Leukemia Research 39 (2015) 828–834

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Influence of donor age in allogeneic stem cell transplant outcome in acute myeloid leukemia and myelodisplastic syndrome

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ARTICLE INFO

Article history:
Received 4 August 2014
Received in revised form 4 May 2015
Accepted 6 May 2015
Available online 14 May 2015

Keywords:
Donor age
Allogeneic stem cell transplant
Overall survival
Transplant related mortality
Myelodisplastic syndrome
Acute myeloid leukemia

ABSTRACT

The impact of donor age in patients with acute myeloid leukemia and myelodysplastic syndrome who underwent allogeneic hematopoietic stem cell transplant (HSCT) remains unclear. In the current study, we evaluate 179 consecutive patients who received an HSCT, from January 2000 to January 2013, in our Institution. Most of the HSCT (91%) were HLA-matched. Patient and donor median age were 51 years (18–69) and 47 years (12–75) respectively, and 81 donors (45%) were older than 50 years. The median follow-up was 38 months (range 1–138), Kaplan–Meier estimated 3-year overall survival (OS) was 63% and disease free survival (DFS) was 56%. Interestingly, patients who received an HSCT from a donor older age (>50 y) showed a poorer OS (51% vs 73%; $p = 0.01$), as well as a higher TRM (20% vs 8%; $p = 0.038$) and higher relapse rate (28% vs 39%; $p = 0.03$). In a stratified subanalysis, 3-year estimated OS was significantly lower among patients undergoing an HSCT from >50 years sibling donors compared to those receiving an HSCT from <50 years unrelated donor (54% vs 72%; $p < 0.001$). In summary, we can conclude that receiving an HSCT from a donor over 50 years old is associated with poorer outcome in patients diagnosed with MDS and AML, and this information may be incorporated into the complex process of donor selection.

1. Introduction

Allogeneic stem cell transplant (HSCT) is the only curative option for some acute myeloid leukemia (AML) and myelodisplastic syndrome (MDS) patients, and nowadays, it can be offered to older patients because of availability of reduced intensity conditioning regimens (RIC) and a better supportive care that have increased the age of candidates to HSCT [1–3]. This fact lead to increase median age of HSCT recipients, mainly in some malignancies whose incidence is higher in older patients, like MDS or AML.

At the same time, HLA-matched related donor age (MRD), is also increasing parallel to patients age. Older donor frequently implies more comorbidity, and potentially, it could be associated with some age-related changes in hematopoietic stem cells whose implication on HSCT outcome remains unknown. In most cases, when a MRD without relevant comorbidity is available, this is considered as donor, regardless of the age. However, previous publications suggest that HSCT from older donors could be associated with poorer outcome [4] as more comorbidity, mobilization failure, increased rates of acute and chronic GVHD and reduced overall survival [5,6], what implies that, in some cases, a younger matched unrelated donor (MUD) or an haploidentical procedure could be preferable [7].

On the other hand, transplant from MUD is an accepted treatment for patients who need an HSCT and do not have MRD. In fact, according to some reports, outcome with MRD and MUD are similar [8–11].

Our goal with this work has been to determine the impact of donor age on overall survival (OS), engraftment, transplant related mortality (TRM) and relapse rate in patients with AML and MDS who consecutively received an HSCT in our center, as well as compared the outcome between those patients receiving an HSCT from younger unrelated vs older related donor.

2. Patients and methods

2.1. Patients and donors

One hundred seventy-nine AML and MDS patients, who consecutively received an HSCT, from January 2000 to January 2013

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http://dx.doi.org/10.1016/j.leukres.2015.05.003
0145-2126/

were analyzed. Data were retrospectively collected from our transplant data-base. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000. Every patient and donor signed the informed consent form before HSCT according to established practice.

Patients and donors were matched for HLA A, B, C, DRB1 and DQB1 by intermediate or high resolution DNA-typing as appropriate.

2.2. Treatment

Myeloablative conditioning regimen consisted of intravenous Fludarabine 40 mg/m^2 on days (−6 to −3), and Busulfan 3.2 mg/kg (−6 to −3), or intravenous Cyclofosfamide 60 mg/kg (−6, −5) and total body irradiation 200cGy on (−3 to −1).

Reduced intensity conditioning (RIC) regimen included intravenous Fludarabine 30 mg/m^2 (−9 to −5), and oral Busulfan 0.8 mg/kg/6 h (−6 to −4).

Graft versus host disease (GVHD) prophylaxis consisted of Cyclosporine (0.5 mg/kg intravenous from day −7 to −2, and 1 mg/kg from day −1) and methotrexate (15 mg/m^2 on day +1 and 10 mg/m^2 on days +3, +6 and +11), in 111 patients. Forty five patients received oral Tacrolimus (0.06 mg/kg/12 h from day −3) and Sirolimus (6 mg on day −5 and 4 mg from day −4) [12], and another 24 patients received intravenous Tacrolimus (0.01 mg/kg/24 h from day −7 to −4 and 0.03 mg/kg/24 h from day −3) and Methotrexate. Immunosuppressive drug levels in peripheral blood were monitored in order to adjust treatment, and tapered from day +56 if patient did not show GVHD symptoms.

2.3. Engraftment, GVHD assessment and follow up evaluation

GVHD diagnosis was based on clinical and histologic criteria[13,14]. Disease response was evaluated by bone marrow analysis on day +21, +56, +100, +180, +270 and 1 year post-transplantation. Complete remission was considered when less than 5% of blasts were observed in bone marrow. Minimal residual disease analysis by multi-parametric 8-colours flow cytometric immunophenotyping analysis and chimerism assessment by RT-PCR was performed in every disease evaluation. In those patients who received a RIC regimen, lineage-specific chimerism assessment was performed by peripheral blood RT-PCR analysis.

2.4. Statistical analysis

The statistical analysis was implemented using SPSS version 20.0 (SPSS, Chicago, IL, USA) and NCSS v.8, 2012 (Number Cruncher Statistical System, Kaysville, UT, USA) for cumulative incidence analysis, considering competitive risk. Categorical factors were compared by X^2 test, and *t*-Student or *U* Mann–Whitney was used to compare continuous variables.

Overall survival (OS) was defined as time from HSCT to death from any cause. Disease free survival (DFS) was time from HSCT to death, progression or relapse. Non-relapse mortality (NRM) was defined as all deaths related to HSCT before disease progression or relapse.

Relapse was considered as demonstration of disease by morphological or immunephenotypical analysis in patients who previously had achieved a complete remission (CR).

Estimated OS and DFS were calculated using Kaplan–Meier (KM) method, and KM curves were compared by the log rank test. Estimated cumulative incidence was calculated for NRM, relapse rate and GVHD by using the cumulative incidence estimator to accommodate competing risks. To evaluate the impact of chronic GVHD, +100 landmark analysis was performed [15]. Multivariate survival analysis was performed using Cox Regression model.

3. Results

3.1. Patients and donors

Baseline characteristics are summarized in Table 1 (patients) and 2 (donors). Among the 179 patients included, diagnosis was AML in 117 (including 25 (14%) pre-existing MDS and 7 (3.9%) therapy-related AML) and MDS in 62 (n = 9 therapy-related MDS). Median age was 51 (18–69) years old in patients, with 96 of them (54%) older than 50. Performance status score (ECOG) was <2 in all except 12 patients (6.7%). Roughly a quarter of patients had poor risk cytogenetic (40.7% in MDS and 20.3% in AML). Donor was unrelated in 51 HSCT [74% of them (n = 37) were 10/10 HLA-identical, 18% (n = 9) had 9/10 HLA in common, 4% (n = 2) 8/10 and 2 patients had 7/8 HLA compatible donor]. In the whole group, 163 patients (91%) underwent HSCT from a HLA identical donor.

Donor's median age was 47 (12–75) years old and 45.3% of them (n = 81) were older than 50 years. Median age was 51 (12–75) and 36 (19–55) years for sibling and unrelated donors respectively. In 41 patients (22.9%), there was a female donor for male patient, while the more common situation was male donor for male patient (36.9%). The most common recognized risk factors were homogenously distributed among younger (<50 y) and older (>50 y) donors (Table 2), except cytomegalovirus (CMV) status [positive donor for negative recipients (76% vs 91%; p = 0.005)], and patient older than 50 years that were more frequent between older donors (31.6% vs 80.2%; p = 0.000); MUD was more frequent in younger donors (44.9% vs 6.2%, p = 0.000). Diagnosis distribution was similar in MRD and MUD (MDS 33% vs 38%, and AML 67% vs 61%, p = 0.4), as well as in younger and older donors (MDS 32% vs 37%, and AML 67% vs 63%, p = 0.54).

Moreover, in order to perform a further comparison among these groups, we assessed the distributions of these common known risk factors between older than 50 y MRD and younger than 50 y MUD (Table 3). Consequently with the data reported before, we also observed older patients in the group of older MRD and consequently more RIC transplants. In addition, HLA identical match was significantly more common in the group of MRD > 50 than in MUD < 50 (96% vs 75%; p = 0.001).

A high proportion of patients were in remission at the moment of the HSCT (106 were in first CR and 24 were second CR or partial response) and 12.8% of patients had refractory disease.

The median number of cells infused was 5.54×10^8/kg of body weight, and in 89% stem cell were collected from peripheral blood.

3.2. Engraftment and GVHD

All but 1 patient engrafted; the median time to neutrophil and platelet engraftment were 17 (2–64) and 11 (1–45) days respectively, defining it as the first of three consecutive days with more than 0.5×10^9/L neutrophils and untransfused platelet count greater than 20×10^9/L.

There was no association between engraftment and donor age (p > 0.05).

In our series, 49.7% of patients developed acute GVHD (aGVHD), with 19% of grade 3–4 aGVHD. Grade ≥3 aGVHD was 17% vs 21% in patients with donor <50 y and >50 y respectively (p > 0.05). After 1-year post-HSCT follow-up, 97 patients had developed chronic GVHD (54.2%); limited and extensive were 25% and 35% respectively. Chronic GVHD (cGVHD) were homogeneously distributed by donor age (<50 y = 61% vs >50 y = 59%; p > 0.05).