The outcome of Autologous Stem Cell Transplantation in First Complete Remission Acute Myeloid Leukemia Patients- Single Center Study

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Abstract

Post-remission treatment in patients with acute myeloid leukemia is still controversial. One potent choice for patients with no donor available is autologous stem cell transplantation. The median follow-up period was 18 months and the median age was 26 years old. In the review of 116 recently diagnosed AML patients (except AML- M3) who underwent autologous stem cell transplantation, 72.4% of patients remained alive and 27.6% relapsed. Relapse was the most common causes of death in patients. The one- year OS and DFS of patients was 73.8% and 59.8%, respectively. There was no statistically significant difference between age, sexuality and waiting time from diagnosis to transplantation. For more comprehensive results, longer follow- up is required.

Keywords: Stem Cell Transplantation, Autologous Stem Cell Transplantation, Acute Myeloid Leukemia, First Complete Remission

Introduction

Acute myeloid leukemia (AML) is a malignant disorder of the blood resulting from blocked differentiation of hematopoietic stem cells and thereby causes abnormal accumulation of immature myeloid precursors.(1) The overall survival of patients with AML has considerably improved over the last decades.(2) This improvement is probably due to the application of intensive post-remission therapies, such as high-dose chemotherapy and stem cell transplantation (SCT).(3-4)

Although most studies have confirmed the superiority of allo-SCT as therapeutic option in AML, many patients do not have suitable Human Leukocyte Antigen (HLA) compatible donors. Auto-SCT is considered as an alternative approach in patients with AML and the results of this trial compare favorably to those of other post-remission strategies.(5) The absence of graft-versus-host disease (GvHD) and the lower incidence of severe complications result in a lower treatment-related mortality (TRM). However, the relapse rate is higher compared with allo-SCT due to the lack of a potential graft-versus-leukemia effect and the possible contamination of the graft with residual leukemia cells.(6)

Here, we report a retrospective analysis on 100 AML patients in first complete remission (CR1) who underwent auto-SCT at our institution.

Materials and Methods

Patients: Between 2003 and 2011, a total of 116 patients with AML (except AML M3) were treated in our institution. HLA- compatible donors were not available for the patients enrolled in this study. All patients underwent autologous SCT after achieving first complete remission (CR1). Complete remissions were confirmed with bone marrow aspiration/biopsy before transplantation.

All patients received granulocyte colony-stimulating factor (G- CSF) on days -8 till -5 of transplantation for mobilizing cells. Conditioning regimen consisted of Busulfan (4mg/kg for 4 days) and etoposide (15 mg/for 2 days). The source of stem cells was peripheral blood in all patients. Trimethoprim/Sulfamethoxazole and acyclovir were given as infection prophylaxis.

End points: Engraftment was defined by achievement of peripheral granulocyte count of

greater than $500\times10^3/\mu L$ for 3 consecutive days without G-CSF administration, and platelet count of greater than $20000\times10^3/\mu L$ for 7 consecutive days, in the absence of platelet transfusion. Relapse was indicated by morphological evidence of leukemia in bone marrow or in any other extramedullary site or by cytogenetic recurrence of the neoplastic clone. Post- transplant disease- free survival (DFS) was defined as the time from HSCT to the date of relapse, death, or last contact. Overall survival (OS) was measured from the time of HSCT to the time of death, or last recorded follow-up.

Statistical method**:** Continuous data were described using median and range while categorical variables were presented as absolute frequencies and percentages. Overall and disease-free survival curves were calculated by the Kaplan-Meier method;(7) and groups were compared using the Log-Rank test statistic.(8) P-values less than 0.05 were considered significant.

Results

Out of 116 patients, 62 were male and 54 were female. The most common subtype of disease was M2 and M4 (54% and 38 % respectively). The median time between diagnosis and transplantation was 6 months (range, 1.5- 34). The median age at transplantation time was 26 years (range, 4- 68 years).The median time for neutrophil and platelet engraftment was 13 days (range, 7- 59 days) and 21 days (range, 8- 70 days), respectively. Nine patients (7.75%) did not have neutrophil recovery by day 100, three of these patients had persistent disease while six had no disease and in two patients ANC never dropped below $500\times10^9/L$. Thirty two patients (27.6%) had Plt<$20\times 10^9/L$ by day 100 and four patients never dropped platelet count below $20\times 10^9/L$. The median follow- up time was 18 months (1- 84 months). Eighty four patients (72.4%) are alive and 32 patients (27.6%) relapsed. The most common causes of death were relapse and progression of disease (Table- 1). The one- year OS and DFS of patients was 73.8% and 59.8%, respectively (Figure- 1).

Table 1. Causes of death in Autologous transplanted AML in CR1

Cause(s)	Number	Percent
Relapse/ Progression of disease	18	56.30%
Infection	5	15.63%
Rejection / graft failure	3	9.38%
Sepsis	2	6.25%
Pulmonary toxicity	2	6.25%
Other	2	6.25%

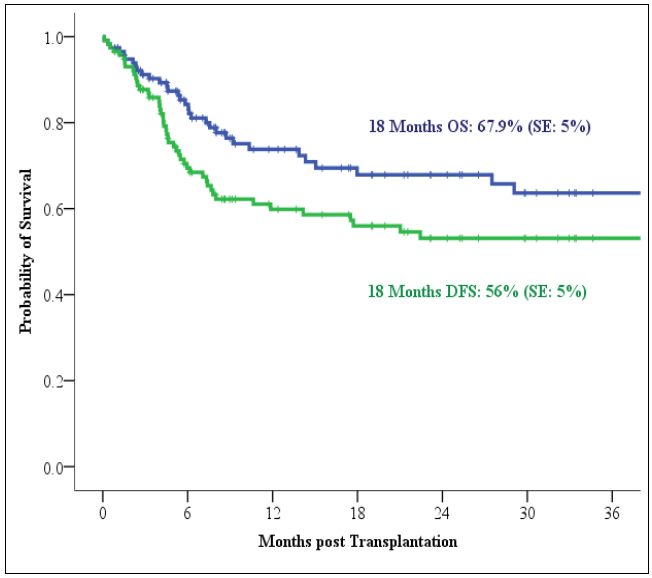

Figure- 1. The overall survival and disease- free survival of patients

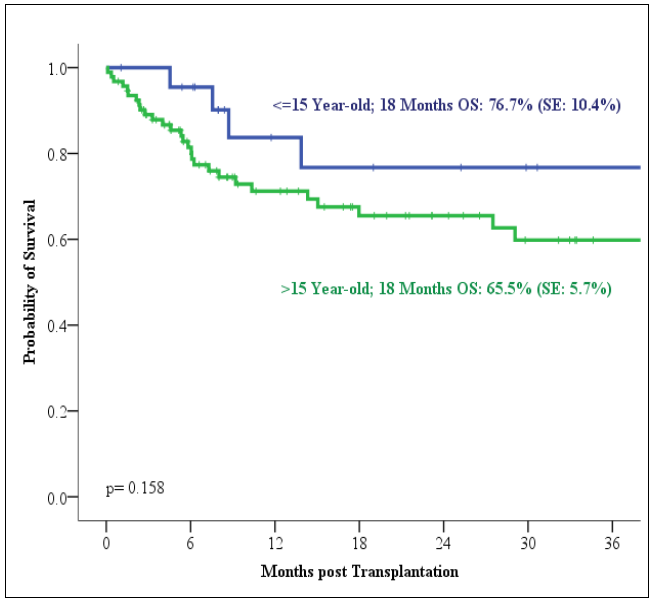

Figure- 2. The overall survival in patients aged ≤ 15 years and > 15 at transplantation

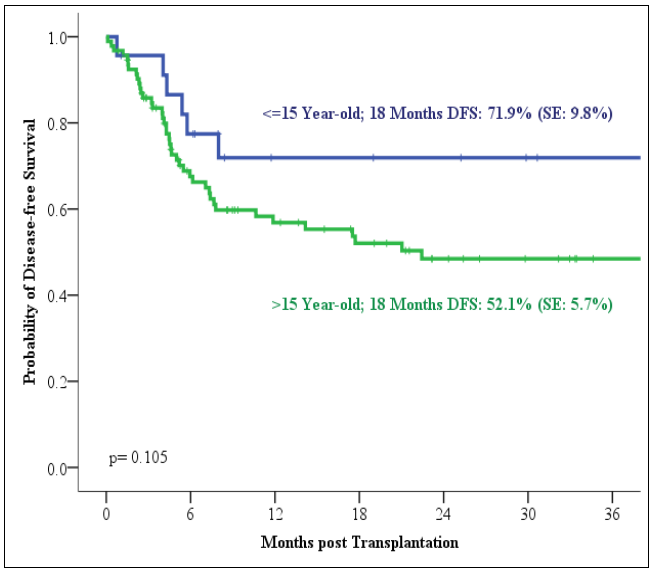

Fig. 3. The disease - free survival in patients aged ≤ 15 years and > 15 at transplantation

The one- year OS and DFS of patients transplanted at 15 years old or less and older than 15 years of age was 83.7%, 71.2% (p- value, 0.158) and 71.9%, 56.8% (p- value: 0.105), respectively (Fig.- 2, Fig.- 3). The one- year OS and DFS of male and female patients was 73.7%, 73.8% (P- value: 0.573) and 56%, 64.3% (p- value: 0.55), respectively. The one-year OS and DFS in patients who had equal to or less than six months between diagnosis and transplantation and more was 70.4%, 77.8% (P-value: 0.457) and 52.5%, 68.5% (P- value: 0.11), respectively.

Discussion

It seems that our retrospective study shows better OS and DFS of autologous SCT in patients with AML in CR1 as compared with Jung et al study.(9) Pretreatment cytogenetic status, number of induction chemotherapy cycles, molecular markers and age are relapse risk factors in AML patients.(10) So, we need to specify the AML patients' subgroups and classify them to favorable, intermediate and poor- risk groups to have a powerful analysis on OS and DFS in autologous SCT among patients with AML in CR1.

We did not find statistically significant difference between OS and DFS with sexuality whereas Martins et al. in univariate analysis found superior DFS in males than females (55% vs. 22%, PV=0.003).(11) Despite Martins et al. study demonstrating significant OS and DFS in patients younger than 15 years old (50% vs. 35%, P-value= 0.05), the results of our study showed no statistically significant difference between OS and DFS with age of patients at transplantation and also waiting time between diagnosis and transplantation. Although several studies have shown that allo-SCT results in superior OS and DFS when compared to auto-SCT,(12-14) Seshadri and Keating found no significant difference in OS between peripheral allo- and auto- SCT.(15) Comparisons between the auto- SCT, Allo- SCT, intensive chemotherapy, or no further treatment showed no significant advantage for the auto- SCT among the patients.(12, 16- 18) On the other hand, faster hematopoietic recovery also reported in patients treated with PBSCT compared with BMSCT.(19-20) Although, they observed a lower TRM in autologous patients, but this difference was not statistically significant. Relapse of disease remains the major problem after autologous SCT. Murillo et al,(21) stated in a report that more than 80% of relapses occurred in CR1 autologous SCT with high level of minimal residual disease after consolidation therapy. Despite of having no evidence at the molecular level and short- term follow- up study, we had lower rates of relapse.

In summary, autologous SCT is an effective therapeutic option for AML patients without suitable donor. Although infection ranked as the second leading cause of death among our patients, auto SCT is a promising approach to prevent Graft-versus- Host Disease (GvHD) and lower risk of infection in other studies. Further prospective clinical trials with intention- to- treat analysis are required to confirm of its effectiveness and benefits as compared to intensive chemotherapy or allogeneic SCT.

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