Busulfan and melphalan as conditioning regimen for allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia in first complete remission

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Background: Allogeneic hematopoietic stem cell transplantation with HLA-identical donors has been established for the treatment of acute myeloid leukemia patients for over 30 years with a cure rate of 50% to 60%.

Objectives: To analyze the overall survival of patients and identify factors that influence the outcomes of this type of transplant in patients in 1st complete remission who received a busulfan and melphalan combination as conditioning regimen.

Methods: Twenty-five consecutive patients with acute myeloid leukemia were enrolled between 2003 and 2008. The median age was 34 years old (Range: 16 - 57 years). All patients received cyclosporine and methotrexate for prophylaxis against graft-versus-host disease. Median neutrophil engraftment time was 16 days (Range: 7 - 22 days) and 17 days (Range: 7 - 46 days) for platelets. Sinusoidal obstructive syndrome was observed in three patients, seven had grade II acute graft-versus-host disease and one extensive chronic graft-versus-host disease.

Results: The overall survival by the Kaplan-Meier method was 48% after 36 months with a plateau at 36 months after transplantation. Intensive consolidation with high-dose arabinoside resulted in an improved survival (p-value = 0.0001), as did grade II acute graft-versus-host disease (p-value = 0.0377) and mild chronic graft-versus-host disease (p-value < 0.0001). Thirteen patients died, five due to infection within 100 days of transplant, two due to hemorrhages, one to infection and graft-versus-host disease and three relapses followed by renal failure (one) and infection (two). The cause of death could not be determined for two patients.

Conclusion: The busulfan and melphalan conditioning regimen is as good as other conditioning regimens providing an excellent survival rate.

Keywords: Stem cell transplantation; Leukemia, myeloid, acute; Drug toxicity; Bone marrow transplantation; Busulfan/administration & dosage; Combined modality therapy; Cyclophosphamide/administration & dosage; Graft vs. Host disease; Survival analysis; Prognosis

Introduction

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) with a HLA-identical donor has been established to treat acute myeloid leukemia (AML) patients for more than 30 years and can cure 50% to 60% of patients.(1) In young patients, with intermediate cytogenetic risk after first complete remission (1st CR), the risk of recurrence is generally less than 20%, but this favorable effect is partly hampered by the toxicity of the procedure, infectious complications and graft-versus-host disease (GvHD). As a result, Allo-HSCT has limited gain in survival despite the low rate of relapse.(2-4)

There is a great difference in the risk of relapse in AML patients according to cytogenetic alterations. After 1st CR, young patients with intermediate or unfavorable cytogenetic risk, have relapse rates of 50% and 80% respectively. In these patients, Allo-HSCT as the first line may represent the best option to prevent relapse, but this depends on the availability of a HLA-matched donor.(2-4) The French-American-British (FAB) classification(5-7) has frequently been used to stratify the degree of risk in combination with cytogenetic alterations.(8-11)

The use of a cyclophosphamide (Cy) and busulfan (BU)(12,13) combination is the most used conditioning for Allo-HSCT, followed by total body irradiation combined with Cy.(14) The association of busulfan and melphalan (BU/Mel)(15-17) is the most used regimen in this service in order to decrease the incidence of hematuria associated with Cy as these agents are active in the treatment of AML.

This study aimed to analyze the overall survival in Allo-HSCT with HLA-identical donors of AML patients in 1st CR who received the BU/Mel combination, to identify factors that influenced the overall survival, to evaluate the toxicity of the conditioning regimen and to determine the causes of death.
Methods

From October 11, 2003 to February 22, 2008, 25 consecutive patients with AML in 1st CR submitted to Allo-HSCT were analyzed retrospectively. The study was closed on March 31, 2009. The study project was submitted and accepted by the Institution's Review Committee on Research Projects and all patients were informed about the nature of the project, signed consent forms and voluntarily participated in the study.

The series is comprised of 13 male and 12 female patients. The median age at time of transplant was 34 years with the youngest being 16 and the oldest 57 years old. Nineteen were Caucasian and six non-Caucasian. Five patients had a history of myelodysplastic syndromes and two had previously received chemotherapy for lupus erythematosus and glioma.

Cytogenetic analysis was performed in 15 patients; one was believed to have a good prognosis, eight intermediate prognoses and six bad. According to the French-American-British (FAB) classification three patients were classified with subtype M1, four M2, one M3, two M4, four M5, two M6, one M7, seven secondary and one biphenotypic.

Twenty patients were induced with a chemotherapy protocol consisting of arabinoside (Ara-C) for seven days and anthracycline for three days (3 + 7). Five received other induction protocols. Intensive consolidation chemotherapy with high-dose Ara-C (HD Ara-C) was performed in 16 patients, while nine did not receive it.

After the first cycle of chemotherapy, nine of 16 achieved CR. This information is unavailable for nine patients as they were referred to the service and the information was lacking at referral.

The median transfusion of concentrated red blood cells before transplantation in 13 patients was 9 U (Range: 0 - 24 U). Four patients, with a median of 6 U, received platelets by apheresis (AP). Multiple donor platelets (MDP) were infused in ten patients with a median of 27 U (Range: 5 - 197 U). Data on the number of previous transfusions in other patients are unavailable either because they received multiple transfusions or because the information was lacking at referral.

Donor and histocompatibility system (HLA)

Of the 25 transplant patients with HLA-identical related donors, 17 donors were male and eight female. Comparative analysis of donor/recipient showed that 15 donors were of the same gender as the patient (five females and ten males) and ten were of different genders (six female patients with male donors and four male patients with female donors).

The median donor age was 35 years old (Range: 14 - 62 years). Data on pregnancy, childbirth and miscarriages of female donors showed that only two donors had had children.

The source of the infused cells was bone marrow (BM) from twenty HLA-identical donors and peripheral stem cells (PSC) after mobilization with filgrastim from five. The median number of total cells infused into twenty patients was $2.7 \times 10^8$/kg (Range: 0.9 to 18.4 $10^8$/kg). In seven donors the median of CD34+ was $5.7 \times 10^6$/kg (Range: 1.5 to 10.0 $10^6$/kg).

The characteristics of transplant patients are shown in Table 1.

| Variable                                      | N° of patients |
|-----------------------------------------------|----------------|
| Gender                                        |                |
| Male                                          | 13             |
| Female                                        | 12             |
| Age in years (median)                         | 34 (range: 16 - 57) |
| Racial background                             |                |
| Caucasian                                     | 19             |
| Not Caucasian                                 | 6              |
| Cytogenetic                                   |                |
| Good / Intermediate                           | 9              |
| Unfavorable                                   | 6              |
| Unknown                                       | 10             |
| French-American-British Classification (FAB)  |                |
| M1                                            | 3              |
| M2                                            | 4              |
| M3                                            | 1              |
| M4                                            | 2              |
| M5                                            | 4              |
| M6                                            | 2              |
| M7                                            | 1              |
| Secondary                                     | 7              |
| Biphenotypic                                  | 1              |
| Toxicity                                      |                |
| Yes                                           | 7              |
| Not                                           | 18             |
| Induction treatment                           |                |
| Anthracyline and arabinoside (3+7)            | 20             |
| Others                                        | 5              |
| Intensive chemotherapy                        |                |
| Yes                                           | 16             |
| Not                                           | 9              |
| Complete remission after 1st cycle of induction|               |
| Yes                                           | 9              |
| Not                                           | 7              |
| Not specified                                 | 9              |
| Source of cells                               |                |
| Bone marrow                                   | 20             |
| Peripheral stem cell (SCP)                    | 5              |
| Median cells infused                          |                |
| Total                                         | 20             |
| CD34+                                         | 7              |
| Conditioning regimen                          |                |

Patients were conditioned with busulfan 16 mg/kg (1 mg/kg orally every six hours on days -7 to -4) and melphalan 140 mg/m² intravenously on the day before transplantation (BU/Mel).
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Prophylaxis

All patients received 10 mg/kg/day of diphenylhydantoin orally, split in four doses to prevent seizures. To prevent infection, patients received trimethoprim-sulfamethoxazole, cefepime, fluconazole and acyclovir, even after engraftment. All patients received cyclosporine and methotrexate as prophylaxis against chronic GvHD.

Statistical analysis

The statistical analysis considered death as the event of interest. The estimated cumulative probability of survival was made by estimating the Kaplan-Meier product limit and making comparisons between curves using the log-rank test. Descriptive statistical analysis was made of follow-up time of surviving patients until March 21, 2009. In every analysis we adopted a significance level (p) of 5% (18).

Patients were evaluated respectively, were in 1st CR, and the indication of Allo-HSCT was due to the existence of HLA-identical donors. We analyzed engraftment, toxicity related to conditioning regimen, while the outcome of the study was overall survival (OS) and associated risk factors.

Definitions

CR is the absence of blasts in peripheral blood, less than 5% blasts in bone marrow, lack of evidence of extra-medullar leukemia or absence of disease recurrence.

Transplant related mortality and relapse was the recurrence of the disease at any time after transplantation.

OS is survival at the end of the follow up period.

Granulocyte engraftment is the presence of more than 0.5 x 10^9/L granulocytes in blood counts on three consecutive days. Platelet engraftment is the presence of more than 20 x 10^9/L platelets for more than seven days without the need of a platelet transfusion. Follow-up time was calculated as the interval between the date of transplant until the date of death, or until March 31, 2009, for those who survived until the end of the follow up period.

The criteria used were those of the FAB classification, cytogenetic risk and toxicity of the World Health Organization (WHO). (19)

Results

Of the 25 patients, the median time between diagnosis and transplantation was 191 days (Range: 73 - 651 days). The median follow up of patients was 768 days (Range: 15 - 5645 days).

The median granulocyte engraftment time was 16 days for 21 patients evaluated with the granulocyte count higher than 0.5 x 10^9/L (Range: 7 - 22 x 10^9/L). The median platelet engraftment time was 15 days for a count higher than 20 x 10^9/L (Range: 0 - 56 x 10^9/L) in 21 patients and for a count higher than 50 x 10^9/L (Range: 7 - 46 x 10^9/L) it was 17 days in 19 patients.

The median transfusion after Allo-HSCT for filtered and irradiated concentrated red blood cells in 21 patients was 5.5 U (Range: 1 - 26 U), for aphaeresis in seven patients it was 17 U (Range: 1 - 18 U) and for multiple donor platelets in eight patients it was 20.5 U (Range: 7 - 60 U).

Infections occurred in all 25 patients including 12 episodes of infection of undetermined origin, six infections by gram-negative bacteria, two gram-positive, 11 viral and five fungal infections. The antigenemia was positive for cytomegalovirus (CMV) in 11 patients and the event occurred from day +25 to day +62 with a median positivity at around day +37.

Sinusoidal obstructive syndrome (SOS) was observed in three patients on days +7, +10 and +10. Hematuria occurred in two patients. Moderate to severe mucositis occurred in 17 patients, nausea and vomiting in eight and diarrhea in seven. The others did not report these symptoms or only had a mild form of the disease.

Acute GvHD was absent in six patients, six had grade I, seven had grade II and two grade III. Four patients were not evaluated for acute GvHD. Four patients did not have chronic GvHD, 14 had mild chronic GvHD and one had extensive chronic GvHD. Six patients were not assessed for chronic GvHD. Analyses of engraftment, toxicity, and acute and chronic GvHD are shown in Tables 2, 3 and 4.

The overall survival rate was 47% after 36 months; 12 patients survived without disease to the end of the study. Descriptive statistics of the patients that survived after the study showed a median survival of 2073 days (Range: 403 - 5645 days).

The probability of survival according to the Kaplan-Meier method showed no significant differences in relation to gender, FAB classification of leukemia, cytogenetic analysis, induction therapy, remission after the 1st induction cycle and source of infused cells (PSC or BM). There were statistically significant differences in relation to intensive consolidation and acute and chronic GvHD; the probability of survival at 36 months of patients who received intensive consolidation with HD Ara-C was 73% and patients who did not...
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Figure 1 - Overall survival of AML patients in 1st complete remission, conditioned with a BU/Mel combination and submitted to allogeneic hematopoietic stem cell transplantation - survival associated to intensive consolidation

Table 5 - Survival probability of AML patients who underwent allogeneic hematopoietic stem cell transplantation in 1st with busulfan and melphalan conditioning

| Variable                  | Category | Survival (in months) | p-value |
|--------------------------|----------|----------------------|---------|
| Gender                   | Male     | 61.4 61.4 53.9       | 0.4396  |
|                          | Female   | 50 50 37.5           |         |
| AML (FAB)                | M1-M2-M4 | 62.5 62.5 62.5       | 0.5347  |
|                          | Others   | 53 53 39.8           |         |
| Citogenetics             | Good/intermediate prognosis | 77.8 77.8 51.9 | 0.1707  |
|                          | Unfavorable prognosis | 16.7 16.7 16.7 |         |
|                          | Unknown prognosis | 60 60 60 |         |
| Induction treatment      | Anthracyleine/arabinoside 3+7 | 60 60 48 | 0.4625  |
|                          | Others   | 40 40 40 |         |
| Intensive consolidation  | Yes      | 81.2 81.2 73.9      | 0.0001  |
|                          | Not      | 11.1 11.1 0         |         |
| Remission after 1st cycle | Yes    | 66.7 66.7 55.6     | 0.62    |
|                          | Not     | 42.9 42.9 42.9      |         |
|                          | Not inform. | 55.6 55.6 41.7   |         |
| Source of cells          | Bone marrow | 50 50 40 | 0.1583  |
|                          | Peripheral stem cells | 80 80 80 |         |
| Acute GVHD               | 0        | 28.6 14.3 14.3      | 0.0377  |
|                          | I        | 80 60 60           |         |
|                          | II       | 85.7 85.7 85.7     |         |
|                          | III      | 50 50 50           |         |
| Chronic GVHD             | absent   | 50 50 50           | <0.0001 |
|                          | limited | 85.7 85.7 85.7     |         |
|                          | extensive | 0 0 0 |         |

Table 4 - Number of patients submitted to allogeneic hematopoietic stem cell transplantation with busulfan and melphalan conditioning who evolved with acute and chronic graft-versus-host disease

| Acute GVHD | No of patients |
|------------|----------------|
| Absent     | 6              |
| I          | 6              |
| II         | 6              |
| III        | 7              |
| Not assessed | 4          |

| Chronic GVHD | No of patients |
|--------------|----------------|
| Absent       | 4              |
| Limited      | 14             |
| Extense      | 1              |
| Not assessed | 6              |

not receive consolidation did not survive. Six of seven patients who presented with grade II acute GvHD or the lack of or limited chronic GvHD had a better chance of survival with a probability of survival of 50% and 66.6%, respectively. The patient with extensive chronic GvHD had died by 12 months.

Table 5 presents the probability of survival at 12, 24 and 36 months in respect to different variables and statistical significance. The survival curves of intensive consolidation with HD Ara-C, acute and chronic GvHD and overall survival are shown in Figures 1, 2, 3 and 4, respectively.

The cause of death of five of 13 patients who died was infection within 100 days of transplantation; three patients died due to relapse on days +189, +274 and +917 followed by renal failure for one and infection for the other two; one had an alveolar hemorrhage on day +18 and one coagulopathy on day +974 after a second mini-allogeneic transplantation. One patient died of chronic GvHD and CMV on day +164. It was not possible to determine the cause of death for two patients (days +103 and +185) as this data was not recorded on their charts.

Of the patients who died after relapse, two had myelodysplastic syndrome before AML, and one had had glioma and had been submitted to chemotherapy before the diagnosis of AML. Cytogenetic analysis after death was normal in three patients; two had trisomy of chromosome 8, five had complex rearrangements and cytogenetics was not performed in three.
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Discussion

Allo-HSCT is the therapy of choice for AML (20,21). However, there are limitations to the applicability of transplantation in most patients, including difficulties in controlling the disease with the initial induction, the lack of HLA-identical donors, toxicity of the conditioning regimen, and long-term complications arising from it.

In this study, 25 patients with AML in first CR who underwent Allo-HSCT received the busulfan and melphalan combination as the conditioning regimen. Analysis of gender, induction therapy, and CR after first cycle of induction chemotherapy showed no statistical significance on survival. However, 73% of patients submitted to intensive consolidation with HD Ara-C survived to the end of the study but all of those who did not receive consolidation died (p-value = 0.0001). The procedure benefited patients with favorable or unknown cytogenetics and good and bad prognoses according to the FAB classification. Despite the small number of patients, our results, unlike the literature (22), show the benefits of intensive consolidation in patients undergoing this type of transplant.

Most patients had severe mucositis, nausea and vomiting. SOS only occurred in three (12%) patients, a lower rate than reported in publications (23). Hematuria occurred in two patients. All patients had post-transplant infection and CMV antigenemia was present in 44%. The median engraftment time did not differ from published data (24,25).

The survival rate was around 47%, with 12 of the 25 patients alive without disease, similar to that observed in the literature (1,3,4,26). Moreover, survival leveled off according to the Kaplan-Meier method 36 months after the procedure. A period when survival leveled off was reported in another study (27) on autologous transplants after 24 months.

In this study, patients with grade II acute GvHD had a survival rate of 85.7%, that is better than other patients, which can be explained by the graft versus leukemia effect in this type of transplant (14). Limited chronic GvHD was observed in 15 patients and one, who presented extensive chronic GvHD, died on day +164 post-transplant.

Of the 13 patients who died, five deaths were due to infection, all within 100 days post-transplant, three due to relapse, one to infection and chronic GvHD, two to bleeding and for two it was not possible to determine the cause of death.

Conditioning with the BU/Mel combination (15-17) is most used in our service as these agents are active in the treatment of AML but cause less hematuria. The conclusion in this study is that Allo-HSCT in AML patients in first CR showed similar results to the literature (1,3,4,26). Patients who received intensive consolidation with HD Ara-C post-induction had better survival than the others. Hence, prospective studies should be performed in Brazil to assess the importance of intensive consolidation in this type of procedure. Acute and chronic GvHD were important in the survival of patients thus...
supporting published data. The BU/Mel conditioning regimen proved to be a valid alternative to BU/Cy as it decreases the incidence of hemorrhagic cystitis and provides a good survival rate.

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