Myeloablative versus Reduced-Intensity Conditioning for Hematopoietic Cell Transplantation in Acute Myelogenous Leukemia and Myelodysplastic Syndromes—Long-Term Follow-Up of the BMT CTN 0901 Clinical Trial

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Abstract

Several prospective randomized trials comparing conditioning intensity before allogeneic hematopoietic cell transplantation (HCT) have been performed, with conflicting results. Although reduced-intensity conditioning (RIC) leads to lower treatment-related mortality (TRM), this is offset by higher rates of relapse. Long-term follow-up of randomized comparative trials are limited. Here we present long-term follow-up of a randomized comparison of myeloablative conditioning (MAC) compared with RIC before HCT for acute myelogenous leukemia (AML) or myelodysplasia (MDS). Long-term comparative analyses of overall survival, relapse, and relapse-free survival were performed. Patients age 18 to 65 years with <5% marrow myeloblasts were randomized to receive MAC (n = 135) or RIC (n = 137), followed by HCT from an HLA-matched donor. The primary endpoint of the trial was an 18-month pointwise comparison of overall survival. The analyses were performed using a proportional hazards model. The median follow-up of the entire cohort was 51 months. At 4 years, the transplant-related mortality (TRM) was 25.1% for MAC, compared with 9.9% for RIC (P < .001). Patients who received RIC had a significantly higher risk of relapse compared to those who received MAC (hazard ratio [HR], 4.06; 95% CI, 3.00 to 5.60).

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Among the patients who relapsed after HCT, postrelapse survival was similar at 3 years (24% for MAC and 26% for RIC). Overall survival was superior for patients who received MAC compared to those who received RIC (HR, 1.54; 95% CI, 1.07 to 2.2; P = .03). Our data show that patients who received MAC were at higher risk of late TRM compared with those who received RIC; however, because of the exceedingly high rates of relapse in the RIC arm, overall survival remained significantly better for patients who received MAC. Among patients with MDS or AML eligible for either MAC or RIC regimens, long-term follow up demonstrates a survival advantage for patients who received MAC.

Keywords
Acute myelogenous leukemia; Myelodysplastic syndrome; Hematopoietic cell; transplantation; Conditioning intensity

INTRODUCTION
Hematopoietic cell transplantation (HCT) is the sole curative option for patients with myelodysplastic syndrome (MDS) and is frequently the preferred consolidative strategy in patients with intermediate- or adverse-risk acute myelogenous leukemia (AML). Although myeloablative conditioning (MAC) before HCT may be curative, there is considerable toxicity and treatment-related mortality (TRM). The understanding that the curative potential of HCT is due in part to the graft-versus-leukemia effect (GVL) mediated by donor cells led to the development of reduced-intensity conditioning (RIC) regimens with reduced transplant-related mortality (TRM).

Multiple retrospective studies have shown similar overall survival (OS) regardless of conditioning intensity, but with lower TRM and higher relapse in patients who received RIC [19]. However, there were concerns regarding inherent patient selection bias in these retrospective comparisons, as patients with comorbidities and lower relapse risk might have been selected to receive RIC, whereas patients at higher relapse risk and with fewer comorbidities might have been selected to receive MAC. Subsequently, 3 randomized trials have evaluated conditioning intensity in patients with MDS or AML [10–12]. These studies yielded conflicting results, used different primary endpoints, had limited follow-up, and were stopped before completion of accrual. Our initial report showed a relapse-free survival (RFS) advantage for patients who received MAC based on multivariate analysis, but with a significantly higher TRM [11]. There were no significant differences in OS based on conditioning intensity in the entire population inclusive of AML and MDS; however, for AML patients specifically, there was a significant improvement in OS with MAC compared with RIC. Following these initial studies, there were several unanswered questions, such as whether the immediate survival advantage seen in AML patients receiving MAC would be subsequently outweighed by long-term TRM, whether a survival advantage would be seen in the patients with longer follow-up, and whether survival following relapse would differ based on initial conditioning intensity. Here we present long-term follow-up results on the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0901 trial.
METHODS

Study Design and Data Sources

The present analysis is a long-term follow-up of patients who were enrolled in a phase III randomized trial comparing RIC to MAC in patients with AML or MDS conducted through the BMT CTN. Details of the study design and enrolled patients have been reported previously [11]. All patients enrolled in BMT CTN clinical trials are also reported to the Center for Blood and Marrow Transplant Research (CIBMTR). Data collected for patients enrolled in these trials were used to capture outcomes beyond the completion of the trial follow-up (18 months). The CIBMTR is a research collaboration between the National Marrow Donor/Be the Match and the Medical College of Wisconsin and operates a longitudinal database of outcomes in HCT and cellular therapy recipients [13].

Patients

Participants had a World Health Organization-defined diagnosis of AML or MDS [14], had receiving a first HCT, and had <5% marrow myeloblasts pre-HCT [15]. They were age 18 to 65 years; had an HLA-A, -B, and -DRB1 (6/6) matched sibling donor or a ≥7/8 HLA-A, -B, -C, and -DRB1 matched unrelated donor; and had a Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) ≤4 [16]. The study cohort included 54 patients with MDS and 218 patients with AML.

Conditioning Regimens and Immune Suppression

The RIC regimens included fludarabine (120 to 180 mg/m²) with busulfan (≤8 mg/kg oral or 6.4 mg/kg i.v.) (Flu/Bu2; n = 110) or melphalan (≤50 mg/m²) (Flu/Mel; n = 27). The MAC regimens included busulfan (16 mg/kg oral or 12.8 mg/kg i.v.) with cyclophosphamide (120 mg/kg) (Bu4/Cy; n = 40) or fludarabine (120 to 180 mg/m²) (Flu/Bu4; n = 87) and cyclophosphamide (120 mg/kg) and total body irradiation (1200 to 1420 cGy) (Cy/TBI; n = 8). Each center selected 1 preferred MAC regimen and 1 preferred RIC regimen. Graftversus-host disease (GVHD) prophylaxis included methotrexate 10 to 15 mg/m² on day 1 and 5 to 10 mg/m² on days 3, 6, and 11 given with cyclosporine or tacrolimus, tacrolimus with sirolimus, or cyclosporine with mycophenolate mofetil. Experimental GVHD therapies were allowed provided that they included a calcineurin inhibitor and no post-HCT Cy or T cell depletion. Antithymocyte globulin was allowed; however, its use was declared before randomization and was administered regardless of conditioning intensity.

Outcomes

The primary endpoint of the initial analysis was OS difference at 18 months postrandomization, compared pointwise and assessed on an intent-to-treat basis. For the long-term follow-up analysis, the primary endpoint was OS as determined by a proportional hazards model. Additional endpoints included relapse, RFS, TRM, and survival following relapse. The primary cause of death was adjudicated using previously described criteria [17], and reviewers were blinded to randomization at the time of determination of cause of death.
**Statistical Analysis**

In the initial analysis, the primary endpoint of an 18-month pointwise comparison of OS was chosen owing to a concern that the proportional hazards model would not hold. It was expected that MAC would result in higher early mortality due to TRM, and that RIC would result in later mortality due to relapse; therefore, the proportional risk of mortality was expected to change over time. Subsequent analysis showed that the proportional hazards model was stable over time without any significant differences in each specific arm of mortality over time.

As reported previously, this study was stopped early by an independent Data and Safety Monitoring Board following the second interim analysis owing to the exceedingly high relapse rates observed in the RIC arm. However, patients who had previously been consented to the trial could complete the planned therapeutic intervention. Owing to the rapid pace of enrollment, by the time the study was stopped, 76% of the anticipated accrual was completed. The first patient was enrolled on June 2, 2011, and the last patient was enrolled on April 10, 2014.

For this long-term analysis, outcome data from the clinical trial were merged with the data collected using the CIBMTR mechanism. Data reported to the CIBMTR during the conduct of the clinical trial was compared with the trial results and found to be similar. Outcomes of patients with >18 months of follow-up were computed using data reported to the CIBMTR. A Cox proportional hazards model was used to compare OS, RFS, relapse, and TRM based on initial randomization to MAC versus RIC. The proportional hazards model was assessed using graphical approaches and time-dependent covariates. Multivariable analysis was performed using the same covariates as in the initial publication [11]. Survival after relapse was based on a pointwise comparison at 3 years postrelapse. Individual time points were compared for OS, RFS, and TRM in a pointwise fashion at 3, 6, and 18 months and 1, 2, and 3 years. Statistical analyses were done using SAS version 9.3 (SAS Institute, Cary, NC), and the cumulative incidence analyses were conducted using R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

**Enrollment**

A total of 285 patients were screened, and 272 patients were enrolled, including 135 randomized to MAC and 137 to RIC. Four patients randomized to MAC and 5 patients randomized to RIC did not undergo the assigned HCT. All participants were included in the long-term follow-up analysis irrespective of whether they underwent allocated HCT. Patient and transplantation characteristics have been described previously [11]. The median duration of follow-up was 51 months (range, 5 to 80 months) for the entire cohort, 50 months (range, 5 to 80 months) for the MAC recipients, and 53 months (range, 13 to 73 months) for the RIC recipients.
OS and RFS

OS at 4 years was significantly better in the MAC recipients (62.0%; 95% confidence interval [CI], 53.5% to 70.1%) compared with the RIC recipients (49.0%; 95% CI, 40.7% to 57.2%; P = .022). Proportional hazards modeling with multivariate analysis showed a survival advantage for MAC recipients compared with RIC recipients (HR, 1.54; 95% CI, 1.07 to 2.2; P = .03) (Figure 1). Although specific subgroup analyses based on underlying disease did not meet statistical significance, the 4-year OS for both MDS and AML was higher in the MAC recipients. For patients with MDS, the 4-year OS was 70.2% (95% CI, 51.8% to 85.7%) for MAC versus 58.3% (95% CI, 39.2% to 76.2%) for RIC (P = .366). For the patients with AML, the 4-year OS was 59.9% (95% CI, 50.3% to 69%) for MAC versus 46.7% (95% CI, 37.3% to 56.2%) for RIC (P = .054). We also examined the impact of specific RIC regimens compared with MAC. The 4-year OS was 68.0% (95% CI, 48.6% to 84.5%) for Flu/Mel, 44.5% (95% CI, 35.3% to 54.0%) for Flu/Bu2, and 61.9% (95% CI, 53.5% to 70.1%) for MAC (P = .01). The 4-year OS was not significantly different between MDS and AML patients (64.2% [95% CI, 50.8% to 76.5%] versus 53.2% [95% CI, 46.4% to 59.9%]; P = .141).

Multivariate analysis showed improved RFS with MAC compared with RIC (HR, 2.06; 95% CI, 1.48 to 2.85; P < .001) (Figure 2). RFS at 4 years was 57.9% (95% CI, 49.7% to 66.2%) with MAC and 33.7% (95% CI, 25.7% to 41.6%) with RIC (P < .0001). Among MDS patients, RFS was not significantly different between the 2 groups at 4 years; however, for AML patients, the 4-year RFS was 55.4% (95% CI 45.8–64.7%) for MAC versus 30.8% (95% CI, 22.4% to 39.8%) for RIC (P < .001).

Relapse

Overall, relapse was the most common cause of mortality for the patients enrolled in this trial. Ninety patients with AML and 13 patients with MDS relapsed by time of last follow-up. The cumulative incidence of relapse was significantly greater among patients who received RIC compared with those who received MAC (HR, 4.06; 95% CI, 2.59 to 6.35; P < .001) (Figure 3). Most patients who relapsed did so in the first year post-HCT. Survival following relapse was not significantly different based on conditioning intensity; 3-year post-relapse survival was 24.0% for MAC and 26.0% for RIC (P = .87). Fifteen patients underwent a second HCT for relapse. The 4-year relapse rate was 19.8% (95% CI, 12.7% to 27.9%) for MAC versus 60.7% (95% CI, 51.2% to 69.8%) for RIC (P < .001).

TRM

The cumulative incidence of TRM was significantly higher with MAC compared to RIC, (HR, 2.00; 95% CI, 1.06 to 3.70; P = .03) (Figure 4). At 4 years, the TRM was 25.1% (95% CI, 18% to 32.9%) for MAC versus 9.9% (95% CI, 5.3% to 15.6%) for RIC (P < .001). We analyzed the cumulative incidence of TRM over time based on conditioning intensity and found a significantly higher proportional increase in TRM over time with MAC compared to RIC. This later mortality in MAC recipients was attributed to causes other than relapse.
Causes of Death

Causes of death are summarized in Table 1. Fifty-four of the 135 patients randomized to MAC died; GVHD was the primary cause of death (39.0%), followed by relapse (33.3%). Seventy-two of the 137 patients randomized to RIC died, with relapse as the primary cause of death (76.4%).

DISCUSSION

These long-term follow-up data demonstrate an OS advantage with MAC compared to RIC. This difference is driven primarily by data from the AML subset, and the small number of MDS patients precludes making specific statements regarding outcomes in this group; nonetheless, the overall trend of increased relapse with RIC is seen in the MDS patients as well. Although there is a higher TRM with MAC that continues to increase over time, this is offset by a much higher relapse rate with RIC.

Since our initial publication, questions have arisen regarding the appropriate choice of RIC regimen in patients who are not candidates for MAC. A large retrospective analysis from the CIBMTR showed a survival advantage with Flu/Mel conditioning compared to Flu/Bu2 conditioning [18]. This advantage is driven by significantly lower rates of relapse seen with Flu/Mel compared to Flu/Bu2 despite a concurrent higher risk of TRM. In the present trial, only 27 patients received Flu/Mel, limiting the ability to specifically analyze this subset of patients owing to limited power. Nevertheless, the 3-year OS was higher in patients who received Flu/Mel compared with recipients of Flu/Bu2, likely due to a lower rate of relapse. This trial was designed to answer not the question of which RIC regimen should be preferred, but rather a broader question of whether conditioning intensity is an important component of allogeneic HCT for MDS and AML patients.

To date, there have been 3 randomized clinical trials evaluating conditioning intensity in patients with MDS or AML. Interestingly, all of these trials were closed before completion of accrual [10–12]. There are key differences among these studies. The initial trial from the German AML study group compared high-dose (12 Gy) and intermediate-dose (8 Gy) TBI-based conditioning and included only patients with AML in first complete remission [10]. The primary endpoint was TRM. With an estimated TRM of 25% in MAC recipients versus 15% in RIC recipients, there would have been 80% power to detect this difference; however, the trial was slow to accrue and was stopped at 77% of accrual (n = 195/252). The TRM was <20% in both arms and not significantly different between the arms. Indeed, there was no significant difference in OS or relapse between these 2 radiotherapy approaches. Concurrent with BMT-CTN 0901 was a trial from the European Society for Blood and Marrow Transplantation (EBMT) randomizing specifically patients with MDS or secondary AML with <20% myeloblasts to either a Flu/Bu2 or a Bu4/Cy regimen [12]. The primary endpoint of this trial was also TRM, with an expected TRM of 40% with Bu4/Cy compared to 20% with RIC, with 90% power to detect this 20% difference. The study was stopped at 80% of the accrual goal (n = 129/160) because of slow accrual. This study was also underpowered to address the primary endpoint, as the TRM with Bu4/Cy was only 25%. The study found no significant differences in TRM, relapse, RFS, or OS. These 3 randomized trials, including our study, have common features. They were all stopped before completion due to either
poor accrual or a mandate from an independent Data and Safety Monitoring Board. In addition, all 3 studies showed a lower-than-expected TRM with MAC. However, there were key differences as well. The German AML study group trial may have been composed of inherently better-risk AML patients owing to a requirement for first complete remission, which was not necessary in our study. In addition, as demonstrated in our study, high-dose TBI was an uncommon selection for MAC in patients with AML. In the EBMT trial, 63% of patients had a World Health Organization diagnosis of myelodysplastic syndrome with excess blasts (MDS-EB) 1 or 2 or secondary AML, and 85% of these patients received cytoreductive therapy before HCT. This likely represents a more favorable group of patients, as our study only required a bone marrow myeloblast count of <5% without count recovery to qualify for enrollment. Finally, both the German AML study and the EBMT trial had TRM as the primary endpoint, whereas our primary endpoint was OS. Based on these differences, it is not surprising that a lower relapse rate was seen with the RIC regimens used in the German AML study group and EBMT trials. An advantage of the German AML study and EBMT studies was the use of more uniform conditioning regimens compared with our study; however, our trial does reflect a more generalizable approach, as before the present publication, multiple different conditioning regimens were used for RIC among participating BMT CTN centers.

The German AML study group has also published long-term follow-up data from their initial randomized trial [19]. There were no statistically significant differences in TRM, OS, and RFS; however, an analysis of TRM in patients age 41 to 60 years as a separate group showed a significantly higher cumulative TRM with 12 Gy TBI compared to 8 Gy TBI (HR, 0.44; 95% CI, 0.2 to 0.95; P= .034). Secondary malignancies were seen at comparable rates in the 2 groups. In addition, there was no increase in late relapse in patients who received RIC. A finding similar to BMT-CTN 0901, in which almost all relapses occurred in the first year post-HCT.

An additional question that all of these trials have elucidated is the current role of minimal residual disease (MRD) and minimal identifiable disease (MID) before HCT [20,21]. Previously published data from BMT-CTN 0901 demonstrated an effect modification of conditioning intensity on relapse risk in patients with AML with MRD at the time of HCT based on MRD [22]. The data suggest that patients without MRD or MID would be better candidates for RIC because of an inherently lower risk of relapse. Patients without MRD/MID do not appear to benefit from increased conditioning intensity, and given the lower TRM seen with RIC, this may be the preferred approach. In the future, clinical trials that evaluate the impact of conditioning intensity and the role of maintenance strategies should consider the impact of MRD and MID at the time of HCT.

Our long-term follow-up analysis was not a planned analysis, and thus statistical comparisons should be interpreted with caution. The primary endpoint of the trial was an 18-month pointwise comparison of OS, and mortality data after that time were obtained by standard CIBMTR reporting. Reporting and ascertainment bias using an outcomes database to supplement clinical trial results is a potential concern. To minimize this effect, BMT CTN trials are designed a priori with the intent of optimizing data collection to decrease the reporting burden. For example, data related to cytogenetics and HCT-CI are collected by the
CIBMTR and merged with clinical trial data. In addition, for this analysis, carefully reviewing any reporting discrepancies between the trial and the CIBMTR data was performed, and an analysis of trials result using CIBMTR-reported data produced similar results. The primary endpoint of BMT-CTN 0901 was an 18-month OS difference pointwise comparison. Initially, there were concerns that the proportional hazards model would not hold; however, analysis of the data showed that the proportional risk of mortality remain constant over time. Given this, we planned to do subsequent analysis based on the Cox proportional hazards model rather than on a pointwise comparison of OS difference at certain time points.

Most patients enrolled in our study had AML and received Bu-based conditioning. Therefore, there is limited power to analyze MDS and Flu/Mel-conditioned patients as separate groups. The proportional risk of TRM increased over time in patients who received MAC, but this increase was not sufficient to overcome the significantly higher earlier relapse rates seen in patients who received RIC. When patients relapsed post-HCT, survival was similar regardless of the initial conditioning intensity. OS remained significantly better in patients who received MAC compared with those who received RIC. For fit patients with AML or MDS who are less than 60 years of age MAC remains the preferred regimen.

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Figure 1.
OS.
Figure 2.
RFS.
Figure 3.
Relapse.
Figure 4.
TRM.
Table 1

Causes of Death

| Cause of Death                              | No. of Patients (%) | MAC | RIC |
|---------------------------------------------|---------------------|-----|-----|
| All causes                                  | 54 (100)            | 72  |     |
| Relapse                                     | 18 (33)             | 55  | 76  |
| Organ failure                               | 9 (17)              | 3 (4.2) |    |
| Cardiac                                     | 2                   | 0    |     |
| Multiorgan failure                          | 1                   | 1    |     |
| Sinusoidal obstruction syndrome             | 1                   | 0    |     |
| Pulmonary failure                           | 4                   | 1    |     |
| Organ failure, NOS                          | 1                   | 1    |     |
| GVHD                                        | 21 (39)             | 8 (11) |    |
| Acute                                       | 6                   | 1    |     |
| Chronic                                     | 11                  | 5    |     |
| Progressive                                 | 4                   | 2    |     |
| Infection                                   | 3                   | 3    |     |
| Graft failure/graft rejection               | 0                   | 0    |     |
| Secondary malignancy                        | 2                   | 1    |     |
| Hemorrhage                                  | 1                   | 0    |     |
| Sudden death                                | 0                   | 1 (2.3) |    |
| Unknown/others                              | 0                   | 1    |     |

NOS indicates not otherwise specified.

There were no deaths before day 28; the earliest death was on day 54 after randomization. Fifty-two deaths were reported at 18 months at randomization.