AbdElFattah et al. *SECI Oncology* 2016
DOI: 10.18056/seci2016.3

Impact of acute graft versus host disease on survival after allogeneic peripheral blood stem cell transplantation

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Published 23 March 2016

Abstract

Background and objectives: Hematopoietic stem cell transplantation (HSCT) is potentially curative treatment for malignant and non-malignant diseases. Graft versus host disease (GVHD) remains a significant cause of morbidity and mortality following HSCT. An increased incidence of GVHD has been suggested following allogeneic peripheral blood stem cell transplantation (PBSCT), however, how this affects survival is not yet clear. In this study, our aim is to assess the impact of acute GVHD (aGVHD) on overall survival (OS) and progression free survival (PFS) following human leukocyte antigens (HLA) identical sibling PBSCT.

Patients and methods: Data of 97 patients undergoing HLA identical sibling allogeneic PBSCT, were analyzed. We studied the incidence of aGVHD and their effects on survival. Survival analysis was done using Kaplan-Meier method to determine OS and PFS.

Results: The overall incidence of aGVHD was 34%. The occurrence of grade 2-4 aGVHD was associated with decreased probability of PFS (P= 0.018). The development of grade 2-4 aGVHD was associated with lower OS compared with the absence of aGVHD (P= 0.021).

Conclusion: These data indicate that the occurrence of aGVHD is an important factor that may influence the survival in HLA-identical sibling allogeneic PBSCT. Patients who developed aGVHD have a high chance of decreased probability of PFS and lower OS.

Keywords: Peripheral blood stem cell transplantation, survival, acute graft-versus host disease.

Background:

HSCT is one of the most unique procedures in medicine. It has become a standard of care for hematologic malignancies, congenital or acquired disorders of the hematopoietic system, and it is also applied as a therapeutic option in some solid tumors [1].

aGVHD is a reaction of donor immune cells against host tissues and is the major limiting factors in successful allogeneic HSCT. It affects at least a third of the patients undergoing matched related donor transplantation and a higher proportion of mismatched and matched unrelated donor (MUD) transplantations [2].

Indeed, one of the major determinants for the development and severity of aGVHD is disparity in major and minor histocompatibility antigens, with an increasing number of mismatched antigens predicting greater risk of aGVHD [3]. As well, more recent insights demonstrated that polymorphism in non HLA genes, including cytokines such as tumor necrosis factor (TNF), interleukin 10 (IL-10), interferon gamma (IFN-γ) [4] and killer immunoglobulin-like receptor (KIR)

polymorphism may also contribute to the development and severity of aGVHD [5].

Other important and consistent risk factors include older patient age, the use of female donors for male recipients, prior alloimmunization of the donor. In addition many other factors have been associated with the risk of GVHD such as increasing intensity of the preparative regimen, the use of peripheral blood stem cells as opposed to bone marrow and the administration of total body irradiation [6].

Traditionally, aGVHD has been defined as a syndrome occurring within the first 100 days following HSCT "classic GVHD", however aGVHD is better defined as a clinical syndrome that can occur both early even before engraftment, and late, beyond day 100. The timing of aGVHD may affect the outcome of the disease, with late aGVHD having a better outcome than "classic" aGVHD [7].

aGVHD primarily affects the skin (81%), gastrointestinal tract (54%), and liver (50%). The syndrome ranges from a mild self-limiting condition to a serious and potentially fatal disorder [8]. The extent of involvement of these organs determines the severity of aGVHD. Overall grades are I (mild), II (moderate), III (severe), and IV (very severe). The overall survival for grades III and IV is very poor with 25% and 5% survival rates respectively [9].

Efforts to prevent aGVHD without compromising graft versus tumor (GVT) effect are a major research objective. The most widely used GVHD prophylaxis following full intensity conditioning includes a combination of a calcineurin inhibitor (e.g. cyclosporine A (CSA), tacrolimus) with methotrexate (MTX). Alternate regimens for GVHD prophylaxis include sirolimus, mycophenolate mofetil (MMF) and manipulation of the graft such as T cell depletion [10].

As GVHD is the major cause of non-relapse mortality after allogeneic HSCT, we conducted this study to evaluate the effect of aGVHD on survival after allogeneic PBSCT.

Patients and Methods:

Patient population

Between January 2014 and February 2015, a total of 97 patients received allogeneic stem cell transplant from fully HLA matched siblings at Bone Marrow Transplantation Centre, Nasser Institute Hospital, Cairo, Egypt were recruited to participate in this study. The median follow-up period was 11 months.

Inclusion criteria

Patients of both genders, aged ≥18 years, with Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, fully HLA identical sibling, and adequate liver and kidney functions, no medical contraindications for HSCT and cardiac ejection fraction ≥ 60%were included in this study.

Exclusion Criteria

Patients with less than fully HLA matched donor or with identical twin donor, pregnancy or lactation, uncontrolled infection, positive human immunodeficiency virus (HIV) and active central nervous system (CNS) disease were excluded from the current study.

Transplant Regimen

PBSCs were mobilized from normal donors with recombinant granulocyte colony-stimulating factor (G-CSF). Conditioning regimens included total-body irradiation/ cyclophosphamide (TBI/CY), busulfan/cyclophosphamide (BU/CY), fludarabine/cyclophosphamide (Flu/CY) and fludarabine/melphalan (Flu/Alk) and fludarabine/Busulfan (Flu/Bu) were used.

Diagnosis of acute GVHD

The patients were evaluated for aGVHD in the first 100 days after HSCT. The diagnosis of aGVHD was based on clinical criteria. The grading criteria of aGVHD are based on dermal, gastrointestinal, and hepatic involvement plus functional impairment. These criteria include a stage for each organ involved between 1 and 4 (Table 1) and are then combined to give an overall grade from I-IV (Table 2) [11].

GVHD prophylaxis consisted of CSA and MTX which given to most of the patients. Only three patients received CSA and MMF. Immunosuppressive drugs were tapered beginning 100 days post-transplant if no signs of GVHD were evident and were gradually discontinued over 3 months.

Statistical analysis

Data was entered on a PC using Excel 2013 (Microsoft Corporation, USA) and was analysis using SPSS version 21 (IBM Inc., USA). Data were described as frequencies (percentages). Differences in distributions between the variables examined were analyzed by chi-square test. PFS was defined as the time from stem cell infusion to progression or death from any cause while OS was defined as the time from stem cell infusion to death from any cause. Survival analysis was done using Kaplan-Meier method to determine OS and PFS. Log rank (Mantel-Cox) test was used to examine difference between survivals of different groups. Probability (p-value) equal or less than 0.05 was considered significant.

Results:

A total of 97 patients with various hematologic disorders underwent allogeneic HSCT. The demographic data of the patients are shown in (Table 3).The mean age of the patients at time of transplantation was 31.2 ± 9.5 years. The median age was 31 years (range 18-56). Ninety-four patients (96.9%) were less than 50 years old while only three patients were ≥50 years old (3.1%).

Diagnoses included acute myeloid leukemia (40.2%), sever aplastic anemia (26.8%), acute lymphocytic leukemia (13.4%), chronic myeloid leukemia (8.2%), myelodysplastic syndrome (4.1%), biphenotypic leukemia (3.1%) and others (4.2%). The other cases included one case of Hodgkin's lymphoma, one case of chronic lymphocytic leukemia, one case of myelofibrosis and one case of paroxysmal nocturnal hemoglobinuria.

Ninety-three patients (96%) underwent myeloablative allogeneic HSCT while only four patients (4%) received reduced-intensity conditioning regimens. Fourteen patients (14.4%) received conditioning with TBI/CY, 48 patients (49.5 %) received BU/CY, 27 patients (27.8%) received FLU/CY and 8 patients (8.2%) received other regimens such as Flu/Alk and Flu/Bu.

The mean age of the donors was 29 ± 10.8 years. The median age was 28 years (range 9-58). Donor–recipient sex compatibility was categorized as follows: male donor to male recipient (47.7%), male donor to female recipient (25.8%), female donor to female recipient (11.3%) and female donor to male recipient (15.5%) (table 3).

After HSCT, thirty-three patients (34%) developed grade II–IV aGVHD. aGVHD primarily affects the skin, gastrointestinal tract and liver (69.7%, 57.6% and 21.2% of patients with aGVHD respectively).

Development of grade 2 to 4 aGVHD decreased probability of PFS compared to the absence of or grade 1 aGVHD (11.5 months versus 15.7 months respectively) (p= 0.018) (figure 1), however PFS not affected by patient diagnosis.

The occurrence of grade 2-4 aGVHD was also associated with lower OS compared to the absence of or grade 1 aGVHD (13 months versus 18 months respectively) (p= 0.021) (figure 2). Development of hepatic aGVHD was associated with the lowest OS compared to other sites of aGVHD (p= <0.001) (table 2). The OS was also affected by patient diagnosis where the OS was decreased among patient diagnosed as myelodysplastic syndrome compared to other diagnosis (p = 0.003) (figure 3).

Table 1: Acute graft-versus-host disease staging

Stage	Skin	Gut	Liver
1	Maculopapular rash < 25% of body area	Diarrhea > 500 <1000 ml/day	Bilirubin 2–3 mg/dl
2	Maculopapular rash 25%–50% of body area	Diarrhea > 1000 <1500 ml/day	Bilirubin 3–6 mg/dl
3	Generalized erythroderma	Diarrhea > 1500 ml/day	Biliribuin 6–15 mg/dl
4	Desquamation and bullae	Diarrhea > 2000 ml/day or pain or ileus	Biliribuin >15 mg/dl

Table 2: Acute graft-versus-host disease grading

Grade	Skin[a]	Gut[a]	Liver[a]	Karnofsky performance scale
I	1-2	0	0	90-100%
II	3	or 1	or 1	70-80%
III	2-3	and 2-3	or 2-3	50-60%
IV	4	or 4	or 4	30-40%

[a] Staging is described in Table 1.

Table (3) Characteristics of 97 patients subjected to allogeneic stem cell transplantation from an identical sibling

	Total		P value
	No	%	
Total	97	100	
Age			
- <50	94	96.9	0.417
- >=50	3	3.1	
Sex			
- Male	71	73.2	0.789
- Female	26	26.8	
Diagnosis			
- SAA	26	26.8	
- AML	39	40.2	
- ALL	13	13.4	0.449
- Biphenotypic	3	3.1	
- CML	8	8.2	
- MDS	4	4.1	
- Others	4	4.2	
Conditioning regimen			
- BU/CY	48	49.5	
- TBI/CY	14	14.4	0.954
- FLU/CY	27	27.8	
- Others	8	8.2	
CMV status			
- Negative	2	2.1	0.778
- Positive	95	97.9	
HCV PCR			
- Negative	84	86.6	0.316
- Positive	13	13.4	
Patient-donor sex matching			
- M-F	25	25.8	
- M-M	46	47.4	0.867
- F-F	11	11.3	
- F-M	15	15.5	

Abbreviations: SAA: severe aplastic anemia; AML: acute myeloid leukemia; ALL: acute lymphocytic leukemia; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome; BU: busulfan; CY: cyclophosphamide; TBI: total body irradiation; CMV: Cytomegalovirus; HCV: hepatitis C virus; PCR: polymerase chain reaction; M: male; F: female.

Table 4: Relation between aGVHD and OS in patients who received HSCT from an identical sibling

Item	OS			Log Rank (Mantel-Cox) P=value
	Mean	Standard Error	95% Confidence Interval (CI)	
Acute GVHD (total)	13.191	1.419	10.409 - 15.973	0.021*
Acute GVHD of skin	14.401	1.614	11.237- 17.565	0.452
Acute GVHD of GIT	12.327	1.706	8.983 - 15.671	0.063
Acute GVHD of liver	3.167	0.792	1.614 -4.720	0.000*

Abbreviations: GVHD: graft-versus-host disease; GIT: Gastrointestinal
*statistically significant

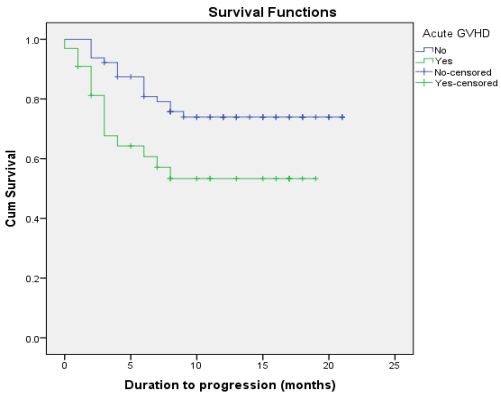

Figure 1: Relation between aGVHD and PFS in patients who received HCST from an identical sibling

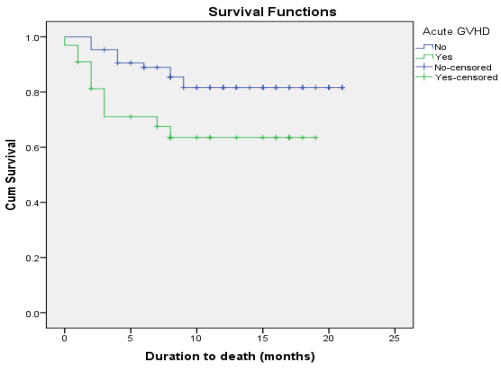

Figure 2: Relation between aGVHD and OS in patients who received HCST from an identical sibling

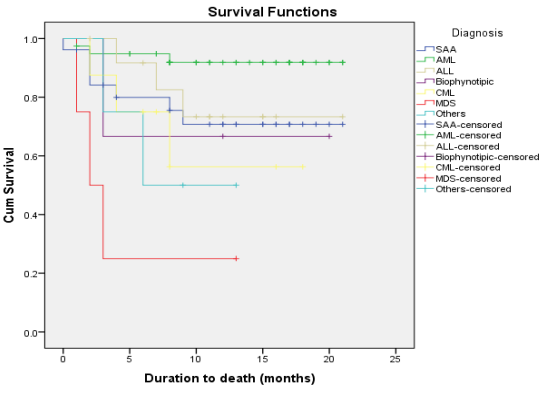

Figure 3: Relation between patient diagnosis and OS in patients who received HCST from an identical sibling

Discussion:

HSCT has significant therapeutic benefits to patients suffering from hematologic disorders but the benefits of the stem cell graft can be limited by the significant morbidity and mortality that can be associated with developing GVHD [12].

This study is to analyze the impact of aGVHD on clinical outcomes of PBSCT including PFS and OS in which we found that the occurrence of grade 2-4 aGVHD was associated with decreased probability of PFS compared to the absence of or grade 1 aGVHD. Our finding appears to be keeping with results published by ***Baron et al*** which demonstrated that grade 2-4 aGVHD had no significant impact on the risk of relapse or progression but was associated with increased risk of non-relapse mortality and decreased probability of PFS [13]. Also our result is consistent with the study done by ***Donato et al*** on 57 patients with multiple myeloma who underwent allogeneic HSCT, in which the occurrence of aGVHD was significantly deleterious to PFS [14]. However, ***Gunhan et al*** who retrospectively evaluated 928 allo-HSCT between 1989 and 2015 and 43% of their patients developed aGVHD. The OS was 59 months and PFS was 33 months. aGVHD had no impact on PFS ,OS or relapse rate [15]. This controversy to our results may be due to a large number of patients and prolonged follow up in ***Gunhan*** study.

In our study the occurrence of grade 2-4 aGVHD was associated with lower OS compared with the absence of or grade 1 aGVHD. Consistent with our results, ***Ishida et al*** studied the impact of GVHD on allogeneic HSCT for adult T cell leukemia/lymphoma and demonstrated an association between grade I-II aGVHD and favorable OS (HR, 0.634; 95% CI, 0.477 to 0.843), whereas grade III-IV aGVHD showed a trend toward unfavorable OS (HR, 1.380; 95% CI, 0.988 to 1.927) compared with no aGVHD [16]. Another study done by ***Ali et al*** showed that in patients with aGVHD, the transplant-related mortality significantly increased and it correlated with the grade and organ of involvement with aGVHD [17]. ***Donato et al*** in his studied 57 patients with multiple myeloma who underwent allogeneic HSCT, demonstrated that the occurrence of aGVHD was significantly deleterious to OS [14].

In summary, Our study concluded that the aGVHD significantly decreased the PFS and OS after allogeneic PBSCT.

Conflict of Interests:

The authors declare that they have no conflict of interests.

Acknowledgements:

We acknowledge the BMT team at the Nasser Institute Hospital, Cairo, Egypt and we thank them for their efforts and support.

References:

1. Appelbaum FR (2007). **Hematopoietic-cell transplantation at 50**. N Engl J Med; **357**:1472–5.
2. Couriel D, Caldera H, Champlin R, Komanduri K (2004). **Acute graft-versus-host disease: pathophysiology, clinical manifestations, and management**. Cancer; **101**:1936-1946.
3. Lee SJ, Klein J, Haagenson M, Baxter-Lowe LA, Confer DL, Eapen M, Fernandez-Vina M, Flomenberg N, Horowitz M, Hurley CK, Noreen H, Oudshoorn M, Petersdorf E, Setterholm M, Spellman S, Weisdorf D, Williams TM, Anasetti C (2007). **High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation**. Blood **110(13**):4576-4583.
4. Dickinson AM and Charron D (2005). **Non-HLA immunogenetics in hematopoietic stem cell transplantation.** Curr Opin Immunol. **17(5):**517-525.
5. Hsu KC, Gooley T, Malkki M, Pinto-Agnello C, Dupont B, Bignon JD, Bornhäuser M, Christiansen F, Gratwohl A, Morishima Y, Oudshoorn M, Ringden O, van Rood JJ, Petersdorf E (2006). **KIR ligands and prediction of relapse after unrelated donor hematopoietic cell transplantation for hematologic malignancy**. Biol Blood Marrow Transplant. **12(8):**828-836.
6. Flowers ME, Inamoto Y, Carpenter PA, Lee SJ, Kiem HP, Petersdorf EW, Pereira SE, Nash RA, Mielcarek M, Fero ML, Warren EH, Sanders JE, Storb RF, Appelbaum FR, Storer BE, Martin PJ (2011). **Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria**. Blood **117**:3214 –3219
7. Mielcarek M, Martin PJ, Leisenring W, Flowers ME, Maloney DG, Sandmaier BM, Maris MB, Storb R (2003). **Graft versus- host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation.** Blood **102**:756-762.
8. Martin PJ, Schoch G, Fisher L, Byers V, Anasetti C, Appelbaum FR, Beatty PG, Doney K, McDonald GB, Sanders JE (1990). **A retrospective analysis of therapy for acute graftversus- host disease: Initial treatment**. Blood **76**:1464 –1472.
9. Cahn JY, Klein JP, Lee SJ, Milpied N, Blaise D, Antin JH, Leblond V, Ifrah N, Jouet JP, Loberiza F, Ringden O, Barrett AJ, Horowitz MM (2005). **Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Société Française de Greffe de Moëlle et Thérapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study**. Blood Aug 15; **106(4):**1495-500.
10. Sophie P, Sung W. Choi and James L.M. Ferrara (2009). **Acute graft-versus-host disease: new treatment strategies**. Current Opinion in Hematology **16**:427–436.
11. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, Thomas ED (1995). **1994 Consensus Conference on Acute GVHD Grading.** Bone Marrow Transpl; **15(6):**825–8.
12. Garnett C, Apperley JF and Pavlů J (2013). **Treatment and management of graft-versus-host disease: improving response and survival.** Ther Adv Hematol. Dec;**4(6):**366-78.
13. Baron F, Maris MB, Sandmaier BM, Storer BE, Sorror M, Diaconescu R, Woolfrey AE, Chauncey TR, Flowers ME, Mielcarek M, Maloney DG, Storb R (2005). **Graft-versus-tumor effects after allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning**. J Clin Oncol. Mar 20; **23(9):**1993-2003.
14. Donato ML, Siegel DS, Vesole DH, McKiernan P, Nyirenda T, Pecora AL, Baker M, Goldberg SL, Mato A, Goy A, Rowley SD (2014). **The graft-versus-myeloma effect: chronic graft-versus-host disease but not acute graft-versus-host disease prolongs survival in patients with multiple myeloma receiving allogeneic transplantation**. Biol Blood Marrow Transplant. Aug; **20(8):**1211-6.
15. Gunhan Gurman, Pinar Ataca, Erden Atilla, Sinem Civriz Bozdag, Selami Kocak ToprakMeltem Kurt Yuksel, Taner Demirer, Hamdi Akan, Onder Arslan, Pervin Topcuoglu, Meral Beksac, Osman Ilhan ,Muhit Ozcan, (2015). 1952 **Positive Impact of Chronic Graft-Versus Host Disease on Survival in 928 Allogeneic Hematopoietic Stem Cell Transplant Recipients**. ASH. 57th Annual Meeting and Exposition. Orlando, FL. December 5-8.
16. Ishida T, Hishizawa M, Kato K, Tanosaki R, Fukuda T, Takatsuka Y, Eto T, Miyazaki Y, Hidaka M, Uike N, Miyamoto T, Tsudo M, Sakamaki H, Morishima Y, Suzuki R, Utsunomiya A (2013) **. Impact of graft-versus-host disease on allogeneic hematopoietic cell transplantation for adult T cell leukemia-lymphoma focusing on preconditioning regimens: nationwide retrospective study**. Biol Blood Marrow Transplant. Dec; **19 (12):**1731-9.
17. Ali N, Adil SN, Shaikh MU, Masood N (2013). **Frequency and Outcome of Graft versus Host Disease after Stem Cell Transplantation: A Six-Year Experience from a Tertiary Care Center in Pakistan**. ISRN Hematol. Jun 27;2013:232519