Should a More Personalized Approach be applied to Hematopoietic Stem-Cell Transplantation?

Stefan O Ciurea**, Piyanuch Kongtim**, Gabriela Rondon¹, Julianne Chen¹, Ciprian Tomuleasa¹ and Richard E Champlin¹

¹Department of Stem Cell Transplant and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
²Iuliu Hatieganu University of Medicine and Pharmacy, Romania

*Equal contribution

Keywords: Allogeneic hematopoietic stem cell transplantation; Transplantation for elderly patients; Personalized transplantation; Melphalan conditioning; Acute myeloid leukemia; High-risk cytogenetics

Introduction

Allogeneic hematopoietic stem-cell transplantation (HSCT) is curative for patients with various hematologic malignancies [1]. It has been traditionally limited to younger individuals and those without significant comorbidities because of higher regimen-related toxicity associated with myeloablative conditioning. In an attempt to extend this therapy to older and unfit patients, a major step forward was the introduction of reduced-intensity conditioning. We hypothesized that differences in intensity of conditioning are needed for different disease status.

Materials and Methods

Patients and transplant procedure

We retrospectively analyzed outcomes of all 115 patients, ≥ 55 years old with a diagnosis of AML who received their first transplant using an HLA matched related (MRD; N=47), matched unrelated (MUD; N=44), mismatched related (haploidentical) or mismatched unrelated donor (MMUD; N=24) at our institution between 01/2000-05/2014 (Table 1). All patients had complete morphologic remission (CR 1 or CR2) at the time of transplant. Cytogenetic and molecular genetic data were appreciated according to both the SWOG and ELN risk categories [10,11]. The conditioning regimen consisted of fludarabine 25–30 mg/m² for 4–5 days (days 6 or 5 to 2) with either melphalan 100 mg/m² (N=42) or 140 mg/m² (N=73) on day 2. Patients who received mismatched transplants received also thiotepa 5-10 mg/kg or 2Gy total body irradiation (TBI) as previously described by us [12]. GVHD prophylaxis for matched transplants consisted of tacrolimus, minidemethoxate. Anti-thymocyte globulin (ATG) was added for MUD and MMUD transplants [13]. Post-transplant cyclophosphamide plus tacrolimus and mycophenolate mofetil was the GVHD prophylaxis used for haploidentical transplants [14].

Abstract

Background: Allogeneic stem cell transplantation for older patients with hematological malignancies has generally been performed with reduced-intensity conditioning, as regimen-related toxicity prohibits a fully myeloablative conditioning regimen. We hypothesized that differences in intensity of conditioning are needed for different disease status.

Patients and Methods: We analyzed 115 older patients with AML (55 years or older) who received conditioning with fludarabine and melphalan, with a melphalan dose of 140 mg/m² (FM140) (N=73) or 100 mg/m² (FM100) (N=42).

Results: Overall, FM100 was associated with less TRM (18.1% versus 43.5%, p=0.007), and acute GVHD (aGVHD) (28.2% versus 36.7%, p=0.021) while relapse was similar (21.5% versus 25.5%, p=0.489). The lower TRM with comparable relapse rate resulted in higher survival for FM100 as compared with FM140 conditioning regimen, 3-year PFS was 60.2% and 28.6% (p=0.014). Conversely, patients with high-risk SWOG cytogenetics and adverse ELN risk had better survival outcomes with FM140 regimen due to lower relapse, while TRM was not different. In multivariable analysis, high-risk SWOG cytogenetics, adverse ELN risk and the development of grade 2-4 aGVHD predicted for worse PFS whereas using FM140 conditioning and aGVHD were an independent factor for TRM.

Conclusion: These results suggest as a proof-of-principle that a differential approach should be applied for patients receiving an allogeneic hematopoietic stem cell transplant, not only based on age, but also on disease characteristics impacting the risk of relapse. Further studies are needed to develop a more personalized approach to hematopoietic stem cell transplant recipients.

Keywords: Allogeneic hematopoietic stem cell transplantation; Transplantation for elderly patients; Personalized transplantation; Melphalan conditioning; Acute myeloid leukemia; High-risk cytogenetics

Acknowledgments

Stefan O Ciurea, MD, Associate Professor, The University of Texas MD Anderson Cancer Centre, 1515 Holcombe Blvd., Unit 423, Houston, Texas-77030, USA, Tel: 713-745-0146; Fax: 713-794-4902; E-mail: sciurea@mdanderson.org

Received January 30, 2015; Accepted March 18, 2015; Published March 20, 2015


Copyright: © 2015 Ciurea SO, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
**Statistical analysis**

The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), relapse, treatment-related mortality (TRM), and incidence of acute and chronic GVHD. OS and PFS were calculated using the Kaplan-Meier method. Cumulative incidence (CI) function with competing risks method was used to estimate the endpoints of relapse, TRM, acute and chronic GVHD. Univariate comparisons of all endpoints were completed by the log-rank test. Variables were included in the multivariate model if they were conceptually important or if they approached (p<0.1) or attained statistical significance in the univariate regression. Analyses were performed using STATA statistics program version 13.

**Results**

Demographics are listed in Table 1. Characteristics were similar between the two groups except more patients in the FM100 group received marrow stem cells (59.5% vs. 31.5%, p=0.006). After a median follow-up duration of 36.5 months, 49 patients (42.6%) were alive and in remission. One hundred and five patients (91.3%) had full donor chimerism at day 30 post-transplant including 37 patients (88.1%) in FM100 and 68 patients (93.2%) in FM140 (p=0.097).

**Outcomes for all patients**

Overall, FM100 was associated with less TRM (18.1% versus 43.5%, p=0.007), and acute GVHD (aGVHD). The Day-100 CI of aGVHD all grades and grade 2-4 in FM100 and FM140 groups was 28.2% versus 36.7% (p=0.021), and 13.2% versus 21.5% (p=0.013), respectively. Infectious death was also lower in FM100 group compared with FM140 (8% versus 19%, p=0.048). However, there was no significant difference in chronic GVHD (cGVHD), the 3-year CI of cGVHD was 39.3% versus 42.4% (p=0.613), whereas extensive cGVHD was 18.7% versus 22.2%, in the FM100 and FM140 group, respectively (p=0.286).

Relapse was similar between FM100 and FM140, 21.5% versus 25.5% at 3 years (p=0.489). The lower TRM with comparable relapse rate resulted in higher OS and PFS for FM100 as compared with FM140 conditioning regimen, 3-year PFS was 60.2% and 28.6% (p=0.014) (Figure 1A), and 3-year OS was 64.1% versus 30.4%, respectively (p=0.005).

**Outcomes for different risk categories**

We first categorized patients according to SWOG cytogenetic risk and found that patients with favorable/intermediate-risk cytogenetics (N=78) had better PFS with FM100 (N=29) compared with FM140 (N=49) regimen (3-year PFS 76.5% versus 48.7%, p=0.05) (Figure 1B), due to lower TRM (1-year TRM 14% in FM100 versus 27.8% in FM140, p=0.03), while relapse was not different (3-year CI or relapse 9.4% in FM100 versus 24.3% in FM140, p=0.06). AML patients with high-risk cytogenetics (N=37) had better outcomes with FM100 (N=24) compared with FM100 conditioning regimen (N=13) (3-year PFS was 39.9% versus 17.6%, p=0.013) (Figure 1C) due to lower relapse with FM100 regimen (3-year CI of relapse 28.5% versus 49.6%, p=0.026), and comparable TRM (1-year TRM was 28.6% versus 20.2%, p=0.14).

When patients were categorized according to ELN risk groups, we have found that patients with favorable, intermediate-I or intermediate-II who received FM100 had a significantly better PFS when compared with FM140 (3-year PFS was 76.9% versus 26.7%, p=0.019) (Figure 1D). This better survival resulted from a lower TRM (1-year TRM was 11.5% in FM100 versus 53.9% in FM140, p=0.006), and comparable relapse (11.6% versus 17.3% at 3-years, p=0.487). Conversely, patients...
Figure 1: Kaplan-Meier estimates of progression-free survival according to the study group.

Panel A shows progression free survival of the entire cohort. Patients who received FM100 conditioning had significantly better progression-free survival compared with those who received FM140 conditioning (p=0.014).

Panel B shows progression free survival of patients with favorable or intermediate SWOG cytogenetic risk. Patients received FM100 conditioning had significantly better progression-free survival compared with those who received FM140 conditioning (p=0.05).

Panel C shows progression-free survival of patients with SWOG high-risk cytogenetics. A higher progression-free survival was seen in patients who received FM140 conditioning as compared to FM100 group (p=0.013).

Panel D shows progression-free survival of patients with favorable or intermediate-I or intermediate-II risk group according to ELN classification. FM 100 was associated with a better progression-free survival as compared to FM140 conditioning (p=0.019).

Panel E shows progression-free survival of patients with adverse risk according to ELN classification. Patients who received FM140 conditioning had a significantly better progression-free survival compared with FM140 conditioning (p=0.041).
with adverse ELN risk had better outcomes with FM140 regimen (3-year PFS was 51.1% in FM140 versus 25.3% in FM100 group, p=0.041) (Figure 1E) due to lower relapse (18.6% versus 47.8%, p=0.031), while TRM was not different (29.9% versus 25.2%, p=0.345).

Univariate and multivariate analysis

Besides conditioning regimen intensity, other factors associated with poor PFS in univariate analysis were high-risk SWOG cytogenetics (p=0.024), adverse ELN risk (p=0.032), transplant beyond 2nd CR (p=0.018), and grade 2-4 aGVHD (p=0.023), while using MRD was associated with a better PFS (p=0.043). Allogeneic transplantation in patients older than 65 years was not associated with poor PFS when compared with patients younger than 65 (p=0.65).

In univariate analysis for TRM and relapse, aGVHD (p=0.021) was associated with higher TRM, while high risk SWOG (p=0.018) and adverse ELN risk (p=0.034) predicted higher relapse rate.

In multivariable analysis, only high-risk SWOG cytogenetics (HR 2.67, 95%CI 2.06-3.24, p=0.017), adverse ELN risk (HR 2.32, 95%CI 1.87-2.64, p=0.021) and the development of grade 2-4 aGVHD (HR 1.79, 95%CI 1.04-2.26, p=0.024) predicted for worse PFS. Using FM140 and aGVHD were an independent factor for TRM with HR of 1.79 (95%CI 1.41-1.97, p=0.032) and 2.13 (95%CI 1.84-2.53, p=0.003). For relapse, both high risk SWOG (HR 2.11, 95%CI 1.86-2.44, p=0.003) and adverse ELN risk (HR 1.94, 95%CI 1.54-2.31, p=0.011) retained their significant in multivariate analysis for relapse.

Discussion

Allogeneic transplantation initially performed using myeloablative conditioning regimens showed feasibility of this procedure for older individuals (Riende O JAMA 1993). However, most older or unfit patients would not be able to tolerate intense conditioning due to prohibitive TRM. While overall transplant outcomes for older individuals were found to be similar with a MAC compared with RIC, patients receiving RIC had lower incidence of aGVHD and TRM at the expense of a higher relapse rate (Aoudhiane Leukemia 2005). Consequently, RIC conditioning has become the new standard for transplantation of these patients [4,15-17].

Still, in hematopoietic stem-cell transplantation one-size-fits-all approach remains the norm, in part because of the relatively small number of patients treated. Here we demonstrate that a more customized approach is needed, and the intensity of conditioning should vary not only with age but also based on the disease treated. Some diseases, like AML with high-risk cytogenetics may not be so responsive to the GVT effects, might be more difficult to eliminate and consequently may require more intense conditioning. Low-risk patients may not need higher intensity conditioning usually associated with a higher TRM, and a lower intensity regimen, which generates reliably a lower TRM, and a lower intensity regimen, which generates reliably a

In conclusion, our results support the use of FM100 conditioning regimen for older individuals with hematological malignancies undergoing transplantation with matched or mismatched donors. We also suggest that a more individualized approach in needed in hematopoietic stem cell transplantation. Limitations in our study are mainly related to the retrospective nature of this study, and relatively small number of patients. These findings should be confirmed in a larger cohort of patients and, if confirmed, should be incorporated in prospective clinical trials of hematopoietic stem cell transplantation.

Authorship Contribution

SOC formulated the hypothesis, contributed to data collection and manuscript writing, PK collected and analyzed the data, and wrote the manuscript, GR, JC contributed to data collection, reviewed and approved the manuscript, CT contributed with manuscript writing, REC contributed with data interpretation and manuscript writing.

References


