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Pre-Transplant Recipient/Donor Cytomegalovirus Serostatus and Graft Failure

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Introduction

Graft failure is complication of Hematopoietic Stem Cell Transplantation (HSCT) which is mostly effected achievement of HSCT. The incidence of graft failure is variable 4% to 20% according to donor types. For instance; incidence of graft failure is 1% at matched sibling donor, 1% to 5% at matched unrelated donor, 5% to 10% at HLA-A, HLA-B and HLA-DR mismatch donor, 20% at cord blood and T cell-depleted haploidentical stem cell transplantation [1,2].

Determination of factors that affect graft failure will help physicians for improving of achievement of HSCT and preventing from graft failure. In this retrospective review, we analyzed some parameters that can have an effect on primary and secondary graft failure and we also reviewed treatment options that had been used on primary and secondary graft failure.

Patients and Methods

We retrospectively evaluated 351 patients who had allogenic HSCT (AHSCT) between 1992 to 2014 years at Gazi University Medical School and Research Hospital. We retrospectively examined Recipient and Donor (R/D) clinicopathologic characteristics. Median age of recipients was 31 years (range, 15 to 64/years); median age of donors was 32 years (range, 2 to 67/years). Two hundred ninety nine (85.2%) of 351 patients had HLA match sibling donor, 14 (4.0%) patients had HLA match relative donor, 31 (8.8%) patients had HLA match unrelated donor, 5 (1.4%) patients had HLA mismatch unrelated donor, 2 (0.6%) patients had haploidentical donor. Lymphocyte depletion was not applied. We treated 226 (64.4%) patients with myeloablative regimen and 125 (35.6%) patients with non-myeloablative regimen. Median CD34+ cell amount was 4.05×10^6/kg (range, 0.20×10^6/kg-12.10×10^6/kg). (Table 1) shows the demographic characteristics of the R/D.

Definition

Neutrophil engraftment was defined as neutrophil count over 0.5 × 109/L on 3 consecutive days. Platelet recovery was defined as independence from platelet transfusion for at least 7 d with a platelet count >20×10^9/l [3].

Graft failure was defined as either primary graft failure or secondary graft failure. Primary graft failure was defined as without hematopoietic reconstitution of donor origin on day +45, Secondary graft failure was defined as patients who had loss of donor cells after a transient engraftment and returned to transfusion dependency [4].

Pre-transplant patients risk classification was defined per Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI/ SORROR) risk stratification [5].

Cytomegalovirus (CMV) Status: R/D CMV status were examined at pre-transplant evaluation. Four groups were defined according to the CMV status. First group R/D CMV status were positive (positive-positive), second group recipient CMV status was positive and donor CMV status was negative, (positive-negative), third group recipient CMV status was negative and donor CMV status was positive (negative-positive), fourth group recipient and donor CMV status were negative (negative-negative).

Statistical Analysis

The MEDCALC software SPPS-16 version (MedCalc Soft- ware bvba, Ostend, Belgium) programme was used for statistical analysis. A chi-square test was used for analyzing categorical values, and Mann-Whitney U test was used for analyzing non-categorical values. A value of $p<0.05$ was considered statistically significant.

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Table 1: Treatment options of graft failure patients.

Patients	GFT	Diagnosis	DLI	Response to DLI	Boost CD34+	Response to CD34+	ST	CR for ST	Response to ST
1	P	AA	-	-	-	-	+	Flu	yes
2	P	AML	-	-	-	-	-	-	-
3	S	AA	-	-	+	no	+	Cy	yes
4	P	PNH	-	-	+	yes	-	-	-
5	S	AML	+	no	-	-	+	ATGAM flu-cy	yes
6	P	AA	-	-	-	-	+	Flu	yes
7	P	MDS	+	yes	-	-	-	-	-
8	P	HD	+	yes	-	-	-	-	-
9	S	AA	+	yes	-	-	-	-	-
10	S	AA	+	no	+	yes	-	-	-
11	S	AA	+	no	-	-	+	ATGAM bu-flu	yes
12	S	AML	-	-	-	-	+	Flu-TBI	yes
13	P	ALL	-	-	-	-	-	-	-
14	P	ALL	-	-	-	-	+	flu	no
15	S	ALL	+	yes	-	-	-	-	-

Abbreviations: GFT: Graft Failure Type; p: primer; s: seconder; AA: Aplastic Anemia; AML: Acute Myeloid Leukemia; PNH: Paroxysmal Nocturnal Hemoglobinuria; MDS: Myelodysplastic Syndrome; HD: Hodgkin Disease; ALL: Acute Lymphoid Leukemia; DLI: Donor Lymphocyte Infusion; post-tx chemo: Posttransplant Chemotherapy; ST: Second Transplant; CR for ST: Conditioning Regimen for Second Transplant; flu: fludarabine; Cy: Cyclophosphamide; ATGAM- flu-cy: Antithymocyte Globuline-fludarabine-cyclophosphamide; bu: busulfan; TBI: Total Body Irradiation

Table 2: Characteristics of primary and secondary graft failure patients.

Patients	GFT	Diagnosis	DLI	Response to DLI	Boost CD34+	Response to CD34+	ST	CR for ST	Response to ST
1	P	AA	-	-	-	-	+	Flu	yes
2	P	AML	-	-	-	-	-	-	-
3	S	AA	-	-	+	no	+	Cy	yes
4	P	PNH	-	-	+	yes	-	-	-
5	S	AML	+	no	-	-	+	ATGAM flu-cy	yes
6	P	AA	-	-	-	-	+	Flu	yes
7	P	MDS	+	yes	-	-	-	-	-
8	P	HD	+	yes	-	-	-	-	-
9	S	AA	+	yes	-	-	-	-	-
10	S	AA	+	no	+	yes	-	-	-
11	S	AA	+	no	-	-	+	ATGAM bu-flu	yes
12	S	AML	-	-	-	-	+	Flu-TBI	yes
13	P	ALL	-	-	-	-	-	-	-
14	P	ALL	-	-	-	-	+	flu	no
15	S	ALL	+	yes	-	-	-	-	-

Abbreviations: GFT: Graft Failure Type; p: primer; s: seconder; AA: Aplastic Anemia; AML: Acute Myeloid Leukemia; PNH: Paroxysmal Nocturnal Hemoglobinuria; MDS: Myelodysplastic Syndrome; HD: Hodgkin Disease; ALL: Acute Lymphoid Leukemia; CMV: Cytomegalovirus

Results

Graft failure was observed in 15 (4.3%) recipient. Of these 15 recipient, 8 (53.3%) had primary graft failure and 7 (46.7%) had secondary graft failure. Median time of secondary graft failure was 60 days (range, 47 to 150 days). Two (25%) primary graft failure recipient had sex-matched donor, 6 (75%) primary graft failure recipient had sex mismatched donor. Three (42.9%) secondary graft failure recipient had sex matched donor, 4 (57.1%) secondary graft failure recipient had sex-mismatched donor. Table 2 show the diagnosis, HLA/ABO/CMV status and median CD34+ cell of patients who had graft failure. According to SORROR risk score; 7 (87.5%) primary graft failure recipient had low risk, 1(12.5%) primary graft failure recipient had high risk, all of the secondary graft failure recipient had low risk. Three (37.5%) primary graft failure recipient had myeloablative conditioning regimen, 5 (62.5%) primary graft failure recipient had non-myeloablative conditioning regimen. Three (42.9%) secondary graft failure recipient had myeloablative conditioning regimen, 4 (57.1%) secondary graft failure recipient had non-myeloablative conditioning regimen. Peripheral stem cell source was used in 6 (75%) primary graft failure recipient, bone morrow stem cell source was used in 2 (25%) primary graft failure recipient, all of the secondary graft failure recipient had peripheral stem cell source.

Ratio of graft failure was high in (R/D); HLA mismatch,

Table 3: Treatment options of graft failure patients.

Patients	GFT	Diagnosis	DLI	Response to DLI	Boost CD34+	Response to CD34+	ST	CR for ST	Response to ST
1	P	AA	-	-	-	-	+	Flu	yes
2	P	AML	-	-	-	-	-	-	-
3	S	AA	-	-	+	no	+	Cy	yes
4	P	PNH	-	-	+	yes	-	-	-
5	S	AML	+	no	-	-	+	ATGAM flu-cy	yes
6	P	AA	-	-	-	-	+	Flu	yes
7	P	MDS	+	yes	-	-	-	-	-
8	P	HD	+	yes	-	-	-	-	-
9	S	AA	+	yes	-	-	-	-	-
10	S	AA	+	no	+	yes	-	-	-
11	S	AA	+	no	-	-	+	ATGAM bu-flu	yes
12	S	AML	-	-	-	-	+	Flu-TBI	yes
13	P	ALL	-	-	-	-	-	-	-
14	P	ALL	-	-	-	-	+	flu	no
15	S	ALL	+	yes	-	-	-	-	-

Abbreviations: GFT: Graft Failure Type; p: primer; s: seconder; AA: Aplastic Anemia; AML: Acute Myeloid Leukemia; PNH: Paroxysmal Nocturnal Hemoglobinuria; MDS: Myelodysplastic Syndrome; HD: Hodgkin Disease; ALL: Acute Lymphoid Leukemia; DLI: Donor Lymphocyte Infusion; post-tx chemo: post transplant chemotherapy; ST: Second Transplant; CR for ST: Conditioning Regimen for Second Transplant; flu: fludarabine; Cy: Cyclophosphamide; ATGAM- flu-cy: Antithymocyte Globuline–fludarabine-cyclophosphamide; bu: busulfan; TBI: Total Body Irradiation

ABO mismatch, CMV +/+ group and recipient who had non-myeloablative conditioning regimen (p=0.023, p=0.03, p=0.029, p=0.044 respectively). Patient age, donor age, R/D gender, Sorror risk score, source and quantity of CD34+ cells have not had significant effect on graft failure (p>0.05).

Seven of 15 recipient received DLI treatment; 5 of 7 recipients had secondary GF, 2 of 7 recipients had primary GF. Four of 7 recipient responded to DLI treatment. Three of 15 recipients had boost CD34+ cells from the same donor. Two of 3 recipients had responded. Seven of 15 recipients underwent a second allogeneic HSCT. Three of 7 recipients had primary GF, 4 of 7 recipients had secondary GF. The entire recipient had second HSCT from same donor. Table 3 shows graft failure of patient's treatment options.

Discussion

Reduced Intensity Regimen (RIC), ABO match R/D, HLA match R/D were factors that had an effect on graft failure according to previous studies [6-8]. These findings are similar in this retrospective review. In additional, another finding in this retrospective review, which are different from previous studies was, significant relationship between R/D CMV statuses with graft failure.

Cytomegalovirus infection is major cause of morbidity and mortality after HSCT and Solid Organ Transplantation (SOT) [10]. However; there are so many clinical research that was showing CMV reactivation after HSCT, might have a beneficial affect protecting from disease relapse, especially Acute Myeloid Leukemia [11-13]. In additional, some of the studies show that CMV infection and reactivation had a close relationship with acute and chronic allograft rejection after SOT and graft failure after HSCT [14-18]. On the other hand; there is not any clinic or research study about showing relationship between D/R pre-transplant CMV statuses with graft failure at HSCT. This retrospective review is showing that pre-transplant D/R CMV status may have related to increase of graft failure risk at HSCT. However, this case series are very small, for this reason we could not claim that there is a definite relationship between them.

Infections are one of the major reasons of graft rejection after SOT [19]. However; infection has not had strong relationship with graft failure at HSCT when comparing to SOT. Previous studies mostly claimed on HLA- mismatching and ABO-mismatching in the D/R pair and use of RIC regimen has related to graft failure [15]. Latent CMV infection in donor tissue or conversely latent CMV infection in recipient can be activated after transplantation [19]. For this reason; pre-transplant evaluation of D/R CMV status are important [20].

There was a bidirectional relationship between CMV disease and acute rejection [21]. For instance; CMV can cause acute rejection *via* immunomodulation and upregulation of alloantigen, conversely acute rejection can cause transactivated of CMV. Cytomegalovirus reactivation had two major effects. These are: CMV disease direct effect and cellular indirect effect (immunologic phenomena) [19]. Natural Killer (NK) cell and CD8+ and CD4+ T cells, some of the cytokines and Major Histocompatibility Complex (MHC) have roles in immunologic phenomena [22].

Donor CMV positive active T cell and NK cell were given to recipient, if T cell or NK cell depletion were not used. Donor and recipient CMV seropositive T and NK cells are confronted in recipient, if recipient have had positive serotype of CMV. Cytomegalovirus reactivation might happen in recipient and can resulted as acute and chronic graft rejection after SOT, especially renal, lung and heart transplantation [23]. At this point; it is possible to think that: donor CMV positive active T and NK cells might have been in a competition with recipient CMV positive active T and NK cells at HSCT. Conversely, graft failure might be occurred from dominancy of recipient CMV positive active NK and T cells at the end of this competition. For this reason; some of graft failure recipient had response to the DLI treatment to which broke down immune reconstruction. Additional; it is always possible to determine recipient who had full chimeric however, who had graft failure. This

also might be related to immune reconstruction of graft environment and it shows early stage of graft failure. Herein; we could suggest using DLI as treatment options of early stage of graft failure.

Boost CD34+ cells and second HSCT are other options at graft failure treatment. Second HSCT is still offering as best treatment option [2,24]. Response rate of second transplant are also better than other treatment options in this retrospective review. Further studies with a large case series are exactly necessary to claim which treatment option is the best and which factors are mostly affecting on graft survival.

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