Age is no Barrier for Adults undergoing HCT for AML in CR1: Contemporary CIBMTR Analysis

Joseph E. Maakaron¹, Mei-Jie Zhang²,³, Karen Chen², Sunil Abhyankar⁴, Vijaya Raj Bhatt⁵, Saurabh Chhabra⁶, Najla El Jurdi⁷, Sherif S. Farag⁸, Fiona He⁷, Mark Juckett⁷, Marcos de Lima⁹, Navneet Majhail¹⁰, Marjolein van der Poel¹¹, Ayman Saad¹², Bipin Savani¹³, Celalettin Ustun¹⁴, Edmund K. Waller¹⁵, Mark Litzow¹⁶, Partow Kebriaei¹⁷, Christopher S. Hourigan¹⁸, Wael Saber², Daniel Weisdorf²

¹Division of Hematology, Oncology, and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, MN
²CIBMTR® (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI
³Division of Biostatistics, Institute for Health and Equity, Medical College of Wisconsin, Milwaukee, WI;
⁴University of Kansas Cancer Center, Westwood, KS

Users may view, print, copy, and download text and data-mine the content in such documents, for the purposes of academic research, subject always to the full Conditions of use.

Corresponding Author Daniel Weisdorf MD, Department of Medicine, University of Minnesota, MMC 480, Minneapolis, MN 55455, weisd001@umn.edu.
Abstract

Acute Myeloid Leukemia (AML) has a median age at diagnosis of 67 years. The most common curative therapy remains an allogeneic hematopoietic stem cell transplantation (HCT), yet it is complicated by treatment-related mortality (TRM) and ongoing morbidity including graft versus host disease (GVHD) that may impact survival, particularly in older patients. We examined the outcomes and predictors of success in 1,321 patients aged 60 years and older receiving a HCT for AML in first complete remission (CR1) from 2007–2017 and reported to the CIBMTR. Outcomes were compared in three age cohorts (60–64; 65–69; 70+). With median follow-up of nearly 3 years, patients aged 60–64 had modestly, though significantly better OS, DFS and lower TRM than those either 65–69 or 70+; cohorts with similar outcomes. Three-year OS for the 3 cohorts was 49.4%, 42.3%, and 44.7% respectively (p=0.026). TRM was higher with increasing age, cord blood as graft source and HCT-CI score of ≥3. Conditioning intensity was not a significant predictor of OS in the 60–69 cohort with 3-year OS of 46% for RIC and 49% for MAC (p=0.38); MAC was rarely used over age 70. There was no difference in the relapse rate, incidence of Grade III/IV acute GVHD, or moderate-severe chronic GVHD across the age cohorts. After adjusting for other predictors, age had a small effect on OS and TRM. High-risk features including poor cytogenetics and measurable residual disease (MRD) prior to HCT were each significantly associated with relapse and accounted for most of the adverse impact on OS and DFS. Age did
not influence the incidence of either acute or chronic GVHD; while graft type and associated GVHD prophylaxis were most important. These data suggest that age alone is not a barrier to successful HCT for AML in CR1 and should not exclude patients from HCT. Efforts should focus on minimizing residual disease and better donor selection.

Introduction

Acute myeloid leukemia (AML) in the elderly carries a poor prognosis with median overall survival measured in months, even in those achieving remission. Treatment of elderly patients with AML is often complicated by their increased burden of comorbid conditions making induction chemotherapy challenging. AML in the elderly is also characterized by higher risk cytogenetic and molecular abnormalities increasing the likelihood of chemoresistance and early relapse. Currently, the only treatment modality that carries the potential for long-term survival remains hematopoietic stem cell transplantation (HCT), but patients are seldom offered transplant, either for lack of ability to achieve a complete remission (CR) or because they are deemed unsuitable for HCT, often without formal guidelines for this determination. Elderly patients undergoing myeloablative conditioning (MAC) HCT may have unacceptable treatment-related mortality (TRM).

The advent of reduced intensity conditioning (RIC) has increased access to HCT, but evidence-based patient selection remains a challenge and a barrier to broader HCT access. The assignment to RIC, MAC, or no transplant is not uniform across transplant centers. Furthermore, relapse remains frequent following RIC HCT and overall mortality remains high. Therefore, observational studies are needed to probe how age, comorbidity, and/or disease factors may inform the optimal approach to transplantation in the older patient population.

Methods

We analyzed prospectively collected data on patients ≥60 years old with a diagnosis of AML in first complete remission (CR1) who underwent HCT and were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is a working group of more than 500 transplantation centers worldwide that contribute detailed data on HCT to a statistical center at the Medical College of Wisconsin (MCW). Participating centers are required to report all transplantations consecutively and compliance is monitored by on-site audits. Definitions used for case report forms are displayed on the CIBMTR website. Eligibility for HCT is determined by the treating center. MRD is reported by each center when available. Computerized checks for discrepancies, physicians’ review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. The MCW and National Marrow Donor Program, Institutional Review Boards approved this study.

Three age groups were considered [60–64] vs [65–69] vs [70+] comparing patient, disease, and HCT treatment characteristics. Consensus criteria were used to define conditioning
intensity. The primary endpoint is overall survival (OS) with death from any cause considered an event. Surviving patients were censored at the time of last follow up. Secondary endpoints included cumulative incidence of acute graft versus host disease (GVHD), chronic GVHD, treatment related mortality (TRM), relapse, and disease-free survival (DFS). TRM was defined as death without preceding disease relapse or death within 28 days regardless of cause. Relapse of AML was defined as clinically detectable disease after HCT with TRM considered a competing event. DFS was defined as survival without relapse or progression.

The incidence of GVHD, relapse, and TRM were calculated using the cumulative incidence estimator to accommodate competing risks. Probabilities of OS and DFS were calculated using the Kaplan-Meier method for univariable analysis. Multivariable regression analysis was performed using regression for acute GVHD, chronic GVHD, relapse, and TRM, and the Cox proportional hazards model for DFS and OS. The assumption of proportional hazards for each factor was tested and forward stepwise selection was used to select significant risk factors. Factors that were significant at a 5% level were retained in the final model. The interaction between the main effect of age and the other significant variables were examined. The variables that were considered in the multivariable models included recipient age, Karnofsky performance status (KPS), comorbidity index (HCT- CI), disease status at transplant, conditioning regimen intensity, GVHD prophylaxis, donor type, graft source, and year of transplant. Adjusted probabilities were calculated based on the final regression models for OS, DFS, relapse, and TRM.

**Results**

A total of 1,321 patients undergoing HCT for AML in CR1 from 2007–2017 were included. The three age cohorts were comparable in terms of clinical characteristics and comorbidities prior to HCT. Patients aged 70+ had more males, more secondary AML, and a higher incidence of MRD pre-HCT. Fewer in the oldest groups had sibling donors and more were performed in recent years. About half had an HCT-CI of 3 or greater. Data for modified ELN risk stratification was only available for about 35% of patients who received HCT in the later years (Table 1).

On univariate analysis, age, poor-risk cytogenetics, presence of MRD, donor type, and year of transplant were found to be associated with OS, while these same variables and graft, but not donor type were associated with DFS. After adjusting for these variables in a multivariate model, age remained a significant predictor of outcomes (Table 2). The youngest cohort age [60–64] had slightly better OS and DFS than the 2 other cohorts with a median follow-up of nearly 3 years (Figure 1). The overall survival of each age cohort is presented in table 3. Hazard ratio (HR) for mortality (worse OS) was 1.27 (p=0.02) for the middle cohort age [65–69] and HR 1.20 (p=0.10) for age 70+; each compared to age [60–64]. Patients age [65–69] and [70+] had similar outcomes with no difference in OS. On adjusted multivariate analysis, three-year OS for the 3 cohorts was 49.4%, 42.3%, and 44.7% respectively (p=0.026; figure 1).
Conditioning intensity was not a significant predictor of outcomes with HR for OS of RIC vs. MAC of 1.13 (CI: 0.93–1.38; p=0.21) for the combined [60–69] cohort with too few age [70+] receiving MAC. Three-year OS was 46% for RIC and 49% for MAC (p=0.38). HCT-CI did not impact OS while poor risk cytogenetics, detectable MRD prior to HCT, cord blood as graft source, and transplant prior to 2016 were each significantly associated with poor OS (Table 2). The use of ATG did not impact DFS or OS (data not shown).

TRM was higher with increasing age (Figure 2), cord blood as graft source and HCT-CI score of ≥ 3. Across the age cohorts there was no difference in the relapse rate, incidence of Grade III/IV acute GVHD, or of moderate-severe chronic GVHD (Figures 2, 3).

Discussion:

Increasing age is associated with a small decrement in OS after transplant that is substantially smaller than that due to other disease-related risk factors. In this large series of HCT for AML in CR1, we quantified the impact of increasing age on outcomes and showed that all age groups achieved 3-year OS of 40–50%; thus, HCT should be considered a standard of care option for patients of all ages with AML achieving CR1 with no upper age limit.

Elderly patients often have comorbid conditions that can complicate their therapy and increase TRM. Nearly 50% of our patients had HCT-CI ≥ 3 which was associated with increasing TRM, but not worse OS. HCT-CI has been shown to be correlated with survival outcomes in other cohorts. This discrepancy is likely reflective of the fact that HCT-CI loses its discriminating power when comorbidities are common, as many older patients with HCT-CI > 3. It also likely reflects better management of comorbidities and improved recent supportive care, while likely influencing patient selection. Elderly AML patients often have higher risk disease with a cytogenetic and molecular profile that confers adverse risk and chemoresistance. Similar to other HCT studies of elderly AML patients we observed a high proportion of patients with poor cytogenetic risk profiles (32%) and detectable MRD at pre-HCT (32%). Presence of MRD was associated with more relapse and consequent worse OS, DFS, particularly using RIC conditioning. MAC conditioning has been hypothesized to abrogate the adverse prognostic significance of MRD, though has not been well studied in this older population. Notably, increasing age was not associated with more frequent acute or chronic GVHD, which was dependent on the type of graft and the GVHD prophylaxis regimen. Patients who received peripheral blood stem cells and a tacrolimus-based prophylaxis regimens had an increased incidence of chronic GVHD, congruent with other reports.

After adjusting for cytogenetic risk, presence of MRD, donor type and year of transplantation, age remained a significant predictor of OS, albeit with a limited impact. Elderly patients with AML are often presumed to have inferior outcomes with treatment and are therefore often undertreated. In SEER database analyses, the reported 5-year OS for patients with AML > 65 years old is < 5%. While this estimate of all patients with AML who are > 65 years, these poor outcomes reflect inability to achieve CR and frequent underutilization of HCT in this age cohort. In a National Cancer Database that looked at
17,000 patients, only 5.5% underwent HCT\textsuperscript{15}, and 0.8% in a SEER report\textsuperscript{1}. These rates, though increasing recently\textsuperscript{16}, remain low despite a novel report showing improved outcomes of patients consolidated with HCT compared to chemotherapy consolidation on clinical trials\textsuperscript{17}. The current cohort of elderly patients has a high prevalence of intermediate and poor risk cytogenetics, secondary AML, significant proportion with MRD, and high HCT-CI, all reflecting patients who are generally considered “high risk”. These patients had an OS > 40% across all age cohorts despite the observed small decrement in survival for those older than 65.

Conditioning intensity did not significantly influence any of the outcomes, including OS, although few in the oldest group received MAC and the outcomes were adjusted for age and HCT-CI. This differs from a randomized trial comparing to MAC vs RIC\textsuperscript{18}. We hypothesize that this reflects important, but perhaps clinically appropriate selection bias where patients deemed unfit for MAC are excluded or assigned a conditioning intensity suitable for their fitness. There is also a spectrum of intensities more refined than the dichotomous MAC vs RIC. Yet chronological age is the main guide to conditioning intensity and treatment options. The arbitrary and varying definitions of “elderly” range from 55 to 70 years\textsuperscript{19,20}, MAC regimens in elderly patients have led to high TRM with early reports up to 50%\textsuperscript{21,22}. In a randomized trial of the preferred conditioning intensity for patients with AML or MDS, patients who received MAC had higher TRM\textsuperscript{18}. Some transplant programs have strict age limits for MAC vs. RIC while in recent years, chronological age has been supplemented with renewed focus on biological age as measured by frailty, sarcopenia, and other indices. Measures of frailty may correlate with survival better than other indices in older patients, and are less subjective than the commonly used KPS score\textsuperscript{23}. Patients undergoing HCT in more recent years also had improved OS\textsuperscript{24,25} and reflects numerous advances and improved supportive care, deeper understanding of mechanisms of failure of HCT and relapse mitigation strategies such as post-HCT maintenance therapy.

In this report, each age group still had 3-year OS > 40% and differences in outcome were better explained by covariates other than age. Because HCT remains the only curative therapy for higher risk AML, all patients with AML should be referred early to a transplant center for evaluation, donor identification, optimization of their disease and organ function, and for psychosocial support planning to maximize the rates of success. More effort should be directed towards investigating barriers to transplant and early referrals\textsuperscript{4}. Women were also underrepresented in this cohort and reasons should be elucidated. Some HCT practices in this patient population cannot be adequately answered by registry data including how to best assess frailty, how to best assess MRD and how to best select a donor for an older adult.

**Acknowledgement:**

Data Sharing

CIBMTR supports accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

Funding
The CIBMTR is supported primarily by Public Health Service U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); HHSH250201700006C from the Health Resources and Services Administration (HRSA); and N00014–20–1–2705 and N00014–20–1–2832 from the Office of Naval Research; Support is also provided by Be the Match Foundation, the Medical College of Wisconsin, the National Marrow Donor Program, and from the following commercial entities: AbbVie; Actinium Pharmaceuticals, Inc.; Adaptive Biotechnologies Corporation; Adienne SA; Allovir, Inc.; Amgen, Inc.; Angioecrine Bioscience; Astellas Pharma US; Bluebird Bio, Inc.; Bristol Myers Squibb Co.; CSL Behring; CytoSen Therapeutics, Inc.; Daiichi Sankyo Co., Ltd.; Eurofins Viracor; ExcellThera; Fate Therapeutics; Gamida-Cell, Ltd.; Genentech Inc.; GlaxoSmithKline; Incyte Corporation; Janssen/Johnson & Johnson; Jasper Therapeutics; Jazz Pharmaceuticals, Inc.; Karyopharm Therapeutics; Kaadis Pharma; Kite, a Gilead Company; Kyowa Kirin; Legend Biotech; Magenta Therapeutics; Medac GmbH; Merck & Co.; Millennium, the Takeda Oncology Co.; Miltenyi Biotec, Inc.; MorphoSys; Novartis Pharmaceuticals Corporation; Omeros Corporation; Oncoimmune, Inc.; Orca Biosystems, Inc.; Pfizer, Inc.; Pharmacyclics, LLC; Sanofi Genzyme; Seagen, Inc.; Stemcyte; Takeda Pharmaceuticals; Tscan; Vertex; Vor Biopharma; Xenikos BV.

Conflicts of interests:

Dr. Weisdorf reports grants from FATE Therapeutics, grants from Incyte, outside the submitted work. Dr. Hourigan reports other from Sellas, outside the submitted work. Dr. Maakaron reports other from CRISPR, other from FortySeven Inc., other from TALARIS, outside the submitted work. Dr. de Lima reports grants from Pfizer grants from Celgene, personal fees from Kadmon personal fees from Pfizer, personal fees from Incyte, personal fees from BMS, outside the submitted work. Dr. Bhatt reports personal fees from Agios, grants and personal fees from Incyte, personal fees from Takeda, personal fees from Partner Therapeutics, personal fees from Omeros, grants and personal fees from Abbvie, grants from Jazz, grants from National Marrow Donor Program, other from Oncoceutics, personal fees from Partnership for health analytic research, LLC, grants and other from Pfizer, personal fees from CSL Behring, grants from Tolero Pharmaceuticals, personal fees from Rigel Pharmaceuticals, other from Novartis, personal fees from Genentech, outside the submitted work. Dr. Saad reports personal fees from Magenta Therapeutics, personal fees from Incyte Pharmaceuticals, personal fees from CareDx, outside the submitted work. Dr. Kebrlai reports grants from Amgen, grants from Ziopharm, other from Kite, other from Novartis, other from Jazz, other from Pfizer, outside the submitted work. Dr. Usut reports not relevant, but honoraria from Novartis and Blueprint for attending advisory board meeting. Dr. He reports personal fees from Magenta Therapeutics, outside the submitted work. Dr. Abhyankar reports other from Incyte Corporation, other from Therkos, outside the submitted work. Dr. Majhail reports personal fees from Incyte, personal fees from Mallinckrodt, outside the submitted work.

References

1. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. Haematologica. 2012;97(12):1916–1924. doi:10.3324/haematol.2012.066100 [PubMed: 22773600]

2. Pollyea DA, Kohrt HE, Medeiros BC. Acute myeloid leukaemia in the elderly: a review. Br J Haematol. 2011;152(5):524–542. [PubMed: 21314823]

3. Estey E, de Lima M, Tibes R, Pierce S, Kantarjian H, Champlin R, et al. Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). Blood. 2007;109(4):1395–1400. doi:10.1182/blood-2006-05-021907 [PubMed: 17038533]

4. Flannelly C, Tan BEX, Tan JL, McHugh CM, Sanapala C, Lagu T, et al. Barriers to Hematopoietic Cell Transplantation for Adults in the United States: A Systematic Review with a Focus on Age. Biol Blood Marrow Transplant. Published online September 20, 2020. doi:10.1016/j.bbmt.2020.09.013

5. Bhatt VR, Chen B, Lee SJ. Use of hematopoietic cell transplantation in younger patients with acute myeloid leukemia: A National Cancer Database Study. Bone Marrow Transplant. 2018;53(7):873–879. doi:10.1038/s41409-018-0105-9 [PubMed: 29403021]

6. Wallen H, Gooley TA, Deeg HJ, Pagel JM, Press OW, Appelbaum FR, et al. Ablative Allogeneic Hematopoietic Cell Transplantation in Adults 60 Years of Age and Older. J Clin Oncol. 2005;23(15):3439–3446. doi:10.1200/JCO.2005.05.694 [PubMed: 15824415]

7. Rashidi A, Ebadi M, Colditz GA, DiPersio JF. Outcomes of allogeneic stem cell transplantation in elderly patients with acute myeloid leukemia: a systematic review and meta-analysis. Biol
8. Bacigalupo A, Ballen K, Rizzo D, Giralt S, Lazarus H, Ho V, et al. Defining the Intensity of Conditioning Regimens: Working Definitions. Biol Blood Marrow Transplant. 2009;15(12):1628–1633. doi:10.1016/j.bbmt.2009.07.004 [PubMed: 19896087]

9. Sorror ML, Storer BE, Fathi AT, Gerds A, Medeiros BC, Shami P, et al. Development and Validation of a Novel Acute Myeloid Leukemia–Composite Model to Estimate Risks of Mortality. JAMA Oncol. 2017;3(12):1675–1682. doi:10.1001/jamaoncol.2017.2714 [PubMed: 28880971]

10. Pohlen M, Groth C, Sauer T, Görlisch D, Mesters R, Schliemann C, et al. Outcome of allogeneic stem cell transplantation for AML and myelodysplastic syndrome in elderly patients (≥60 years). Bone Marrow Transplant. 2016;51(11):1441–1448. doi:10.1038/bmt.2016.156 [PubMed: 27295269]

11. Hourigan CS, Dillon LW, Gui G, Logan BR, Fei M, Ghannam J, et al. Impact of Conditioning Intensity of Allogeneic Transplantation for Acute Myeloid Leukemia With Genomic Evidence of Residual Disease. J Clin Oncol. Published online December 20, 2019:JCO.19.03011. doi:10.1200/JCO.19.03011

12. De Jong CN, Meijer E, Bakunina K, et al. Post-Transplantation Cyclophosphamide after Allogeneic Hematopoietic Stem Cell Transplantation: Results of the Prospective Randomized HOVON-96 Trial in Recipients of Matched Related and Unrelated Donors. Blood. 2019;134(Supplement_1):1–1. doi:10.1182/blood-2019-124659 [PubMed: 31273001]

13. Lee SJ, Logan B, Westervelt P, Cutler CC, Woolfrey AE, Khan S, et al. 5 Year Results of BMT CTN 0201: Unrelated Donor Bone Marrow Is Associated with Better Psychological Well-Being and Less Burdensome Chronic Gvhd Symptoms Than Peripheral Blood. Blood. 2015;126(23):270–270. doi:10.1182/blood.V126.23.270.270 [PubMed: 26012570]

14. Thein MS, Ershler WB, Jemal A, Yates JW, Baer MR. Outcome of older patients with acute myeloid leukemia. Cancer. 2013;119(15):2720–2727. doi:10.1002/cncr.28129 [PubMed: 23633441]

15. Bhatt VR, Chen B, Gyawali B, Lee SJ. Socioeconomic and health system factors associated with lower utilization of hematopoietic cell transplantation in older patients with acute myeloid leukemia. Bone Marrow Transplant. 2018;53(10):1288–1294. doi:10.1038/s41409-018-0164-y [PubMed: 29588500]

16. Muffly L, Pasquini MC, Martens M, Brazauskas R, Zhu Z, Adekola K, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. Blood. 2017;130(9):1156–1164. doi:10.1182/blood-2017-03-772368 [PubMed: 28674027]

17. Ustun C, Le-Rademacher J, Wang HL, Othus M, Sun Z, Major B, et al. Allogeneic hematopoietic cell transplantation compared to chemotherapy consolidation in older acute myeloid leukemia (AML) patients 60–75 years in first complete remission (CR1): an alliance (A151509), SWOG, ECOG-ACRIN, and CIBMTR study. Leukemia. 2019;33(11):2599–2609. doi:10.1038/s41375-019-0477-x [PubMed: 31073153]

18. Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, et al. Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes. J Clin Oncol. 2017;35(11):1154–1161. doi:10.1200/JCO.2016.70.7091 [PubMed: 28380315]

19. Finke J, Nagler A. Viewpoint: What is the role of allogeneic hematopoietic cell transplantation in the era of reduced-intensity conditioning – is there still an upper age limit? A focus on myeloid neoplasia. Leukemia. 2007;21(7):1357–1362. doi:10.1038/sj.leu.2404741 [PubMed: 17508002]

20. Hegenbart U, Niederwieser D, Sandmaier BM, Maris M, Shizuru JA, Greinix H, 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. [PubMed: 16344316]

21. Deeg HJ, Storer B, Slattery JT, Anasetti C, Doney KC, Hansen JA, et al. Conditioning with targeted busulfan and cyclophosphamide for hematopoietic stem cell transplantation from related and unrelated donors in patients with myelodysplastic syndrome. Blood J Am Soc Hematol. 2002;100(4):1201–1207.
22. Ditschkowski M, Elmaagacli AH, Trenschel R, Steckel NK, Koldehoff M, Beelen DW. Myeloablative allogeneic hematopoietic stem cell transplantation in elderly patients. Clin Transplant. 2006;20(1):127–131. doi:10.1111/j.1399-0012.2005.00453.x [PubMed: 16556167]

23. Polverelli N, Tura P, Battipaglia G, Malagola M, Bernardi S, Gandolfi L, et al. Multidimensional geriatric assessment for elderly hematological patients (≥60 years) submitted to allogeneic stem cell transplantation. A French–Italian 10-year experience on 228 patients. Bone Marrow Transplant. Published online May 12, 2020:1–10. doi:10.1038/s41409-020-0934-1

24. Munshi PN, Vesole D, Jurczyszyn A, Zaucha JM, St Martin A, Davila O, et al. Age no bar: A CIBMTR analysis of elderly patients undergoing autologous hematopoietic cell transplantation for multiple myeloma. Cancer. n/a(n/a). doi:10.1002/cncr.33171

25. D’Souza A, Fretham C, Lee SJ, Arora M, Brunner J, Chhabra S, Devine S, et al. Current Use of and Trends in Hematopoietic Cell Transplantation in the United States. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2020;26(8):e177–e182. doi:10.1016/j.bbmt.2020.04.013
Figure 1.
A. Adjusted probability of OS stratified by age cohorts. B. Adjusted probability of DFS
A

Adjusted Cumulative Incidence of Relapse

60-64 (N=607)

65-69 (N=504)

70+ (N=194)

Months Since Transplant
Figure 2.
A. Cumulative incidence of relapse and B. Cumulative incidence of TRM stratified by age.
A Adjusted Cumulative Incidence of Acute GVHD (grade III/IV)

- 60-64 (N=610)
- 65-69 (N=507)
- 70+ (N=196)

Days Since Transplant

%
Figure 3.
A. Grade III/IV Acute GVHD and B. Moderate/Severe Chronic GVHD
# Table 1.

## Baseline characteristics

| Characteristic                               | Age 60–64 | 65–69 | ≥70  |
|----------------------------------------------|-----------|-------|------|
| No. of patients                              | 612       | 512   | 197  |
| Age at HCT (years) - median (range)          | 62 (60–65)| 67 (65.1–69.9)| 72 (70–77.7)|
| Gender - no. (%)                             |           |       |      |
| Male                                         | 340 (56)  | 296 (58)| 133 (68)|
| Female                                       | 272 (44)  | 216 (42)| 64 (32)|
| Clinical onset of AML - no. (%)              |           |       |      |
| De-novo                                      | 467 (76)  | 376 (73)| 139 (71)|
| sAML/TAML                                    | 145 (24)  | 136 (27)| 58 (29)|
| Karnofsky score - no. (%)                    |           |       |      |
| <90                                          | 251 (41)  | 236 (46)| 78 (40)|
| ≥90                                          | 355 (58)  | 271 (53)| 119 (60)|
| Missing                                      | 6 (1)     | 5 (1) | 0    |
| HCT-CI - no. (%)                             |           |       |      |
| 0                                            | 115 (19)  | 80 (16)| 31 (16)|
| 1                                            | 93 (15)   | 74 (14)| 20 (10)|
| 2                                            | 94 (15)   | 67 (13)| 39 (20)|
| 3+                                           | 285 (47)  | 271 (53)| 100 (51)|
| Missing                                      | 25 (4)    | 20 (4) | 7 (4) |
| Cytogenetic risk group - no. (%)             |           |       |      |
| Favorable                                    | 8 (1)     | 8 (2) | 5 (3) |
| Intermediate                                 | 401 (66)  | 325 (63)| 131 (66)|
| Poor                                         | 191 (31)  | 168 (33)| 59 (30)|
| Missing                                      | 12 (2)    | 11 (2)| 2 (1) |
| No. of patients                              | 612       | 512   | 197  |
| ELN cytogenetic score                        |           |       |      |
| Favorable                                    | 50 (8)    | 55 (11)| 28 (14)|
| Intermediate                                 | 185 (30)  | 185 (36)| 80 (41)|
| Adverse                                      | 109 (18)  | 107 (21)| 48 (24)|
| Missing                                      | 268 (44)  | 165 (32)| 41 (21)|
| MRD at time of HCT - no. (%)                 |           |       |      |
| Negative                                     | 416 (68)  | 338 (66)| 127 (64)|
| Positive                                     | 154 (25)  | 141 (28)| 64 (32)|
| Missing                                      | 42 (7)    | 33 (6) | 6 (3) |
| Donor type - no. (%)                         |           |       |      |
| HLA-identical sibling                        | 159 (26)  | 109 (21)| 24 (12)|
| Haploidentical                               | 57 (9)    | 46 (9) | 21 (11)|
| Other relative                               | 30 (5)    | 30 (6) | 9 (5) |
| Well-matched URD (8/8 alleles)               | 240 (39)  | 228 (45)| 110 (56)|
| Partially-matched URD (7/8)                  | 24 (4)    | 23 (4) | 5 (3) |
| Characteristic                  | Age 60–64 | 65–69 | ≥70  |
|-------------------------------|-----------|-------|------|
| Cord blood                    | 102 (17)  | 76 (15)| 28 (14) |
| Graft type - no. (%)          |           |       |      |
| Bone marrow                   | 69 (11)   | 53 (10)| 23 (12) |
| Peripheral blood              | 441 (72)  | 383 (75)| 146 (74) |
| Cord blood                    | 102 (17)  | 76 (15)| 28 (14) |
| Conditioning intensity - no. (%)|       |       |      |
| MAC                           | 184 (30)  | 82 (16)| 13 (7) |
| RIC/NMA                       | 428 (70)  | 430 (84)| 184 (93) |
| ATG as part of regimen        |           |       |      |
| No                            | 451 (74)  | 378 (74)| 148 (75) |
| Yes                           | 158 (26)  | 131 (26)| 48 (24) |
| GVHD prophylaxis - no. (%)    |           |       |      |
| Post-cy +/- other             | 61 (10)   | 64 (13)| 35 (18) |
| TAC/CSA +/- other             | 497 (81)  | 418 (82)| 153 (78) |
| Other                         | 54 (9)    | 30 (6)| 9 (5) |
| Year of transplant - no. (%)  |           |       |      |
| 2007–2013                     | 261 (43)  | 156 (30)| 40 (20) |
| 2014–2015                     | 225 (37)  | 217 (42)| 96 (49) |
| 2016–2017                     | 126 (21)  | 139 (27)| 61 (31) |
| Follow-up of survivors (months) - median (min-max) | 49 (0.4–142.9) | 47.9 (0.2–126.1) | 43.6 (0.4–122.5) |

sAML=secondary AML; tAML=Therapy-related AML; MAC=Myeloablative conditioning; RIC=Reduced intensity conditioning; URD=unrelated donor; mELN=modified European Leukemia Net classification; MRD=Minimal residual disease; Tac=tacrolimus; CSA=cyclosporine; Post-Cy=post-transplant cyclophosphamide
**Table 2.**

Multivariate model outcomes

| Covariates                        | N    | HR (95% CI)       | p-value |
|-----------------------------------|------|-------------------|---------|
| Overall survival                  |      |                   |         |
| Age at HCT (years) - main effect  |      |                   |         |
| 60–64                             | 612  | Reference         | 0.008   |
| 65–69                             | 512  | 1.27 (1.09–1.49)  | 0.002   |
| ≥70                               | 197  | 1.20 (0.96–1.50)  | 0.11    |
| Cytogenetic risk group            |      |                   | <0.001  |
| Favorable/Intermediate            | 878  | Reference         |         |
| Poor                              | 418  | 1.42 (1.22–1.65)  | <0.001  |
| Missing                           | 25   | 0.70 (0.40–1.22)  | 0.21    |
| MRD status at HCT                 |      |                   | 0.004   |
| Negative                          | 881  | Reference         |         |
| Positive                          | 359  | 1.33 (1.12–1.57)  | 0.001   |
| Missing                           | 81   | 1.12 (0.83–1.52)  | 0.45    |
| Donor type                        |      |                   | <0.001  |
| HLA-identical sibling             | 292  | Reference         |         |
| Other relative                    | 193  | 1.22 (0.95–1.57)  | 0.12    |
| Well-matched URD (8/8)            | 578  | 0.90 (0.74–1.10)  | 0.29    |
| Partially-matched URD (7/8)       | 52   | 0.98 (0.67–1.43)  | 0.91    |
| Cord blood                        | 206  | 1.49 (1.19–1.87)  | 0.001   |
| Year of HCT                       |      |                   | 0.034   |
| 2007–2013                         | 457  | Reference         |         |
| 2014–2015                         | 538  | 0.96 (0.81–1.14)  | 0.63    |
| 2016–2017                         | 326  | 0.76 (0.61–0.94)  | 0.01    |
| Non-relapse mortality             |      |                   |         |
| Age at HCT (years) - main effect  |      |                   | 0.018   |
| 60–64                             | 607  | Reference         |         |
| 65–69                             | 504  | 1.34 (1.06–1.69)  | 0.016   |
| ≥70                               | 194  | 1.44 (1.05–1.96)  | 0.023   |
| HCT-CI                            |      |                   | 0.009   |
| 0–1                               | 406  | Reference         |         |
| 2                                 | 199  | 1.10 (0.78–1.57)  | 0.58    |
| 3+                                | 648  | 1.40 (1.09–1.79)  | 0.01    |
| Missing                           | 52   | 0.56 (0.26–1.22)  | 0.23    |
| Donor type                        |      |                   | 0.001   |
| HLA-identical sibling             | 286  | Reference         |         |
| Other relative                    | 189  | 0.91 (0.61–1.35)  | 0.63    |
| Covariates                        | N     | HR (95% CI)     | p-value |
|----------------------------------|-------|----------------|---------|
| Well-matched URD (8/8)           | 575   | 0.99 (0.74–1.32)| 0.94    |
| Partially-matched URD (7/8)      | 52    | 1.58 (0.98–2.56)| 0.063   |
| Cord blood                       | 203   | 1.69 (1.20–2.37)| 0.003   |

**Relapse**

| Age at HCT (years) - main effect |       |                |         |
|----------------------------------|-------|----------------|---------|
| 60–64                            | 607   | Reference      |         |
| 65–69                            | 504   | 1.19 (0.98–1.44)| 0.083   |
| ≥70                              | 194   | 0.99 (0.75–1.32)| 0.95    |

| Cytogenetic risk group           |       |                |         |
|----------------------------------|-------|----------------|---------|
| Favorable/Intermediate           | 868   | Reference      | <0.001  |
| Poor                             | 412   | 1.83 (1.52–2.20)| <0.001  |
| Missing                          | 25    | 0.98 (0.50–1.90)| 0.95    |

| MRD status at HCT                |       |                |         |
|----------------------------------|-------|----------------|---------|
| Negative                         | 873   | Reference      | <0.001  |
| Positive                         | 352   | 1.54 (1.27–1.88)| <0.001  |
| Missing                          | 80    | 1.37 (0.96–1.97)| 0.085   |

| Donor type                       |       |                |         |
|----------------------------------|-------|----------------|---------|
| HLA-identical sibling            | 286   | Reference      | 0.013   |
| Other relative                   | 189   | 1.06 (0.78–1.44)| 0.72    |
| Well-matched URD (8/8)           | 575   | 0.77 (0.61–0.97)| 0.027   |
| Partially-matched URD (7/8)      | 52    | 0.48 (0.27–0.88)| 0.017   |
| Cord blood                       | 203   | 0.83 (0.56–1.23)| 0.35    |

| Graft type                       |       |                |         |
|----------------------------------|-------|----------------|---------|
| Bone marrow                      | 143   | Reference      | 0.02    |
| Peripheral blood                 | 959   | 0.72 (0.54–0.95)| 0.02    |

**Acute GVHD (grade III/IV)**

| Age at HCT (years) - main effect |       |                |         |
|----------------------------------|-------|----------------|---------|
| 60–64                            | 610   | Reference      | 0.65    |
| 65–69                            | 507   | 1.12 (0.81–1.54)| 0.5     |
| ≥70                              | 196   | 1.20 (0.79–1.82)| 0.41    |

**Chronic GVHD (moderate-severe)**

| Age at HCT (years) - main effect |       |                |         |
|----------------------------------|-------|----------------|---------|
| 60–64                            | 612   | Reference      | 0.20    |
| 65–69                            | 510   | 0.84 (0.66–1.08)| 0.17    |
| ≥70                              | 197   | 0.76 (0.53–1.09)| 0.14    |

| Graft type                       |       |                | <0.001  |
|----------------------------------|-------|----------------|---------|
| Bone marrow                      | 145   | Reference      |         |
| Peripheral blood                 | 968   | 1.74 (1.11–2.74)| 0.017   |

*Bone Marrow Transplant. Author manuscript; available in PMC 2022 October 02.*
| Covariates          | N   | HR (95% CI) | p-value |
|---------------------|-----|-------------|---------|
| Cord blood          | 206 | 0.61 (0.32–1.16) | 0.13    |
| GVHD prophylaxis    |     |             | 0.001   |
| Post-cy +/- other   | 160 | Reference   |         |
| TAC/CSA +/- other   | 1066| 1.76 (1.15–2.70) | 0.02    |
| Other               | 73  | 0.37 (0.13–1.08) | 0.068   |
| Missing             | 20  | 1.48 (0.51–4.28) | 0.47    |
Table 3.

Five-year overall survival

| Prob (95% CI) | 60–64 (n=612) | 65–69 (n=512) | >=70 (n=197) | P Value |
|---------------|--------------|--------------|-------------|---------|
| 1-year        | 67.6 (63.9–71.3)% | 59.2 (54.9–63.4)% | 59.9 (53–66.6)% | 0.008   |
| 2-year        | 55.4 (51.3–59.3)% | 49.7 (45.3–54.1)% | 51.7 (44.7–58.7)% | 0.172   |
| 3-year        | 49.4 (45.3–53.5)% | 42.3 (37.8–46.8)% | 44.7 (37.5–52)% | 0.068   |
| 4-year        | 44.3 (40.1–48.5)% | 38.1 (33.6–42.8)% | 43.8 (36.5–51.2)% | 0.135   |
| 5-year        | 42 (37.7–46.4)% | 35.8 (31–40.7)% | 40.6 (32.7–48.7)% | 0.166   |