Impact of conditioning intensity on outcomes of haploidentical stem cell transplantation for patients with acute myeloid leukemia 45 years of age and over

Impact of Conditioning Intensity on Outcomes of Haploidentical Stem Cell Transplantation for Patients With Acute Myeloid Leukemia 45 Years of Age and Over

Nicole Santoro, MD [1]; Myriam Labopin, MD[2,3]; Fabio Ciceri, MD[4]; Maria Teresa Van Lint, MD[5]; Daniela Nasso, MD[6]; Didier Blaise, MD[7]; William Arcese, MD[6]; Johanna Tischer, MD[8]; Benedetto Bruno, MD[9]; Gerhard Ehninger, MD[10]; Yener Koc, MD[11]; Stella Santarone, MD[12]; Xiao-Jun Huang, MD [13]; Bipin N. Savani, MD [3,14]; Mohamad Mohty, MD[2,3]; Annalisa Ruggeri, MD [15,16]; and Arnon Nagler, MD[3,17]

BACKGROUND: T cell–replete haploidentical stem cell transplantation (haplo-SCT) is a valid therapeutic option for adult patients with high-risk acute myeloid leukemia (AML) lacking an HLA-matched sibling or unrelated donor. METHOD: We retrospectively analyzed the outcomes of 912 AML patients ≥45 years of age who had undergone haplo-SCT with either myeloablative conditioning (MAC; n = 373) or reduced intensity conditioning (RIC; n = 539) regimens. RESULTS: The median follow-up was 31.1 and 25.7 months for MAC and RIC, respectively. The incidence of relapse and nonrelapse mortality (NRM) were 25.1% versus 28.7% and 31.0% versus 30.3% for MAC and RIC, respectively; 2-year leukemia-free survival (LFS) was 43.9% for MAC versus 41.0% for RIC. In multivariate analysis, the use of MAC versus RIC was not associated with a difference in the outcomes. Results were confirmed in the propensity score–weighted analysis. Disease status and performance status at transplantation were associated with outcomes. Notably, the use of posttransplantation cyclophosphamide was associated with reduced acute graft-versus-host disease (aGVHD) stage III-IV, and NRM and increased overall survival, LFS, and GVHD-free, relapse-free survival. The use of mobilized peripheral blood stem cells was associated with an increased risk of stage II-IV aGVHD. CONCLUSION: No differences were found between MAC and RIC regimens for haplo-SCT in adults with AML who were ≥45 years of age. The type of GVHD prophylaxis, disease status, and performance status were the major predictors of transplantation outcome. These results may serve as the background for randomized study comparing RIC versus MAC for haplo-SCT in adults with AML. *Cancer* 2019;125:1499-1506. *© 2019 American Cancer Society.*

KEYWORDS: acute myeloid leukemia, haploidentical stem cell transplantation, myeloablative conditioning, reduced intensity conditioning.

INTRODUCTION

Haploidentical stem cell transplantation (haplo-SCT) is a valid and rapidly available therapeutic option for patients with high-risk acute myeloid leukemia (AML) who do not have an HLA-identical sibling or unrelated donor.[1] In recent years, most haplo-SCTs are being performed without T cell depletion (T cell-replete haplo-SCT) with improving outcomes due to faster immune reconstitution and a lower incidence of nonrelapse mortality (NRM) related to graft-versus-host disease (GVHD), graft rejection, and life-threatening infections.[2,3] Notably, the results of haplo-SCT also improved in patients with AML who were ≥60 years of age.[4,5]

The optimal conditioning intensity regimen for allogeneic transplantation for patients with AML is a debated topic. Reduced-intensity conditioning (RIC), which is based mainly on the graft-versus-leukemia effect and less on the cytotoxicity of the chemotherapy or radiotherapy was originally developed for older and less-fit patients, those with comorbidities, and those unable to undergo myeloablative conditioning (MAC).[6-8] Indeed, RIC resulted in a

[1]Section of Hematology, Department of Medicine, University of Perugia, Centro Ricerche Emato-Oncologiche, Perugia, Italy; [2]Department of Hematology and Cell Therapy, Saint-Antoine Hospital, Paris, France; [3]ALWP Office, Saint-Antoine Hospital, Paris, France; [4]Hematology and Bone Marrow Transplantation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; [5]San Martino Hospital, Department of Haematology II, Genova, Italy; [6]Rome Transplant Network, Tor Vergata, University of Rome, Stem Cell Transplant Unit, Policlinico Universitario Tor Vergata, Rome, Italy; [7]Bone Marrow Transplantation Unit, Cancer Research Center, Institute Paoli Calmettes, Marseille, France; [8]University Hospital of Munich-Grosshadern, LMU, Department of Internal Medicine III, Munich, Germany; [9]S.S.C.V.D Trapianto di Cellule Staminali, A.O.U Citta della Salute e della Scienza di Torino, Presidio Molinette, Torino, Italy; [10]Universitaets Klinikum Dresden, Medizinische Klinik und Poliklinik I, Dresden, Germany; [11]Medical Park Hospitals, Stem Cell Transplant Unit, Antalya, Turkey; [12]Ospedale Civile, Dipartimento di Ematologia, Medicina Trasfusionale e Biotecnologie, Pescara, Italy; [13]Peking University People's Hospital, Institute of Haematology, Beijing, China; [14]Vanderbilt University Medical center, Nashville, Tennessee; [15]Department of Pediatric Hematology and Oncology, IRCCS Bambino Gesù Children's Hospital, Rome, Italy; [16]Cellular Therapy and Immunobiology Working Party of EBMT; [17]Department of Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel Hashomer, Israel.

significant reduction in organ toxicity and NRM and is now widely used, even in patients who are eligible for MAC.[9] Different groups have investigated the influence of the conditioning intensity on outcomes of allo-SCT from matched related or unrelated donors.[10-13] Overall, MAC is associated with a good antileukemic effect and therefore fewer relapses but with increased NRM, whereas RIC could result in higher relapse incidence (RI) but reduced NRM, and both approaches have similar leukemia-free survival (LFS) and overall survival (OS).[14] The similar net outcome is despite the fact that RIC was generally applied to older patients and those with comor- bidities.[8] Recent randomized clinical trial showed that age-adapted strategy could be considered in the choice of conditioning.[12,15,16]

In the haplo setting, the broad HLA mismatch could theoretically increase the risk of immunological complications, such as acute GVHD (aGVHD) and chronic GVHD (cGVHD) and graft rejection leading to an increase in NRM.[3] For this reason, the intensity of conditioning, especially in different age subgroups, could have an important influence on outcomes and may be even more imperative and subtle than HLA- matched sibling and unrelated donor transplants.[17] The majority of studies addressing conditioning intensity in the setting of haplo-SCT have focused on the feasibility of RIC regimens using posttransplanta- tion cyclophosphamide (PT-Cy) as a GVHD prophy- laxis.[18-21] In these studies, relapse remains the major cause of treatment failure, despite the low GVHD. In contrast, MAC has been studied for both PT-Cy and other GVHD prophylaxes, including anti-thymocyte globulin (ATG).[22-25] To date, the choice of the condi- tioning intensity for haplo-SCT in AML depends on patient and disease characteristics and transplantation center experience, but there are no clear indications. There are very few data comparing MAC and RIC in adult patients with AML transplanted with hap- lo-SCT.[26,27] The aim of our study was to evaluate the impact of conditioning regimens on the outcomes of adult AML patients ≥45 years of age who underwent T cell–replete haplo-SCT.

METHODS

Study Design and Definition

This was a retrospective registry-based analysis on behalf of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT is a

nonprofit scientific society representing more than 600 transplantation centers, mainly in Europe, that are required to report all consecutive stem cell transplanta- tions and follow-ups once a year. Data are entered, man- aged, andmaintainedinacentralonlinedatabaseinwhich each EBMT center is represented. For original data, the database is available at the ALWP-EBMT, Saint Antoine Hospital, Paris, France. Audits are routinely performed to determine the accuracy of the data. Patients or legal guardians provide informed consent to authorize the use of their personal information for research purposes. The study was approved by the ALWP institutional review board.

Eligibility criteria for the study included all patients ≥45 years of age with AML who underwent a haplo-SCT (as first transplantation) between January 2007 and December 2016, using either PT-Cy or ATG as a GVHD prophylaxis. Transplantations were performed in 162 EBMT centers.

MAC was defined as a regimen containing either total body irradiation with a dose >6 Gy, a total dose of oral busulfan >8 mg/kg, or a total dose of intravenous busulfan >6.4 mg/kg. All other regimens were defined as RIC.[28] Cytogenetics abnormalities were classified by cytogenetic status according to UK Medical Research Council criteria.[29]

Endpoints

The primary endpoint was LFS. Secondary endpoints were OS; refined GVHD-free, relapse-free survival (GRFS)[30]; neutrophil engraftment; aGVHD and cGVHD; RI; and NRM. LFS was defined as the interval from haplo-SCT to either relapse or death in remission. OS was defined as the time to death from all causes. GRFS events have been defined as stage III-IV aGVHD, severe cGVHD, disease relapse, or death from any cause after SCT.[30] Engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count >0.5×10^9/L. aGVHD was graded according to the modified Glucksberg criteria[31] and cGVHD according to the revised Seattle criteria.[32]

Statistical Analysis

Follow-up was calculated using the reverse Kaplan- Meier method. Patient-, disease-, and transplant-related variables were compared between the 2 groups (MAC or RIC) using the chi-square statistic for categorical variables and the Mann-Whitney test for continuous variables. Cumulative incidence (CI) of relapse and NRM was calculated from the date of transplantation

to the date of relapse or death in remission, respectively, with the other event being the competing risk. For studying GVHD, both relapse and death were con- sidered as competing events. Univariate comparisons of time-dependent endpoints were done using the log- rank test for OS and LFS and GRFS and the Grays test for cumulative incidence functions. A Cox propor- tional hazards model was used for multivariate regres- sion. All variables differing significantly between the 2 groups or factors known to influence outcomes were included in the Cox model. In order to test for a center effect, we introduced a random effect or frailty for each center into the model.[33,34]

We used propensity scores (PS) weighting to control for pretreatment imbalances on observed vari- ables.[35] The following factors were included in the propensity score model: patient age, disease status at transplantation, secondary versus de novo AML, cy- togenetics, female donor to male recipient versus other combinations, Karnofsky performance status less or more than 90%, previous autograft, stem cell source, patient and donor CMV serology, and PT-Cy versus others. The weights equal the ratio of the propensity score to 1 minus the propensity score in the 2 groups. Results are expressed as the hazard ratio (HR) with the 95% confidence interval (95% CI). All tests were 2-sided. The type 1 error rate was fixed at 0.05 for determination of factors associated with time to event. Analyses were performed using the R statistical soft- ware version 3.4.0 (R Development Core Team, Vienna, Austria); propensity score analysis was performed using the ipw and the npsurv packages.

RESULTS

Patients, Disease, and Transplantation Characteristics

We analyzed 912 AML patients ≥45 years of age who underwent haplo-SCT. The conditioning regimens sued were MAC (n = 373 [40.9%)] and RIC (n = 539 [59.1%]). Patients and transplantation characteristics are summarized in Supporting Table S1.

For MAC and RIC, the median follow-up was 31.1 months (range, 0.5-119.9 months) and 25.7 (range, 0.43-113.8 months), respectively, and the median year of transplantation was 2014 and 2015, respectively. RIC recipients were older (MAC, 55.2 years vs RIC, 61.3 years; $P < .05$). The majority of patients had a Karnofsky per- formance status (KPS) ≥90% (MAC, 71.6% vs RIC, 64.1%; $P < .05$). There were no differences in disease

status at transplantation: for MAC and RIC, 48.5% versus 47.7% were in CR1, 20.1% versus 18.9% were in CR ≥ 2, and 31.4% versus 33.4% were in active disease, respectively ($P = .79$). Cytogenetic analysis revealed an intermediate risk in 40.8% of MAC patients and 49.2% of RIC patients, whereas 15.3% and 19.5% of the pa- tients undergoing MAC and RIC, respectively, harbored poor risk ($P < .05$). Secondary AML was reported in 19.1% and 24.1% of patients undergoing MAC and RIC, respectively ($P = .07$).

The kinship of haplo-SCT donors for MAC and RIC was a child in 68.4% and 77.4%, respectively, and a sibling in 30.5% and 20.8%, respectively ($P = .31$).

Details regarding transplantation characteristics, conditioning regimens, and GVHD prophylaxis are provided in Supporting Table S2. RIC regimens were more frequently associated with the use of peripheral blood as a stem cell source (MAC, 47.4% vs RIC, 60.3%; $P < .05$).

The most frequent MAC conditioning regimen was TBF (thiotepa, fludarabine, busulfan) that was adminis- tered to 54.2% of MAC. Reduced-dose TBF was also the most frequent RIC preparative regimen (35.1%). Total body irradiation-based regimens were used in 6.4% and 32.2% of patients receiving MAC and RIC, respectively. PT-Cy–based GVHD prophylaxis was used in 78% of patients undergoing RIC and 77.9% of patients un- dergoing MAC, whereas ATG was administered in 16.9% and 18.4% of patients undergoing MAC and RIC, respectively ($P = .53$). The combination of both PT-Cy and ATG regimens was used in 5.1% and 3.7% of patients receiving MAC and RIC, respectively.

Engraftment and aGVHD/cGVHD

Neutrophil engraftment was achieved in 91% of haplo-SCTs following MAC and in 92% of transplanta- tions following RIC ($P = .49$). At 100 days, the CI for aGVHD stage II-IV was 24.8% versus 32.4% ($P < .05$), whereas the CI for stage III-IV aGVHD was 8.3% ver- sus 10.5% for MAC and RIC, respectively ($P = .29$). At 2 years, the CI for cGVHD was 27.4 versus 26.8% ($P = .83$) and the CI for extensive cGVHD was 11% ver- sus 15.1% ($P = .13$) for MAC and RIC, respectively. The propensity score analysis did not show differences in acute and cGVHD between the 2 groups (Supporting Table S3). In multivariate analysis (Supporting Table S4), the conditioning regimen did not influence the risk of grade 2-4 and 3-4 aGVHD (HR, 0.80; 95% CI, 0.59-1.09, $P = .14$; HR, 0.81; 95% CI, 0.49-1.35, $P = .41$ for MAC vs RIC, respectively) or cGVHD (HR, 0.79; 95% CI, 0.56-1.11; $P = .17$). The risk of stage II-IV

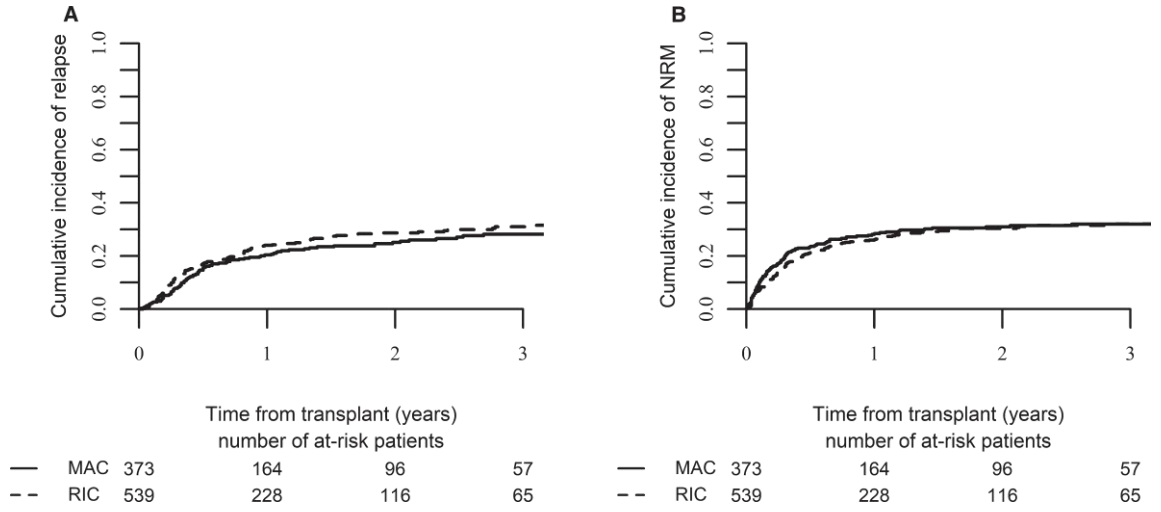

Figure 1. Probability of relapse incidence (A) and nonrelapse mortality (NRM) (B) after myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) haploidentical stem cell transplantation in acute myeloid leukemia patients ≥45 years of age.

aGVHD was higher with mobilized peripheral blood as a stem cell source (HR, 1.83; 95% CI, 1.35-2.47; $P < .05$) and in patients who underwent transplantation while in CR ≥ 2 (HR, 1.69; 95% CI, 1.18-2.42; $P < .05$).

Furthermore, the use of PT-Cy versus ATG (HR, 0.56; 95% CI, 0.33-0.93; $P < .05$) was associated with a reduced risk of stage III-IV aGVHD. In addition, patients with a KPS ≥90 had a reduced risk of cGVHD (HR, 0.69; 95% CI, 0.49-0.99; $P < .05$).

Relapse Incidence and NRM

At 2 years, the CI of relapse after haplo-SCT differed little between MAC and RIC (25.1% vs 28.7%, respec- tively; $P = .20$) (Fig. 1A). This was confirmed also by multivariate analysis (Supporting Table S4), no differ- ence in RI according to the conditioning intensity was observed (HR, 0.85; 95% CI, 0.62-1.16; $P = .29$).

Factors independently associated with increased risk of relapse were disease status at transplantation (HR, 2.81; 95% CI, 2.06-3.83; $P < .05$) and poor cytogenetics risk (HR, 1.44; 95% CI, 1.04-2.00; $P < .05$).

The CI of NRM at 2 years was 31% for MAC versus 30.3% for RIC ($P = .56$) (Fig. 1B).

The most common causes of death were infection (MAC, 37.8% vs RIC, 36.1%), disease recurrence (MAC, 31.6% vs RIC, 35.4%), and GVHD (MAC, 15.2% vs RIC, 15.1%) (Supporting Table S5). On multivariate analysis, NRM was not statistically different between the 2 groups (HR, 1.23; 95% CI, 0.93-1.67; $P = .16$).

Increased age (at 10-year intervals) was associated with increased risk of NRM (HR, 1.27; 95% CI, 1.04-1.55; $P < .05$). In addition, a KPS ≥90 (HR, 0.56; 95% CI, 0.42-0.75; $P < .05$) and the use of PT-Cy as GVHD prophylaxis (HR, 0.69; 95% CI, 0.48-0.99; $P < .05$) were independently associated with reduced mortality risk (Supporting Table S4).

OS, LFS, and GRFS

At 2 years, OS was 48.3% versus 44.1% ($P = .49$), LFS was 43.9% versus 41.0% ($P = .63$), and GRFS was 39.1% versus 33.7% ($P = .17$) for MAC and RIC, respectively (Fig. 2). On multivariate analysis (Supporting Table S4), OS, LFS, and GRFS did not differ between MAC and RIC. Advanced disease status at transplantation was allocated as the main factor associated with poor LFS (HR, 1.88; 95% CI, 1.51-2.35; $P < .05$), OS (HR, 1.81; 95% CI, 1.45-2.28, $P < .05$), and GRFS (HR, 1.77; 95% CI, 1.44-2.18, $P < .05$).

KPS ≥90 (HR, 0.66; 95% CI, 0.53-0.81, $P < .05$; HR, 0.63; 95% CI, 0.51-0.79, $P < .05$; HR, 0.69; 95% CI, 0.57-0.84, $P < .05$) and the use of PT-Cy for GVHD prophylaxis (HR, 0.74; 95% CI, 0.56-0.97, $P < .05$; HR, 0.75; 95% CI, 0.57-0.99, $P < .05$; HR, 0.77; 95% CI, 0.60-0.99, $P < .05$) were the prognos- tic factors independently associated with higher LFS, OS, and GRFS, respectively. Overall, these results were confirmed in the propensity score analysis (Supporting Table S3).

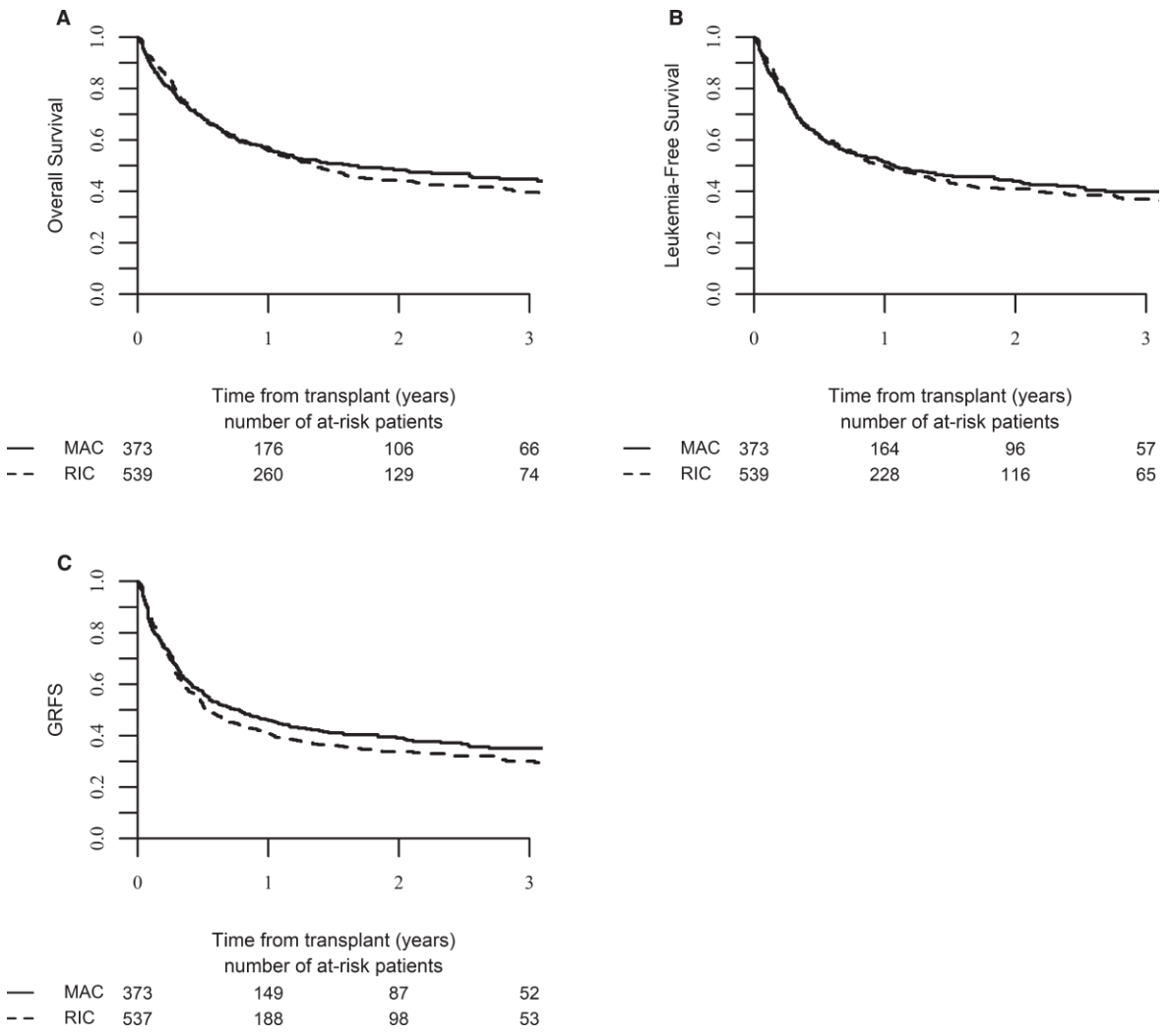

Figure 2. Probability of overall survival (A), leukemia-free survival (B), and graft-versus-host disease–free, relapse-free survival (GRFS) (C), after myeloablative conditioning (MAC) or reduced-intensity conditioning (RIC) haploidentical stem cell transplantation in acute myeloid leukemia patients ≥45 years of age.

Analysis of Outcomes According to Age Stratification

With the aim to analyze the effect of conditioning intensity according to patients' age, we performed a subgroup analysis for outcomes. Age was categorized in 3 subgroups: 45-55 years, 55-60 years, >60 years. Of note, the intensity of the conditioning being MAC or RIC had no effect on transplantation outcome (Supporting Table S6).

DISCUSSION

Our study focused on adult patients with AML who underwent haplo-SCT between 2007 and 2016 with

the aim of identifying how conditioning intensity may influence outcomes. We analyzed a homogenous popula- tion in terms of disease, patient characteristics, and trans- plantation characteristics. Our results showed no impact of the regimen intensity, with no significant differences in the incidence of aGVHD, cGVHD, RI, NRM, or in LFS, OS, and GRFS following MAC or RIC in the haplo-SCT setting. These findings were also confirmed in matched paired analysis.

In a previous survey on behalf of the ALWP of EBMT, Rubio et al[26] studied the impact of condition- ing intensity in a small cohort of patients with both ALL and AML who had been treated with heterogeneous

pretransplantation preparative regimens between 2001 and 2012 and observed no differences between MAC and RIC. The main limitation of our previous study is that the RIC group included young patients (range, 18-76 years) even though RIC is more applicable for patients ≥45 years of age. Our current study focused on a larger group of patients ≥45 years of age with AML who underwent transplantation in more recent years. Moreover, we also stratified the patient population by 3 different age subgroups (45-55 years, 55-60 years, >60 years) to analyze whether patients at different ages would benefit from different conditioning inten- sity regimens, hypothesizing that younger patients may benefit from MAC, whereas older patients may have better outcomes with RIC. Our current results showed no differences in the outcomes of haplo-SCT follow- ing MAC versus RIC according to age stratification. These results are in agreement with previous studies analyzing the impact of age and conditioning intensity in matched related or unrelated SCT.[16,36]

Huselton et al[27] recently published a propensity score analysis of conditioning intensity in peripheral blood haplo-SCT with PT-Cy. The study included 61 patients receiving MAC and 87 receiving RIC, with a median follow-up of 20.3 and 8.2 months, respectively. Patients were transplanted for different hematological malignancies (95 patients were transplanted for AML: 45 in the MAC and 50 in the RIC groups). In line with our findings, survival outcomes (OS, LFS) and aGVHD and cGVHD were not significantly different between the 2 groups. Furthermore, they showed a significant reduc- tion of RI and increased NRM with MAC.

In our study, the most representative condition- ing regimen was TBF, followed by BF (busulphan and fludarabine) both in MAC and RIC (Supporting Table S2). We recently published a study reporting the out- comes of TBF versus BF in AML patients undergoing to matched related or unrelated transplantation both in the MAC and RIC setting[37]; our results showed similar sur- vival outcomes despite an increased NRM and reduced RI with TBF, but these results need to be confirmed in prospective clinical trials.

In our analysis, the main factors associated with outcomes were performance status and disease status at transplantation. In particular, a KPS ≥90% was asso- ciated with better LFS, OS, and GRFS and a reduced risk of cGVHD and NRM. Disease status (active disease versus CR1) had a significant impacted on RI, LFS, OS, and GRFS. The risk of RI correlates with the cytogenetic category. Finally, higher age correlated with increased risk of NRM. These results highlight the importance of the early referral of patients with AML with indica- tion for transplantation to haplo-SCT and the need for transplantation as soon as possible once first complete remission is achieved.

Another factor associated with reduced mortality and better LFS, OS, and GRFS was the use of PT-Cy as the main GVHD prophylaxis. In vivo TCD is a known risk factor associated with high incidence of infection and NRM, as reported also in the unrelated donor setting.[38] Moreover, a very favorable toxicity profile of PT-Cy Haplo-SCT has been observed, also in older patients.[39]

Our group[40] recently compared the outcomes of PT-Cy-based versus ATG-based GVHD prophylaxis in the haplo-SCT setting, showing improved LFS and GRFS with PT-Cy; however, prospective randomized studies focusing on the best platform of GVHD prophy- laxis for unmanipulated haplo-SCT are lacking.

Another important finding of our current study is the comparable survival with the use of peripheral blood as a stem cell source compared with bone marrow, despite an increase risk of grade 2-4 aGVHD. These data are in agreement with recent reports by Ruggeri et al[41] and Bashey et al[42] that focused on the role of stem cell source in the haplo setting using PT-Cy. Importantly, our study revealed a strong center effect influencing NRM, OS, and LFS. In previous reports from our group, the center effect was demonstrated in the T cell-depleted setting as well,[43] and more recently in unmanipulated haplo.[44] It is conceivable that the observed center effect is due to differences in management of posttransplantation complications, life-threating infections, and relapse between the various centers.

In conclusion, while in the matched related or unrelated transplant setting, data from prospective trials showed higher NRM after MAC counterbal- anced by higher RI after RIC with similar survival outcomes,[12,13,16] our results in the haplo setting showed no differences in outcomes. These results are important for transplant physicians to keep in mind when choos- ing the appropriate regimen for the patients according to disease risk features, comorbidities, and transplan- tation characteristics. Although our study has some limitations due to its retrospective nature—namely, the theoretic possibility of patient selection, the unavail- ability of the Sorror score in the EBMT registry, and some missing data (mainly of molecular markers)—we were able to demonstrate that both MAC and RIC are suitable preparative regimens for AML patients ≥45 years of age who undergo haplo-SCT. The use of

RIC may offer the possibility of lowering early toxicity and enhance posttransplantation maintenance therapy to prevent relapse in this high-risk setting. Finally, the optimal regimen and GVHD prophylaxis should be chosen according to patient and disease characteristics. Our study may serve as the background for a well- designed prospective clinical trial to investigate the best conditioning intensity platform in AML patients ≥45 years of age who undergo haplo-SCT.

REFERENCES

1. Passweg JR, Baldomero H, Bader P, et al. Is the use of unrelated donor transplantation leveling off in Europe? The 2016 European Society for Blood and Marrow Transplant activity survey report. *Bone Marrow Transplant*. 2018;53:1139-1148.
2. Chang Y-J, Huang X-J. Improving the clinical outcome of unma- nipulated haploidentical blood and marrow transplantation. *Bone Marrow Transplant*. 2015;50(suppl 2):S21-S23.
3. Kanakry CG, Fuchs EJ, Luznik L. Modern approaches to HLA- haploidentical blood or marrow transplantation. *Nat Rev Clin Oncol*. 2016;13:10-24.
4. Santoro N, Labopin M, Giannotti F, et al. Unmanipulated haploiden- tical in comparison to matched unrelated donor stem cell transplan- tation in patients 60 years and older with acute myeloid leukemia: a comparative study on behalf of the ALWP of the EBMT. *J Hematol Oncol*. 2018;11:55.
5. Muffly L, Pasquini MC, Martens M, et al. Increasing use of alloge- neic hematopoietic cell transplantation in patients aged 70 years and older in the United States. *Blood*. 2017;130:1156-1164.
6. Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hema- topoietic progenitor cells with purine analog-containing chemother- apy: harnessing graft-versus-leukemia without myeloablative therapy. *Blood*. 1997;89:4531-4536.
7. Rizzieri DA, Koh LP, Long GD, et al. Partially matched, nonmye- loablative allogeneic transplantation: clinical outcomes and immune reconstitution. *J Clin Oncol*. 2007;25:690-697.
8. Savani BN, Labopin M, Kröger N, et al. Expanding transplant options to patients over 50 years. Improved outcome after reduced intensity conditioning mismatched-unrelated donor transplan- tation for patients with acute myeloid leukemia: a report from the acute leukemia working party of the EBMT. *Haematologica*. 2016;101:773-780.
9. Pasquini MC, Wang Z, Horowitz MM, Gale RP. 2010 report from the Center for International Blood and Marrow Transplant Research (CIBMTR): current uses and outcomes of hematopoietic

cell transplants for blood and bone marrow disorders. *Clin Transpl*. 2010:87-105.
10. Sengsayadeth S, Savani BN, Blaise D, Malard F, Nagler A, Mohty
M. Reduced intensity conditioning allogeneic hematopoietic cell transplantation for adult acute myeloid leukemia in complete remis- sion—a review from the acute leukemia working party of the EBMT. *Haematologica*. 2015;100:859-869.
11. Luger SM, Ringdén O, Zhang MJ, et al. Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant prepara- tive regimens for AML or MDS. *Bone Marrow Transplant*. 2012;47: 203-211.
12. 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;35:1154-1161.
13. Zeng W, Huang L, Meng F, Liu Z, Zhou J, Sun H. Reduced-intensity and myeloablative conditioning allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia and myelo-dysplastic syndrome: a meta-analysis and systematic review. *Int J Clin Exp Med*. 2014;7:4357-4368.
14. Weisdorf DJ. Reduced-intensity versus myeloablative allogeneic transplantation. *Hematol Oncol Stem Cell Ther*. 2017;10:321-326.
15. Lioure B, Béné MC, Pigneux A, et al. Early matched sibling hemato- poietic cell transplantation for adult AML in first remission using an age-adapted strategy: long-term results of a prospective GOELAMS study. *Blood*. 2012;119:2943-2948.
16. Bornhäuser M, Kienast J, Trenschel R, et al. Reduced-intensity con- ditioning versus standard conditioning before allogeneic haemopoi- etic cell transplantation in patients with acute myeloid leukaemia in first complete remission: a prospective, open-label randomised phase 3 trial. *Lancet Oncol*. 2012;13:1035-1044.
17. Jagasia M, Arora M, Flowers MED, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. *Blood*. 2012;119:296-307.
18. Luznik L, ODonnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant*. 2008;14:641-650.
19. Munchel AT, Kasamon YL, Fuchs EJ. Treatment of hematological malignancies with nonmyeloablative, HLA-haploidentical bone marrow transplantation and high dose, post-transplantation cyclo- phosphamide. *Best Pract Res Clin Haematol*. 2011;24:359-368.
20. McCurdy SR, Kanakry JA, Showel MM, et al. Risk-stratified out- comes of nonmyeloablative HLA-haploidentical BMT with high-dose posttransplantation cyclophosphamide. *Blood*. 2015;125:3024-3031.
21. Ciurea SO, Zhang MJ, Bacigalupo AA, et al. Haploidentical transplant with posttransplant cyclophosphamide vs matched unrelated donor transplant for acute myeloid leukemia. *Blood*. 2015;126:1033-1040.
22. Bacigalupo A, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and post-transplant cyclophosphamide for hematologic malignanices following a mye- loablative conditioning: an update. *Bone Marrow Transplant*. 2015;50 (suppl 2):S37-S39.
23. Solomon SR, Sizemore CA, Sanacore M, et al. Haploidentical transplantation using T cell replete peripheral blood stem cells and myeloablative conditioning in patients with high-risk hematologic malignancies who lack conventional donors is well tolerated and pro- duces excellent relapse-free survival. *Biol Blood Marrow Transplant*. 2012;18:1859-1866.
24. Raiola AM, Dominietto A, Ghiso A, et al. Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. *Biol Blood Marrow Transplant*. 2013;19:117-122.
25. Solomon SR, Sizemore CA, Sanacore M, et al. Total body irradia- tion-based myeloablative haploidentical stem cell transplantation is a safe and effective alternative to unrelated donor transplantation in patients without matched sibling donors. *Biol Blood Marrow Transplant*. 2015;21:1299-1307.

26. Rubio MT, Savani BN, Labopin M, et al. Impact of conditioning intensity in T-replete haplo-identical stem cell transplantation for acute leukemia: a report from the acute leukemia working party of the EBMT. *J Hematol Oncol*. 2016;9:25.
27. Huselton E, Slade M, Trinkaus KM, DiPersio JF, Westervelt P, Romee R. Propensity score analysis of conditioning intensity in pe- ripheral blood haploidentical hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2018;24:2047-2055.
28. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant*. 2009;15:1628-1633.
29. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determi- nation of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*. 2010;116:354-365.
30. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-free survival for registry-based studies: an ALWP-EBMT analysis on patients with AML in remission. *Bone Marrow Transplant*. 2016;51:610-611.
31. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825-828.
32. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease.
Biol Blood Marrow Transpl. 2003;9:215-233.
33. Hougaard P. Frailty models for survival data. *Lifetime Data Anal*. 1995;1:255-273.
34. Andersen PK, Klein JP, Zhang MJ. Testing for centre effects in multi-centre survival studies: A Monte Carlo comparison of fixed and random effects tests. *Stat Med*. 1999;18:1489-1500.
35. Mccaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for mul- tiple treatments using generalized boosted models. *Stat Med*. 2013;32:3388-3414.
36. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first com- plete remission or with myelodysplastic syndrome. *J Clin Oncol*. 2010;28:1878-1887.
37. Saraceni F, Labopin M, Hamladji RM, et al. Thiotepa-busulfan- fludarabine compared to busulfan-fludarabine for sibling and unre- lated donor transplant in acute myeloid leukemia in first remission. *Oncotarget*. 2017;9:3379-3393.
38. Walker I, Panzarella T, Couban S, et al. Pretreatment with anti-thymocyte globulin versus no anti-thymocyte globulin in pa- tients with haematological malignancies undergoing haemopoietic cell transplantation from unrelated donors: a randomised, controlled, open-label, phase 3, multicentre trial. *Lancet Oncol*. 2016;17:164-173.
39. Blaise D, Fürst S, Crocchiolo R, et al. Haploidentical T cell-replete transplantation with post-transplantation cyclophosphamide for pa- tients in or above the sixth decade of age compared with allogeneic hematopoietic stem cell transplantation from an human leukocyte antigen-matched related or unrelated donor. *Biol Blood Marrow Transplant*. 2016;22:119-124.
40. Ruggeri A, Sun Y, Labopin M, et al. Post-transplant cyclophos- phamide versus antithymocyte-globulin as graft versus host dis- ease prophylaxis in haploidentical transplant. *Haematologica*. 2017;102:401-410.
41. Ruggeri A, Labopin M, Bacigalupo A, et al. Bone marrow versus mo- bilized peripheral blood stem cells in haploidentical transplants using posttransplantation cyclophosphamide. *Cancer*. 2018;124:1428-1437.
42. Bashey A, Zhang MJ, McCurdy SR, et al. Mobilized peripheral blood stem cells versus unstimulated bone marrow as a graft source for T-cell-replete haploidentical donor transplantation using post- transplant cyclophosphamide. *J Clin Oncol*. 2017;35:3002-3009.
43. Ciceri F, Labopin M, Aversa F, et al. A survey of fully haploidentical hematopoietic stem cell transplantation in adults with high-risk acute leukemia: a risk factor analysis of outcomes for patients in remission at transplantation. *Blood*. 2008;112:3574-3581.
44. Ruggeri A, Labopin M, Sanz G, et al. Comparison of outcomes after unrelated cord blood and unmanipulated haploidentical stem cell transplantation in adults with acute leukemia. *Leukemia*. 2015;29:1891-1900.