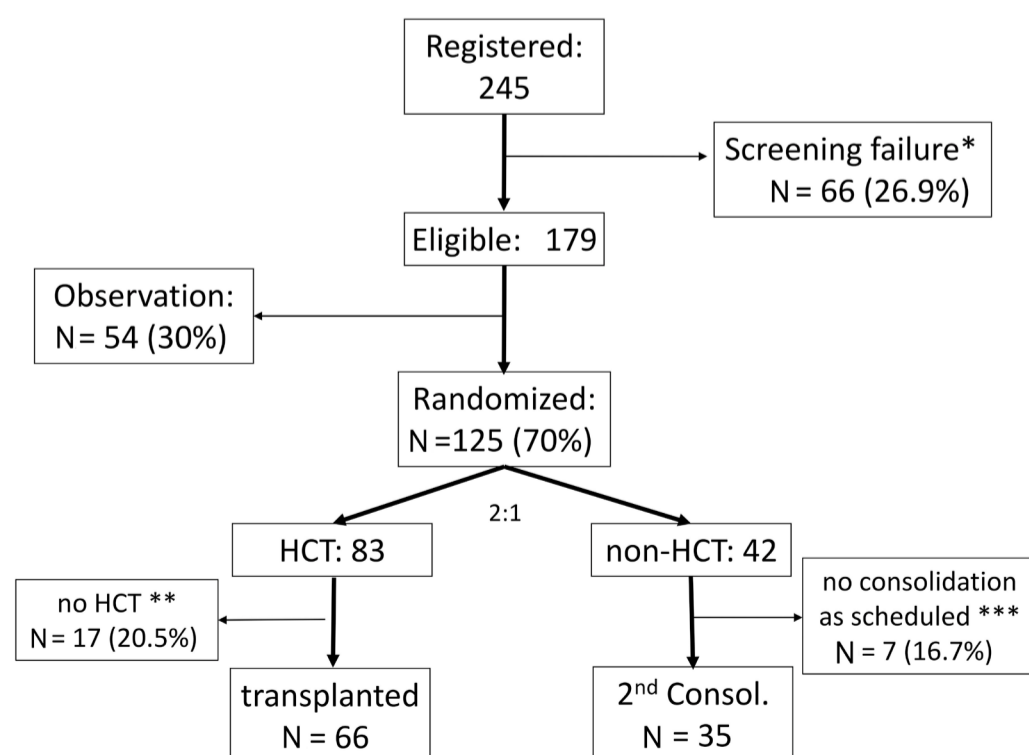


Figure 1. Flow chart. *Reason for dropout: 34 patients (morbidity, withdrawal of informed consent, no donor available, or unknown reasons), 26 no longer in first complete remission (CR1) (relapse, non-CR1, no hematological recovery) and 6 patients died. **Patients not receiving treatment according to randomization 20.5% (relapse N=7; morbidity N=4; withdrawal N=3; unavailable donor N=3). ***Patients not receiving treatment according to therapy as planned 16.7% (relapse N=2; morbidity N=2; withdrawal N=3). HCT: hematopoietic cell transplantation; CT: chemotherapy; Consol.: consolidation.

morbidity N=4; withdrawal N=3; unavailable donor N=3) and 16.7% in the non-HCT arm (relapse N=2; morbidity N=2; withdrawal N=3; Figure 1). In total, 66 of the 83 patients in the HCT arm finally received HCT. In the non-HCT arm 35 of the 42 patients local non-HCT therapy. In those transplanted, mean time from diagnosis to transplant was 4.5 months, with 62 of 66 (94%) within less than 6 months (*Online Supplementary Figure S3B*).

The median follow-up time of surviving patients was 62 months. Figure 2A shows LFS in the ITT analysis. Kaplan Meier curves cross within the first year. Five-year LFS rates were 28.8% (95% confidence interval [CI]: 20.4-40.6) in the

HCT and 8.9% (95% CI: 3.1-25.7) in the non-HCT arm; the LFS rate difference at 5-years was +19.9% (95% CI: 6.2-33.6), favoring HCT.

The primary endpoint RM-LFS up to 5 years (i.e., the expected lifetime in CR1 on a time horizon of 5 years) was 24.5 months (95% CI: 18.9-29.8) in the HCT and 15.6 months (95% CI: 10.4-20.8) in the non-HCT arm (Table 2). The difference in RM-LFS of +6.4 months (95% CI: 0.2-12.6) at 4 years ($P=0.04$) increased to +8.9 months (95% CI: 1.3-16.6) at 5 years ($P=0.022$) and +10.8 months (95% CI: 1.7-19.9) at 6 years ($P=0.019$) favoring HCT (Table 3). This treatment effect is confirmed in regression analysis as 9.5 months (95%

Table 1. Patient characteristics at randomization.

| Variable | Total | | | HCT | | non-HCT | | P |
|---------------------------------|-------|----------------------|-------------------|------------------|-------------------|------------------|-------------------|------|
| | N | Available % of total | % tested positive | N=83 | % tested positive | N=42 | % tested positive | |
| Age in years, median (IQR) | 125 | 100 | - | 67.3 (64.7-70.4) | | 66.4 (63.6-69.9) | | 0.23 |
| Sex | | | | | | | | |
| male | 86 | 68.8 | - | 57 | 68.7 | 29 | 69 | 1 |
| female | 39 | 31.2 | - | 26 | 31.3 | 13 | 31 | - |
| Diagnosis | | | | | | | | |
| AML | 122 | 97.6 | - | 81 | 97.6 | 41 | 97.6 | 1 |
| RAEB | 3 | 2.4 | - | 2 | 2.4 | 1 | 2.4 | - |
| Cytogenetic risk [§] | | | | | | | | |
| low | 16 | 12.8 | - | 11 | 13.3 | 5 | 11.9 | 0.62 |
| intermediate | 73 | 58.4 | - | 46 | 55.4 | 27 | 64.3 | |
| high | 36 | 28.8 | - | 26 | 31.3 | 10 | 23.8 | |
| Molecular analysis [#] | | | | | | | | |
| BCR::ABL1 | 41 | 33 | 0.0 | 29 | 0.0 | 12 | 0.0 | NA |
| FLT3-ITD | 111 | 89 | 19.8 | 75 | 21.3 | 36 | 16.7 | 0.75 |
| FLT3-TKD | 31 | 25 | 0.0 | 20 | 0.0 | 11 | 0.0 | NA |
| NPM1mut | 109 | 87 | 33.9 | 74 | 28.4 | 35 | 45.7 | 0.12 |
| ASXL1 | 25 | 20 | 0.0 | 18 | 0.0 | 7 | 0.0 | NA |
| IDH1 | 35 | 28 | 5.79 | 26 | 7.7 | 9 | 0.0 | 1 |
| IDH2 | 35 | 28 | 17.1 | 27 | 18.5 | 8 | 12.5 | 1 |
| RUNX1 | 25 | 20 | 16.0 | 18 | 16.7 | 7 | 14.3 | 1 |
| TP53 | 24 | 19 | 25.0 | 18 | 16.7 | 6 | 50.0 | 0.07 |
| Donor type | | | | | | | | |
| related | 28 | 22.4 | - | 19 | 22.9 | 9 | 21.4 | 1 |
| unrelated | 97 | 77.6 | - | 64 | 77.1 | 33 | 78.6 | - |
| HCT-CI Comorbidity Index | | | | | | | | |
| 0 | 53 | 44.9 | - | 33 | 42.3 | 20 | 50 | 0.23 |
| 1 | 44 | 37.3 | - | 27 | 34.6 | 17 | 42.5 | - |
| 2 | 13 | 11.0 | - | 10 | 12.8 | 3 | 7.5 | - |
| 3 | 6 | 5.1 | - | 6 | 7.7 | 0 | 0 | - |
| 4 | 2 | 1.7 | - | 2 | 2.6 | 0 | 0 | - |
| valid | 118 | 94.4 | - | 78 | - | 40 | - | - |
| Integrated NRM score* | | | | | | | | |
| 0-3 | 69 | 55.2 | - | 38 | 45.8 | 31 | 73.8 | 0.01 |
| 4+ | 56 | 44.8 | - | 45 | 54.2 | 11 | 26.2 | - |

AML: acute myeloid leukemia; RAEB: refractory anemia with excess of blasts; NA: not applicable; [§]cytogenetic risk according to;²⁰ [#]data of full molecular analyses are presented in the *Online Supplementary Table S1*; HCT: hematopoietic cell transplantation; *integrated non-relapse mortality (NRM) score.²⁸

CI: 2.1-17.0), when adjusting for stratification parameters, cytogenetic risk group and donor type (*Online Supplementary Table S5*). No difference in LFS was observed between patients transplanted from related and unrelated donors (*Online Supplementary Figure S7*). Analyses of LFS as per protocol revealed similar results.

Online Supplementary Figure S8A depicts the dependence of the treatment effect in RM-LFS as a function of the time horizon. After an early disadvantage of HCT due to NRM in the

first year, the benefit of HCT over non-HCT emerges starting at about 36 months and reaches statistical significance after 48 months.

The study does not allow for a robust analysis of molecular AML subsets. The distribution of *NPM1*-mutated AML in both treatment groups was not significantly different (28.4 vs. 45.7%, respectively; $P=0.12$). Proportions of continuous CR, relapse and NRM among *NPM1*-mutated and *NPM1* wild-type patients between HCT and non-HCT treatment groups

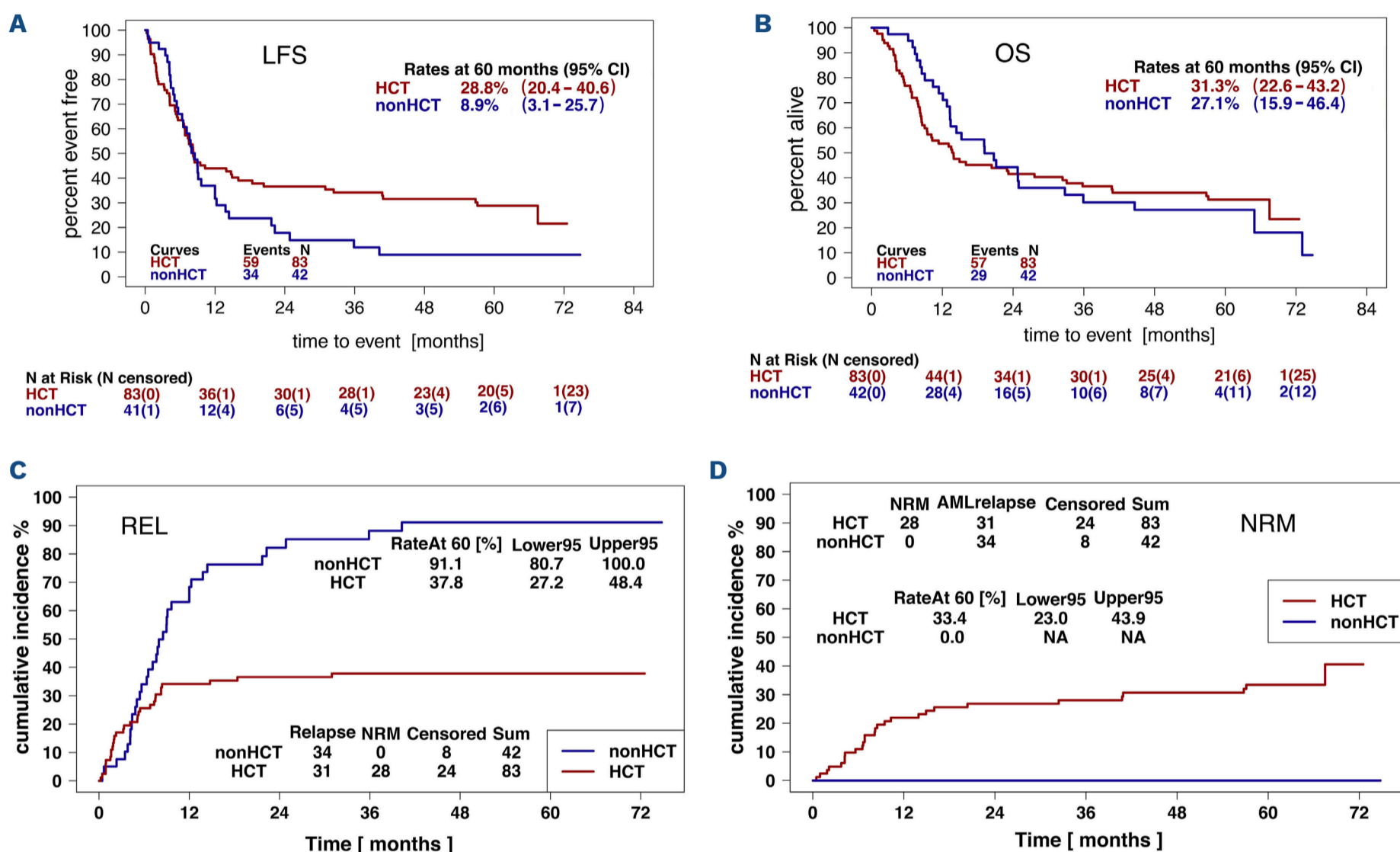


Figure 2. Outcome according to randomization to hematopoietic cell transplantation (HCT) or non-HCT analyzed following the intention to treat principles. Numbers below leukemia-free survival (LFS) and overall survival (OS) are number of patients at risk (number of patients censored). (A) LFS, (B) OS, (C) cumulative relapse incidence (RI) and (D) non-relapse mortality (NRM).

Table 2. Patient outcome.

| | HCT (95% CI) | Non-HCT (95% CI) | P |
|--------------------------------|------------------|-------------------|----------------------|
| RM-LFS up to 5 years in months | 24.5 (18.9-30.1) | 15.6 (10.4-20.8) | 0.02 |
| RM-OS up to 5 years in months | 27.7 (22.2-33.0) | 28.5 (21.7-35.3) | 0.85 |
| LFS 5 years % | 28.8 (20.4-40.6) | 8.9 (3.1-25.7) | 0.02* |
| OS 5 years % | 31.3 (22.6-43.2) | 27.1 (15.9-46.4) | 0.16* |
| Cum. RI 5 years % | 37.8 (27.2-48.4) | 91.1 (80.7-100.0) | <0.0001 |
| Cum. NRM 5 years % | 33.4 (23.0-43.9) | 0 NA | <0.0001 [#] |

HCT: hematopoietic cell transplantation; CI: confidence interval; RM-LFS: restricted mean leukemia-free survival; RM-OS: restricted mean overall survival; OS: overall survival; cum. RI: cumulative relapse incidence; Cum. NRM: cumulative non-relapse mortality; *derived from the Kaplan Meier rate estimates, [#]Fisher's exact test (0 in 1 arm); NA: not available (0 events).

were too small to allow for a meaningful analysis (*Online Supplementary Table S6*). The distributions of *FLT3*-internal tandem duplication (ITD)-positive patients were neither different in the HCT and non-HCT treatment groups (21.3% vs. 16.7%; $P=0.75$; Table 1), respectively. *TP53* mutant was present in six of 24 patients tested and distributed equally between the two arms (3 in each).

LFS events were either AML relapse, NRM or initiation of anti-leukemic treatment. Cumulative incidence curves of relapse with NRM as a competing risk show a potent anti-leukemic effect after HCT treatment (Figure 2C). Almost all patients in the non-HCT arm relapsed early with a 5-year RI of 91.1% (95% CI: 80.7-100.0). In contrast, RI in the HCT was 37.8% (95% CI: 27.2-48.4) at 5 years (hazard ratio [HR]=3.1; 95% CI: 1.93-4.98; $P<0.0001$).

On the other hand, NRM was exclusively observed in the HCT arm with a 5-year NRM cumulative incidence (with RI as a competing risk) of 33.4% (95% CI: 23.0-43.9) (Figure 2D). Cumulative incidence of NRM, broken down by the integrated NRM score²⁸ was 25.0% (95% CI: 6.9-43.1) in patients with lower score (0-3) versus 45.7% (95% CI: 30.2-61.2) in higher scores (4+) (*Online Supplementary Figure S4*).

Relapses were the predominant cause of death in both treatment groups, i.e., 50.9% in the HCT and 100% in the non-HCT group. Infections (22.8%; bacterial 19.3% and viral 3.5%) and GVHD (10.5%; *Online Supplementary Table S7*) were the most frequent cause of death after relapse in the HCT arm. Cumulative incidence of acute GVHD grade 3-4 was noted in 13.1% and chronic GVHD in 33.5% at 5 years

(*Online Supplementary Figures S5, S6*).

OS curves cross at about 20 months (Figure 2B). Five-year OS rates were 31.3% (95% CI: 22.6-43.2) in the HCT arm and 27.1% (95% CI: 15.9-46.4) in the non-HCT arm (not significant). The secondary outcome RM-OS up to 5 years (i.e., the expected lifetime on a time horizon of 5 years) is 27.8 months (95% CI: 22.2-33.0) in the HCT and 28.6 months (95% CI: 21.7-35.3) in the non-HCT arm ($P=0.85$; *Online Supplementary Figure S8B*). Thus, the long-term RM-LFS benefit does not translate into a benefit in the secondary endpoint RM-OS - at least not within the study period. Of note, 19 of 34 (56%) non-HCT patients with an AML relapse received HCT in CR2 as part of second line treatment. OS of patients after relapse in the non-HCT arm according to HCT and non-HCT after relapse is given in *Online Supplementary Figure S9* and results of patients in the observation arm in *Online Supplementary Figure S10*.

Discussion

HCT has become a commonly applied treatment modality in younger and middle-aged adults with AML, particularly for those patients with a comparatively high prognostic risk of recurrence of disease following chemotherapy.^{27,29} The incidence of AML increases with age and older patients generally have an unfavorable outcome even in so called low or intermediate genetic risk, making them potential candidates for HCT.^{2,20} The age-dependent risk of

Table 3. Restricted mean leukemia-free survival and restricted mean overall survival for different time horizons.

| RM-LFS | HCT | HCT 95% CI | non-HCT | Non-HCT 95% CI | Difference RM-LFS | Difference 95% CI | P |
|-----------|------|------------|---------|----------------|-------------------|-------------------|-------|
| 12 months | 7.80 | 6.8-8.7 | 8.1 | 7.0-9.2 | -0.3 | -1.8 to 1.2 | 0.8 |
| 24 months | 12.5 | 10.4-14.6 | 11.0 | 8.6-13.3 | 1.5 | -1.7 to 4.7 | 0.35 |
| 36 months | 16.8 | 13.5-20.1 | 13.0 | 9.5-16.4 | 3.9 | -0.9 to 8.6 | 0.11 |
| 48 months | 20.8 | 16.3-25.2 | 14.3 | 10.0-18.6 | 6.4 | 0.2-12.6 | 0.042 |
| 60 months | 24.5 | 18.9-30.1 | 15.6 | 10.4-20.8 | 8.9 | 1.3-16.6 | 0.022 |
| 72 months | 27.6 | 21.0-34.39 | 16.8 | 10.7-23.0 | 10.8 | 1.7-19.9 | 0.019 |
| RM-OS | HCT | HCT 95% CI | non-HCT | Non-HCT 95%CI | Difference RM-OS | Difference 95% CI | P |
| 12 months | 9.2 | 8.4-10.0 | 10.9 | 10.2-11.5 | -1.65 | -2.7 to -0.6 | 0.002 |
| 24 months | 14.7 | 12.8-16.7 | 17.3 | 15.2-19.4 | -2.57 | -5.5 to 0.3 | 0.078 |
| 36 months | 19.5 | 16.4-22.7 | 21.7 | 18.1-25.2 | -2.11 | -6.9 to 2.6 | 0.38 |
| 48 months | 23.8 | 19.5-28.0 | 25.2 | 20.3-30.2 | -1.48 | -8.0 to 5.1 | 0.66 |
| 60 months | 27.8 | 22.3-33.2 | 28.6 | 22.2-35.0 | -0.79 | -9.2 to 7.6 | 0.85 |
| 72 months | 31.2 | 24.6-37.7 | 31.1 | 23.3-38.8 | 0.09 | -10.0 to 10.2 | 0.98 |

LFS: leukemia-free survival; OS: overall survival; HCT: hematopoietic cell transplantation; RM-LFS: restricted mean leukemia-free survival; RM-OS: restricted mean overall survival; OS: overall survival; CI: confidence interval.

transplant-related complications and the likely potential selection bias in older patients proceeding to HCT have created doubts about the comparative therapeutic value of HCT in older patients. Prospective randomized studies concerning the value of HCT treatment have proved difficult to conduct - particularly in elderly patients.

The present study with RM-LFS as primary endpoint represents the first randomized intention to treat cooperative effort of evaluating HCT in the setting of older patient in CR1 after intensive or low-intensive induction therapy and a matched donor. Our study confirms both the potent anti-leukemic effect as well the NRM with HCT after NMA conditioning as compared with conventional consolidation therapy. Starting after 4 years, RM-LFS is significantly better with HCT compared to non-HCT consolidation outweighing the disadvantage of increased NRM. Previous studies in patients with hematopoietic donors have documented the potent anti-leukemic potential of HCT, but these were non-randomized.^{12,16,18} By starting registration of the patients at CR1 immediately after induction and by randomization after subsequent first consolidation with a time limit of 5 months from diagnosis to randomization, this trial set out to avoid biases previously considered major issues in the evaluation of HCT in older patients. By choosing a uniform NMA, less toxic conditioning and short aplasia time without outcome differences between ages 60-64, 65-69 and ≥ 70 years as previously published and confirmed in our study (*Online Supplementary Figure S11*), the selection of patients ineligible for HCT has been reduced as much as possible.¹⁸ RI (91.1% at 5 years) was extremely high in the non-HCT arm of elderly AML despite low, intermediate- and high-risk cytogenetic as published previously.^{2,20} In contrast, RI after HCT was 37.8% in a range similar to the 50% after related, and 16% after unrelated HCT, described previously.¹⁵ Furthermore, the study was performed over a period when subpopulation chimerism guided immune suppression, shown to decrease RI early after HCT, was not available to all participating centers.³⁰ Moreover, the NRM of 33.4% at 60 months seems similar to the 29.0% previously observed in phase II trials in this age group.^{12,14,15} A high proportion of deaths (22.8% of deaths) was caused by bacterial or viral infections in this elderly patient population, which exceeded the proportion of deaths from GVHD (10.5%). Future HCT protocols including better infectious prophylaxis are expected to increase even more the outcome in this elderly patient population with excessively high RI of 91.1% with non-HCT consolidation.

The improved 5-year RM-LFS after HCT in comparison to non-HCT does not translate into a RM-OS benefit during the study period (*Online Supplementary Figure S8; Online Supplementary Table 3*). The rescue possibility in the non-HCT arm after relapse by HCT impedes RM-OS comparisons. Of note, 19 of the 34 (55.8%) relapsing non-HCT patients were transplanted in CR2.

The results of our study raise some additional points of

interest. First, a considerable proportion of CR patients relapse within a few weeks after CR1 during consolidation and before randomization to HCT or non-HCT underscoring the need to generate more stable or deeper remissions with induction therapy. Unfortunately, we could not determine the MRD status pre- or post-HCT in patients in this study. In the meantime, new treatment strategies and techniques for determining MRD have become available, which allow for more personalized management of additional therapeutic interventions following one or two induction chemotherapies. In addition, new remission induction approaches e.g., hypomethylating therapy in combination with venetoclax, may induce MRD-negativity prior to transplant with less toxicity. As extensively discussed before, the immunotherapeutic effect of HCT as a consolidation therapy is strong and extends across different sub-types of AML resulting in a reduction of relapse of at least a third of what can be observed in patients consolidated with chemotherapy, as shown again in the present study.^{27,29} However, especially in older and medically less fit patients, NRM reduces the net effect on LFS and OS, necessitating the selection of patients for whom NRM can be predicted to be acceptable. Several predictive scores have been developed. For instance, the integrated EBMT/HCT-CI score by Versluis *et al.*²⁸ and the HCT-CI score can be used to tailor the application of HCT and preclude excessive toxicities. However, the predictive value of such scores may be valued differently by physicians and patients and did not influence RI or OS (*Online Supplementary Figure S4; data not shown*) in our trial.

For 75.4% of patients in our study, an HLA-identical related or unrelated donor was identified within a few weeks of CR1 and during consolidation, allowing HCT to be scheduled within 5 months from diagnosis of the disease. The best time for a donor search is as early as possible and may already be started at CR1 or even at diagnosis, although depending on local institutional circumstances the time needed to find a donor and the possibility to cancel a donor search in patients not undergoing HCT will impact on the choice for an early donor search strategy. Increasing donor availability and shorter diagnosis-HCT time intervals are foreseen in the future due to the increased use of haploidentical donors in clinical practice worldwide.³¹ This trial has a few limitations. During the trial period transplant strategies evolved, but none of them have been proven to be superior to low-dose total-body irradiation (TBI) in a prospective trial with unbiased patient inclusion. The use of this minimally toxic, low-dose TBI based, nonmyeloablative regimen conditioning with CyA/MMF immunosuppression has been developed in a dog model,³² translated to clinical phase II studies with long-term outcomes on more than thousand patients^{13-15,18} and is now studied in a phase III study. While short-term results are available on heterogeneous patients populations with newer transplant strategies, long-term results are missing in elderly patients with post-Cy or newer immunosuppressive therapies.³³

While new drugs including venetoclax combinations have become available as consolidation and/or maintenance for non-HCT treatment since study start, most of these have yet to demonstrate improvement of long-term outcome in the broader AML population; e.g., maintenance with CC-486 in comparison to placebo prolonged median relapse-free survival and 2-year survival, but long-term LFS and OS was unaffected.³⁴ Combinations of apoptosis-interacting drugs with HMA and targeted therapy, where possible, have high CR rates and longer median OS, but resistance caused by e.g., loss of p53 function, activating kinase mutations and alternative anti-apoptotic proteins are considered reasons for failing better long-term LFS and OS.³⁵

The preparative regimen described here is currently used less frequently (8.5% of 6289 AML patients >60 years transplanted from 2020-2022) according to the EBMT registry in comparison to RIC (EBMT personal communication). The latter regimen requires significant expertise and MRD or subpopulation chimerism guided immunosuppression. However, it exerts potent anti-leukemic activity.¹³⁻¹⁵ The NMA regimen has been used intentionally to avoid selection of elderly patients to HCT being associated with an extremely short duration of aplasia and a missing age effect in this elderly patients.¹⁸ As a possible sign of selection, only 35% of patients transplanted in 2020-2022 according to the EBMT registry were older than 60 years of age, despite the highest incidence of the disease in this age group as compared to a younger age group. In our trial, only one patient in CR1 after consolidation was considered unfit for HCT. The extent of selection for HCT using RIC cannot be reliably estimated, but is assumed to be substantial by looking at the HCT activity of elderly patients with AML. It might well be that RIC or even myeloablative conditioning (MAC) may reduce the RI in selected patients in comparison to NMA, but prospective randomized studies in similar patient populations are missing or have similar RI.³⁶ Preemptive or post-HCT MRD driven targeted therapy may improve results further. Unfortunately, no ancillary quality of life studies were performed in this trial.

Furthermore, our study was not intended to answer the question, if HCT in CR2 ultimately leads to similar results as HCT in CR1. As reported previously, patients with hematological relapse, and especially elderly patients, have a dismal outcome. Only 28.6% of patients >60 years achieve CR2 after relapse and LFS has been described to be only 13.8% at 5 years in this age group.²

Even if induction therapy of AML has changed (and will continuously change), the study provides a solid basis for further trials and an essential backbone for evidence-based AML therapy in elderly aiming at improving long-term LFS from diagnosis. Achievement of molecular CR1 after induction therapy remains the goal to decrease early relapses before consolidation and improve results of HCT consolidation. Since none of the available targeted therapies and combinations have shown to be superior in long-term outcome by inducing resistance, consolidation treatment

for long-term LFS is urgently needed. Perceptions of main treatment goals/chances of cure (80%) from patients and of chances of cure (7%) from physicians are clearly discordant in elderly patients with AML.³⁷ The only treatment able to improve long-term LFS is HCT as shown in our unbiased randomized ITT study. The current study provides the rationale to increase the use of HCT in elderly patients (currently performed only in a small proportion). Further advances in elderly AML can be reached only by improving the different steps of therapy: decrease relapse after CR1 by increasing molecular remissions and better timing of HCT, decrease relapse incidence after HCT or non-HCT by better maintenance, decrease NRM after HCT and increase long- (not only short-) term outcome using the results of our study as baseline. The need to analyze the different steps within studies will be the main aim for the next years and the only way to improve long-term outcome of AML in a population of increasing life-expectancy today of >82 years (<https://www.worldometers.info/demographics/life-expectancy/>).

Disclosures

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Contributions

Protocol writing by DN, DH, BL and JC. Data contribution by DN, DH, WB, BJB, HA-A, YC, MvG, CJ, GG, MH, RH, TH, AH, SI, RvMR, NK, JJ, MJ, FB, MM, SM-L, GO, JP, WP, JS, CS, SS, MS, LFV, VV, BL and JC. Data analysis by DN, DH, BL and JC. Discussion of results by DN, DH, WB, BJB, HA-A, YC, MvG, CJ, GG, MH, RH, TH, AH, SI, RvMR, NK, JJ, MJ, FB, MM, SM-L, GO, JP, WP, JS, CS, SS, MS, LFV, VV, BL and JC. Manuscript writing by DN, DH, BL and JC. Manuscript discussion and approval by DN, DH, WB, BJB, HA-A, YC, MvG, CJ, GG, MH, RH, TH, AH, SI, RvMR, NK, JJ, MJ, FB, MM, SM-L, GO, JP, WP, JS, CS, SS, MS, LFV, VV, BL and JC.

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Data-sharing statement

Individual participant data that underlie the results reported in this article (text, tables, figures, and appendices) will be shared after de-identification to researchers who provide a methodologically sound and ethically approved proposal. Proposals can be submitted up to at least 36 months after article publication. Proposals should be directed to dirk.hasenclever@imise.uni-leipzig.de; to gain access, data requestors will need to sign a data access agreement.

References

1. Fitzmaurice C, Abate D, Abbasi N, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: a systematic analysis for the global burden of disease study. *JAMA Oncol.* 2019;5(12):1749-1768.
2. Heinicke T, Krahl R, Kahl C, et al. Allogeneic hematopoietic stem cell transplantation improves long-term outcome for relapsed AML patients across all ages: results from two East German Study Group Hematology and Oncology (OSHO) trials. *Ann Hematol.* 2021;100(9):2387-2398.
3. McCurdy SR, Luger SM. Dose intensity for induction in acute myeloid leukemia: what, when, and for whom? *Haematologica.* 2021;106(10):2544-2554.
4. Medeiros BC, Satram-Hoang S, Hurst D, Hoang KQ, Momin F, Reyes C. Big data analysis of treatment patterns and outcomes among elderly acute myeloid leukemia patients in the United States. *Ann Hematol.* 2015;94(7):1127-1138.
5. Niederwieser D, Lang T, Krahl R, et al. Different treatment strategies versus a common standard arm (CSA) in patients with newly diagnosed AML over the age of 60 years: a randomized German inter-group study. *Ann Hematol.* 2023;102(3):547-561.
6. Al-Ali HK, Jaekel N, Junghanss C, et al. Azacitidine in patients with acute myeloid leukemia medically unfit for or resistant to chemotherapy: a multicenter phase I/II study. *Leuk Lymphoma.* 2012;53(1):110-117.
7. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med.* 2020;383(7):617-629.
8. Cortes JE, Khaled S, Martinelli G, et al. Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* 2019;20(7):984-997.
9. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med.* 2019;381(18):1728-1740.
10. Erba H, Montesinos P, Vrhovac R, et al. Quizartinib prolonged survival vs. placebo plus intensive induction and consolidation therapy followed by single-agent continuation in patients aged 18-75 years with newly diagnosed FLT3-ITD+ AML. *Hemasphere.* 2022;6:1-2.
11. Erba HP, Montesinos P, Kim H-J, et al. Quizartinib plus chemotherapy in newly diagnosed patients with FLT3-internal-tandem-duplication-positive acute myeloid leukaemia (QuANTUM-First): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2023;401(10388):1571-1583.
12. Storb R, Gyurkocza B, Storer BE, et al. Graft-versus-host disease and graft-versus-tumor effects after allogeneic hematopoietic cell transplantation. *J Clin Oncol.* 2013;31(12):1530-1538.
13. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood.* 2001;97(11):3390-3400.
14. Niederwieser D, Maris M, Shizuru JA, et al. Low-dose total body irradiation (TBI) and fludarabine followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases. *Blood.* 2003;101(4):1620-1629.
15. Hegenbart U, Niederwieser D, Sandmaier BM, et al. Treatment for acute myelogenous leukemia by low-dose, total-body, irradiation-based conditioning and hematopoietic cell transplantation from related and unrelated donors. *J Clin Oncol.* 2006;24(3):444-453.
16. Versluis J, Hazenberg CLE, Passweg JR, et al. Post-remission treatment with allogeneic stem cell transplantation in patients aged 60 years and older with acute myeloid leukaemia: a time-dependent analysis. *Lancet Haematol.* 2015;2(10):e427-e436.
17. Aoudjhane M, Labopin M, Gorin NC, et al. Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). *Leukemia.* 2005;19(12):2304-2312.
18. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning

- and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA*. 2011;306(17):1874-1883.
19. Kröger N, Iacobelli S, Franke G-N, et al. Dose-reduced versus standard conditioning followed by allogeneic stem-cell transplantation for patients with myelodysplastic syndrome: a prospective randomized phase III study of the EBMT (RICMAC Trial). *J Clin Oncol*. 2017;35(19):2157-2164.
 20. Grimwade D, Walker H, Oliver F, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukaemia Working Parties. *Blood*. 1998;92(7):2322-2333.
 21. Andersen PK, Hansen MG, Klein JP. Regression analysis of restricted mean survival time based on pseudo-observations. *Lifetime Data Anal*. 2004;10(4):335-350.
 22. Klein JP, Gerster M, Andersen PK, Tarima S, Perme MP. SAS and R functions to compute pseudo-values for censored data regression. *Comput Methods Programs Biomed*. 2008;89(3):289-300.
 23. Andersen PK, Perme MP. Pseudo-observations in survival analysis. *Stat Methods Med Res*. 2010;(19):71-99.
 24. Royston P, Parmar MKB. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. *Stat Med*. 2011;30(19):2409-2421.
 25. Royston P, Parmar MKB. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. *BMC Med Res Methodol*. 2013;13:152.
 26. A'Hern RP. Restricted mean survival time: an obligatory end point for time-to-event analysis in cancer trials? *J Clin Oncol*. 2016;34(28):3474-3476.
 27. Cornelissen JJ, Blaise D. Hematopoietic stem cell transplantation for patients with AML in first complete remission. *Blood*. 2016;127(1):62-70.
 28. Versluis J, Labopin M, Niederwieser D, et al. Prediction of non-relapse mortality in recipients of reduced intensity conditioning allogeneic stem cell transplantation with AML in first complete remission. *Leukemia*. 2015;29(1):51-57.
 29. Cornelissen JJ, Gratwohl A, Schlenk RF, et al. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. *Nat Rev Clin Oncol*. 2012;9(10):579-590.
 30. Hell S, Jentzsch M, Franke G-N, et al. Prospective phase II study of preemptive chimerism-driven reduction of immunosuppression after non-myeloablative conditioning-Eudract #: 2007-002420-15. *Bone Marrow Transplant*. 2022;57(5):824-826.
 31. Niederwieser D, Baldomero H, Bazuaye N, et al. One and a half million hematopoietic stem cell transplants: continuous and differential improvement in worldwide access with the use of non-identical family donors. *Haematologica*. 2022;107(5):1045-1053.
 32. Storb R, Yu C, Wagner JL, et al. Stable mixed hematopoietic chimerism in DLA identical littermate dogs given sublethal total body irradiation before and pharmacological immunosuppression after marrow transplantation. *Blood*. 1997;89(8):3048-3054.
 33. Bolaños-Meade J, Hamadani M, Wu J, et al. Post-transplantation cyclophosphamide-based graft-versus-host disease prophylaxis. *N Engl J Med*. 2023;388(25):2338-2348.
 34. Wei AH, Döhner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383(26):2526-2537.
 35. Saxena K, DiNardo C, Daver N, Konopleva M. SOHO state of the art updates and next questions: harnessing apoptosis in AML. *Clin Lymphoma Myeloma Leuk*. 2022;22(3):133-139.
 36. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35(11):1154-1161.
 37. Sorror ML, Gooley TA, Storer BE, et al. An 8-year pragmatic observation evaluation of the benefits of allogeneic HCT in older and medically infirm patients with AML. *Blood*. 2023;141(3):295-308.