Comparison of Prognostic Factors and Death Hazard Function of Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) Patients after Bone Marrow Transplantation

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Abstract

Introduction: The majority of leukemia patients are acute leukemia patients, so that about 70.8% lymphoblastic leukemia were acute lymphoblastic leukemia (ALL) patients and 66.4 % of myeloid leukemia patients were acute myeloid leukemia (AML) in Tehran metropolitan. During the last two decades, intensification of therapy by the use of high-dose Cytarabine allogeneic stem cell transplantation in selected cases, paralleled by improvement in supportive care may have contributed to the impotent. In this article we use parametric survival models for recognizing prognostic factors in acute leukemia patients.

Patients and methods: Data on patients who underwent bone marrow or peripheral blood transplantation were obtained from the Hematology- Oncology and bone marrow transplantation research center at Shariati hospital, Tehran, Iran. Transplantations were performed between Oct. 17, 1993 to Jan. 31, 2007. Written informed consents for hematopoietic cell collection and transplantation were obtained from patients and donors. The study included patients 2 to 56 years of age who had received either an HLA-matched marrow transplant or a marrow transplant with a single HLA mismatch from an unrelated donor. The mean follow- up period was about 2 years after transplantation.

Results: Five hundred and seven patients were included in the study. There were 301 with acute myeloid leukemia (AML) and 206 with acute lymphoblastic leukemia (ALL). The median ages of the AML and ALL patients were 27 (2-55) and 20 years (2-52), respectively. In ALL patients, Prior viral exposure- cytomegalovirus antibody was positive in 143 patients and negative in 30 patients. In AML patients' Prior viral exposure- cytomegalovirus antibody was positive in 220 patients and negative in 41patients. Table- 1 shows the characteristics of 507 patients who included in the study.

Conclusion: In spite of no significant difference in follow-up time, serological status (CMV), donor-recipients sex match, bone marrow cell dose(WBC, CD34, MNC), donor type, source of stem cell, graft type, and conditioning regimen, (Busulfan- Oral, Cyclophosphamide, ALG/AIS/ATG, Stoposide)(Table- 1) in both AML and ALL patients, generalized gamma distribution shows that the mean of SBMT in AML patients is 2.52 times of ALL patients.

Keywords: AML, ALL, Prognostic Factor, Death Hazard Function

Introduction

The majority of leukemia patients are acute leukemia patients, so that about 70.8% lymphoblastic leukemia were acute lymphoblastic leukemia(ALL) patients and 66.4% of myeloid leukemia patients were acute myeloid leukemia (AML) in Tehran metropolitan.(1)

During the last two decades, intensification of therapy by the use of high-dose Cytarabine allogeneic stem cell transplantation in selected cases, paralleled by improvement in supportive care may have contributed to the impotent.(2)

Historically, the prognosis of acute leukemia was based on morphology and cytochemistry. Several factors are known to predict the long-term survival of acute leukemia, including age, cytogenetic, leukocyte count at presentation, previous hematologic disease and prior exposure to

chemotherapy.(3) Identification of prognostic factors related to survival time in patients after bone marrow transplant is very important because we can understand that changing which factors have affect the patients survival time, so it helps a physician making the best decision about patients treatment.

Prognostic factors of acute leukemia were considered by using non-parametric survival methods such as life table, Kaplan-Meier and Cox proportional hazard in many studies.(4, 5, 6, 7) However, the Cox proportional hazard regression model is used extensively, when proportional hazard assumptions are not met, using the Cox proportional hazard model is wrong. Parametric models are attractive because standard method such as maximum likelihood is available for parameter estimation and testing, and proportional hazard assumption is not required.(8)

If the survival time has a specific statistical distribution, the statistical power of parametric survival models is higher than non-parametric survival models.

A parametric survival model is one in which survival time (the outcome) is assumed to follow a known distribution. Examples of distributions that are commonly used for survival time are: the Weibull, the exponential, the Log-Logistic, the lognormal and the generalized gamma.(9) Survival estimates obtained from parametric survival models typically yield plots more consistent with a theoretical survival curve. If an investigator is comfortable with the underlying distribution assumption, the parameters can be estimated in such away that completely specify the survival and hazard functions. This simplicity and completeness are the main appeals of using a parametric approach.(9) Thus, in this article we use parametric survival models for recognizing prognostic factors in acute leukemia patients.

Patients and methods

Data on patients who underwent bone marrow or peripheral blood transplantation were obtained from the Hematology- Oncology and bone marrow transplantation research center at Shariati hospital, Tehran, Iran. Transplantations were performed between Oct 17, 1993 to Jan 31, 2007. Written informed consents for hematopoietic cell collection and transplantation were obtained from patients and donors.

All patients received a BuCy regimen (busulfan 4 mg/kg/day orally on days -6 to -3 and cyclophosphamide 60 mg/kg/day by intravenous infusion on days -2 to -1) for conditioning therapy with subsequent infusion of donor marrow cells on day 0 for GVHD prophelaxy in ALL patients.

All patients were monitored prospectively for the occurrence of adverse events, including GVHD, regimen-related toxicities. Two patients who received cord blood transplants were excluded from the study. 507 eligible patients were enrolled in the study (206 patients were diagnosed with acute Myeloid leukemia and 301 were diagnosed as having acute lymphoblastic leukemia).

The study included patients 2 to 56 years of age who had received either an HLA-matched marrow transplant or a marrow transplant with a single HLA mismatch from an unrelated donor. The mean follow- up period was about 2 years after transplantation.

End points: Platelet recovery was defined by a count of at least 20,000 platelets per cubic millimeters, unsupported by transfusion, for seven days: Neutrophil recovery was defined by an absolute neutrophil count of at least 500 cells per cubic millimeter on three consecutive days. The incidence of acute GVHD was determined in all patients. Patients who developed grades I to IV GVHD, were considered as having AGVHD.(10) The incidence of chronic GVHD was determined in patients who survived for at least 90 days.(11)

Relapse was defined as a recurrence of leukemia. Survival time after bone marrow transplant (STABMT) was defined as the time-interval between bone marrow transplantation and death or censoring. Censoring was defined as being alive at the last follow-up.

Statistical analysis: The probability of STABMT was estimated by using Kaplan-Meier estimator.(12) The probabilities of neutrophil, platelet recovery, AGVHD, CGVHD, death and relapse were calculated with the use of cumulative-incidence-function methods.(12) Confidence intervals were calculated by the use of Log failure transformation. The accelerated time (AFT) models such as: the Weibull, the exponential, the Log-Logistic, the lognormal and the Generalized Gamma distributions were used for finding the distribution of time-to-event (death) after bone marrow transplantation. Discrimination among the Weibull, the exponential, the Log-Logistic, the lognormal the Generalized Gamma distributions and Cox proportional hazard model were done using Maximum likelihood(LL), Akaike criteria (AIC), Cox-snell residuals and graphical methods. By adding different covariates in models,

conditional distributions of parametric and non-parametric survival time models were estimated. The Generalized Gamma distribution was used to determine prognostic factors for survival after bone marrow transplantation. Cox, proportional hazards regression analysis was used when convergence in Generalized Gamma distribution was in question.

In Cox proportional hazards regression models, multivariate models were built using a stepwise forward selection, with a P value of .05 or less considered to indicate statistical significance. Proportional hazards assumption was checked using graphical method, a goodness-of-fit testing procedure [the test of Harrel and Lee (1986)] and the procedure of using time-dependent variables.(9) Smoothed hazard function was estimated using Kernel smoothing method (Ramlu-Hansen 1983).(13) A P-value<0.05 was considered statistically significant. Analyses were completed using SAS ver. 9.1 and SPSS ver. 16 and stata ver. 10.

Results

Five hundred and seven patients were included in the study. There were 301 with acute myeloid leukemia (AML) and 206 with acute lymphoblastic leukemia (ALL). The median ages of the AML and ALL patients were 27 (2-55) and 20 years (2-52), respectively. In ALL patients, Prior viral exposure-cytomegalovirus antibody was positive in 143 patients and negative in 30 patients. In AML patients' Prior viral exposure- cytomegalovirus antibody was positive in 220 patients and negative in 41patients. Table- 1 shows the characteristics of 507 patients who included in the study. The 5-year survival rate based on Kaplan-Meir curve in ALL and AML patients were 52% (95% CI: 47.3-56.7), 65% (95% CI: 60.7-69.3), respectively (Figure- 1). The five-year survival rate in ALL and AML patients in CR1 disease stage was 65% (95% CI: 60.1- 69.9) and 84% (95% CI: 81.3- 86.7), respectively. The shape of hazard function in ALL patients showed that the hazard function had a decreasing trend so that, hazard of dying in the first 6 months after transplantation was higher than, the second six months after transplantation (Figure- 2). The hazard function in AML patients is U- shaped in a way that it decreases till about two years after transplant and then increases till 3 years (Figure- 3).

Prognosis factors of survival after bone marrow transplants, univariate analysis: A number of demographics and transplant-related factors were evaluated using the Gamma distribution as potential risk factors for SABMT. There was statistical deference between SABMT in AML and ALL patients [P=.000, EXP(b) =2.52]; so that, SABMT in AML patients was 2.52 times longer than ALL patients. There were just statistically significant associations among donor age, WBC, CD3, relapse, AGVHD, CGVHD and platelet recovery with SABMT in univariate analysis (Table- 2). There was not any statistically significant association among other variables with SABMT. Every 1000-unit increase in WBC dose cell will increase survival time by 6%. No significant association was observed between SABMT and WBC dose cell in AML patients (P= .18, Exp(b)= 1.1) but in ALL patients this association was considered significant (P= .047, Exp(b)= 1.03). There was a significant association between CD3 dose cell and SABMT (P=.0001, Exp(b)=1.046 CI 95% (1.037, 1.55). Exp(b)= 1.046 shows that with increasing every unit to CD3 cell dose, patients survival time increase about 4.6%.

Three patients in AML group were HLA-mismatched-sibling. There was a significant association between donor type and SABMT (P=.000, Exp (b) =20.45, CI 95% (10.5, 39.2), SABMT of HLA-identical-sibling patients was 19.45 times longer than, HLA-mismatched-sibling patients. The rate of relapse in AML and ALL patients were 16.9% and 28.6%, respectively. Figure- 4 shows cumulative relapse incidence among AML and ALL patients. There was a strong correlation between SABMT and leukemia recurred after transplantation in both ALL and AML patients (p=.000, Table- 2). The patients who had relapsed following transplantation the SABMT of them was about 11.5 time shorter than other patients. The effects of relapse on survival time were similar among patients with ALL and AML. Acute GVHD of grade 1, 2, 3, or 4 developed in 136 patients (77.7%) of ALL group and of 175 (71.8%) of AML patients. The mean of AGVHD time was 13.3 (sd= 16.5) and 15.16 (sd= 14.1) days in ALL and AML patients, respectively. There was no significant difference in the mean time of AGVHD in ALL and AML patients (P= .28). ADVHD have had a significant effect on SABMT in ALL patients (P= .021, Exp(b)= 2.29 CI 95% (1.13, 4.71), but in AML patients its effect was not significant on SABMT (P= .11 Exp(b)= .59 CI 95% (.30, 1.13). The occurrence of AGVHD had a negative effect on SABMT in AML patients, whereas it had a positive effect on SABMT in ALL counterparts. The cumulative incidence of AGVHD after bone marrow among ALL and AML patients has been shown in Figures- 5, 6.

Table- 1. Patients and transplants characteristics.

Characteristics	ALL (n=301)	AML(206)	P-value
Sex, No. (%)			.000
Male	139(67.5)	165(54.8)	
Female	67(32.5)	136(42.2)	
Age mean (sd)	22.5(8.73)	27.4(11.64)	.000
Age group, No. (%)			.000
<15 yr	37(18)	49(16.3)	
16-20 yr	72(35)	55(18.3)	
21-30 yr	64(31.1)	76(25.2)	
31-40 yr	22(10.7)	72(23.9)	
>40 yr	11(5.3)	49(16.3)	
Disease status, No. (%)			.000
CR1	138(67)	218(74.7)	
>CR1	52(25.2)	57(19.5)	
PIF	5(2.4)	9(3.1)	
Relapse 1,2,3,other	11(5.3)	8(2.7)	
FAB or immunophenotype classification, No. (%)	B-lineage: 88(42.7) L1:1(.5) Mature B-cell(L3):4(1.9) Other,specify:93(45.1) T-lineage:6(2.9) Unspecified:14(6.8)	M0:4(1.3) M1:18(6) M2:131(43.5) M3:23(7.6) M4:78(25.2) M5:31(10.3) M6:7(2.3) Other,specify:3(1) Unspecified:3(1)	
Conditioning regimen, No. (%)	185(89.8)	247 (83.2)	.024
BuCy	0	8(2.7)	.04
BuFluATG	204(99)	294(99)	.67
Busulfan - Oral	4(1.9)	2(.7)	.19
Stoposide	186(90.3)	250(84.2)	.031
Cyclophosphamide	4(3.7)	11(3.7)	.192
ALG/AIS/ATG			
Donor age (years), median (range)	21(2-55)	25(1-54)	
Patients age (years), median(range)	20(2-51)	27(2-55)	
Donor sex, No. (%)			
Female	85(41.3)	112(37.2)	
Male	121(58.7)	189(62.8)	
Graft type, No. (%)			.175
Allogeniec	200(97.1)	297(98.7)	
Syngeneic	6(2.9)	6(2.9)	
Source of stem cells, No. (%)			.43
Bone marrow	14(6.8)	23(7.8)	
Peripheral blood	192(93.2)	278(92.4)	
Donor type, No. (%)			.35
HLA-identical sibling	198(99)	293(99.7)	
HLA-mismatch - sibling	2(1)	1(.3)	
Bone marrow cell dose, median (range)			
WBC	10.5(2.1-33.3)	10.32(2.1-24.5)	.12
CD3	29(1-81.1)	25(.2-74.6)	.46
$CD34^{+}$cells($\times 10^{6}$/kg)	2.15(.2-18.6)	1.9(.2-79.2)	.42
MNC	6.44(.94-19.93)	6.95(1.04-17.6)	.22
Donor– recipient sex match，No. (%)			.19
Male-male	85(41.3)	106(35.2)	
Male-female	54(26.2)	59(19.6)	
Female-male	36(17.5)	83(27.6)	
Female-female	31(15)	53(17.6)	
Donor- Negative-negative recipient serological status For cytomegalovirus, No. (%)			.96
Negative-negative	16(9.3)	24(9.4)	
Negative-positive	19(11)	32(12.5)	
Positive-negative	14(8.1)	17(6.7)	
Positive-positive	123(71.5)	182(71.4)	

Outcomes, No. (%)			
Death	76(39.9)	67(22.3)	.000
Relapse	59(28.6)	51(16.9)	.002
AGVHD	136(77.7)	188(71.8)	.136
CGVHD	34(24.1)	62(25.5)	.76
Platelet recovery	141(75)	224(80)	.175
AGVHD time			
Mean(sd)	13.3(16.5)	15.16(14.12)	.28
Median	9	10	.003
Range	3-90	2-90	
CGVHD time			
Mean(sd)	160.26(73.4)	181.80(83.1)	.25
Median	140	168	.15
Range	91-327	91-492	
Relapse time			
Mean(sd)	580(555)	703.2(645)	.056
Median	412	479	.036
Range	10-2661	21-4301	
Platelet recovery time			
Mean(sd)	20.8(19.2)	19.2(10.1)	.32
Median	17	17	.80
Range	1-165	2-90.8	
Neutrophil recovery time			
Mean(sd)			
Median			
Range			
Follow up-month			.30
Median	16	17	
range	3-89	3-143	

Among patients who survived for 90 days or longer, chronic GVHD developed in 62 (25.5%) AML and 34 (24.1%) ALL patients. The median time of CGVHD was 123 (SD=74.1) and 156 (SD=84.9) days in ALL and AML patients, respectively. There was a significant association between CGVHD and SABMT in both AML and ALL patients (P=.000), so that in the acute leukemia patients with CGVHD, survival time was about 3.11 times longer than the patients without CGVHD (Figures-.7, 8). The cumulative incidence of CGVHD after transplantation in AML and ALL patients has been shown in Figure- 9.

Among patients who had platelet recovery, the mean time was 19.88 days, CI 95% (18.4- 21.36). There was strong association between platelet recovery and SABMT in acute leukemia patients [P= .000, Exp(b)= 3.11, CI 95% (1.95-4.95) Table-2, Figures- 10, 11]. The STABMT in ALL patients who had platelet recovery was 3.39 time longer than the patients how did not have platelet recovery. The cumulative incidence of platelet recovery in ALL and AML patients has been shown in Figure-12.

Prognostic factors of survival after bone marrow transplants, multivariate analysis: The variables that showed a significance level of P-value<.2 on univariate analysis were considered in the multivariate models, also the patients age and sex were considered in the variable selection process. Several multivariate models were considered because of strong association between SABMT and relapse and avoiding of missing data in cd3 and WBC variables. Discrimination among exponential, Weibull, log-normal, log- logistic and gamma distributions was done by likelihood ratio test.(14) The three-parameter generalized gamma distribution was shown to be appropriate for data set. All models were estimated using Generalized Gamma distribution. When the assumption of the Cox proportional hazard regression model was met and generalized gamma distribution was known to have convergence problem we used proportional hazard regression model in our study.

Death risk adjusted for patients sex and age in ALL group was 2.14 times of AML counterparts (All vs. AML, Hazard ratio (HR)= 2.14 CI 95% (1.52-3.10) P=.000). Other models were estimated in AML and ALL patients, separately. In ALL patients, a strong association between relapse adjusted for patients' sex and age and SABMT (exp(b)= 10 CI 95% (5.2-19.3) p= .000) showed that SABMT in the patients who did not have relapse was about 10 times longer than the patients with relapsed disease. CGVHD adjusted for patients' sex and age had significant association with SABMT (exp (b) =5.4 CI 95 % (2.57-10.38) P=.0001).

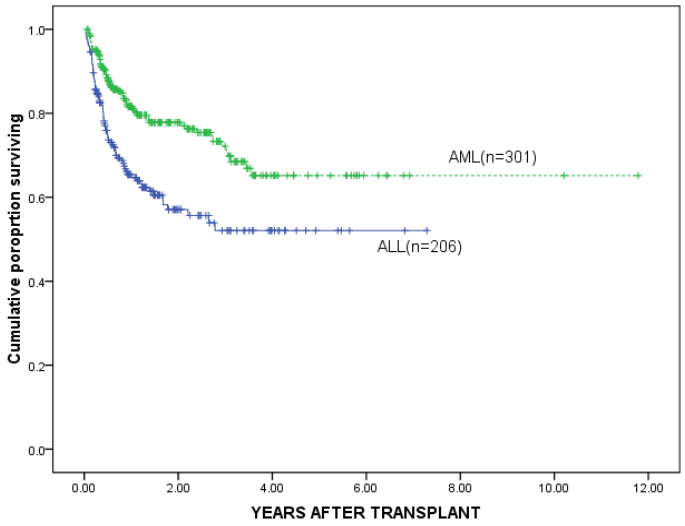

Figure- 1. Kaplan-Meir estimated survival after transportation for patients diagnosed with AML compared with ALL. Differences did reach statistical significance as determined by the log-rank test (p=.000)

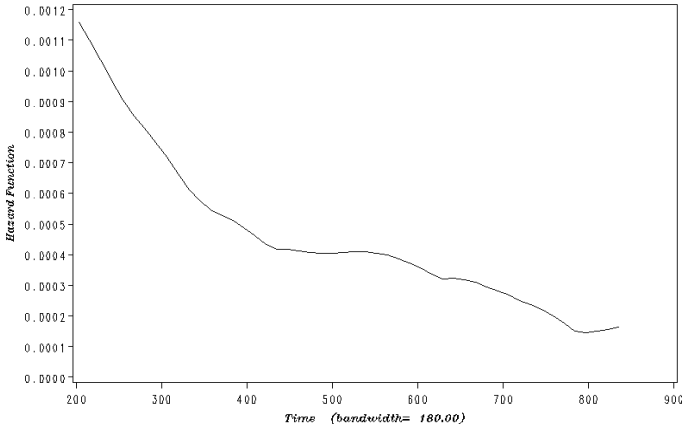

Figure- 2. Hazard function in ALL patients.

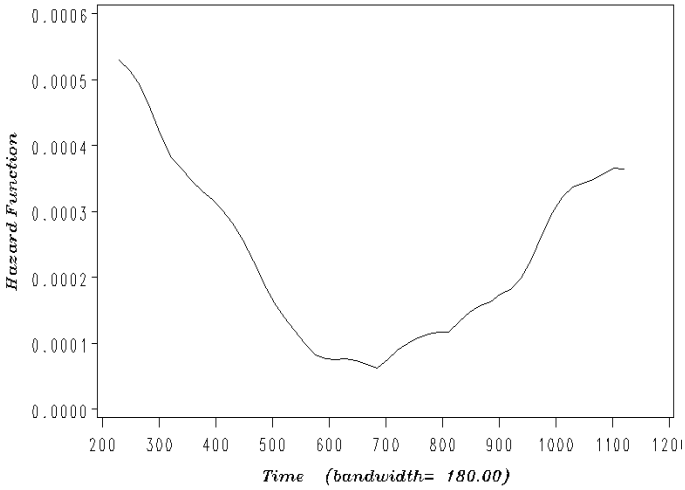

Figure- 3. The hazard function in AML patients.

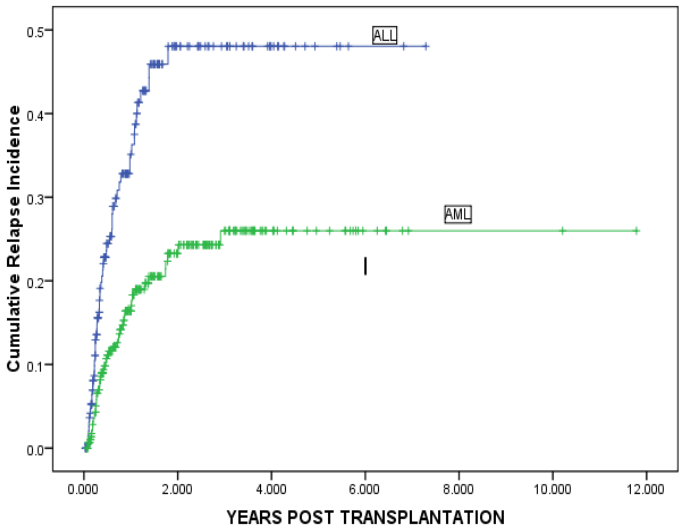

Figure- 4. Cumulative relapse incidence after transportation for patients diagnosed with AML compared with ALL. Differences did reach statistical significance as determined by the log-rank test (p=.000).

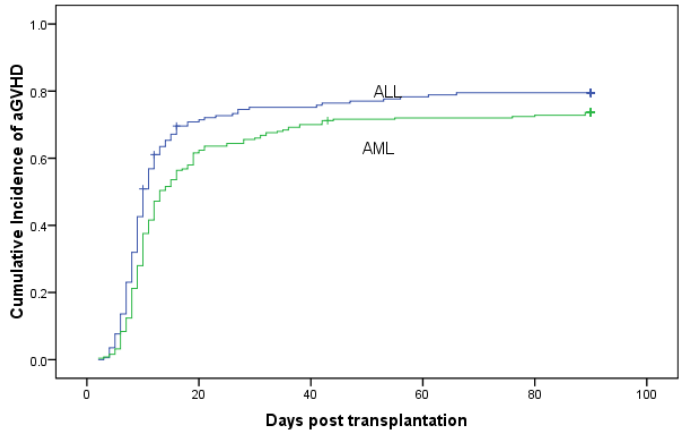

Figure- 5. Cumulative Incidence of aGVHD for patients diagnosis with AML compared with ALL.

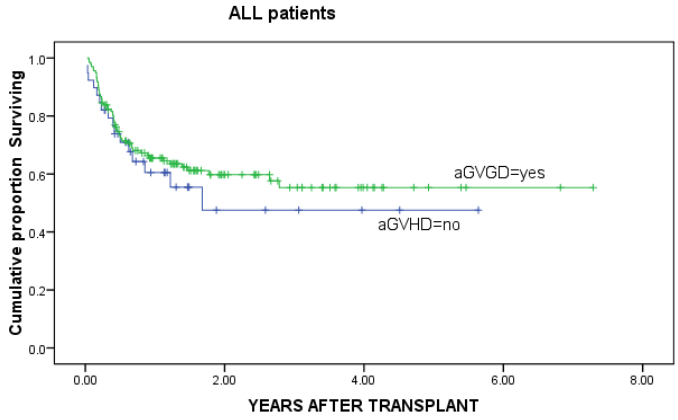

Figure- 6. Survival of ALL patients after transplantation grouped according to aGVHD development.

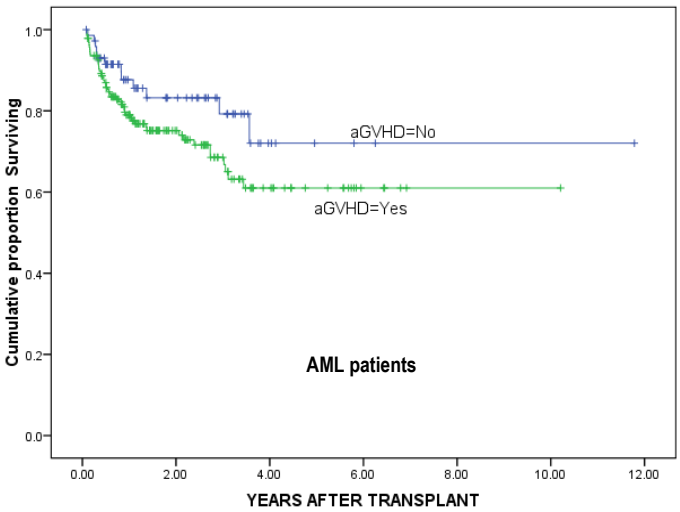

Figure-7. Survival of AML patients after transplantation grouped according to aGVHD development.

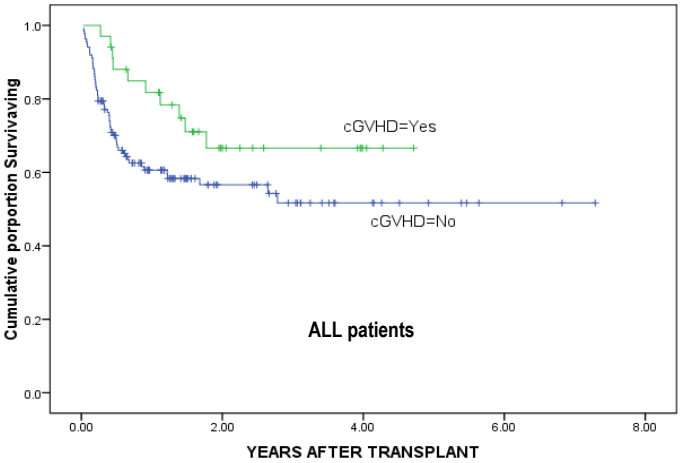

Figure- 8. Survival of ALL patients after transplantation grouped according to cGVHD development.

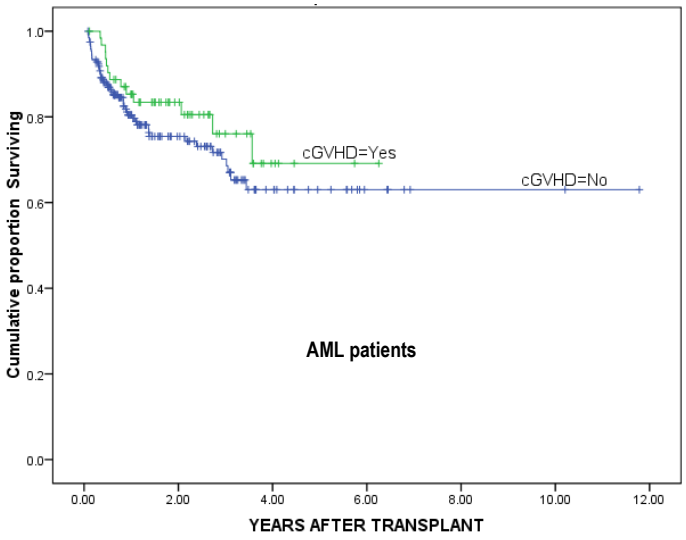

Figure- 9. Survival of AML patients after transplantation grouped according to aGVHD development.

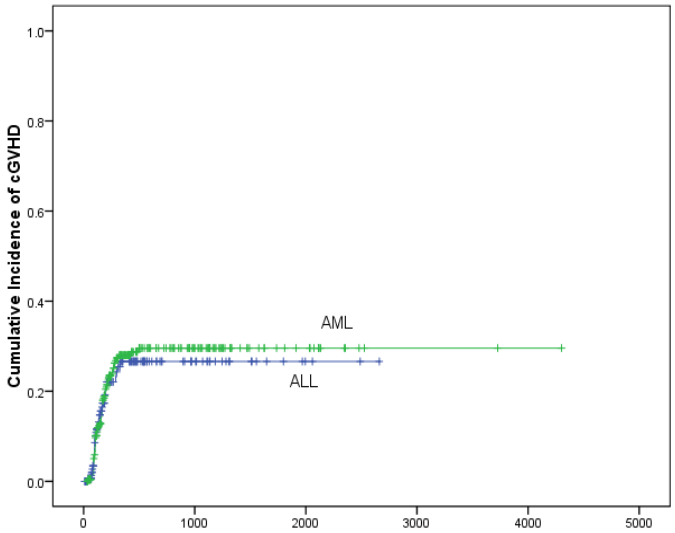

Figure- 10. Cumulative Incidence of platelet recovery.

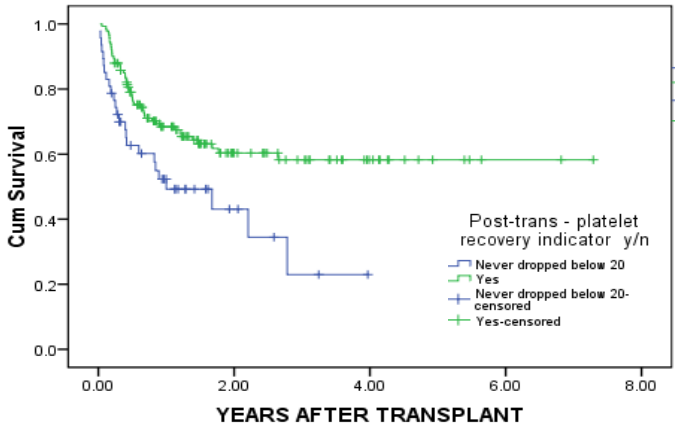

Figure- 11. Survival of ALL patients after transplantation grouped according

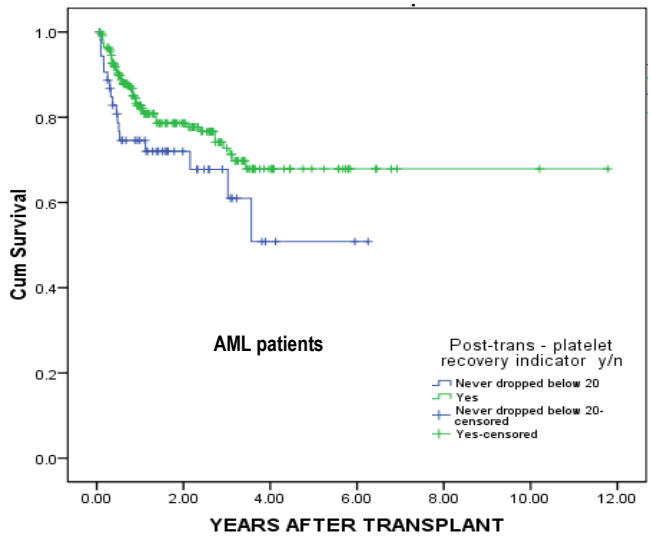

Figure- 12. Survival of AML patients after transplantation grouped according to platelet recovery.

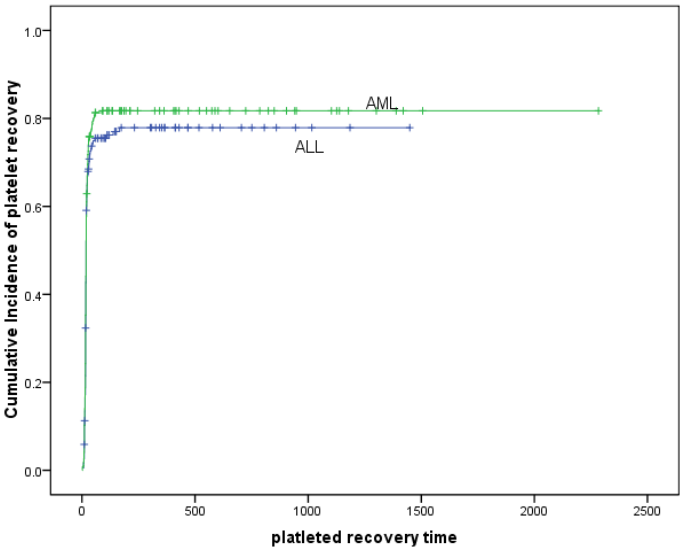

Figure- 13. Cumulative Incidence of platelet recovery.

Platelet recovery adjusted for patients' sex and age had significant association with SABMT (exp (b)= 3.7 CI 95 %(2.34-5.68) P=.0001). Because of convergence problems we could not use GG distribution for considering the relation of AGVHD adjusted for patients' sex and age. Cox proportional hazard regression model showed there was no association between AGVHD and SABMT adjusted for patients' sex and age (AGVHD no vr yes HR=1.01 CI 95 % (.98-1.039). CGVHD adjusted for AGVHD and Platelet recovery had significant association with SABMT (exp (b) =3.6 CI 95 % (1.95-6.8 P=.0001). Platelet recovery adjusted for AGVHD and CGVHD had significant association with SABMT (exp(b)= 3.3 CI 95% (1.61-6.7 P=.001). There was no significant association between WBC dose cell adjusted for patients' sex and age and SABMT (exp(b)= 1.02 CI 95% (.92-1.13) P= .65).

In AML patients, in a model including relapse, patients sex and age, there was strong association between relapse and SABMT (exp(b)=10.58, CI 95% (5.4-20.7) P= .000) In this model, the significant association between patients' sex and SABMT(exp(b)= 2.05 male vr. Female CI 95 % (1.1-3.7) (P=.000), showed that SABMT in males was about two times of females. There was no significant association between SABMT and patients age (Exp (b) =.97 CI 95% (.95-1.01) P=.098).

In AML patients, significant association between WBC dose cell adjusted for patients' sex and age and SABMT (Exp (b)= 1.13, CI 95 % (1.037-1.23), P=.005) showed that with increasing every unit in WBC dose cell, SABMT of patients increased about 13%, CI 95% (3.7% to 23%). Because of convergence problems in the generalized gamma model, Cox proportional- hazard regression model was used to consider the relationship among AGVHD, CGVHD, patients' sex and age and platelet recovery in a multivariate model. In this model the significant association between platelet recovery and SABMT (HR=2.42, CI 95% (1.3-4.45) P=.004) showed that death risk in patients with no platelet recovery is 2.42 times of those who had platelet recovery. AGVHD effect adjusted for platelet recovery, CGVHD, patients' age and sex had significant association with SABMT (HR=.47 CI 95 % (.24- .93) P=.03) which showed that death risk in AML patients who developed AGVHD was about 2.12 (1/.47) of the patients without developing AGVHD.

Discussion

Our objectives were to find hazard function shape in AML and ALL patients with HLA-matched bone marrow and to identify prognostic factors of SABMT using parametric and non-parametric model. Risk of death after bone marrow transplantation had different patterns in ALL and AML patients so that hazard function had a decreasing rate in ALL patients, that is it decreased after transplant until about 2 years and then increased until 3 years after transplant .The reasons of difference in shape of hazard function in ALL and AML patients were not clear but it seems that relapse of disease after two years leads to increase in the hazard of death in AML patients. The Generalized gamma distribution provides better fit than other parametric survival models such as: exponential, Weibull, log-normal, log- logistic. Hazard function in the Generalized gamma distribution can take a wide variety of shapes.(13) When I executed PubMed search, I could not find any research regarding generalized gamma distribution for finding hazard shape after bone marrow transplant or finding prognosis factors of SABMT in ALL and AML patients. In many researches Log- rank test or Cox proportional-hazard regression models were used to consider prognostic factor's of SABMT.(4- 7, 15, 16)

In our study the five-year survival rate based on Kaplan-Meir curve in ALL and AML patients with sibling donors in CR1 disease stage was 65% CI 95% (60.1 -69.9%) and 84% CI 95%(81.3 -86.7%), respectively Based on Kaplan-Meir curves of data from the center for international blood1 and marrow transplant research (CIBMTR) and the national marrow donor program (NMPD) data the rates were 65% and 65% ,respectively.(17) The five-year survival rate in AML and ALL patients is ranging from 11% for patients over 55 years to 71% in

infants and children.(18- 22) The five- year survival rate was only 5% CI 95% (1-15%) among patients who were not transplanted in first remission.(20) Thus, improvement in patients survival seems to be associated with the increasing use of transplant.

In spite of no significant difference in follow-up time, serological status (CMV), donor-recipients sex match, bone marrow cell dose (WBC, CD34, MNC), donor type, source of stem cell, graft type, and conditioning regimen, (Busulfan- Oral, Cyclophosphamide, ALG/AIS/ATG, Stoposide) (Table- 1) in both AML and ALL patients, generalized gamma distribution shows that the mean of SBMT in AML patients is 2.52 times of ALL patients.

Cox proportional- hazard regression models show that death hazard in ALL patients is 2.14 times of (CI 95 %) AML patients.

One of the reasons that the survival of AML patients is better than ALL patients is the higher relapse rate in ALL group.

The rate of relapse in AML patients was 16.9%, whereas it was 28.6% in ALL counterparts.

In this study CGVHD developed in 24.1 % of ALL patients and in 25.5% of AML patients.

Refrencess

1. Mohaghegi M, Mosavi A. Cancer Incidence in the Population of Tehran Metropolice, 1998-2001. The Cancer Institute Center Research Center, Tehran, Iran, 2006.
2. Lowenberg B, Downning JR, Burnett A. Acute Myeloid Leukemia. N Engl J Med 1999; 341:1051-1062.
3. Avivi Irit, M Rowe Jacob. Prognostic Factors in Acute Myeloid Leukemia. Current Opinion in Hematology 2005, 12:62- 67.
4. Mayer RJ, Davis RB, Shiffer CA, et al. Intensive Post-remission Chemotherapy in Adults with Acute Myeloid Leukemia N Engl J. Med 1994; 331: 896-903.
5. Baillargeon J, Langevin AM, Lewis M, et al. Obesity and Survival in a Cohort of Predominantly Hispanic Children with Acute Lymphoblastic Leukemia. J Pediatr Hematol Oncol. 2006 Sep; 28(9):575-8.
6. Lottick NS, Ness KK, Bhatia S, Gurney JG. Survival Variability by Race and Ethnicity in Childhood Acute Lymphoblastic Leukemia. JAMA. 2003 Oct 15; 290(15): 2061-3.
7. Hotowiecki J, Wojnar J, Krawczyk-Kuliś M, et al. Allogeneic and Autologous Bone Marrow Transplantation in Single Centre Experience. Bone Marrow Transplant. 1998 Dec; 22 Suppl 4:S100-3.
8. Christopher Cox, Haitao Chu, Michael F Shneider, et al. Parametric Survival Analysis and Taxonomy of Hazard Functions for the Generalized Gamma distribution. Statistics in medicine. 2007; 26:4352-4374
9. Kleinbaum DG, Klein M. Survival Analysis -A Self-Learning Text. 2005, Second Edition. New York: Springer -Verlag.
10. Nannya Y, Kanda Y, Oshima K, et al. Prognostic Factors in Elderly Patients with Acute Myelogenous Leukemia: a Single Center Study in Japan. Leuk Lymphoma. 2002 Jan; 43.
11. Johnson PR, Hunt LP, Yin JA. Prognostic Factors in Elderly Patients with Acute Myeloid Leukaemia: Development of a Model to Predict Survival. Br J Haematol. 1993 Oct; 85(2): 300.
12. Klien John P, Moeschberger M. Survival Analysis Techniques for Censored and Trancated Data. New York: Springer- Verlag. 1997.
13. Allison Paul D. Survival Analysis Using the Sas System a Practical Guide
14. ShaoXM . Parametric Survival Analysis for Gating Kinetics of SingleP otassium Channels. Brain Res. 1997 Oct 3; 770(1-2): 96-104.
15. Verstovsek S, Estey E, Manshouri T, et al. Clinical Relevance of Vascular Endothelial Growth Factor Receptors 1 and 2 in Acute Myeloid Leukaemia and Myelodysplastic Syndrome. Br J Haematol. 2002 Jul; 118(1): 151-6.
16. Sakamoto S, Kurata H, Miwa A. Multivariate Analysis of Prognostic Factors Influencing Survival in Chronic Myelogenous Leukemia. Rinsho Ketsueki. 1989 Aug; 30(8): 1180- 4.
17. E Anders Kolb, Pooja Gidwani, Stephan A Grupp. Hematopoietic Stem Cell Transplantation. eMedicine Specialties> Pediatrics: General Medicine> Oncology.
18. Barrett AJ, Horowitz MM, Gale RP, et al. Marrow Transplantation for Acute Lymphoblastic Leukemia: Factors Affecting Relapse and Survival. Blood 1989 Aug 1; 74(2): 862- 71.
19. Vernant JP, Marit G, Maraninchi D, et al. Allogeneic Bone Marrow Transplantation in Adults with Acute Lymphoblastic Leukemia in First Complete Remission. J Clin Oncol 1988 Feb; 6(2): 227- 31.
20. Blaise D, Gaspard MH, Stoppa AM, et al. Allogeneic or Autologous Bone Marrow Transplantation for Acute Lymphoblastic Leukemia in First Complete Remission. Bone Marrow Transplant 1990 Jan;5(1):7-12.

21. Wingard JR, Piantadosi S, Santos GW, et al. Allogeneic Bone Marrow Transplantation for Patients with High-risk Acute Lymphoblastic Leukemia. J Clin Oncol, 1990 May; 8(5): 820- 30.
22. Anders1 W, Markevärn B, Golovleva I, Nilsson M. Improved Outcome in Adult Acute Myeloid Leukemia is almost Entirely Restricted to Young Patients and Associated with Stem Cell Transplantation. European Journal of Haematology, Volume 68, Number 1, January 2002, pp. 54- 63 (10).