GRAFT-VERSUS-HOST DISEASE IN PEDIATRIC PATIENTS UNDERGOING ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR BENIGN DISORDERS (A SINGLE CENTER STUDY)

Mona Hassan Eltagui, Khaled Salama, Ahmed M Kaddah, Monica Ashraf Nashed[*], Mai Abd EL Salam

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Abstract

Background: Despite great advances in hematopoietic stem cell transplantation (HSCT) procedure, post-transplant complications -especially after allogenic transplant (allo-HSCT) - remain a great challenge. Graft versus host disease (GVHD) is the most important complication following allo-HSCT.

Objective: To evaluate the post-transplant GVHD in pediatric patients undergoing allo-HSCT for benign conditions.

Methods: The study included 36 pediatric patients, with benign hematological or immunological disorders, who underwent allo-HSCT in Hematology and Bone Marrow Transplantation Unit - Cairo University Children Hospital (2014-2020). Transplant-related data were recorded. Data regarding GVHD incidence, characteristics, management and outcome were collected.

Results: GVHD occurred in 58.3% of patients, with early onset GVHD in 47.2% while late GVHD in 36.1%; 9 patients developed both early and late GVHD (25%). Cutaneous GVHD occurred in 95.2% of GVHD patients while gut and hepatic involvement occurred in 19% and 14.3% respectively. Regarding acute GVHD cases, Grades I, II, III and IV occurred in 41.2%, 23.5%, 29.4% and 5.9% respectively. As for chronic GVHD cases, 53.8% developed mild disease while 30.8% developed severe disease. and only 15.4% had moderate affection. GVHD completely resolved in 12 patients (57.1%), 3 patients (14.3%) had residual stationary lesions not requiring treatment and 6 cases (28.6%) had controlled disease on immunosuppression.

Conclusion: Although GVHD is a common complication post allo-HSCT, especially when using Peripheral blood stem cells, prognosis with current treatment modalities is relatively good. Skin GVHD represents the most common form of GVHD followed by gut GVHD then hepatic GVHD.

Keywords: Hematopoietic stem cell transplantation, allogeneic, graft-versus-host disease

Department of Pediatrics (Pediatric Hematology Unit), Cairo University Kasr Alainy Faculty of Medicine, Cairo University, Cairo, Egypt
[*]Corresponding Email: monicaachraf@cu.edu.eg

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1. INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is defined as any procedure where hematopoietic stem cells are given to a recipient with the aim of repopulating and replacing the recipient's hematopoietic system either totally or partially. (1). Nowadays it is considered a potentially curative and life-saving therapeutic modality for many otherwise incurable malignant, hematological, immunological, or metabolic conditions (2,3)

Based on the donor, HSCT is either autologous (patient himself), syngeneic (identical twin), or allogenic (related or unrelated donor) (3). Different sources for stem cells include bone marrow harvest (BM), mobilized peripheral blood stem cells (PBSC), and cord blood (CB) (4).

Despite great advances in HSCT procedure, post-transplant complications -especially after allogenic

transplant (allo-HSCT) - remain a great challenge (1,5) Graft versus host disease (GVHD) is the most important complication following allo-HSCT. It may be as a self- limiting presentation up to being a life - threatening condition (6). The aim of this study was to assess GVHD incidence, characteristics, management and outcome in pediatric patients who underwent allo-HSCT for benign conditions.

2. PATIENTS AND METHODS

The study included 36 pediatric patients, diagnosed with benign hematological or immunological disorders, who underwent allo-HSCT in Hematology and Bone Marrow Transplantation Unit - Cairo University Children Hospital. Ethical committee approval was obtained (Code M D-5-2019). Parental written consents were obtained before enrolment. According to diagnosis, our patients were either transfusion- dependent chronic anemia (TDCA), primary immunodeficiency (PID) or severe aplastic anemia (SAA). TDCA included β- thalassemia major or sideroblastic anemia. PID diagnoses included severe combined immunodeficiency (SCID) and non-SCID conditions including severe congenital neutropenia, Chediak-Higashi syndrome, DOCK 8-Hyper-IgE syndrome, major histocompatibility complex class II (MHCII) defect and Interleukin-10 signaling defects. SAA group included transfusion-dependent cytopenias (acquired severe aplastic anemia and osteopetrosis). Pretransplant and transplant data were collected for all patients.

In our study, GVHD was classified as either early-onset (occurring between D0 and D+100) or late (occurring after D+100). Late GVHD in our study included acute GVHD (aGVHD) (persistent, recurrent, or late onset), and chronic GVHD (cGVHD) (classic cGVHD or overlap syndrome) (6,7). Main GVHD affected organs (skin, liver and GIT), treatments used, and outcome were recorded. Line of treatments evaluated included resuming Cyclosporin A (CSA) or adding any of the following: systemic steroids (oral or parentral), Mycophenolate Mofetil (MMF), topical steroids (for oral, skin or GIT lesions) or topical Tacrolimus (skin lesions).

Grading of severity of aGVHD was done in 4 grades (I to IV) based on the classification developed by **Glucksberg et al.** (6,8). Grading of cGVHD was done into three categories: mild, moderate and severe according to the organ-specific grading (7). Patients were followed up at least 1 year post transplant.

STATISTICAL ANALYSIS:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data was found non-parametric. Also, qualitative variables were presented as numbers and percentages.

3. RESULTS

Our study included 36 patients who underwent allo-HSCT: 22 males (61.1%) and 14 females (38.9%) with a median age at transplant of 3.8 (1.08 – 6) years, ranging from 0.16 to 14 years. The initial diagnosis was primary immunodeficiency (PID) in 18 patients (50%), severe aplastic anemia (SAA) in 11 patients (30.6%) and transfusion-dependent chronic anemia (TDCA) in 7 patients (19.4%). Pre-transplant patients' characteristics are shown in **Table (1).**

Regarding conditioning, reduced intensity conditioning (RIC) was used in 55.6% of cases, myeloablative (MA) conditioning in 25% while 19.4% didn't receive any pre-transplant conditioning. The GVHD prophylaxis in our patients was based on CSA either alone (19.4%) or in combination with another immunosuppressive (80.6%). CSA was combined with one or more of the following: Mycophenolate mofetil (MMF), methotrexate (MTX), antithymocyte globulin (ATG), or post-transplant cyclophosphamide (PT-CY), the latter being used in haploidentical transplants. All patients received mobilized PBSC.

Mean Total CD34 count was 10.17 ± 2.01, ranging from 7.2 to 15. Engraftment occurred between D+11 to D+35 with mean value 16.38 ± 5.00 Main transplant-related data is shown in **Table (2)**

Twenty-one of our patients (58.3%) developed GVHD. Early onset GVHD occurred in 17 patients (47.2%) while 13 patients (36.1%) had Late GVHD. Nine patients suffered from both early and late GVHD (25%)

Regarding GVHD patients, 95.2% (20/21 patients) developed skin involvement (cutaneous GVHD) while GIT and hepatic involvement occurred in only 19% and 14.3% respectively.

Regarding acute GVHD cases, 41.2% (7/17 patients) were Grade I, while grade II, III and IV occurred in 23.5%, 29.4% and 5.9% respectively. As for chronic GVHD cases, 53.8% (7/13 patients) developed mild disease while 30.8% (4/13 patients) developed severe disease. Moderate cGVHD occurred only in 2 patients (15.4%, 2/13 patients)

All of our GVHD patients were treated by adding steroids (either parenteral or oral).

Topical steroids were added in 81% of GVHD cases in the form of topical creams for skin lesions, steroids mouth wash for oral cavity lesions and GIT-locally-acting steroids for GIT symptoms. MMF was added in 33.3% of cases, while CSA was resumed in 19% of the patients. Topical Tacrolimus cream was added for skin lesions in 19% of cases.

At the time of our study, GVHD had completely resolved in 12 patients (57.1%) while symptoms improved in 3 patients (14.3%) with residual stationary old lesions but not requiring treatment. However, 6 of our GVHD cases (28.6%) were still on immunosuppressive treatment at the time of this study but their GVHD symptoms were controlled. All GVHD data are summarized in **Table (3).** Median duration of immunosuppression in our patients was 443.5 days ranging between 106 and 1620 days.

Table (1): Pre-transplant Data of transplanted patients

		Total No. = 36	Percentage
Repeated infections (pre-transplant)	No	9	25.0%
	Yes	27	75.0%
Blood Transfusions (pre-transplant)	None	10	27.8%
	Once	5	13.9%
	Multi	21	58.3%
Platelet Transfusions (pre-transplant)	None	25	69.4%
	Once	1	2.8%
	Multi	10	27.8%
Iron overload (pre-transplant)	No	18	50.0%
	Yes	18	50.0%
Patient CMV status pre-transplant	Negative	8	22.2%
	Seropositive	28	77.8%
Patient HCV status pre-transplant	Negative	31	86.1%
	Positive	5	13.9%

CMV: Cytomegalovirus, HCV: Hepatitis C virus

Table (2): Donor Characteristics and transplant related data

		Total = 36
Donor Diagnosis	Normal	32 (88.9%)
	Carrier	4 (11.1%)
Donor Type	Matched Sibling donor	28 (77.8%)
	Matched Family donor	7 (19.4%)
	Haploidentical Sibling donor	1 (2.8%)
Relationship of donor to patient	Brother	15 (41.7%)
	Sister	14 (38.9%)
	Mother	7 (19.4%)
Donor CMV status (pre-transplant)	Seropositive	31 (86.1%)
	Negative	5 (13.9%)
Type of Conditioning Regimen	Reduced intensity conditioning	20 (55.6%)
	Myeloablative	9 (25.0%)
	No conditioning	7 (19.4%)
Graft versus host disease prophylaxis	Cyclosporin A alone	7 (19.4%)
	Combined	29 (80.6%)
Total CD34 count dose ($x10^6$ /kg)	Mean ± SD	10.17 ± 2.01
	Range	7.2 – 15
Day of engraftment	Mean ± SD	16.38 ± 5.00
	Range	11 – 35
Duration of hospital stay during transplantation (days)	Mean ± SD Range	49.11 ± 18.81 27-108
Chimerism analysis at D+28 *	Complete chimerism	23 (65.7%)
	Mixed chimerism	11 (31.4%)
	Autologous	1 (2.9%)
Chimerism analysis at D+100	Complete chimerism	22 (61.1%)
	Mixed chimerism	14 (38.9%)
Chimerism analysis at D+180	Complete chimerism	21 (58.3%)
	Mixed chimerism	15 (41.7%)

Chimerism analysis at D+356	Complete chimerism	24 (66.7%)
	Mixed chimerism	12 (33.3%)

* At D+28, chimerism was not done for one patient due to non-engraftment.
CMV: Cytomegalovirus, D:Day SD: Standard deviation

Table (3): Graft versus host disease characteristics

Organs involved and treatment given to GVHD cases (No=21)		**No.**	**%**	**% (Total cases)**
Cutaneous GVHD	No	1	4.8%	2.8%
	Yes	20	95.2%	55.6%
Hepatic GVHD	No	18	85.7%	50.0%
	Yes	3	14.3%	8.3%
GIT GVHD	No	17	81.0%	47.2%
	Yes	4	19.0%	11.1%
GVHD treatment "added Steroids"	No	0	0.0%	
	Yes	21	100.0%	N/A
GVHD treatment "added MMF"	No	14	66.7%	
	Yes	7	33.3%	N/A
GVHD treatment "CSA resumed"	No	17	81.0%	
	Yes	4	19.0%	N/A
GVHD treatment "Topical Tacrolimus"	No	17	81.0%	
	Yes	4	19.0%	N/A
GVHD treatment "Topical steroids"	No	4	19.0%	
	Yes	17	81.0%	N/A
Outcome of GVHD	Controlled on ttt	6	28.6%	
	Resolved	12	57.1%	N/A
	Improved	3	14.3%	
Grading Of GVHD Cases				
Grade of acute GVHD (No=17)	Grade I	7	41.2%	19.4%
	Grade II	4	23.5%	11.1%
	Grade III	5	29.4%	13.9%
	Grade IV	1	5.9%	2.8%
Grade of Chronic GVHD (No=13)	Mild	7	53.8%	19.4%
	Moderate	2	15.4%	5.6%
	Severe	4	30.8%	11.1%

CSA: cyclosporin A, GIT: gastrointestinal tract, GVHD: graft versus host disease, MMF: Mycophenolate mofetil, N/A: not applicable, ttt: treatment

4. DISCUSSION

Among our 36 patients, males were more prevalent representing 61.1%. The median age at transplant in our patients was 3.8 (1.08 – 6) years, ranging from 0.16-14 years. The wide range starting from 2 month till 14 years is attributed to the different indications, since our PID patients are usually transplanted at a very early age.

The GVHD prophylaxis in our patients was based mainly on combined therapy (80.6%) including CSA with one or more immunosuppressive. Previous trials showed the superiority of combined therapy over CSA alone (9).

The overall incidence of GVHD in our patients was 58.3%: seventeen patients (47.2%) had early onset GVHD, this is in concordance with the incidence mentioned in the previous studies (9–11). Thirteen patients (36.1%) had late onset GVHD; late onset GVHD in our patients was due to cGVHD. The incidence of cGVHD in literature is 20-40% in pediatrics (12). The relatively high incidence of GVHD in our patients may be due to the use of PBSC in all patients (9,13).

In our study, aGVHD (II-IV) and (III-IV) occurred in 27.8% (10/36) and 16.7% (6/36) of patients respectively. **Holler et al.,** estimate that 40% of recipients of allo-HSCT develop moderate to severe

aGVHD (grade II to IV); **Zeiser and Blazar** estimate that severe disease (grade III-IV) occurs in 14% of overall allo-transplant recipients (6,9).

In our study, cutaneous GVHD was present in most of the patients with GVHD (95.2%). In the literature, skin is the most frequently affected organ in GVHD (5,12).

All of our patients received systemic steroids since the first-line treatment of GVHD -either acute or chronic- remain Corticosteroids therapy (14,15). Topical therapies were widely used in our patients since more than half of our patients had mild disease; **Jagasia et al.** confirmed the efficacy of local treatment in mild cases and of intensive local treatment in oral lesions. (7)

Graft-versus host disease remain a major complication after allo-HSCT, however, outcome has improved with more understanding of the underlying pathophysiology of the disease and the development of new treatment modalities.

Our results could be limited by the small sample size and that it involves a heterogenous group of patients.

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