A Comparison of Allogeneic and Autologous Hematopoietic Stem Cell Transplantation for Acute Myeloblastic Leukemia

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Abstract

Introduction: Acute Myelogenous Leukemia (AML) is a clonal malignant disease of hematopoietic tissue. The early use of Hematopoietic Stem Cell Transplantation (HSCT) for AML was for patients with advanced stages of disease, usually while in relapse, in second or subsequent remission, or with resistant disease.

Patients and Methods: From March 1991 until February 2008, 356(65%) registered allogeneic transplantation and 192(35%) of registered autologous transplantation had comprehensive data available for analysis and were included in this study and all patients have followed through January 2008.

Result: In allogeneic and autologous groups, 263 (73.9%) and 160 (88.3%) patients were in first complete remission, respectively. The stem cells sources of transplantation in allogeneic recipients were Peripheral Blood (92.4%), Bone Marrow (7%), Bone Marrow combined Peripheral Blood (0.3%) and Cord Blood (0.3%). The source of stem cell transplantation for 157 (82.3%) autologous patients was Peripheral Blood, for 33(17.2%) patients was Bone marrow and there was one recipient (0.5%) with combined Peripheral Blood and Bone marrow. Totally, 279 (78.4%) allogeneic patients and 123 (64.1%) autologous patients were alive since the end of this study. Relapse was the most common cause of death in both groups. Five years Overall Survival (OS) and Disease Free Survival (DFS) in allogeneic patients were 70.6% and 62.3% (SE=3%) and in autologous patients were 53.6% and 46.8% (SE=5%, 4%). The median follow up time for this study was 1.5 years (19 months).

Conclusion: According to this study and our experience, the acceptable treatment for Acute Myeloblastic Leukemia, especially in first complete remission is allogeneic Hematopoietic Stem Cell Transplantation.

Keywords: Acute Myeloblastic Leukemia, Hematopoietic Stem Cell Transplantation, Allogeneic

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Introduction

Acute myelogenous leukemia (AML) is a clonal malignant disease of Hematopoietic tissue that is characterized by, accumulation of abnormal blastic cells, principally in the marrow and impaired production of normal blood cell. AML accounts for 15 to 20% of the acute leukemia in children and 80% of it in adults. It's slightly more common in males. A somewhat lower incidence is seen in persons of Asian descent.(1) Remission rates have improved dramatically but remission, 5-year survival and cure rates are most dependent on the patient's age when AML occurs.

Relapse in long- term survivors occurring as late as 8 years after remission has been reported in adults and after more than 16 years in children and always occurs in the marrow in adults and usually in the marrow in children. Better survival has been reported for young patients who have received allogeneic bone marrow transplantation in first remission.(1) The role of Hematopoietic Cell Transplantation (HCT) for AML has progressed from early reports of syngeneic marrow transplantation to the extensive data now available on allogeneic HCT from matched –sibling donors with evidence of a beneficial graft vs. leukemia (GVL) effect.(2) The early use of HCT for AML was for patients with advanced stages of disease, usually while in relapse, in second or subsequent remission, or with resistant disease. The first successful autologous hematopoietic cell transplantation for AML was reported in 1977.(1) Similar to the strategy with allogeneic HCT, autologous HCT was then used earlier in the clinical course of disease to enable high-dose consolidation therapy for patients who were in

complete remission and lacked a histocompatible sibling donor.(1)
We undertook a retrospective study of patients who underwent either autologous or allogeneic transplantation and analyzed the effect of several important factors including stem cell source, sexuality, age and disease status before receiving transplantation, karnofsky performance score at transplantation on survival.

Patients and Methods

Iran has a population of about 70 million people. The incidence of transplantable disease is estimated at about 2 per 100000 or 1400 patients per year. The cost of transplant procedures is borne by insurance companies and board of trustees.(3) This study includes patients with AML who underwent autologous or allogeneic transplantation from the year 1991 to 2008 in hematology-oncology and stem cell transplantation research center (HORCSCT) of Tehran university of medical sciences which is located in Shariati Hospital and established since 1991 and were reported to the CIBMTR(Central International Bone Marrow Transplantation Registry).(4) Atonal of 356 (65%) registered allogeneic transplantation and 192 (35%) of registered autologous transplantation had comprehensive data available for analysis and were included in the study. The pretransplantation statuses of patients were: first, second or third complete remission, primary induction failure and relapse. There were several sources for HSCT consist of Bone Marrow, Peripheral Blood, Bone Marrow associated with Peripheral Blood and Cord Blood.In this study Karnofsky scale (for recipient age >16 years) and lansky scale (for recipient age <16 years) describes the activity status of the recipient before transplantation

Statistical Analysis: Univariate probabilities of Disease Free Survival (DFS) and Overall Survival (OS) were calculated using the Kaplan-Meier estimator; the log-rank test was used for univariate comparisons.(5, 6) Chi-square test used in comparison of the rate between autologous and allogeneic patients who were in first complete remission. Relapse, disease free survival and overall survival after autologous versus allogeneic transplantation were evaluated in multivariate analyses using Cox proportional hazards regression to adjust for other potentially confounding differences between the cohorts.(5-7) Variables considered in multivariate analysis are as fallows: type of stem cell transplantation, age at stem cell transplantation, sexuality, karnofsky performance score at stem cell transplantation, graft source and disease status at stem cell transplantation.
End Points: The end points were Disease Free Survival (DFS) - Overall Survival (OS) and relapse. Relapse was defined as persistent or recurrent disease. Disease Free Survival was defined as survival without evidence of disease. For analysis of disease free survival, relapse, or death from any cause were considered as events. For analysis of overall survival, event were death from any cause.

Results

There were 356(190 males and 166 females) allogeneic stem cell transplantation patients available for analysis. The median age of allogeneic recipients was 27 years (range: 2 – 57 years). There were 263 (73.9%) allogeneic patients in first complete remission (CR1) before receiving HSCT. Fifty five (15.4%) allogeneic recipients were in second complete remission and 16 (4.5%) of them were in third complete remission. Just 6 (1.7%) patients were in first relapse before stem cell transplantation. we didn't have any patients in second relapse status in allogeneic group. Approximately 9 (2.5%) allogeneic patients were in primary induction failure. The stem cells source of transplantation for 330 (92.7 %) allogeneic recipients was Peripheral Blood and for 25 (7%) allogeneic recipients was Bone Marrow. Only 1 (0.3%) recipient in allogeneic group had Bone Marrow associated with Peripheral Blood as stem cell source. Also there was 1 (0.3%) patient with Cord Blood source of stem cell.(8) Two hundred thirty one (64.9%) of all allogeneic recipients had most karnofsky or lansky score between 90 to 100.

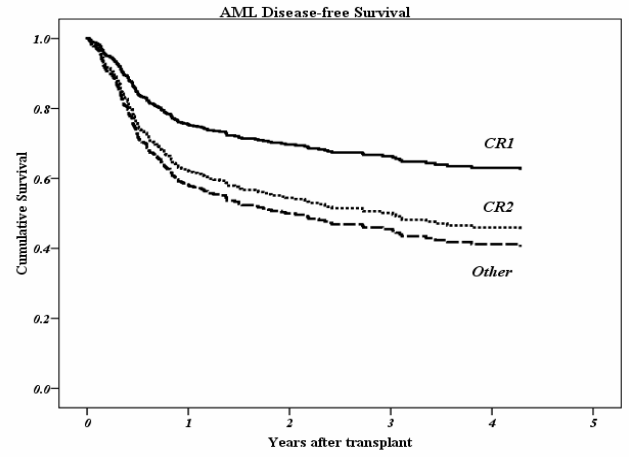

Figure 1. Probability of Disease-free survival by type of Disease status at transplant adjusted for graft type, Gender and Karnofsky performance score

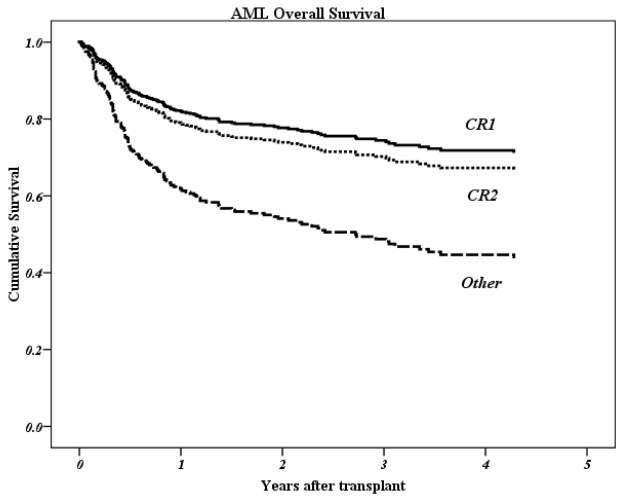

Figure 2. Probability of survival by type of Disease status at transplant adjusted for graft type, Gender and Karnofsky performance score

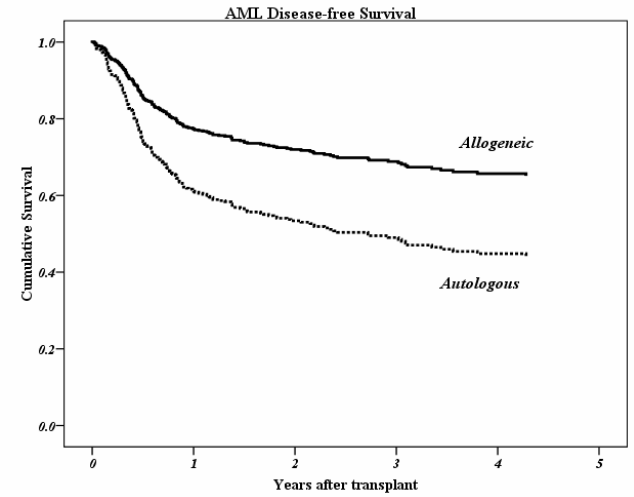

Figure 3. Probability of Disease-free survival by type of transplant adjusted for Gender, Karnofsky performance score and Disease status transplantation

Ninthy two (25.8%) recipients had karnofsky or lansky score between 80 to 90 and 26(7.3%) recipients had the score of lower than 80. At the end of this study, from 356 allogeneic recipients, Two hundred seventy nine (78.4%) patients were alive.

The common cause of death in allogeneic patients was relapse (31.2%). The second cause of death in 23 patients with allogeneic HSCT (31.2%) was Graft Versus Host Disease (GVHD). The other causes of death in allogeneic HSCT were infection (16.9%), intracranial hemorrhage (3.9%), cardiac

Table 1. Multivariate analysis of Relapse

Variables	Relative Risk of Relapse	p
Graft Type		
Allogeneic	1	
Autologous	3.12	<0.001
Age at Transplant		
<=16	1	
>16	1.19	0.389
Gender		
Male	1	
Female	0.69	0.031
Source of SCT		
Peripheral Blood	1	
Bone Marrow	1.18	0.497
Disease status at transplantation		
CR 1	1	
CR 2	2	0.002
Other	1.84	0.023
Karnofsky Score		
<= 80	1	
>80, <= 90	0.94	0.754
>90	0.95	0.904
Unknown	0.37	0.323

Table2. Multivariate analysis of Disease Free Survival

Variables	Relative Risk of treatment failure	p
Graft Type		
Allogeneic	1	
Autologous	1.91	<0.001
Age at Transplant		
<=16	1	
>16	1.35	0.097
Gender		
Male	1	
Female	0.79	0.11
Source of SCT		
Peripheral Blood	1	
Bone Marrow	1.22	0.34
Disease status at transplantation		
CR 1	1	
CR 2	1.68	0.008
Other	1.92	0.002
Karnofsky Score		
<= 80	1	
>80, <= 90	1.1	0.546
>90	1.19	0.563
Unknown	0.3	0.217

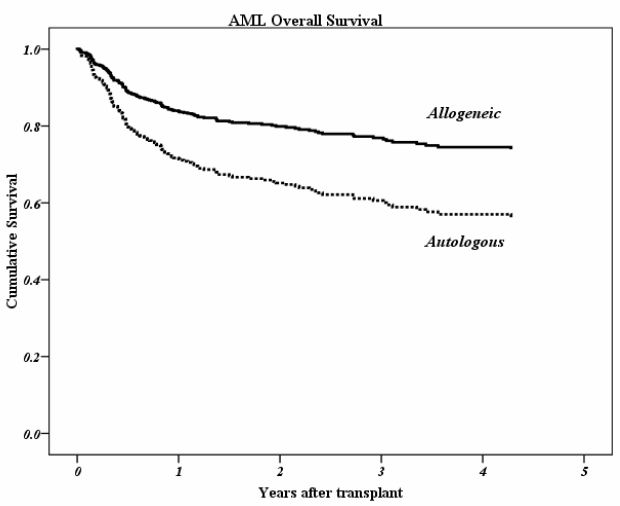

Figure 4. Probability of survival by type of transplant adjusted for Gender, Karnofsky performance score and Disease status transplantation

toxicity (2.6%), post transplant lymphoprolifrative disease (2.6%), pulmonary toxicity (2.6%), rejection (1.3%) and others (7.7%).

In autologous group, the median age of recipients was 22 years (range: 2 – 68 years). About 160 (88.3%) autologous recipients were in first complete remission status at the start of stem cell transplantation. Eighteen (9.4%) of them were in second complete remission status and eight (4.3%) ones were in third complete remission status. Just two (1%) autologous patients were in first relapse status and one (0.5%) of them was in second relapse status. The stem cells source of transplantation for 158 (82.3%) autologous patients was Peripheral Blood and for 33 (17.2%) patients were Bone Marrow. There was just one autologous patient (0.5%) with combined Peripheral Blood and Bone marrow as source of HSCT.(8) There was no Cord Blood HSCT for autologous group. One hundred eighteen (61.5%) of all autologous recipients had most karnofsky or lansky score between 90 to 100. Sixty-two (32.3%) recipients had karnofsky score between 80 to 90 and 7(3.6%) ones had karnofsky score of lower than 80. Finally 122 (63.9 %) of autologous patients were alive since the end of this study. Most important causes of death in 53 (76.8%) autologous patients were relapse, progression, and persistent disease. Six (8.7%) patients died on cause of infection, four patients (5.8%) died due to rejection, one patient (1.4 %) died due to Veno-Occlusive Disease and 2 patients (2.8%) died due to Vascular thromboembolic and DIC.

Disease Free- Overall Survival and relapse: One, three and five years probabilities of overall survival in patients who received allogeneic stem cells transplantation were 82%, -76% and 71% (SE=2%-3%-3%; P<0.0001) and in patients with autologous stem cells transplantation were 69%, 56% and 54% (SE=4%-4%-5%; P<0.0001), One, three and five years probabilities of DFS in patients who received allogeneic stem cell transplantation were 76%, 68% and 62% (SE=2%- 3%-3%) and in patients with autologous transplantation were 56%, 47% and 47% (SE=4%)(P<0.0001).

The relative risk of relapse in autologous recipients to allogeneic recipients was 3.12 (p<0.001) (Table 2).

Discussion

Hematopoietic stem cells transplantation is an option for some patients with acute myelogenous leukemia (AML). In this study approximately three fourth of all patients in allogeneic and autologous group received their stem cells transplantation in first complete remission.

Disease status at transplantation was so important where as the relative risk of relapse in patients who received their transplantation in second complete remission (RR=2; P=0.002)or in other statuses (RR=1.84; P=0.023) was greater than the patients who received transplantation in their first complete

Table3. Multivariate analysis of Overall Survival

Variables	Relative Risk of death (95% CI)	p
Graft Type		
Allogeneic	1	
Autologous	1.91	<0.001
Age at Transplant		
<=16	1	
>16	1.3	0.2
Gender		
Male	1	
Female	1.14	0.42
Source of SCT		
Peripheral Blood	1	
Bone Marrow	1.65	0.024
Disease status at transplantation		
CR 1	1	
CR 2	1.2	0.49
Other	2.43	<0.001
Karnofsky Score		
<= 80	1	
>80, <= 90	1.1	0.61
>90	1.11	0.77
Unknown	0.42	0.38

remission, as the relative risk of treatment failure in patients in second complete remission (RR=1.68; P=0.002) or in other statuses (RR=1.92; P=0.002) which were greater than the patients in first complete remission. (Table1, Table2, Figure1)

On the other hand, all of the patients who received stem cell transplantation in first complete remission had higher disease free survival (DFS) than transplant recipients who were in second complete remission (P=0.008) or in more advanced disease (P=0.002). (Table=2)

Surprisingly the present study revealed that there is no significant difference between relative risk of death in patients in first complete remission and second complete remission (RR=1.2; P=0.49) (Table3, Figure2).

There is no significant difference between relative risk of death for recipients with karnofsky or lansky score of lower than 80 with karnofsky or lansky score of 80 to 90 (RR=1.1; P=0.61) and upper than 90 (RR=1.1; P=0.77) (Table 3); as same as relative risk of treatment failure in karnofsky or lansky score of 80 to 90 (RR=1.1; P=0.546) and upper than 90 (RR=1.19; P=0.563) (Table2),also there is no sigcnificant difference between relative risk of relapse in karnofsky or lansky score of lower than 80 (RR=1) and karnofsky or lansky score of 80 to 90 (RR=0.94; P=754) and upper than 90 (RR=0.95; P=0.904). (Table1)

Multivariate analysis of Disease Free Survival found that autologous stem cell transplantation had inferior DFS than allogeneic one (P<0.001) (Figure3).

Also the Autologous stem cell transplantation had inferior OS than the Allogeneic one (P<0.001) (Figure 4)

As a result of this study, the relative risk of death, relapse and treatment failure in autologous recipients was significantly higher than the allogeneic recipients (P<0.001) (Table 1, 2, 3). In addition, one, three, and five years probabilities of overall survival in autologous patients were lower than allogeneic ones. It means that in this study the overall survival of allogeneic patients was higher than the autologous patients.(Figure 4)

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