Published in final edited form as:

Bone Marrow Transplant. 2012 February ; 47(2): 203–211. doi:10.1038/bmt.2011.69.

SIMILAR OUTCOMES USING MYELOABLATIVE VERSUS REDUCED INTENSITY ALLOGENEIC TRANSPLANT PREPARATIVE REGIMENS FOR AML OR MDS

Selina M. Luger, MD[1], **Olle Ringdén, MD, PhD**[2], **Mei-Jie Zhang, PhD**[3], **Waleska S. Pérez, MPH**[3], **Michael R. Bishop, MD**[4], **Martin Bornhauser, MD**[5], **Christopher N. Bredeson, MD, MSc**[6], **Mitchell S. Cairo, MD**[7], **Edward A. Copelan, MD**[8], **Robert Peter Gale, MD, PhD, DSc**[9], **Sergio A. Giralt, MD**[10], **Zafer Gulbas, MD**[11], **Vikas Gupta, MD**[12], **Gregory A. Hale, MD**[13], **Hillard M. Lazarus, MD**[14], **Victor Anthony Lewis, MD**[15], **Michael C. Lill, MD**[16], **Philip L. McCarthy, MD**[17], **Daniel J. Weisdorf, MD**[18], and **Michael A. Pulsipher, MD**[19]

[1] Hospital of the University of Pennsylvania, Philadelphia, PA

[2] Karolinska University Hospital, Huddinge, Sweden

[3] Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI

[4] National Cancer Institute, Bethesda, MD

[5] Universitatsklinikum Carl Gustav Carus, Dresden, Germany

[6] Froedtert Memorial Lutheran Hospital, Milwaukee, WI

[7] Morgan Stanley Children's Hospital of New York, New York

[8] Cleveland Clinic, Taussig Cancer Center, Cleveland, OH

[9] Celgene Corporation, Summit, NJ

[10] MD Anderson Cancer Center, Houston, TX

[11] Osman Gazi University Medical School, Eskisehir, Turkey

[12] Princess Margaret Hospital, Ontario, Canada

[13] All Children's Hospital, St. Petersburg, FL

[14] University Hospitals Case Medical Center, Cleveland, OH

[15] Alberta Children's Hospital, Calgary-Alberta, Canada

[16] Cedars Sinai Medical Center, Los Angeles, CA

[17] Roswell Park Cancer Institute, Buffalo, NY

Correspondence and reprint requests to: Daniel J. Weisdorf, MD, University of Minnesota Medical Center, 420 Delaware Street SE, MMC 480, Minneapolis, Minnesota, 55455; Telephone: 612-624-3101; Fax: 612-625-6919; weisd001@umn.edu.

CONFLICT OF INTEREST: None

[18] University of Minnesota Medical Center, Minneapolis, MN

[19] University of Utah Health Science Center, Salt Lake City, UT

Abstract

Although reduced intensity (RIC) and nonmyeloablative (NMA) conditioning regimens have been used for over a decade, their relative efficacy versus myeloablative (MA) approaches to allogeneic hematopoietic cell transplantation (HCT) in patients with acute myelogenous leukemia (AML) and myelodysplasia (MDS) is unknown. We compared disease status, donor, graft and recipient characteristics with outcomes of 3731 MA with 1448 RIC/NMA procedures performed at 217 centers between 1997 and 2004. Five year univariate probabilities and multivariate relative risk (RR) outcomes of relapse, transplant related mortality (TRM), disease free survival (DFS) and overall survival (OS) are reported. Adjusted OS at 5 years was 34%, 33%, and 26% for MA, RIC and NMA transplants, respectively. NMA conditioning resulted in inferior DFS and OS but there was no difference in DFS and OS between RIC and MA regimens. Late TRM negates early decreases in toxicity with RIC and NMA regimens. Our data suggest higher regimen intensity may contribute to optimal survival in patients with AML/MDS, suggesting roles for both regimen intensity and graft vs. leukemia in these diseases. Prospective studies comparing regimens are needed to confirm this finding and determine the optimal approach to patients who are eligible for either MA or RIC/NMA conditioning.

Keywords

allogeneic transplant; reduced intensity; AML

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) offers a chance of long-term disease free survival to patients with high–risk AML or MDS, with five-year survival ranging from 30–50%(1–3). Many patients with AML are not considered candidates for standard myeloablative (MA) procedures because of advanced age, prior therapies or comorbidities. Nonmyeloablative (NMA) and reduced intensity conditioning (RIC) regimens were developed over a decade ago to reduce the transplant related mortality (TRM) of myeloablative (MA) HCT, and to allow patients otherwise ineligible for allogeneic transplant to benefit from the graft-versus leukemia effect(4–7). AML and MDS are now considered standard indications for NMA or RIC transplants, and a number of studies have demonstrated durable long-term remissions using these approaches(8–14).

Several groups have retrospectively compared RIC to MA conditioning for allotransplantation in AML and MDS(15–18) and suggest that RIC allografts can yield satisfactory survival for patients who are ineligible for myeloablative allografts. To better address the important question of whether the intensity of the preparative regimens used for AML/MDS is correlated with survival and other key outcomes we performed a comparative analysis of outcomes of transplants reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) after MA, RIC, and NMA preparatory regimens. In

addition, we report the association of specific donor, graft and recipient characteristics with key outcomes when each of these three approaches is utilized.

PATIENTS AND METHODS

Data Sources

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR), Autologous Blood and Marrow Transplant Registry (ABMTR) and the National Marrow Donor Program (NMDP) established in 2004 that comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on allogeneic and autologous hematopoietic SCT to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the NMDP Coordinating Center in Minneapolis. Participating centers are required to report all transplants consecutively. Patients are followed longitudinally, with yearly follow-up. Computerized checks for discrepancies, physicians' review of submitted data and on-site audits of participating centers ensure data quality and compliance. Observational studies conducted by the CIBMTR are performed in compliance with the Privacy Rule (HIPAA) as a Public Health Authority, and in compliance with all applicable federal regulations pertaining to the protection of human research participants as determined by continuous review of the Institutional Review Boards of the NMDP and the Medical College of Wisconsin since 1985.

The CIBMTR collects data at two levels: Transplant Essential Data (TED) and Comprehensive Report Form (CRF) data. TED include disease type, age, sex, pretransplant disease stage and chemotherapy-responsiveness, date of diagnosis, graft type (bone marrow- and/or blood-derived stem cells), high-dose conditioning regimen, post-transplant disease progression and survival, development of a new malignancy and cause of death. All CIBMTR teams contribute TED. More detailed disease, and pre- and post-transplant clinical information are collected on a subset of registered patients selected for CRF data by a weighted randomization scheme. TED and CRF level data are collected pre-transplant, 100 days and six months post transplant and annually thereafter or until death.

Patients, donors and graft source

The study included all patients between the ages of 18 and 70 who received peripheral blood stem cell (PB) or bone marrow (BM) grafts from a related or volunteer unrelated donor (URD) for MDS or non-M3 AML reported to the CIBMTR between 1997 and 2004 on whom adequate data was available for analysis. Excluded were recipients of cord blood transplants, transplants performed with a conditioning regimen that was used in fewer than 30 patients, and transplants in which patients received T cell depleted grafts.

Conditioning regimens

The regimens were defined as MA, RIC and NMA using previously defined guidelines as follows(19, 20): MA regimens included: 1) TBI dose >500cGy single dose or TBI dose >=800 cGy fractionated, with or without cyclophosphamide, 2) standard dose busulfan and cyclophosphamide, 3) melphalan ≥150mg/m^2 +/− other agents, and 4) busulfan total dose >9 mg/kg +/− other agents. RIC regimens included: 1) TBI dose >200cGy and <500cGY single

dose or TBI dose <800cGY fractionated +/− other agents, 2) melphalan dose ≤150 mg/m^2 +/− other agents, 3) busulfan dose ≤9 mg/kg +/− other agents. NMA regimens included were: 1) TBI alone: dose = 200cGY, 2) fludarabine + TBI 200cGY or 3) fludarabine + cyclophosphamide.

Endpoints

Primary endpoints were hematopoietic recovery, GVHD, TRM, clinical disease relapse (hematologic or extramedullary), disease-free survival (DFS), and overall survival (OS). TRM was defined as death during continuous complete remission post-transplant. Relapse was defined as clinical or hematologic recurrence. For analyses of DFS, failures were clinical or hematologic relapses or deaths from any cause; patients alive and in complete remission were censored at time of last follow-up. For analyses of OS, failure was death from any cause; surviving patients were censored at the date of last contact. The date of the transplant was the starting time point for calculating all outcomes.

Statistical analysis

Patient-, disease-, and transplant related variables for patients receiving MA, RIC and NMA conditioning regimens were compared using the chi-square statistic for categorical variables and the Kruskal-Wallis test for continuous variables. Univariate probabilities of DFS and OS were calculated using the Kaplan-Meier estimator; the log-rank test was used for univariate comparisons. Probabilities of hematopoietic recovery, acute and chronic GVHD, TRM and relapse were calculated using cumulative incidence curves to accommodate competing risks(21). Assessment of potential potential risk factors for outcomes of interest were evaluated in multivariate analyses using Cox proportional hazards regression(22). The variables considered in the multivariate analysis were age at transplant, gender, Karnofsky performance score (<90% vs. ≥90% vs. unknown), disease (AML vs. MDS), French-American-British subtype at diagnosis (M0–M2 vs. M4–M7 vs. other/unclassified (for AML); refractory anemia or acquired idiopathic sideroblastic anemia, vs. other MDS (for MDS)), therapy related leukemia (no vs. yes vs. unknown), cytogenetics (good vs. intermediate vs. poor prognosis vs. unknown), blast percentage at transplant (<5% vs. 5–10% vs. >10% vs. unknown), duration of first complete remission (CR) for AML patients transplanted in second CR (<6 vs. 6–12 months vs. unknown), disease status at transplant (primary induction failure vs. first CR vs. ≥ second CR vs. relapse (for AML); treated vs. untreated (for MDS), time from remission to transplant for AML patients transplanted in first CR (≤3 months vs. >3 months vs. unknown), type of donor (HLA-identical sibling vs. unrelated well-matched vs. unrelated partially matched vs. unrelated mismatched vs. unrelated matching unknown), donor age, donor-recipient sex match (female-male vs. others), donor recipient cytomegalovirus status (donor−/recipient− vs. donor+/recipient− vs. recipient+ vs. unknown), graft type (BM vs. PB stem cells), year of transplant, previous autologous transplant (no vs. yes), ATG (no vs. yes) and GVHD prophylaxis (tacrolimus+ methotrexate +/− other vs. tacrolimus +/− other vs. cyclosporine + methotrexate +/− other vs. cyclosporine +/− other). A backward stepwise model selection approach was used to identify all significant risk factors. Each step of model building contained the main effect for conditioning regimen. Factors which were significant at a 5% level were kept in the final model. The potential interactions between main effect and all significant risk factors were

tested. A significant interaction was found between graft type and reduced-intensity conditioning regimen. A model with this interaction was considered for this group. The proportionality assumption was tested by adding a time-dependent covariate for each factor. When tests indicated differential effects over time (non-proportional hazards), models were constructed breaking the post-transplant course into two time periods, using the maximized partial likelihood method to find the most appropriate breakpoint. The proportionality assumptions were further tested. After the above modeling of time varying effects, the final multivariate model was built. Adjusted probabilities of DFS and OS were generated from the final Cox models stratified on treatment of conditioning regimen and weighted averages of covariate values using the pooled sample proportion as the weight function. These adjusted probabilities were used to estimate likelihood of outcomes in populations with similar prognostic factors.

RESULTS

Patient and Transplant Characteristics

Five thousand one hundred and seventy-nine patients met the study inclusion criteria. There were 3731 HCT with MA conditioning regimens and 1448 RIC/NMA procedures performed at 223 centers from 37 different countries. Median follow up of survivors was as follows: 58 (3–128) months for MA, 38 (3–124) months for the RIC group, and 48 (3–87) months for the NMA group. Table 1 shows patient, disease and transplant characteristics of the 5179 transplant recipients. Patients in the MA group were younger than those in the RIC or NMA groups ($p<0.001$). MA and RIC PB recipients were more likely to receive cells from an HLA identical sibling, compared to RIC BM recipients or NMA conditioned recipients. Patients who received NMA/RIC conditioning were less often transplanted with >10% blast in the bone marrow compared to the MA group (6% vs. 12%) and were less likely to have a Karnofsky score ≥90% ($p<0.001$). The groups were similar with respect to percentage of patients with AML vs. MDS, FAB categorization, and cytogenetic prognostic group. Fewer patients who received MA conditioning had therapy related leukemia. Patients who were in the NMA group were more likely to be transplanted more than 3 months after attaining remission ($p<0.002$).

Hematopoietic Recovery

Hematopoietic recovery at 100 days was similar for the conditioning regimen categories. The likelihood of achieving an ANC of 500 on day 100 was 93% vs. 92% vs. 95% vs. 94% for MA vs. RIC conditioning with BM, RIC with PB, and NMA conditioning.

Graft versus Host Disease

The incidence of grade II–IV acute GVHD (aGVHD) by day 100 was lower in the RIC BM group (RR 0.66 (0.51–0.85), $p=0.001$), with 41% of patients developing aGVHD compared to 45–47% in the MA, RIC PB and NMA groups (Figure 1a).

Chronic GVHD (cGVHD) was more likely in RIC PB and NMA conditioned recipients (almost all of whom received PBSC) when compared to MA conditioned recipients and least likely with RIC conditioned recipients who received BM (Figure 1b).

Treatment Related Mortality

Table 2 demonstrates the results of the multivariate analysis of TRM. There was no statistically significant difference in TRM between the 4 groups. Early on (at 3 and 6 months), there was slightly higher TRM in the MA and RIC BM groups when compared to RIC PB and NMA (3 month TRM 18%, 16%, 12 %, and 13% for MA vs. RIC BM vs. RIC PB vs. NMA, respectively). However, by 3 years, TRM was equivalent between the four groups (Figure 2a) and this continued at 5 years.

Relapse and Survival

Relapse was more likely in the RIC BM and NMA groups than in the MA group ($p<0.001$) (Table 2). At 5 years, cumulative incidence of relapse was 32%, 42%, 39% and 43% for the MA vs. RIC BM vs. RIC PB vs. NMA conditioned groups, respectively (Figure 2b).

Treatment failure (relapse or death in remission) was greatest and DFS was lowest among the NMA group ($p<0.001$, Table 2). The adjusted DFS probability at 5 years was 33%, 29%, 30% and 24% for the MA, RIC PB, RIC BM and NMA conditioned groups, respectively ($p<0.001$ for NMA compared to MA conditioning) (Figure 3a).

Overall mortality was highest for patients who underwent NMA transplants (RR 1.2, $p=0.006$). Adjusted overall survival (OS) at 5 years was 34%, 33%, 33% and 26% for MA, RIC PB, RIC BM and NMA transplants, respectively (Figure 3b).

Primary disease, infection and GVHD accounted for the majority of deaths. Patients in the NMA group were more likely to die of primary disease (43% vs. 37% for MA/RIC PB and 34% for RIC BM). Death from infection was more likely in RIC transplants than MA and NMA transplants (22% vs. 16% for RIC vs. MA/NMA, respectively, $p=0.009$).

Potential candidates for ablative and nonablative conditioning

We performed a subset analysis of patients who had better risk disease, a high performance score, and were in an age range where many clinicians would consider using any of the three approaches. This subgroup consisted of patients between the ages of 40–60 years with AML in CR1 or with early MDS (<5% blasts) and with a Karnofsky score of ≥90%. Similar to the entire group, DFS at five years was 43%, 37%, 33% and 26% for MA vs. RIC BM vs. RIC PB vs. NMA (Table 3). Only the NMA group had an inferior outcome compared to the MA group ($p=0.006$).

DISCUSSION

This study describes the largest group of patients with AML and MDS who have received allogeneic transplant with MA, RIC, and NMA conditioning reported to date. It includes transplantation from both related and unrelated donors from multiple centers. The key finding of our study is that in spite of varying regimen intensities for older and sicker patients previously ineligible for allogeneic transplantation, differences in survival outcomes are very small. RIC and NMA yielded similar OS and DFS. Only NMA conditioning (defined here as TBI 200cGy +/− Fludarabine, or fludarabine + cyclophosphamide) resulted

in significantly worse long-term DFS and OS compared to the more intense preparative approaches.

Although RIC and NMA regimens are thought to decrease the risk of early morbidity and acute GVHD because of decreased tissue damage, conditioning intensity did not significantly impact the incidence of acute GVHD. While donor type impacted on the probability of both acute and chronic GHVD, in multivariate analysis only age and type of GVHD prophylaxis impacted the incidence of chronic GVHD.

MA regimens were associated with less relapse than the RIC BM and NMA groups. Increased blast percentage at transplant, late disease status, and poor-risk cytogenetics were associated with relapse, but surprisingly, so was a lower Karnofsky score. Age, performance status and disease status at transplant were significant covariates for TRM and were significantly different between the various transplant types. While early TRM was less with RIC/NMA approaches, the data indicate that late TRM negates any early advantage offered by RIC regimens, resulting in similar 5 year DFS and OS in recipients of MA conditioning. Late TRM after RIC/NMA approaches was due to similar causes compared to MA approaches, primarily infections and GVHD.

In a retrospective review of RIC vs. MA sibling matched transplants in 722 patients with AML over the age of 50 from the EBMT(23), acute GVHD (grade II–IV) and TRM (at 2 years) were decreased and relapse rate was increased following RIC procedures on univariate analysis. The study was not, however, able to demonstrate any difference in leukemia free survival (LFS) and OS at 2 years. A recent EBMT study comparing MA conditioning vs. RIC in patients with AML receiving URD transplants showed that in patients below 50 years of age, relapse was increased following RIC, but TRM and LFS were the same in each group(23–25). In patients above 50 years of age, TRM was increased in the MA group, but relapse and LFS were the same.

Martino et al(26) reported results on 836 patients with MDS or secondary AML who received RIC vs. MA sibling transplants. They noted an increase in relapse rate with RIC but no difference in progression free or OS. For patients under the age of 50, however, the 3 year incidence of relapse and TRM was lower for those who received MA conditioning compared to RIC (57%vs 69%). It is possible that patients under 50 years who received RIC had other comorbidities or risk factors that would have contributed to an inferior outcome. In their study, for patients who were transplanted not in CR, there was a lower incidence of relapse and TRM for those patients who had MA rather than RIC (68% vs. 90%). In our study, multivariate analysis showed that blast percentage and disease status at transplant were also found to be significant covariates for both DFS and OS. Also, DFS and OS were also not different for the t-AML/MDS subgroup. In our sub-analysis of patients between the ages of 40–60 with AML in CR1 or with MDS potentially eligible for any conditioning approach, we observed similar DFS when comparing MA to RIC transplant approaches, but inferior survival using NMA regimens.

As with all retrospective registry studies, heterogeneity of patients may affect our analysis. Additionally the reason for choice of preparative regimens is not known. The NMA group

was older and had a lower Karnofsky score at transplant. Many patients who received RIC or NMA transplants would not have been candidates for MA transplants. Detailed comorbidity descriptions or data allowing formal comorbidity scoring were not available. While the known cofactors affecting outcome are accounted for as much as possible in our analyses and adjusted for in the DFS and OS assessments, the analysis presented here cannot be used to determine the optimal treatment for any given patient. These data do suggest, however, that NMA/RIC conditioning yields durable long term survival for a sizeable fraction of patients with AML/MDS, and therefore is a treatment option that can be considered. NMA conditioning is associated with more relapse, resulting in inferior DFS and OS compared to the other levels of regimen intensity. This finding supports a hypothesis that some level of conditioning intensity above typical NMA approaches may improve survival in AML/MDS. Further support for this hypothesis is provided by the higher rate of relapse and decrease in DFS after NMA regimens noted in the subgroup analysis we performed on patients with better risk disease between ages 40–60, who had the potential of receiving MA, RIC or NMA approaches. That said, patients receiving NMA conditioning may differ in unknown ways from patients receiving the more intensive regimens. Prospective studies randomizing these regimens in defined populations are warranted to determine optimal approaches for patients based upon patient, disease, and donor characteristics.

Acknowledgments

The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement U24-CA76518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a Grant/Cooperative Agreement 5U01HL069294 from NHLBI and NCI; a contract HHSH234200637015C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-06-1-0704 and N00014-08-1-0058 from the Office of Naval Research; and grants from AABB; Aetna; American Society for Blood and Marrow Transplantation; Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Astellas Pharma US, Inc.; Baxter International, Inc.; Bayer HealthCare Pharmaceuticals; Be the Match Foundation; Biogen IDEC; BioMarin Pharmaceutical, Inc.; Biovitrum AB; BloodCenter of Wisconsin; Blue Cross and Blue Shield Association; Bone Marrow Foundation; Canadian Blood and Marrow Transplant Group; CaridianBCT; Celgene Corporation; CellGenix, GmbH; Centers for Disease Control and Prevention; Children's Leukemia Research Association; ClinImmune Labs; CTI Clinical Trial and Consulting Services; Cubist Pharmaceuticals; Cylex Inc.; CytoTherm; DOR BioPharma, Inc.; Dynal Biotech, an Invitrogen Company; Eisai, Inc.; Enzon Pharmaceuticals, Inc.; European Group for Blood and Marrow Transplantation; Gamida Cell, Ltd.; GE Healthcare; Genentech, Inc.; Genzyme Corporation; Histogenetics, Inc.; HKS Medical Information Systems; Hospira, Inc.; Infectious Diseases Society of America; Kiadis Pharma; Kirin Brewery Co., Ltd.; The Leukemia & Lymphoma Society; Merck & Company; The Medical College of Wisconsin; MGI Pharma, Inc.; Michigan Community Blood Centers; Millennium Pharmaceuticals, Inc.; Miller Pharmacal Group; Milliman USA, Inc.; Miltenyi Biotec, Inc.; National Marrow Donor Program; Nature Publishing Group; New York Blood Center; Novartis Oncology; Oncology Nursing Society; Osiris Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; Pall Life Sciences; Pfizer Inc; Saladax Biomedical, Inc.; Schering Corporation; Society for Healthcare Epidemiology of America; StemCyte, Inc.; StemSoft Software, Inc.; Sysmex America, Inc.; Teva Pharmaceutical Industries;; THERAKOS, Inc.; Thermogenesis Corporation; Vidacare Corporation; Vion Pharmaceuticals, Inc.; ViraCor Laboratories; ViroPharma, Inc.; and Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, or any other agency of the U.S. Government.

We thank Karen Ballen, Willem Bujan, Steven Goldstein, Roger Herzig, Osman Ilhan, Luis Isola, Jane Liesveld, Gustavo Milone, David Rizzieri, James Russell, Mitchell Sabloff, Stella Santarone, Gary Schiller, Robert Soiffer, Edmund Waller, Roy Weiner, and Peter Wiernik for helpful comments and insights.

References

1. Vicente D, Lamparelli T, Gualandi F, Occhini D, Raiola AM, Ibatici A, et al. Improved outcome in young adults with de novo acute myeloid leukemia in first remission, undergoing an allogeneic bone marrow transplant. Bone Marrow Transplant. 2007; 40(4):349–54. [PubMed: 17589537]
2. Blaise D, Maraninchi D, Archimbaud E, Reiffers J, Devergie A, Jouet JP, et al. Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: a randomized trial of a busulfan-Cytoxan versus Cytoxan-total body irradiation as preparative regimen: a report from the Group d'Etudes de la Greffe de Moelle Osseuse. Blood. 1992; 79(10):2578–82. [PubMed: 1586710]
3. Chang C, Storer BE, Scott BL, Bryant EM, Shulman HM, Flowers ME, et al. Hematopoietic cell transplantation in patients with myelodysplastic syndrome or acute myeloid leukemia arising from myelodysplastic syndrome: similar outcomes in patients with de novo disease and disease following prior therapy or antecedent hematologic disorders. Blood. 2007; 110(4):1379–87. [PubMed: 17488876]
4. Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M, Cividalli G, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood. 1998; 91 (3):756–63. [PubMed: 9446633]
5. McSweeney PA, Niederwieser D, Shizuru JA, Sandmaier BM, Molina AJ, Maloney DG, 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):3390–400. [PubMed: 11369628]
6. Giralt S, Estey E, Albitar M, van Besien K, Rondon G, Anderlini P, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood. 1997; 89(12):4531–6. [PubMed: 9192777]
7. Khouri IF, Keating M, Korbling M, Przepiorka D, Anderlini P, O'Brien S, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. J Clin Oncol. 1998; 16(8):2817–24. [PubMed: 9704734]
8. Hegenbart U, Niederwieser D, Sandmaier BM, Maris MB, 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): 444–53. [PubMed: 16344316]
9. Gratwohl A, Baldomero H, Frauendorfer K, Urbano-Ispizua A. EBMT activity survey 2004 and changes in disease indication over the past 15 years. Bone Marrow Transplant. 2006; 37(12):1069–85. [PubMed: 16757972]
10. Bertz H, Potthoff K, Finke J. Allogeneic stem-cell transplantation from related and unrelated donors in older patients with myeloid leukemia. J Clin Oncol. 2003; 21 (8):1480–4. [PubMed: 12697870]
11. Martino R, Caballero MD, Perez-Simon JA, Canals C, Solano C, Urbano-Ispizua A, et al. Evidence for a graft-versus-leukemia effect after allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning in acute myelogenous leukemia and myelodysplastic syndromes. Blood. 2002; 100(6):2243–5. [PubMed: 12200391]
12. Tauro S, Craddock C, Peggs K, Begum G, Mahendra P, Cook G, et al. Allogeneic stem-cell transplantation using a reduced-intensity conditioning regimen has the capacity to produce durable remissions and long-term disease-free survival in patients with high-risk acute myeloid leukemia and myelodysplasia. J Clin Oncol. 2005; 23(36):9387–93. [PubMed: 16314618]
13. Mohty M, Bay JO, Faucher C, Choufi B, Bilger K, Tournilhac O, et al. Graft-versus-host disease following allogeneic transplantation from HLA-identical sibling with antithymocyte globulin-based reduced-intensity preparative regimen. Blood. 2003; 102(2):470–6. [PubMed: 12649133]
14. Niederwieser D, Maris M, Shizuru JA, Petersdorf E, Hegenbart U, Sandmaier BM, 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):1620–9. [PubMed: 12393457]

15. Flynn CM, Hirsch B, Defor T, Barker JN, Miller JS, Wagner JE, et al. Reduced intensity compared with high dose conditioning for allotransplantation in acute myeloid leukemia and myelodysplastic syndrome: a comparative clinical analysis. Am J Hematol. 2007; 82(10):867–72. [PubMed: 17616969]
16. Scott BL, Sandmaier BM, Storer B, Maris MB, Sorror ML, Maloney DG, et al. Myeloablative vs nonmyeloablative allogeneic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. Leukemia. 2006; 20(1):128–35. [PubMed: 16270037]
17. Massenkeil G, Nagy M, Neuburger S, Tamm I, Lutz C, le Coutre P, et al. Survival after reduced-intensity conditioning is not inferior to standard high-dose conditioning before allogeneic haematopoietic cell transplantation in acute leukaemias. Bone Marrow Transplant. 2005; 36(8): 683–9. [PubMed: 16113673]
18. Alyea EP, Kim HT, Ho V, Cutler C, DeAngelo DJ, Stone R, et al. Impact of conditioning regimen intensity on outcome of allogeneic hematopoietic cell transplantation for advanced acute myelogenous leukemia and myelodysplastic syndrome. Biol Blood Marrow Transplant. 2006; 12(10):1047–55. [PubMed: 17067911]
19. Giralt S, Ballen K, Rizzo D, Bacigalupo A, Horowitz M, Pasquini M, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. 2009; 15(3):367–9. [PubMed: 19203728]
20. Giralt S, Logan B, Rizzo D, Zhang MJ, Ballen K, Emmanouilides C, et al. Reduced-intensity conditioning for unrelated donor progenitor cell transplantation: long-term follow-up of the first 285 reported to the national marrow donor program. Biol Blood Marrow Transplant. 2007; 13(7): 844–52. [PubMed: 17580263]
21. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999; 18(6):695–706. [PubMed: 10204198]
22. Klein, J.; Moeschberger, M. Survival Analysis: Techniques of censored and truncated data. 2. Springer-Verlag; New York, N.Y: 2003.
23. Aoudjhane M, Labopin M, Gorin NC, Shimoni A, Ruutu T, Kolb HJ, 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): 2304–12. [PubMed: 16193083]
24. Ringden O, Labopin M, Ehninger G, Niederwieser D, Olsson R, Basara N, et al. Reduced intensity conditioning compared with myeloablative conditioning using unrelated donor transplants in patients with acute myeloid leukemia. J Clin Oncol. 2009; 27(27):4570–7. [PubMed: 19652066]
25. Report from the International Bone Marrow Transplant Registry. Advisory Committee of the International Bone Marrow Transplant Registry. Bone Marrow Transplant. 1989; 4(3):221–8. [PubMed: 2659107]
26. Martino R, Iacobelli S, Brand R, Jansen T, van Biezen A, Finke J, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood. 2006; 108(3):836–46. [PubMed: 16597592]

Figure 1a

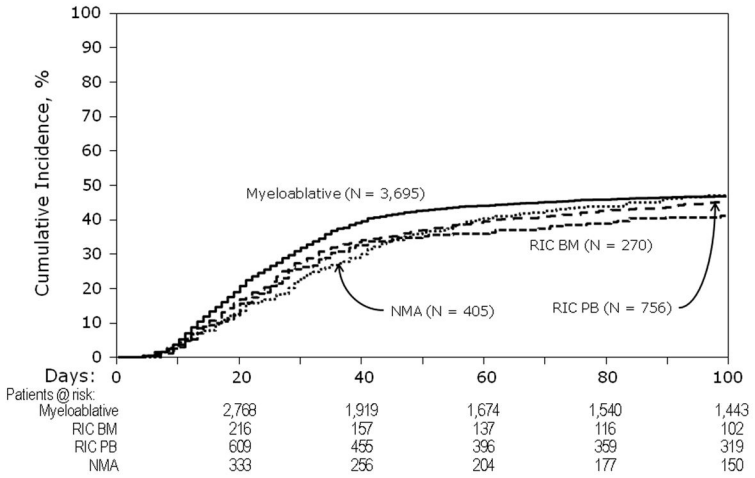

Figure 1b

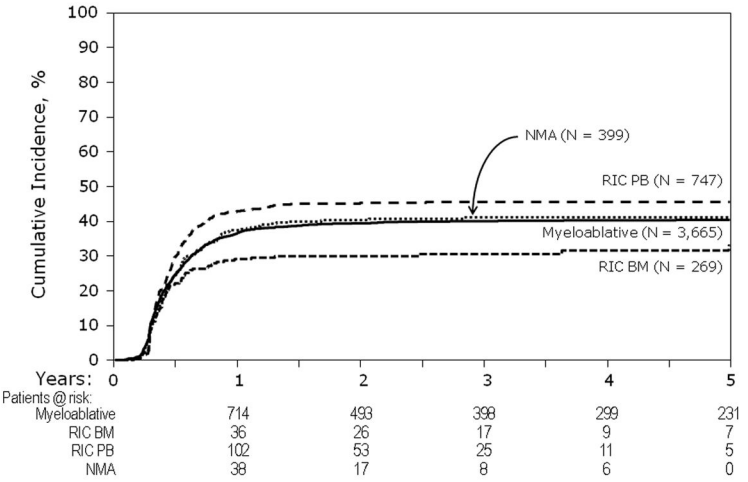

Figure 1.

Cumulative incidence of (a) acute and (b) chronic GVHD after peripheral blood stem cell or bone marrow allogeneic transplant for AML or MDS, by conditioning regimen.

Figure 2a

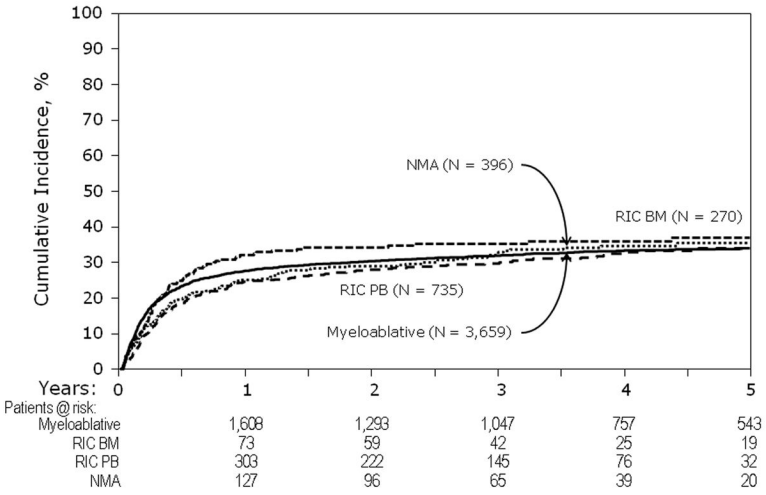

Figure 2b

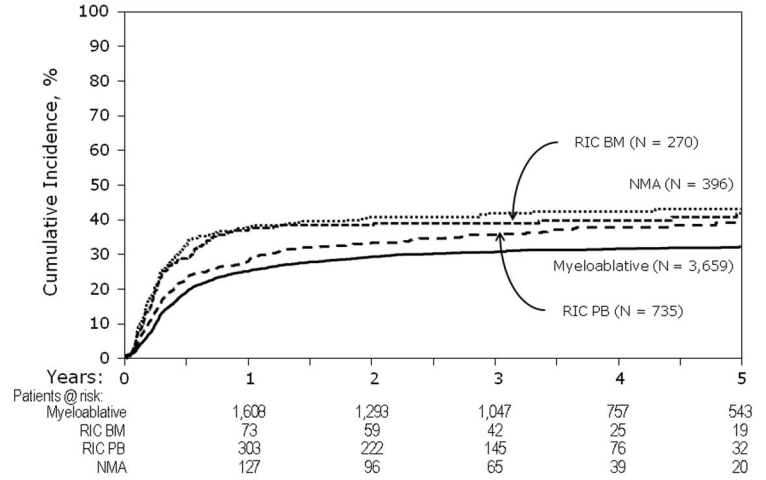

Figure 2.

Cumulative incidence of (a) treatment-related mortality and (b) relapse after peripheral blood stem cell or bone marrow allogeneic transplant for AML or MDS, by conditioning regimen.

Figure 3a

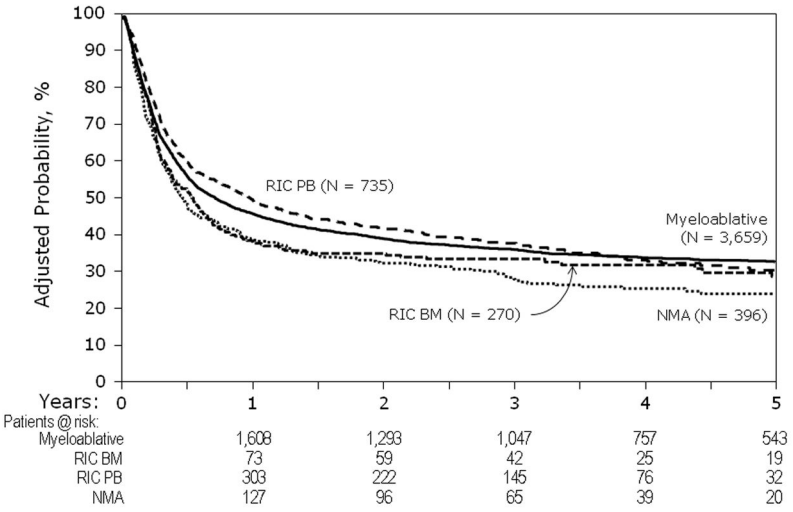

Figure 3b

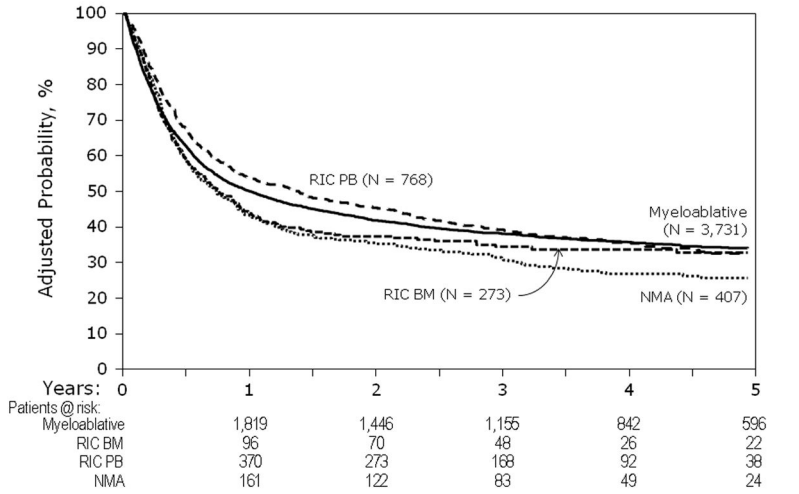

Figure 3.

Adjusted probability of (a) disease-free and (b) overall survival after peripheral blood stem cell or bone marrow allogeneic transplant for AML or MDS, by conditioning regimen.

Table 1

Characteristics of patients 18–70 years of age who underwent allogeneic bone marrow and/or peripheral blood HLA-identical sibling or URD SCT for AML or MDS, reported to the CIBMTR between 1997 and 2004

Characteristics of patients	Myeloablative	RIC BM	RIC PBSC	NMA	P-value
Number of patients	3731	273	768	407	
Number of centers	217	77	128	85	
Age, median (range), yrs	42 (18–68)	51 (19–69)	56 (18–70)	57 (18–70)	<0.001
Age at transplant					<0.001
18–39 y	1662 (44)	71 (26)	107 (14)	45 (11)	
40–59 y	1972 (53)	165 (60)	439 (57)	215 (53)	
60–70 y	97 (3)	37 (14)	222 (29)	147 (36)	
Male sex	1991 (53)	166 (61)	438 (57)	253 (62)	<0.001
Donor-recipient sex match					0.003
M-M	1272 (34)	114 (42)	277 (36)	169 (42)	
M-F	945 (25)	64 (23)	193 (25)	94 (23)	
F-M	719 (19)	52 (19)	161 (21)	84 (21)	
F-F	795 (21)	43 (16)	137 (18)	60 (15)	
FAB subtype					<0.001
AML					
M0–M2	1233 (33)	71 (26)	220 (29)	115 (28)	
M4–M7	1037 (28)	61 (22)	177 (23)	90 (22)	
Transformed from MDS	54 (2)	7 (2)	46 (6)	17 (4)	
Unclassified/Other AML	490 (13)	40 (15)	109 (14)	67 (17)	
MDS					
RA/RARS	229 (6)	29 (11)	70 (9)	37 (9)	
RAEB	274 (7)	29 (11)	79 (10)	41 (10)	
RAEB-t	137 (4)	14 (5)	21 (3)	7 (2)	
CMML	86 (2)	3 (1)	11 (1)	10 (2)	
Unclassified/Other MDS	191 (5)	19 (7)	35 (5)	23 (6)	
Karnofsky score at transplant					<0.001
<90%	1190 (32)	80 (29)	242 (32)	167 (41)	
≥90%	2341 (63)	168 (62)	487 (65)	210 (52)	

Characteristics of patients	Myeloablative	RIC BM	RIC PBSC	NMA	P-value
Unknown	200 (5)	25 (9)	39 (5)	30 (7)	
Therapy-related leukemia					<0.001
No	3382 (91)	231 (84)	672 (88)	338 (83)	
Yes	312 (8)	40 (15)	88 (11)	60 (15)	
Unknown	37 (1)	2 (1)	8 (1)	9 (2)	
Cytogenetics					0.05
Good prognosis	189 (5)	12 (4)	41 (5)	14 (4)	
Intermediate prognosis	2232 (60)	145 (53)	456 (60)	249 (61)	
Poor prognosis	691 (17)	64 (24)	163 (21)	90 (22)	
Unknown	619 (17)	52 (19)	108 (14)	54 (13)	
IPSS score at transplant (*for MDS*)					0.86
Low	45 (5)	3 (3)	15 (7)	9 (9)	
Intermediate-1	301 (33)	29 (31)	64 (29)	37 (31)	
Intermediate-2	199 (21)	19 (20)	49 (23)	24 (20)	
High	108 (12)	9 (10)	26 (12)	11 (9)	
Unknown	264 (29)	34 (36)	62 (29)	37 (31)	
Disease status at transplant					<0.001
1st complete remission	1200 (32)	50 (18)	187 (24)	124 (31)	
≥ 2nd complete remission	565 (15)	50 (18)	121 (16)	85 (21)	
Relapse	606 (16)	51 (19)	121 (16)	51 (13)	
Primary induction failure	410 (11)	25 (9)	105 (14)	27 (6)	
MDS treated	474 (13)	61 (22)	120 (15)	75 (18)	
MDS untreated	429 (12)	32 (12)	91 (12)	40 (10)	
Unknown	47 (1)	4 (2)	23 (3)	5 (1)	
Duration of CR1 (*AML in CR2*)					0.53
Median (range), months	11 (<1–79)	12 (2–45)	11 (1–60)	11 (<1–60)	
≤6 months	112 (21)	7 (17)	15 (14)	14 (19)	
6–12 months	159 (30)	13 (31)	31 (29)	20 (27)	
≥12 months	187 (35)	20 (47)	42 (40)	30 (41)	
Unknown	73 (14)	2 (5)	18 (17)	10 (13)	
Time from remission to transplant, months (*for AML patients in CR1*)					0.002

Characteristics of patients	Myeloablative	RIC BM	RIC PBSC	NMA	P-value
≤3 months	600 (50)	21 (42)	94 (50)	43 (35)	
>3 months	569 (47)	29 (58)	85 (46)	81 (65)	
Unknown	31 (3)	0	8 (4)	0	
Blast in BM at transplant, %					<0.001
Median (range), months	0 (0–99)	0 (0–97)	0 (0–99)	0 (0–92)	
<5%	2842 (76)	195 (72)	575 (75)	346 (85)	
5–10%	168 (5)	14 (5)	43 (6)	13 (3)	
>10%	413 (11)	44 (16)	73 (9)	22 (6)	
Unknown	308 (8)	20 (7)	77 (10)	26 (6)	
Type of donor					<0.001
HLA-identical sibling	1560 (42)	36 (13)	340 (44)	143 (35)	
Unrelated well matched	999 (27)	85 (31)	222 (29)	173 (43)	
Unrelated partially matched	726 (19)	88 (32)	128 (14)	56 (14)	
Unrelated mismatched	313 (8)	39 (14)	41 (5)	24 (6)	
Unrelated matching unknown	133 (4)	25 (9)	37 (5)	11 (3)	
Donor age, years					<0.001
Median (range), months	37 (<1–82)	35 (16–69)	41 (1–78)	41 (19–75)	
18–39 y	2191 (59)	174 (64)	335 (44)	196 (48)	
40–59 y	1363 (37)	86 (32)	328 (43)	160 (39)	
≥60 y	93 (3)	4 (1)	85 (11)	46 (11)	
Unknown	84 (2)	9 (3)	20 (3)	5 (1)	
Donor-recipient CMV match					<0.001
+/+	1242 (33)	75 (27)	298 (39)	120 (30)	
+/−	426 (11)	34 (12)	68 (9)	48 (12)	
−/+	960 (26)	87 (32)	218 (28)	110 (27)	
−/−	990 (27)	58 (22)	150 (20)	119 (29)	
Unknown	113 (3)	19 (7)	34 (4)	10 (2)	
Prior autologous transplant	0	40 (15)	67 (9)		---
Graft type					---
BM	2011 (54)	273 (100)	0	49 (12)	
PBSC	1720 (46)	0	768 (100)	358 (88)	

Characteristics of patients	Myeloablative	RIC BM	RIC PBSC	NMA	P-value
Year of transplant					<0.001
1997–2000	1728 (46)	83 (30)	101 (13)	58 (14)	
2001–2004	2003 (54)	190 (70)	667 (87)	349 (86)	
ATG					<0.001
No	3079 (82)	160 (59)	497 (65)	346 (85)	
Yes	631 (17)	112 (41)	269 (35)	57 (14)	
Unknown	21 (1)	1 (<1)	2 (<1)	4 (1)	
GVHD prophylaxis					<0.001
FK506+MTX±other	851 (23)	88 (32)	145 (19)	35 (9)	
FK506±other	202 (5)	25 (9)	153 (20)	43 (11)	
CsA+MTX±other	2442 (65)	103 (38)	202 (26)	57 (14)	
CsA±other	236 (6)	57 (21)	268 (35)	272 (67)	
Median follow-up of survivors, m	58 (3–128)	38 (4–124)	38 (3–90)	48 (3–87)	

Abbreviations: CMV = cytomegalovirus; CsA = cyclosporine; MTX = methotrexate; FK506=tacrolimus; FLUD = fludarabine.

Table 2

Multivariate analysis of treatment-related mortality, relapse, treatment failure (inverse of disease-free survival) and mortality (inverse of overall survival)

Main effect:	N	RR (95% CI)	P-value
TRM[a]			
Myeloablative	3659	1.00	$P_{overall}$ = 0.49
RIC BM	270	0.96 (0.77–1.19)	0.72
RIC PB	735	0.90 (0.77–1.05)	0.19
NMA	396	1.05 (0.87–1.28)	0.60
RELAPSE[b]			
Myeloablative	3659	1.00[a]	$P_{overall}$ <0.001
RIC BM	270	1.46 (1.19 – 1.80)	<0.001
RIC PB	735	1.08 (0.94 – 1.24)	0.27
NMA	396	1.73 (1.46 – 2.04)	<0.001
TREATMENT FAILURE[c]			
Myeloablative	3659	1.00	$P_{overall}$ <0.001
RIC BM	270	1.15 (0.99–1.34)	0.07
RIC PB	735	0.93 (0.83–1.03)	0.14
NMA	396	1.28 (1.12–1.45)	<0.001
MORTALITY[d]			
Myeloablative	3731	1.00	$P_{overall}$ = 0.003
RIC BM	273	1.10 (0.95–1.28)	0.20
RIC PB	768	0.92 (0.82–1.02)	0.11
NMA	407	1.20 (1.05–1.36)	0.006

[a] Other significant covariates were: age at transplant (≥40 years vs. <40 years: RR=1.36, 95% CI, 1.21–1.52, P<0.001), Karnofsky score (≥90% vs. <90%: RR=0.75, 95% CI, 0.67–0.83, P<0.001), therapy-related leukemia (yes vs. no: RR=1.29, 95% CI, 1.11–1.51, P=0.001), blast percentage at transplant (>10% vs. <5%: RR=1.43, 95% CI, 1.20–1.70, P<0.001), disease status at transplant (CR2, duration of CR1≤12m vs. CR1: RR=1.35, 95% CI, 1.11–1.65, P=0.003; relapse vs. CR1: RR=1.30, 95% CI, 1.09–1.55, P=0.004; treated MDS vs. CR1: RR=1.38, 95% CI=1.18–1.62, P<0.001; untreated MDS vs. CR1: RR=1.39, 95% CI=1.18–1.64, P<0.001), cytogenetics (poor vs. good: RR=1.40, 95% CI, 1.07–1.82, P=0.013), type of donor (URD well matched vs. HLA-identical sibling: RR=1.57, 95% CI, 1.36–1.81, P<0.001; URD partially matched vs. HLA-identical sibling: RR=2.22, 95% CI, 1.92–2.56, P<0.001, URD mismatched vs. HLA-identical sibling: RR=2.74, 95% CI, 2.29–3.27, P<0.001), donor age (≥50 years vs. <50 years: RR=1.29, 95% CI, 1.12–1.50, P=0.001), donor-recipient sex match (F-M vs. others: RR=1.21, 95% CI, 1.08–1.37, P=0.002) and year of transplant (2002–2004 vs. 1998–2001: RR=0.81, 95% CI, 0.72–0.90, P<0.001).

[b] Other significant covariates were: Karnofsky score (≥90% vs. <90%: RR=0.71, 95% CI, 0.64–0.79, P<0.001), FAB subtype (M4–M7 vs. M0–M2: RR=1.24, 95% CI, 1.10–1.40, P=0.001), blast percentage at transplant (5–10% vs. <5%: RR=1.49, 95% CI, 1.22–1.83, P<0.001; >10% vs. <5%: RR=1.80, 95% CI, 1.55–2.08, P<0.001), disease status at transplant (CR1 vs. PIF: RR=0.35, 95% CI, 0.30–0.42, P<0.001; CR2, duration of CR1≤12m vs. PIF: RR=0.61, 95% CI, 0.49–0.77, P<0.001; duration of CR1>12m vs. PIF: RR=0.30, 95% CI, 0.22–0.40, P<0.001; treated MDS vs. PIF: RR=0.31, 95% CI, 0.12–0.81, P=0.017), cytogenetics (intermediate vs. good: RR=1.51, 95% CI, 1.16–1.97, P=0.002; poor vs. good: RR=2.45, 95% CI, 1.85–3.23, P<0.001) and donor age (≥50 years vs. <50 years: RR=1.15, 95% CI, 1.01–1.31, P=0.035).

[c] Other significant covariates were: age at transplant (≥40 years vs. <40 years: RR=1.22, 95% CI, 1.13–1.32, P<0.001), Karnofsky score (≥90% vs. <90%: RR=0.73, 95% CI, 0.68–0.79, P<0.001), therapy-related leukemia (yes vs. no: RR=1.20, 95% CI, 1.07–1.35, P=0.002), blast percentage at transplant (5–10% vs. <5%: RR=1.29, 95% CI, 1.11–1.51, P=0.001; >10% vs. <5%: RR=1.64, 95% CI, 1.47–1.83, P<0.001), disease status at transplant (CR1 vs. PIF: RR=0.53, 95% CI, 0.47–0.60, P<0.001; CR2, duration of CR1≤12m vs. PIF: RR=0.82, 95% CI, 0.70–0.97, P=0.016; duration of CR1>12m vs. PIF: RR=0.58, 95% CI, 0.48–0.70, P<0.001; relapse vs. PIF: RR=1.14, 95% CI, 1.01–1.29, P=0.035; untreated MDS vs. PIF: RR=0.69, 95% CI, 0.61–0.79, P<0.001; treated MDS vs. PIF: RR=0.63, 95% CI, 0.54–0.72, P<0.001), cytogenetics (intermediate vs. good: RR=1.31, 95% CI, 1.10–1.57, P=0.003; poor vs. good: RR=1.83, 95% CI, 1.51–2.22, P<0.001), type of donor (URD well matched vs. HLA-

identical sibling: RR=1.26, 95% CI, 1.14–1.38, P<0.001; URD partially matched vs. HLA-identical sibling: RR=1.42, 95% CI, 1.29–1.58, P<0.001, URD mismatched vs. HLA-identical sibling: RR=1.81, 95% CI, 1.58–2.06, P<0.001) and donor age (≥50 years vs. <50 years: RR=1.22, 95% CI, 1.10–1.35, P<0.001).

[d]Other significant covariates were: age at transplant (≥40 years vs. <40 years: RR=1.26, 95% CI, 1.16–1.36, P<0.001), Karnofsky score (≥90% vs. <90%: RR=0.72, 95% CI, 0.67–0.77, P<0.001), therapy-related leukemia (yes vs. no: RR=1.24, 95% CI, 1.11–1.39, P<0.001), blast percentage at transplant (5–10% vs. <5%: RR=1.30, 95% CI, 1.11–1.52, P=0.001; >10% vs. <5%: RR=1.65, 95% CI, 1.48–1.84, P<0.001), disease status at transplant (CR1 vs. PIF: RR=0.58, 95% CI, 0.52–0.66, P<0.001; duration of CR1>12m vs. PIF: RR=0.64, 95% CI, 0.53–0.78, P<0.001; relapse vs. PIF: RR=1.16, 95% CI, 1.03–1.31, P=0.018; untreated MDS vs. PIF: RR=0.76, 95% CI, 0.66–0.87, P<0.001; treated MDS vs. PIF: RR=0.71, 95% CI, 0.62–0.82, P<0.001), cytogenetics (intermediate vs. good: RR=1.26, 95% CI, 1.05–1.50, P=0.011; poor vs. good: RR=1.68, 95% CI, 1.39–2.03, P<0.001), type of donor (URD well matched vs. HLA-identical sibling: RR=1.27, 95% CI, 1.15–1.39, P<0.001; URD partially matched vs. HLA-identical sibling: RR=1.48, 95% CI, 1.33–1.64, P<0.001, URD mismatched vs. HLA-identical sibling: RR=1.90, 95% CI, 1.67–2.16, P<0.001), donor age (≥50 years vs. <50 years: RR=1.22, 95% CI, 1.10–1.35, P<0.001) and year of transplant (2002–2004 vs. 1998–2001: RR=0.91, 95% CI, 0.84–0.98, P=0.009).

Table 3

Multivariate analysis of disease-free survival in patients 40–60 years of age with a Karnofsky score ≥90% for AML in first complete remission or MDS with <5% blasts

Main effect:	N	RR (95% CI) of relapse or death[a]	P-value	Adjusted DFS probability at 5y[b]	P-value
Myeloablative	811	1.00	$P_{overall}$ = 0.08	43 (39 – 46)	$P_{overall}$ = 0.016
RIC BM	65	1.21 (0.87 – 1.68)	0.27	37 (24 – 50)	0.46
RIC PB	188	1.14 (0.91 – 1.42)	0.25	33 (25 – 42)	0.06
NMA	93	1.38 (1.05 – 1.82)	0.020	26 (16 – 38)	0.006

[a] Other significant covariates were: therapy-related leukemia (yes vs. no: RR=1.30, 95% CI, 1.03–1.65, P=0.029), cytogenetics (poor vs. intermediate: RR=1.52, 95% CI, 1.24–1.86, P<0.001) and type of donor (URD well matched vs. HLA-identical sibling: RR=1.35, 95% CI, 1.10–1.65, P=0.004; URD partially matched vs. HLA-identical sibling: RR=1.46, 95% CI, 1.15–1.86, P=0.002; URD mismatched vs. HLA-identical sibling: RR=1.99, 95% CI, 1.45–2.73, P<0.001).

[b] Based on multivariate regression model.

Pairwise comparisons: RIC PB vs. RIC BM = 0.63, NMA vs. RIC BM = 0.20, NMA vs. RIC PB = 0.33