

Allogeneic stem cell transplantation outcome in acute lymphoblastic leukemia patients

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Abstract

Introduction: Despite achievement to complete remission (CR) with current treatments and new multiple chemotherapeutic agents in Acute Lymphoblastic Leukemia (ALL) patients, the majority of them still relapse during long-term follow-up. The use of post-remission therapy will reduce early relapse in these cases, but the best option is still debatable.

Patients and Methods: In this retrospective review, we assessed the outcome of allogeneic hematopoietic stem cell Transplantation (HSCT) in ALL patients treated in our center. All cases received cyclophosphamide and busulfan as conditioning regimen, cyclosporine A and methotrexate for graft versus host disease prophylaxis (GVHD) and trimethoprim/sulfamethoxazole, acyclovir and fluconazol as prophylaxis of bacterial / viral and fungal infections.

Results: From March 1991 till August 2011, 446 ALL patients with a median age of 20 (range: 2 -53) years old underwent allogeneic HSCT. The male to female ratio was 300/146. At the time of transplantation 63 % of cases were in first CR, 23 % in second CR and 6% in third CR. Thirty eight (9%) patients were transplanted in primary induction failure or relapse. Sources of hematopoietic stem cell included peripheral blood (n=412, 92.3%), bone marrow (n=23, 5.1%), cord blood (n=8, 1.7%) and peripheral blood with bone marrow (n=3, 0.9%). Almost 93.2% of patients received stem cells from their HLA- identical siblings. HLA-mismatched sibling or other relatives, HLA-matched other relative and HLA-mismatched unrelated donors were 3.4%, 2% and 1.4%, respectively. Female patients received stem cells from 16% of female and 17% of male donors. Male patients received stem cells from 26% of female and 41% of male donors. The median time of neutrophil recovery was 16 (range: 6-58) days and platelet recovery was 12 (range: 9-43) days. Relapses occurred in 106 (24%) patients. 18-month LFS and OS were 58.9% (SE: 2.6%) and 68.1% (SE: 2.5%), respectively.

Conclusion: According to these results, allogeneic HSCT as a post-remission therapy can improve OS and DFS in ALL patients with a reduction in relapse rate.

Keywords: Acute Lymphoblastic Leukemia, Allogeneic, Post-Remission Maintenance Therapy, Hematopoietic Stem Cell Transplantation (HSCT).

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Introduction

Acute Lymphoblastic Leukemia (ALL) is much harder to treat in adults than in children. Although with current treatments and new multiple chemotherapeutic agents, 80- 90% of ALL cases achieve complete remission, the majority of patients still relapse during long term follow-up. (1-3). Post-remission

maintenance therapy is critical point in the treatment of ALL. It includes consolidation / maintenance chemotherapy and allogeneic or autologous stem cell transplantation. Recently, new immunotherapeutic agents like monoclonal antibodies have been used successfully in the treatment of special subtypes of ALL like Philadelphia positive cases. Without post-

remission maintenance therapy, most of ALL cases will relapse early (4). Post-remission therapy should be done to achieve best treatment results, but the best option is still debatable. Despite too many chronic illnesses and morbidities which will occur for ALL children in lifelong period and years after treatment (3), the cure rate is acceptable in children rather than adults (1, 5). ALL treatment in adults is still a point of challenge. Hematopoietic stem cell transplantation (HSCT) provides the most potent anti-leukemic effect of any post-remission therapy in adults with ALL. Allogeneic HSCT can cure some patients with ALL but the complications like graft-versus-host disease (GvHD), transplant-related mortality (TRM) and relapse are still problematic. On the other hand, recent use of minimal residual disease (MRD) detection in risk classification of ALL changed the point of view in the use of allogeneic HSCT for the treatment of ALL patients. In MRD positive patients HSCT is still the best choice of treatment in both standard and high risk patients. Some trials have confirmed that the use of allogeneic HSCT is a reasonable option for the patients with ALL in the first complete remission (CR1), while it remains controversial in standard-risk patients. Allo-HSCT after first complete remission has been shown to decrease the relapse rate among patients (10). Although allo-HSCT is a suitable choice for prevention of relapse after CR1 in ALL patients, it still has own complications including toxicities from the conditioning regimen and transplant-related morbidities. Use of newly reduced-intensity conditioning (RIC) regimens and alternative stem cell sources like cord blood cells improve these restrictions (11). New techniques in stem cell harvesting, preservation and transplantation along with precise molecular and cytogenetic studies, as well as use of stem cells in gene therapies open a new window to best results of HSCT for ALL treatment. Detection of minimal residual disease can predict the results of allogeneic HSCT in ALL patients (12). In high-risk ALL patients such as Philadelphia positive (Ph+) cases, we must use allogeneic stem cell transplantation as much as possible. Recent studies are based on new approaches to overcome allogeneic HSCT restrictions, especially relapse after HSCT in ALL patients.

In this retrospective review, we attempt to assess the outcome of allogeneic HSCT without total body irradiation (TBI) conditioning regimens in ALL patients treated in the Hematology-Oncology and Stem Cell Transplantation Research center, affiliated to Tehran University of Medical Science

Patients and methods

Patients: The analysis includes ALL patients (Adults and children) underwent allogeneic HSCT at the Hematology-Oncology and Stem Cell Transplantation Research Center between 1991 and 2011.

Conditioning Regimens: All patients received endoxan (cyclophosphamide) and busulfan as our center-approved protocol for conditioning regimen utilized for allogeneic HSCT in ALL. They were given endoxan (cyclophosphamide) 60 mg/kg for 2 days and busulfan 4 mg/kg for 4 days. Antithymocyte globulin (ATG 2.5 mg daily for 4 days) was added to the regimen of patients who received haploidentical HSCT.

Stem cell source: In most patients, peripheral blood stem cells were used as the stem cell source. Bone marrow and cord blood were two other sources of stem cells.

Engraftment: Neutrophil engraftment was defined as the first of three consecutive days on which the absolute neutrophil exceeds $500 \times 10^9/L$. Platelet engraftment was defined as the first of seven days with platelet counts of $> 50,000 \times 10^9/L$ without substitution. Chimerism analysis (STR) was used to confirm engraftment of donor cells over time.

GvHD prophylaxis: Patients received cyclosporine A and methotrexate for GvHD prophylaxis.

Infection prophylaxis: Patients received trimethoprim/Sulfamethoxazole, fluconazole and acyclovir as prophylaxis of bacterial, viral and fungal infections. They received irradiated packed cell or platelet as supportive care when needed. However, supportive cares and infection prophylaxis (antimicrobial, viral, fungal) improved over the time, but all patients treated in the same isolated, HEPA-filtered rooms in one center.

Definitions: Overall survival (OS) was measured from the time of transplantation until death or last follow-up. TRM was defined as death without evidence of relapse. Leukemia-

free survival (LFS) includes patients alive without relapse. Relapse was defined as hematologic and pathologic recurrence of leukemia.

Statistics: The data were analyzed for patients who achieved CR, progression-free survival (PFS), overall survival (OS), relapse rate, TRM and causes of death.

Results

From March 1991 till August 2011, 446 adults and children with ALL underwent allogeneic HSCT in this center. The median age of patients was 20 (range: 2 -53) years old. The male to female ratio was 300/146.

Sixty-three percent of patients were in first complete remission at the time of transplantation. Twenty-three percent and 6% of patients were in second and third complete remission, respectively. Thirty eight (9%) patients were transplanted in primary induction failure or relapse.

Sources of hematopoietic stem cell include peripheral blood (n=412, 92.3%), bone marrow (n=23, 5.1%), cord blood (n=8, 1.7%) and peripheral blood with bone marrow (n=3, 0.9%). Almost 93.2% of patients received stem cells from their HLA- identical siblings. HLA-mismatched sibling or other relatives, HLA-matched other relative and HLA-mismatched unrelated donors were 3.4%, 2% and 1.4%, respectively. Female patients received stem cells from 16% of female and 17% of male donors. Male patients received stem cells from 26% of female and 41% of male donors.

Stem cell harvest was successful in all of these patients. All of patients had successful engraftment procedure.

The median time of neutrophil and platelet recovery was 16 (range: 6-58) and 12 (range: 9-43) days, respectively.

Relapses occurred in 106 (24%) patients.

18-month LFS: 58.9% (SE: 2.6%)

18-month OS: 68.1% (SE: 2.5%)

Discussion

Consolidation chemotherapy, autologous hematopoietic cell transplantation (HSCT) and allogeneic HSCT are potential treatment alternatives for post-remission therapy in adult acute lymphoblastic leukemia (ALL), but there is actual uncertainty about the optimal approach

for the treatment of ALL patients. Despite all these improvements in ALL treatment approximately half of adult ALL patients have long term survival (14, 15). Allogeneic stem cell transplantation (SCT) from HLA- matched sibling is shown as optimal post- remission therapy for the patients who are in first complete remission aged 15 years old and more in one meta-analysis (10). Another meta-analysis with intention to treat analysis on clinical trials.comparing allo-HSCT with autologous or chemotherapy, also confirmed significant event-free survival (EFS) in allogeneic patients (p=0.011) rather than autologous or chemotherapy. It had acceptable cost-effectiveness too. (16)

Study on MRD after transplantation showed significant difference on relapse rate and overall survival of MRD positive patients before transplantation. In order to reduce relapse rate after allogeneic HSCT must check the MRD status after transplantation. If it is positive, should consider prescribing DLI or other new drugs after transplantation (12). Hereby, we can overcome problem of relapse after allo- HSCT. For example, use of tyrosin kinase inhibitors before and after transplantation can improve survival and reduce relapse rate (17).

To assess the effect of matched sibling donor allogeneic HSCT in adults with ALL, we analyzed the results of allogeneic HSCT in our patients.

In Pidala study, HR of OS and DFS in donor group to no-donor group was 0.86 and 0.82, respectively (10).

Fortunately, almost all of our patients had a suitable donor. Our conditioning regimens do not include total body irradiation. Allogeneic HSCT can improve OS and DFS in ALL patients with a reduction in relapse rate.

References

1. Copelan EA, McGuire EA. The biology and treatment of acute lymphoblastic leukemia in adults. *Blood*. 1995;85(5):1151-68. Epub 1995/03/01.
2. Laport GF, Larson RA. Treatment of adult acute lymphoblastic leukemia. *Semin Oncol*. 1997;24(1):70-82. Epub 1997/02/01.
3. Hoelzer D, Gokbuget N. New approaches to acute lymphoblastic leukemia in adults: where do we go? *Semin Oncol*. 2000;27(5):540-59. Epub 2000/10/26.
4. Lonsdale D, Gehan EA, Fernbach DJ, Sullivan MP, Lane DM, Ragab AH. Interrupted vs. continued

- maintenance therapy in childhood acute leukemia. *Cancer*. 1975;36(2):341-52. Epub 1975/08/01.
5. Faderl S, O'Brien S, Pui CH, Stock W, Wetzler M, Hoelzer D, et al. Adult acute lymphoblastic leukemia: concepts and strategies. *Cancer*. 2010;116(5):1165-76. Epub 2010/01/27.
 6. Ljungman P, Bregni M, Brune M, Cornelissen J, de Witte T, Dini G, et al. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe 2009. *Bone Marrow Transplant*. 2010;45(2):219-34. Epub 2009/07/09.
 7. Goldstone AH, Rowe JM. Transplantation in adult ALL. *Hematology Am Soc Hematol Educ Program*. 2009:593-601. Epub 2009/12/17.
 8. Yanada M, Matsuo K, Suzuki T, Naoe T. Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a metaanalysis. *Cancer*. 2006; 106(12):2657-63. Epub 2006/05/17.
 9. Ram R, Gafter-Gvili A, Vidal L, Paul M, Ben-Bassat I, Shpilberg O, et al. Management of adult patients with acute lymphoblastic leukemia in first complete remission: systematic review and meta-analysis. *Cancer*. 2010;116(14):3447-57. Epub 2010/06/22.
 10. Pidala J, Djulbegovic B, Anasetti C, Kharfan-Dabaja M, Kumar A. Allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia (ALL) in first complete remission. *Cochrane Database Syst Rev*. 2011(10):CD008818. Epub 2011/10/07.
 11. Paulson K, Szwajcer D, Seftel MD. The role of allogeneic stem cell transplantation for adult acute lymphoblastic leukemia. *Transfus Apher Sci*. 2011;44(2):197-203. Epub 2011/02/19.
 12. Spinelli O, Peruta B, Tosi M, Guerini V, Salvi A, Zanotti MC, et al. Clearance of minimal residual disease after allogeneic stem cell transplantation and the prediction of the clinical outcome of adult patients with high-risk acute lymphoblastic leukemia. *Haematologica*. 2007;92(5):612-8. Epub 2007/05/10.
 13. Onishi Y, Sasaki O, Ichikawa S, Inokura K, Katsuoka Y, Ohtsuka Ohba R, et al. Favorable outcome of unrelated cord blood transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2011;17(7):1093-7. Epub 2011/02/01.
 14. Fielding AK. Current therapeutic strategies in adult acute lymphoblastic leukemia. *Hematol Oncol Clin North Am*. 2011;25(6):1255-79, viii. Epub 2011/11/19.
 15. Ribera JM. Advances in acute lymphoblastic leukemia in adults. *Curr Opin Oncol*. 2011;23(6):692-9. Epub 2011/09/06.
 16. Orsi C, Bartolozzi B, Messori A, Bosi A. Event-free survival and cost-effectiveness in adult acute lymphoblastic leukaemia in first remission treated with allogeneic transplantation. *Bone Marrow Transplant*. 2007;40(7):643-9. Epub 2007/07/31.
 17. Khaled SK, Thomas SH, Forman SJ. Allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia in adults. *Curr Opin Oncol*. 2012;24(2):182-90. Epub 2012/01/12.