INTRODUCTION

Autologous hematopoietic stem cell transplantation (auto-HSCT) is a technique widely used in patients with hematological cancers and some solid tumors. It is also called high-dose chemotherapy with hematopoietic stem-cell support or, simply, autologous bone marrow transplantation. The technique consists of the collection of hematopoietic stem cells from the patient, administration of high-dose chemotherapy, followed by the infusion of previously collected hematopoietic stem-cells. Unlike allogeneic transplantation, in autologous transplantation, there is no need for a donor because the patient himself/herself is the donor.

The number of hematopoietic stem cell (HSCT) transplants has gradually increased over the years. In 1985, it was limited to 10,000 transplants worldwide, ten years later it accounted for around 100,000 transplants, increasing to 500,000 in 2005, and doubled to around one million HSCT by the end of 2012. The availability of resources and evidence and the positive regulatory environment was associated with the high number of transplants.

In Brazil, autologous HSCT has been practiced in large hospital centers for at least 30 years, when autologous HSCT was established as part of the rescue...
treatment, with curative intent, for patients with relapsed lymphomas. It has also been incorporated into the first-line treatment of multiple myeloma, with the aim of increasing survival.[2,3] Of the total of 2,794 stem cell transplants (HSCT) performed in Brazil in 2017, 59.7% were autologous, which shows the current importance of this type of transplant in the treatment of onco-hematological diseases.[4]

The objectives of this study are to describe the characteristics of autologous transplants performed for 30 years in a single institution and to analyze the results of autologous transplantation in the most frequent diseases.

METHODS

This is an observational retrospective cohort study, which included all patients who underwent autologous HSCT between June 1987 and December 2016 at the HSCT unit of a philanthropic hospital. Only patients with multiple myeloma (MM), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and acute myeloid leukemia (AML) were included in the analysis of results. The study was approved by the local Ethics Committee. The Ethics Committee waived the need to sign a specific consent form for this study.

The data for this study were collected from the patients’ medical records and data reported by the hospital to the Center for International Blood and Marrow Transplant Research (CIBMTR).

Demographic data, such as age and gender, were collected. The following clinical data were also computed: underlying disease, disease status, source of stem cells for transplantation, number of cells infused and performance status. The primary outcome was death. Secondary outcomes were the time for neutrophil and platelet grafting and relapse. The disease condition (status) before transplantation was classified as complete remission, partial remission or with refractory disease.

The characteristics of the patients were described as absolute and relative frequencies. The overall survival (OS) and disease-free survival (DFS) curves were estimated using the Kaplan-Meier method and compared using the log rank test.

For each disease, hazard ratios (HR) were estimated with the respective 95% confidence intervals, using a single and multiple Cox proportional hazard model. A two-tailed p-value less than 5% was considered statistically significant. All analyses were made in R, version [3.6.1].

RESULTS

Since the first autologous HSCT in the institution, in 1987, until December 2016, 583 autologous transplants were performed in 526 patients. Of these, 378 were transplanted for multiple myeloma (MM), acute myeloid leukemia (AML), Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL). The characteristics of the patients and the first transplants are shown in Table 1. Briefly, the median age was 43 years, 56% were men, and the most common diagnosis was MM.

All patients had neutrophil engraftment, at a median of 10 days. Factors related to faster recovery were the number of infused CD34 (hazard ratio, HR = 1.05 for each increase in 1x10E6/kg, p = 0.0001) and, for slower recovery, diagnosis of AML (HR = 0.33, p = 0.003, compared with MM).

With a median follow-up of 6.4 years, the 5-year overall survival (OS) was 61%. Survival was significantly worse in patients with non-Hodgkin’s lymphoma (Figure 1). In the multivariate analysis, both Hodgkin’s lymphoma (HR = 3.02, p = 0.0006) and non-Hodgkin’s lymphoma (HR = 2.00, p = 0.0003) were associated with worse survival. Age was also a poor-prognosis factor (HR = 1.04, for each year older, p <0.0001). Transplantation in the most recent period (2008 - 2017) was a protective factor (HR = 0.42, p <0.0001).

The 5-year incidence of disease relapse was 42% for AML, 49% for MM, 41% for HL and 41% for NHL (p = 0.88). For MM, the incidence of relapse was significantly higher in patients who did not achieve a partial response (HR = 4.02, p = 0.03). For lymphomas, both patients who achieved partial response (HR = 5.16, p = 0.003) and those who were refractory (HR = 5.06, p = 0.007) had higher relapse rate.

Progression-free survival (PFS) was 41% at 5 years, with no difference between diagnoses (44% for AML, 39% for MM, 51% for LH, and 41% for NHL; p = 0.50). In the multivariate analysis, the factors of poor prognosis were age (HR = 1.03 for each additional year, p = 0.003), partial remission (HR = 3.22, p = 0.0003) and refractory disease (HR = 4.73, p = 0.003) for lymphomas. For MM, only pre-transplant disease status (HR = 2.11, p = 0.01 for partial remission, and HR = 19.5, p <0.0001 for patients who did not achieve partial response) were identified as risk factors.

Non-relapse mortality was 13% in 1 year. We did not find any factors associated with non-relapse mortality.
DISCUSSION

This analysis of the results of a single autologous transplant center in multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's lymphoma and acute myeloid leukemia is one of the largest in the world. [5,6,7,8,9] It shows that the modality rendered an overall survival of 61%. There were no grafting failures and the times for neutrophil and platelet engrafting were compatible with literature data.[10]

The indication of autologous transplantation for patients with multiple myeloma should be maintained even with the advent of novel treatments. Several studies show that, even with the new proteasome inhibitors and pre-transplant immunomodulators, autologous HSCT increased progression-free survival, especially in patients younger than 70 years old. At the American Association of Hematology last meeting, the importance of the procedure for this group of patients was also demonstrated.[9,11] Current studies comparing transplanted versus non-transplanted patients corroborate our findings. They show an advantage for autologous transplantation as a complement to treatment instead of following with observation or even maintenance.[9,12,13]

Possibly, one of the reasons for the success is the adequate selection of patients in conditions to be transplanted, with good functional status. All patients selected for transplantation in this sample were generally in good clinical condition, usually less than 75 years old and without major comorbidities. In our institution, for patients older than 65 years old (which represented 11% of patients), we use the Comprehensive Geriatric Assessment. [14,15] Still, mortality was higher in older patients. However, when considering only mortality up to 100 days, age was not a prognostic factor. Also, we have seen an improvement in overall survival in the most recent period.

Our results showed that patients with multiple myeloma with a median age of 58 years had 39% disease-free survival at 5 years. The overall survival was 69%. This data is compatible with other findings in the literature.[16] As with most diseases, we also demonstrated that patients’ pre-transplant disease status is fundamental in the outcome. That is, patients with stable disease have worse disease-free survival.[16]

Patients with non-Hodgkin's lymphoma are usually transplanted as part of the treatment of relapsed chemosensitive patients. The cure rate of patients with aggressive B lymphoma in first remission varies from 50% to 90% depending on the prognostic indexes.[17] Our results show that, following relapse, 41% of the patients remained in complete remission after 5 years. The prognosis of patients who were not at complete remission was poor and even worse for refractory patients. CD19+ Non-Hodgkin lymphomas are discussed for their future replacement by other methods of cell therapy, such as the chimeric antigen receptor T-cells (CAR-T cells) against CD19, but this is not yet established.

This situation is similar to that with Hodgkin's lymphomas. These have high cure rates with the initial treatments, ranging from 75 to 90%. In relapses, autologous transplantation is a treatment option, and our data show that 51% remained in complete remission in five years. Literature data point to 40 to 70%, depending on the prognostic index. 18,19 In our sample, we did not classify patients because it is a retrospective study in which data were not always available. The only data we had was pre-transplant status. As with multiple myeloma, autologous transplantation in Hodgkin's and non-Hodgkin's lymphoma continues to be used even with the advent of new therapies and transplant modalities.

In the case of acute myeloid leukemia, the situation is different, as this modality, more defended by the Europeans and less by the Americans, had only one reference at the ASH 2018 meeting, presented on a poster precisely by Europeans. In that study, they suggest that patients who achieve complete remission after induction, depending on their cytogenetics and molecular factors, should undergo allogeneic transplantation or four to five consolidations or one to two consolidations and autologous transplantation.[20,21] These patients are those with good prognosis or intermediate prognosis who do not have a compatible donor. In our population, the disease-free survival in 5 years was 44%, and the global was 65%. The choice between several consolidations versus autologous transplantation in this group of patients is still controversial and is the subject of several comparative studies.[22,23] In patients at intermediate risk, data showing that haploidentical transplants are similar to allogeneic transplants from unrelated donors end up endorsing its use in this category at detriment of autologous ones.[24,25]

The results showing a 50% long-term survival rate agree with data from the literature, which reveals the recurrence rate as a major concern in this type of transplant compared to allogeneic transplants. In these, the leading cause of death is procedure toxicity, with a higher rate of infections and the presence
of graft versus host disease.[26] Patients with poor prognoses, such as those with complex cytogenetics or presence of FLT3 mutated gene (tyrosine kinase 3 Fms-related), if they are not submitted to allogeneic transplantation, have a high chance of recurrence of the disease in a short period.[27] On the other hand, patients with good prognostic cytogenetics, such as t[8:21] or inv16, and those with normal karyotype, with negative FLT3 and positive NPM1, would have a higher risk with allogeneic transplantation28, which presents greater toxicity compared to intensive chemotherapy such as consolidation or autologous transplantation. Only randomized studies will demonstrate the superiority or otherwise of autologous transplantation over chemotherapy in these low-risk or intermediate-risk patients.[8]

In summary, the profile and historical path of autologous transplants for oncological and onco-hematological diseases performed in the last 30 years in a Brazilian institution demonstrated evolution according to the medical literature, giving the possibility of recovering a significant number of patients with Hodgkin’s lymphoma, non-Hodgkin lymphoma, multiple myeloma and acute myeloid leukemia. The continuous study of the performance of autologous transplants in the light of new therapies allows reframing their indications when compared to new therapies. Thus, even with the advent of new therapies, the indications for autologous first-line transplantation for young and fit patients with multiple myeloma remain, and their use in relapsed or refractory patients with Hodgkin’s and non-Hodgkin’s lymphoma as second-line consolidation of treatment. However, in acute myeloid leukemia, autologous transplants would only have some indication in patients with a favorable prognosis. Only prospective studies will show whether its use exceeds the performance of several cycles of consolidation with cytarabine.

**TABLE 1 - Patients’ characteristics**

<table>
<thead>
<tr>
<th></th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>526</td>
</tr>
<tr>
<td><strong>Age – mean (SD)</strong></td>
<td>44.6 (17.9)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>292 (55.5%)</td>
</tr>
<tr>
<td>Female</td>
<td>234 (44.5%)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>44 (8.4%)</td>
</tr>
<tr>
<td>MM</td>
<td>159 (30.3%)</td>
</tr>
<tr>
<td>HL</td>
<td>45 (8.6%)</td>
</tr>
<tr>
<td>NHL</td>
<td>129 (24.6%)</td>
</tr>
<tr>
<td>Others</td>
<td>148 (28.2%)</td>
</tr>
<tr>
<td><strong>Status prior to transplant</strong></td>
<td></td>
</tr>
<tr>
<td>Complete remission</td>
<td>97 (36.3%)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>137 (51.3%)</td>
</tr>
<tr>
<td>REF</td>
<td>33 (12.4%)</td>
</tr>
<tr>
<td><strong>Stem cell source</strong></td>
<td></td>
</tr>
<tr>
<td>PBSC</td>
<td>451 (85.7%)</td>
</tr>
<tr>
<td>BM</td>
<td>25 (4.8%)</td>
</tr>
<tr>
<td>BM+PBSC</td>
<td>50 (9.5%)</td>
</tr>
<tr>
<td><strong>CD34 – mean (SD)</strong></td>
<td>5.9 (4.5%)</td>
</tr>
<tr>
<td><strong>Period</strong></td>
<td></td>
</tr>
<tr>
<td>1987-1997</td>
<td>144 (28.6%)</td>
</tr>
<tr>
<td>1998-2007</td>
<td>201 (40%)</td>
</tr>
<tr>
<td>2008-2017</td>
<td>158 (31.4%)</td>
</tr>
</tbody>
</table>

SD = standard deviation; AML = acute myeloid leukemia; MM = multiple myeloma; HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; PBSC = peripheral blood stem cell; BM = bone marrow
REFERENCES


5. Lévy V, Katsahian S, Fermand JP, Mary JY, Chevret S. A meta-analysis on data from 575 patients with multiple myeloma randomly assigned to either high-dose therapy or conventional therapy. Medicine (Baltimore). 2005v.84, n.4, p.250–60.


