

Original Article

Hematopoietic Stem Cell Transplantation in Acute Promyelocytic Leukemia, Experience in Iran

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Abstract

Background: Acute promyelocytic leukemia is a rare indication for hematopoietic stem cell transplantation. Usually it is indicated as consolidation of salvage regimens following relapse. Here we report our experience with stem cell transplantation in acute promyelocytic leukemia patients.

Methods: Between 1989 and 2011, we performed 40 hematopoietic stem cell transplantation in first complete remission or relapsed acute promyelocytic leukemia patients. Median age of patients was 23.5 years. Patients received 11 autologous and 29 allogeneic hematopoietic stem cell transplantation from their HLA fully-matched sibling donors. Different conditioning regimens were applied. A total of 24 patients received hematopoietic stem cell transplantation who were in first complete remission and the remainder with a second or more complete remission.

Results: Hematopoietic stem cell engraftment was observed in all cases. There were no deaths prior to 100 days after hematopoietic stem cell transplantation. Acute graft versus host disease was mild to moderate in the majority of patients, whereas it was grade III in 4 patients. Chronic graft versus host disease was extensive in 2 cases. With a 4-year median follow up, the relapse rate was 25%. A total of 26 patients are alive. Five year overall survival was 65.5% and 46.8% for allogeneic and autologous hematopoietic stem cell transplantation, respectively.

Conclusion: Hematopoietic stem cell transplantation is an acceptable treatment for acute promyelocytic leukemia. Although there is a statistical difference for overall survival between allogeneic or autologous hematopoietic stem cell transplantation, the choice between autologous or allogeneic transplantation needs to have reliable methods for the detection of molecular remission before hematopoietic stem cell transplantation as well as close, reliable follow up of patients with clinical and molecular parameters.

Keywords: acute promyelocytic leukemia, allogeneic vs. autologous, stem cell transplantation

Introduction

Acute promyelocytic leukemia (APL) is a highly curable type of myeloid leukemia.¹⁻³ Despite improvements in prognosis with current treatments, 5% – 30% of patients relapse.^{3,4} Today, rarely is hematopoietic stem cell transplantation (HSCT) used for APL during the first complete remission (CR), however before implementation of new therapeutic agents (including All transretinoic acid and Arsenic trioxide), it was a common therapeutic modality. For relapse cases, Patients can achieve second 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,² but the choice of autologous versus allogeneic stem cell transplantation (in the presence of an HLA fully matched sibling donor) remains challenging. Because of the low numbers of cases who need HSCT and the difficulty for randomization of patients to allogeneic and autologous stem cell transplantation, conducting a prospective phase

III study is difficult. Conventionally, patients in molecular CR are candidates for autologous HSCT whereas for other cases must do search for allogeneic HSCT donors.^{2,8}

This study is a retrospective study on all cases of APL who underwent transplantation in our center.

Materials and Methods

Patient characteristics

We performed 40 HSCT for APL from 1989 until 2011. This cohort consisted of cases treated in other centers by conventional chemotherapy and/or All transretinoic acid (29 cases) who referred to us for HSCT as well as 11 patients treated with Arsenic trioxide at our center, as frontline therapy from the time of diagnosis. After relapse this group underwent salvage treatment again with Arsenic trioxide. When CR achieved, we performed hematopoietic stem cell transplantation in this group.

APL was diagnosed according to histomorphologic criteria. In 20 cases, APL was confirmed by RT-PCR and detection of PML-RARa.³ Cases that did not have RT-PCR results, were cases who were treated before the RT-PCR availability, or who were treated in other centers without cytogenetic or molecular confirmation. This cohort consisted of 22 females and 18 males. Median age was 23.5 (3 – 46) years. Between them, 24 patients received HSCT in the first CR, 8 in the second remission and 8 in the third remission. All cases transplanted in the first CR, had undergone previous treat-

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ment with chemotherapy and/or ATRA; and none of them were treated with arsenic trioxide. Regarding remission status at transplantation time, 9 out of 11 autologous transplanted patients were in the first CR, and 15 of 29 allogeneic transplanted patients were in the first CR.

Graft type and conditioning regimens

Graft type consisted of 29 allogeneic transplantations from HLA fully matched sibling donors and 11 autologous stem cell transplantations. In case of allogeneic transplantation, there were 11 female and 18 male donors. All patients and donors were screened for Hepatitis B and C, HIV and cytomegalovirus (CMV) before HSCT. All recipients and donors were CMV positive before HSCT.

The conditioning regimen for allogeneic transplantation was either Busulfan and cyclophosphamide (29 cases) or fludarabine and busulfan (3 cases). For autologous HSCT, we used cyclophosphamide, cytarabine and etoposide (2 cases) and busulfan/etoposide (7 cases) or busulfan/idarubicine (2 cases) as the conditioning regimen. Bone marrow was the source for HSCT in 8 cases and peripheral blood in 32 cases.

GVHD prophylaxis after HSCT was cyclosporine and methotrexate. For reporting and treatment of acute and chronic GVHD, we used standard scoring and treatment reported elsewhere (modified Seattle criteria).

Definition of outcomes and statistical analysis

CR was defined as the presence of normal peripheral blood cells and less than 5% promyelocytes and blasts in bone marrow at the time of HSCT. Neutrophil and platelet engraftment was defined as 3 consecutive days of ANC $>0.5 \times 10^9/L$ and platelet more than $20 \times 10^9/L$.

Overall survival (OS) was defined as the time from HSCT to death or the last follow up. Disease-free survival (DFS) was defined as the time from HSCT to relapse, death, or last follow up. We used the Kaplan-Meier method for survival analysis.

Results

HSCT was successful in all patients and engraftment was observed in all patients. The median time to neutrophil and platelet engraftment were 12 (9–34) and 18 (9–41) days post-HSCT.

Acute GVHD occurred in 18 cases, which consisted of grade I (2), grade II (12), and grade III (4) acute GVHDs in allogeneic transplanted patients. Chronic GVHD was observed in 9 cases. The maximum grade of chronic GVHD was limited in 7 cases and extensive in 2 cases.

Patients were followed for a median of 4 years (1.5 months - 16 years). Overall, 14 (35%) patients died and 26 (65%) survived. The cause of death was relapse in 8 cases and complications due to transplantation (GVHD and infection) in 6 other cases. From autologous transplanted cases, a total of 3 relapsed, whereas 7 allogeneic transplanted patients relapsed. DFS analysis showed that 2 year disease-free survival rate was $74.2\% \pm 8.4\%$ for allogeneic and $72.7\% \pm 13.4\%$ for autologous transplantations (Figure 1). This rate for 5 years was $61.8\% \pm 9.6\%$ for allogeneic and $51.9\% \pm 15.7\%$ for autologous cases ($P=0.64$). The majority of relapses occurred in the bone marrow. One patient relapsed in the bone marrow, underwent salvage treatment with arsenic trioxide and then experienced CNS relapse.

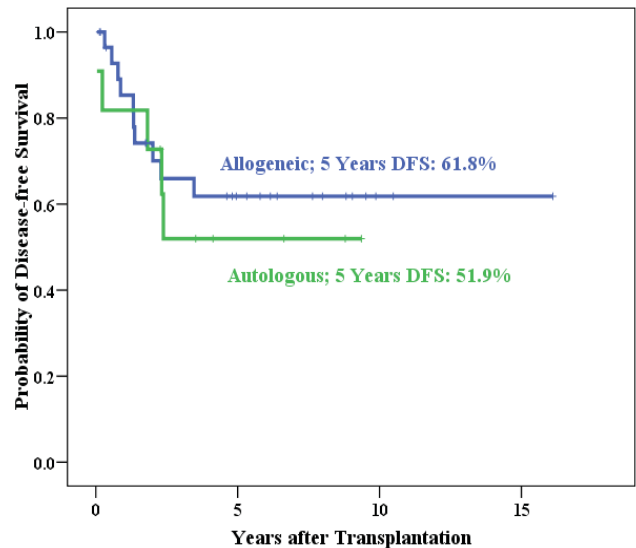


Figure 1. DFS for APL patients who underwent transplantation in CR.

We compared OS for allogeneic and autologous HSCT (Figure 2). Survival analysis showed 2-year OS was $77.9\% \pm 8\%$ for allogeneic transplanted cases and $72.7\% \pm 13.4\%$ for autologous cases, which difference was not statistically significant. The 5 year OS was $65.6\% \pm 9.4\%$ for allogeneic cases and $46.8\% \pm 17.6\%$ for autologous recipients.

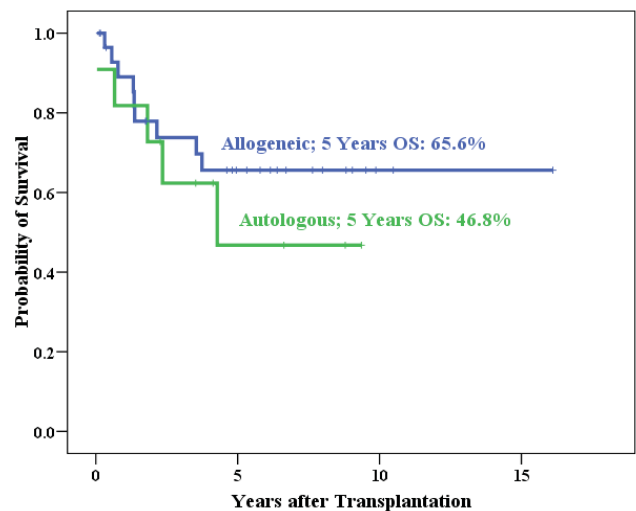


Figure 2. OS analysis for APL.

Discussion

Despite successful experiences with HSCT in acute leukemia, its role in APL, especially after the ATRA and arsenic era, remains controversial. Many authors suggest HSCT for patients in 2 or more CR.^{4,6-9} In our study, we performed HSCT for 24 cases who were in first CR. These patients were referred by their primary physicians due to concerns about optimal treatment after the first CR or were referred before ATRA or arsenic became available in our country. Additionally, many were transplanted before accurate molecular or cytogenetic diagnosis. We observed acceptable 2 and 5 years DFS and OS, which was comparable to other reports.^{6,7,9}

In a large retrospective study from multicenter data collection by

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EBMT, if patients transplanted in first CR, the chance of 5-year LFS for autologous vs. allogeneic transplantation were 69% and 68%, respectively. If patients received transplants beyond the first CR, this rate decreased to 51% and 59%.⁷ One reason for our good results was the higher number of first CR patients in our cohort. Another reason was relatively younger age of our patients.

If patients underwent transplantation in molecular CR, some reports have shown equal efficacy between allogeneic and autologous HSCT.⁹ Although autologous HSCT is easier to perform and transplant related mortality is lower than allogeneic transplantation,¹⁰ however, the relapse rate is higher in acute leukemia. Thus, to prevent relapse in autologous stem cell transplantation, a standard molecular method for detection of molecular remission and reliable molecular method for patient follow up to detect molecular relapse before clinical relapse are needed.

In our study, the majority of patients who received autologous HSCT were in the first CR (9 out of 11 cases) but only half of the allogeneic transplanted patients were in the first CR. Although our analysis did not show statistically significant OS and DFS differences between allogeneic and autologous HSCT, this confounding factor may affect our results. Because of obscure long-term results with other methods of leukemia salvage, it seems that HSCT is a possible choice for patients who relapse after first line treatment for APL.

References

1. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Woods WG, et al. All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. *Blood*. 2002; **100**: 4298 – 4302.
2. Sanz M, Grimwade D, Tallman M. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European Leukemia Net. *Blood*. 2009; **113**: 1875 – 1891.
3. Ghavamzadeh A, Alimoghaddam K, Rostami S, Ghaffari SH, Jahani M, Iravani M, et al. Phase II study of single-agent arsenic trioxide for the front-line therapy of acute promyelocytic leukemia. *J Clin Oncol*. 2011; **29**: 2753 – 2757.
4. Tallman MS. Treatment of relapsed or refractory acute promyelocytic leukemia. *Best Pract Res Clin Haematol*. 2007; **20**: 57 – 65.
5. Douer D, Tallman MS. Arsenic trioxide: new clinical experience with an old medication in hematologic malignancies. *J Clin Oncol*. 2005; **23**: 2396 – 2410.
6. Thirugnanam R, George B, Chendamarai E, Lakshmi KM, Balasubramanian P, Viswabandya A, et al. Comparison of clinical outcomes of patients with relapsed acute promyelocytic leukemia induced with arsenic trioxide and consolidated with either an autologous stem cell transplant or an arsenic trioxide-based regimen. *Biol Blood Marrow Transplant*. 2009; **15**: 1479 – 1484.
7. Sanz MA, Labopin M, Gorin NC, de la Rubia J, Arcese W, Meloni G, et al. Hematopoietic stem cell transplantation for adults with acute promyelocytic leukemia in the ATRA era: a survey of the European Cooperative Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2007; **39**: 461 – 467.
8. Tallman M, Altman J. How I treat acute promyelocytic leukemia. *Blood*. 2009; **114**: 5126 – 5135.
9. deBotton S, Fawaz A, Chevret S, Dombret H, Thomas X, Sanz M, et al. Autologous and allogeneic stem-cell transplantation as salvage treatment of acute promyelocytic leukemia initially treated with all-trans retinoic acid: a retrospective analysis of the European Acute Promyelocytic Leukemia Group. *J Clin Oncol*. 2005; **23**: 120 – 126.
10. Gorin NC. Autologous stem cell transplantation in acute myelocytic leukemia. *Blood*. 1998; **92**: 1073 – 1090.