Hematopoietic Stem Cell Transplantation in PML-RARa Positive Acute Promyelocytic Leukemia

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Abstract:
Introduction: Acute promyelocytic leukemia treatment revolutionized by new tretaMNETS. Currently number of patinets who undergoe hematopoietic stem cell transplantation decrased so experience with this modality is limited. Here we report our experience with stem cell transplantation in acute promyelocytic leukemia patients.
Design and setting: retrospective, single center
Methods: between year 2000 and 2011 we performed 20 HSCT in APL. Median age of patients was 25 year old. Patients received 3 autologous and 17 allogeneic HSCT from their HLA full match sibling donor. Different type of conditioning regimens applied for them. We used Cyclosporine and Methotraxtae as prophylaxis of GVHD after allogeneic HSCT.
Results: Hematopoietic stem cell engraftment observed in all cases. Acute GVHD was mild to moderate in all except one and was manageable.one patient dies due to aGVHD. Chronic GVHD was extensive in 2 cases and one mortality observed due to sever cGVHD. Mortality rate was 35% with a median follow up of 3.5 years. Five patinets died due to their primary disease relapse after HSCT.
Three years DFS and OS were 63.1 and 77.2% respectively.
Conclusion: hematopoietic stem cell transplantation is an acceptable consolidation for APL. Choosing between autologous or allogeneic transplantation, need facilities such as reliable method for molecular remission detection before HSCT and also close and reliable follow up of patients with clinical and molecular parameters.

Keywords: Hematopoietic Stem Cell Transplantation, Acute Promyelocytic Leukemia, APL, PML-RARa Positive APL

Introduction

Acute promyelocytic leukemia is a highly curable type of myeloid leukemia.(1-3) Despite of prognosis improvement with current treatments, 5%-30% patients relapse.(3,4)

Currently these patients rarly undergo transplantation in first complete remission. Also after relapse these patients can achieve to second complete remission (CR) with salvage regimens (1,5) but optimal consolidation/treatment is controversial. One of the possible salvage consolidations is hematopoietic stem cell transplantation (HSCT).

This treatment seems to be superior to consolidation/maintenance therapy with Arsenic Trioxide or conventional chemotherapies,(5,7) but choosing autologous vs allogeneic stem cell transplantation (in the presence of HLA full mach sibling donor) remained challenging.Because of low number of cases who need HSCT and difficulty for randomization of patients to allogeneic and autologous stem cell transplantation, running a prospective phase III study is difficult. Conventionally patients in molecular CR candidate for autologous HSCT and other cases undergo search for allogeneic HSCT donor.(2,8)

We did a retrospective study on all cases of APL who transplanted in our center and reporting them here.

Material and Methods

Patients characteristic: 1- We performed 20 HSCT for APL disease from year2000 till Jan 2011. This cohort consist cases that treated in other centers by conventional ATRA and chemotherapy (9 cases) and referred to us for HSCT.These patients refered by their primary physician for HSCT in first CR due to their concern for adequacy of chemotherapy protocol or inadequate follow up of patinets by molecular methods. Another 11 patients treated by Arsenic Trioxide at our center, as first line therapy from diagnosis time. After relapse, this group, recivede salvage again by Arsenic Trioxide and then transplanted in morphologic CR.

APL diagnosed according to histomorphologic criteria and confirmation by RT-PCR and detection of PML-RARa (3) This cohort consist 10 females and 10 males. Median age was 25(3-46) years old. Between them 6 patients received HSCT in first complete remission, 6 in second remission and 8 in third remission. All cases who transplanted in CR1, treated before with ATRA and chemotherapy and nobody who treated by Arsenic Trioxide transplanted in CR1.

Graft type and conditioning regimens: Graft type consists, 17 allogeneic transplantation from HLA full match sibling donor and 3 autologous stem cell transplantation. In case of allogeneic transplantation, donors sex were 7 females and 10 males.

All patients and donor screened for Hepatitis B and C, HIV and CMV before HSCT. All of the recipients and donors were CMV positive before HSCT.

Conditioning regimen for allogeneic transplantation was Busulfan and Cyclophosphamide (15 cases)

or Fludarabine and Busulfan (2 cases). For autologous HSCT we used Cyclophosphamide, Cytarabin and Etoposide (2 cases) and Busulfan and Etoposide(I case) as conditioning regimen. BM was source of HSC in 2 and peripheral blood was in 18 cases.

GVHD prophylaxis after HSCT was Cyclosporine and MTX. For reporting and treatment of Acute GVHD and chronic GVHD we used standard modified seattle scoring and treatment reported elsewhere.

Definition of outcomes and Statistical analysis: CR defined as Normal peripheral blood cells and less than 5% promyelocte and blasts in BM at time of HSCT.

Neutrophil and platelet engraftment defined as three consecutive day of ANC>0.5X109/L and platelet more than 20X109/L.

For acute and chronic GVHD definition we used modified Seattle scoring.

Overall survival (OS) defined as time from HSCT to death or last follow up. Disease free survival (DFS) defined as time from HSCT to relapse, death or last follow up.

We used Kaplan-Meier method for survival analysis.

Results

Hematopoietic stem cell transplantation was successful in all patients and engraftment observed in all patients.

Median days to Neutrophil and platelet engraftment were 12(9-19) and 16(9 26) days post HSCT.

Acute GVHD happened in 9 cases, which consist 8 grade II, and one grade III. GVHD in these patients were manageable and nobody, except one, died due to aGVHD. In autologous transplanted patients no body had sever complication or mortality due to transplantation.

Chronic GVHD observed in 6 cases. Maximum grade of cGVHD was limited in 4 cases and extensive in 2 cases.

Patients followed up for a median 3.5 years (1.5 month-9years).

Survival analysis showed 2 years DFS and OS, both are 83.6%+/-8.7%. (Fig-1). Disease free survival and OS for three years were 63.1%+/-12.2% and 77.2%+/-10.10%.

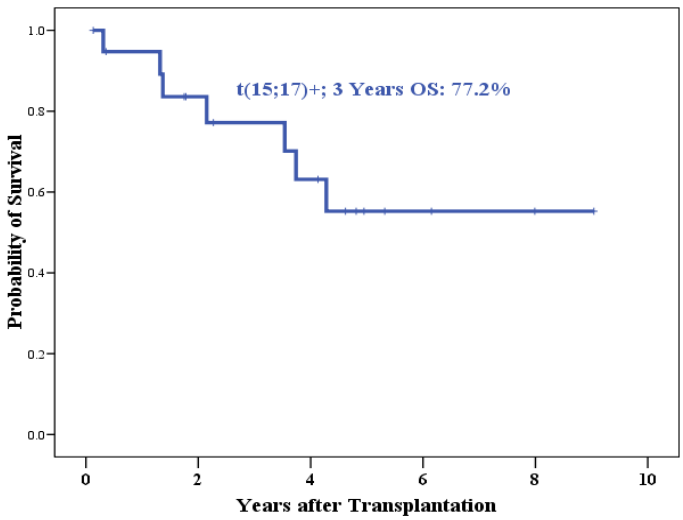

Figure- 1: survival analysis for APL patients who transplanted in CR

Overall 7(35%) death happened between our patients and 13 (65%) patients are alive. Cause of death was relapse in 5 cases and complications of transplantation in two other cases (aGVHD and infection in one case and extensive cGVHD and renal failure in another one). Median time of relapse after transplantation was 27 month.

Between autologous transplanted, one patient relapsed and from allogeneic transplanted 4 patients experienced their primary disease recurred. All patients who relapsed after HSCT died.

Two patients, who relapsed, were transplanted in CR1 and other cases were transplanted in CR2 or experienced more relapses before transplantation. Two Transplant related mortality, transplanted in CR3.

Discussion

Despite of successful experiences with HSCT in Acute Leukemia its role in APL, especially after ATRA and Arsenic era, remained controversial. Many authors suggest HSCT for patients in CR2 or more.(4,6-9) In our study we did HSCT for 6 cases in CR1. These patients referred by their primary physician due to their concern about optimal treatment after CR1.Between our cases we observed acceptable 3 years DFS and OS, which is comparable to other reports.(6,7,9)

In a large retrospective study from multicenter data collection by EBMT, if patients transplanted in first CR, 5 years LFS for autologous vs allogeneic transplantation was 69% and 68%. If patients received transplantation beyond CR1, this rate was 51% and 59%.(7)

If patient transplanted in molecular complete remission, some reports show equal efficacy of allogeneic HSCT and autologous HSCT.(9) Although autologous HSCT is easier to perform and TRM is lower than allogeneic transplantation,(10) but relapse rate is higher in acute leukemia. So to prevent excess relapse if we choose Autologous stem cell transplantation, we need a standard molecular method for detection of molecular remission and also reliable molecular method for patient follow up to detect molecular relapse before clinical relapse.

Because of obscure long term results with other methods of leukemia salvage it seems that HSCT is a possible choice for patients who relapsed after first line treatment of APL.

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