

Autologous Hematopoietic Stem Cell Transplantation in Acute Lymphoblastic Lymphoma

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Abstract

Introduction: Despite high remission rates in acute lymphoblastic leukemia (ALL) patients after induction chemotherapies, post-remission therapies needed to avoid relapse. Autologous hematopoietic stem cell transplantation (HSCT) role in the treatment of ALL is still controversial. In this retrospective study, we assessed the outcome of auto-HSCT in the treatment of ALL patients treated in this center.

Patients and methods: From March 1991 to December 2005, 25 ALL patients with no suitable donors underwent auto-HSCT. All patients received Endoxan, Cytarabine and Etoposide according to the center-approved protocol for conditioning regimen. The sources of graft were peripheral blood and bone marrow. The patients hospitalized in same special rooms and circumstances. The Kaplan-Meier method was used for the data analysis.

Results: The median age of patients was 18 years old (range: 8-54). The majority of patients were male. The mean number of WBC count at diagnosis was $48.5 \times 10^3/\mu\text{l}$. Seventy-two percent of patients received autologous HSCT in CR1. Eighty percent of ALL subtypes were B-lineage. Primary central nervous system involvement at diagnosis time was observed in 16%. The median number of harvested nucleated cells: $4.16 \times 10^8/\text{kg}$, MNC: $3.69 \times 10^8/\text{kg}$, CD3: $1.52 \times 10^8/\text{kg}$ and CD34+ cells were $0.07 \times 10^8/\text{kg}$ of recipient weight. The median time of neutrophil and platelet recovery was 12 (range: 9-37) and 17 (range: 10-74) days, respectively. The median follow-up period for survivors was 12 months (range: 4-110 months). Relapse occurred in 17(68%) of patients. Relapse was the only cause of death in patients. The one-year overall survival (OS) and disease-free survival (DFS) were 46% (SE: 10.2%) and 38% (SE: 9.9%), respectively. Age at transplantation and WBC count at diagnosis time had no significant effect on DFS and OS. Source of stem cells had no significant effect on survival outcome too. Transplantation in first complete remission had the best survival outcome ($p=0.01$).

Conclusion: The role of autologous HSCT in ALL patients who do not have suitable donors is still inferior to chemotherapy alone. Regarding poor results of the current study, further studies on the role of auto-HSCT in specific subtypes of ALL patients is suggested.

Keywords: Precursor Cell Lymphoblastic Leukemia-Lymphoma, Stem Cell Transplantation, Disease-Free Survival

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Introduction

Acute lymphoblastic Leukemia (ALL) is a heterogeneous disease that constitutes about 20% of newly diagnosed leukemias in adults. Despite high remission rates with new chemotherapy agents (80–90%), the 4-5 years overall survival (OS) rate in adults are within

the 30–40% range (1). In the last decade, the treatment outcome of these patients has been substantially improved mainly by the intensification and optimization of chemotherapy, the risk-adapted use of stem cell transplantation, and improved supportive cares (2-3). Autologous hematopoietic stem cell

transplantation (HSCT) in post-remission treatment of ALL has been used for many years, but its effectiveness is still debatable. In some studies autologous HSCT has superiority than conventional chemotherapy on patients' survival (4), whereas others emphasized that despite the lower rate of transplant-related mortality (TRM) in autologous patients, the relapse rate is still significant (5). Some studies like the MRC/ Eastern Cooperative Oncology Group study also showed in adult patients with any risk groups, autologous HSCT has no favorable position rather than standard consolidation and maintenance therapy (6). Studies from the Center for International Blood and Marrow Transplant Research have also confirmed the superiority of allogeneic over autologous HSCT (7-8). Allogeneic HSCT was first used for relapsed ALL patients (9). Although allogeneic HSCT is associated with higher TRM, especially in older patients due to drug toxicities, complications of acute and chronic graft-versus-host disease (GvHD), and post-transplant delayed immune system reconstitution, many working groups do not recommend autologous HSCT in the treatment of ALL patients (10-12). In this study, we retrospectively reviewed the results of autologous HSCT undertaken in patients with ALL at Hematology- Oncology and Stem Cell Transplantation Research center, affiliated to Tehran University of Medical Sciences.

Patients and Methods

This analysis includes ALL patients (children and adults) who underwent autologous HSCT at Hematology- Oncology and Stem Cell Transplantation Research Center between March 1991 and December 2005.

Treatment

All patients received Endoxan, Cytarabin and Etoposide as our center-approved protocol for conditioning regimen. They were taken Endoxan (Cyclophosphamide) 60 mg/kg for 1 day on day 12 before transplantation, for stem cell mobilization and then Granulocyte-Colony Stimulating Factor (GCSF) 5 µg/kg for 4 days (-7 to -4) for peripheral blood stem cell harvesting. They also received Vp16, 500 mg/m² for 3 days (-3 to -1), Cytosar (ARA-C) 1500 mg/m² for 3 days (-3 to -1) and Endoxan

(Cyclophosphamide) 60 mg/kg for 2 days (-3, -2). Between 1991 and 1993, bone marrow was the major source of stem cells for twelve transplantations and from 1996 to 2005, peripheral blood was used in thirteen patients. Although supportive cares and infection prophylaxis (antimicrobial, viral, fungal) improved over the time, all patients were treated in isolated, High-Efficiency Particulate Air (HEPA) - filtered rooms in one center and same circumstances. They received irradiated packed cell or platelet as supportive care when needed.

Definitions

Overall survival (OS) was measured from the time of transplantation until death or last follow-up. Leukemia-free survival (LFS) includes patients alive without relapse. Relapse was defined as hematologic recurrence of leukemia.

Statistics

Categorical data were presented with frequencies and percentages, while continuous variables were described using median and range. Overall survival (OS) and disease-free survival (DFS) curves were calculated by the Kaplan-Meier method and groups were compared using the Log-Rank test statistic.

Results

Patients and Treatments

This study includes 25 ALL patients who underwent autologous HSCT between March 1991 and December 2005. Demographic characteristics of patients are summarized in Table 1. The median age of patients was 18 years old (range: 8 -54). The majority of patients were male. The mean number of WBC count at diagnosis was $48.5 \times 10^3/\mu\text{l}$. Seventy-two percent of patients received autologous HSCT in CR1, 24% in CR2, whereas one patient was in primary induction failure (PIF). Among patients tested (10 of 25) for immunophenotype, 80% were of B- lineage versus 20% of T- lineage ALL cases. Patients were referred from other centers did not have cytogenetic tests. BCR-ABL detection test was done only on ten patients, three of whom were positive (3/10: 30%). Primary central nervous system involvement at diagnosis time was

observed in 4 patients (16%). The median follow-up period for survivors was 12 months (range: 4 -110 months). Among them, three cases (75%) relapsed. Generally, patients with no central nervous system (CNS) involvement received cranial irradiation and intrathecal chemotherapy for prophylaxis of CNS involvement. Stem cell harvest was successful in all of these patients. The median number of harvested nucleated cells: 4.16×10^8 /kg, MNC: 3.69×10^8 /kg, CD3: 1.52×10^8 /kg and CD34+ cells were 0.07×10^8 /kg of recipient weight. Potential sources of graft were bone marrow (n=12) and peripheral blood (n=13). The median time of neutrophil and platelet recovery was 12 (range: 9-37) and 17 (range: 10-74) days, respectively. One patient failed to engraft by 100 days after transplantation, and the other one did not achieve platelet engraftment. One patient had never dropped platelets below than $20 \times 10^3/\mu\text{l}$.

Table 1. The characteristics of ALL patients who underwent autologous HSCT

Characteristic	Number (%)
Total no of patients	25 (100)
Age at HSCT, years	
<18	11 (44)
≥18	14 (56)
Sexuality	
Male	13 (52)
Female	12 (48)
Disease Status at HSCT	
CR1	18 (72)
CR2	6 (24)
PIF	1 (4)
Philadelphia Chromosome+	3 (30)
Immunophenotype	
B-lineage	8 (32)
T-lineage	2 (8)
Not tested	15 (60)
CMV Serostatus	
Negative	7 (28)
Positive	18 (72)

+ Philadelphia chromosome tested in 10 patients

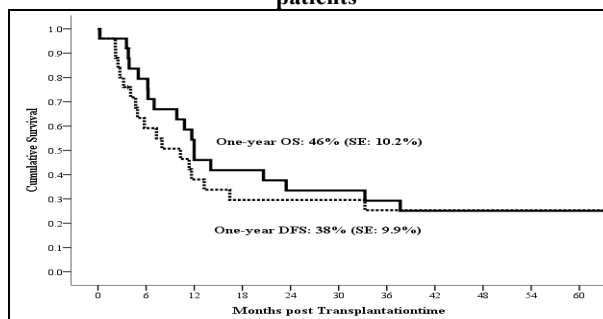
TRM and relapse

Relapse occurred in 17 (68%) of patients. Seven patients (28%) were alive by the end of the follow-up period. Relapse was the only cause of death in patients except one who was a 13- year old male patient. He died on +7 day because of drug toxicity and cardiac arrest.

Survival

One - year overall survival (OS) was 46% (SE: 10.2%). One - year disease free survival (DFS) was 38% (SE: 9.9%) (Fig.1).

Fig 1. One-year DFS and OS in autologous HSCT ALL patients



Age at transplantation had no significant effect on DFS and OS (P value= 0.74, 0.58), respectively. The effect of age and sex on survival is shown in Fig.2. There is no significant relationship between the WBC count at diagnosis (less or more than $50 \times 10^3/\mu\text{l}$) and the transplantation outcome (DFS: P value= 0.67, OS: P value= 0.79). Source of stem cells (peripheral blood vs. bone marrow) had no significant effect on survival outcome (DFS: P value= 0.51, OS: P value= 0.52). Transplantation in first complete remission (CR1) had the best survival outcome (P value= 0.01). (Fig.3).

Fig 2. Age and sex effects on DFS in autologous HSCT ALL patients

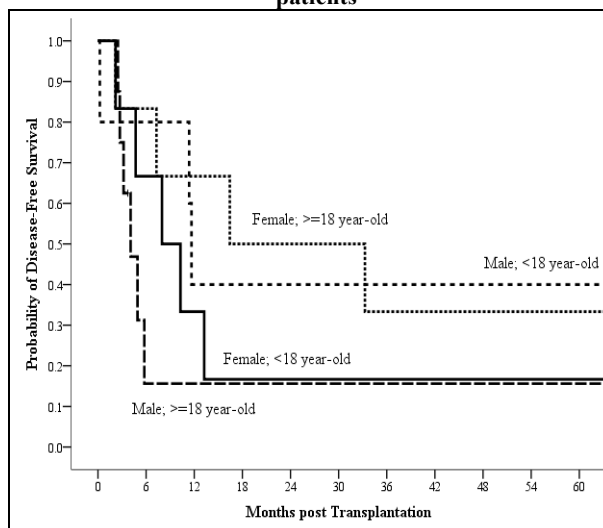
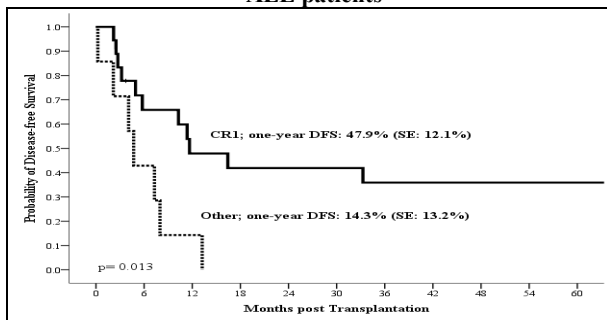


Fig 3. The effect of CR on survival in autologous HSCT ALL patients



Discussion

Despite intensive investigation to date, the role of autologous HSCT as post-remission therapy in ALL is still under debate (13). Although allogeneic HSCT is associated with higher TRM, especially in older patients due to drug toxicities, complications of acute and chronic graft-versus-host disease (GvHD) and post-transplant delayed immune system reconstitution, many working groups do not recommend autologous HSCT in the treatment of ALL patients (10-12). Several studies compared autologous HSCT versus chemotherapy in patients without a suitable donor. Most studies demonstrated that autologous HSCT had no better results or even inferior outcome compared to conventional chemotherapy for adult patients (6, 14-17), while some studies found that autologous HSCT was superior to conventional chemotherapy (4, 18). Autologous HSCT is an optional post-remission therapy for ALL patients with no human leukocyte antigen (HLA)-identical sibling or unrelated donors and patients with contraindications for allogeneic HSCT or not interested in the use of other stem cell sources like umbilical cord blood or conventional chemotherapies. Autologous HSCT is obviously inferior to allogeneic because of higher relapse rates, lack of Graft-versus-Leukemia (GvL) effect and contamination with leukemic blasts, albeit these results may be due to selecting high-risk patients for autologous HSCT too (19). Maintenance therapy after autologous stem cell transplantation significantly increases the OS rather than only chemotherapy even after excluding the Philadelphia positive patients (4). There are no significant differences between sex and white blood cells (WBC) count at diagnosis on survival of patients that might be

due to low study power of our research. We did not have enough tested subtypes of ALL allowing us to compare them like Zhang YL, et al. study which showed significant effect of these factors in the B-ALL group (20). Although age alone had no significant effect on survival with this sample size, we found interesting results in the analysis of two variables included sex and age. As shown in Figure 2, DFS and OS was better in females ≥ 18 years old than male < 18 during three years after transplantation and then the ratio became inverted in this study. Again, we emphasize the small number of cases should be mentioned in these results interpretation.

Due to lack of HLA-identical donor, most of our patients underwent autologous HSCT. One of them had HLA-identical sibling donor but unfortunately the donor was HCV-RNA positive. At that time, we had no cord blood bank or unrelated stem cell donor banks for transplantation. The patients were referred here from other centers had no cytogenetic or flow cytometry tests. Maintenance therapy is still standard for ALL patients and the absence of this treatment can lead to poor patient outcomes (13). In this study, the poor survival rates might be due to lack of maintenance therapy after transplantation. Like the study conducted by Chim CS et al. (21), thirty percent of patients were found to be Philadelphia positive. All Philadelphia positive patients relapsed, while only 57% of Ph negative patients experienced relapse. So, according to above-mentioned findings Philadelphia chromosome plays an important role in the prognosis of ALL. In case of availability of suitable donors, allogeneic HSCT is recommended for Philadelphia positive patients (22). The better survival in patients transplanted in CR1 confirms the importance of time to make decision for transplantation in ALL patients (7, 12).

However, the question about autologous HSCT advantages in ALL patients still remains controversial. Autologous HSCT in combination with maintenance chemotherapy may improve OS and DFS in patients without suitable donors and high-risk ALL patients (4). The MRC/ Eastern Cooperative Oncology Group study in all-risk groups of adult patients also showed that autologous HSCT has no significant efficacy compared to standard

consolidation and maintenance therapy (6). Studies from the Center for International Blood and Marrow Transplant Research have also confirmed the superiority of allogeneic over autologous HSCT (7-8). Dhedin et al in a report released by French LALA group showed that autologous HSCT had a reduced incidence of relapse and better disease-free survival compared to the conventional chemotherapy during the 10-year follow-up (18). Compared to our unpublished data gathered from ALL patients who treated with conventional chemotherapy in this center, one- year overall survival and disease- free survival in chemotherapy patients were 84.1% (SE: 3.8%) and 61.5% (SE:5%), respectively which showed better survival than autologous patients (OS: 46% (SE: 10.2%), DFS: 38% (SE:9.9%)). Our study confirmed the conclusions of other studies that showed no advantage for autologous HSCT over conventional maintenance chemotherapy in ALL patients (6). The results of this study should be interpreted cautiously because of retrospective analysis, small number of patients and no risk stratification based on Minimal Residual Disease (MRD). Regarding poor results of the current study, further studies on the role of autologous HSCT in specific subtypes of ALL patients is required.

Conclusion

The role of autologous HSCT in ALL patients who do not have suitable donors is still inferior to chemotherapy alone. Regarding poor results of the current study, further studies on the role of auto- HSCT in specific subtypes of ALL patients is suggested

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