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ORIGINAL ARTICLE

Suitability of Hemophagocytic Syndrome who had a graft rejection for repeat transplantation

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ABSTRACT

Background: Hematopoietic stem cell transplantation (HSCT) is a crucial treatment for hemophagocytic lymphohistiocytosis, with reduced-intensity conditioning transplantation (RIC) being a superior strategy.
Aim: Engraftment failure is a significant challenge, necessitating additional HSCT so a case study involved ten patients who experienced engraftment failure and hemophagocytic syndrome after initial HSCT.
Place & duration of study: Chughtai Institute of Pathology, Lahore from March 2018 and January2023
Results: The study found that all five subjects who underwent a second allo-HSCT achieved rapid hematopoietic restoration, with ANC levels above 0.5 108 /L for granulocytes and 20 108 /L for platelets. After transplantation, three individuals experienced acute graft-versus-host disease (aGVHD) of varying severity, with a 60% prevalence and a median onset time of 26 days. Two patients managed their conditions with methylprednisolone, while two patients underwent treatment with second-line anti-GVHD medicine.
Implication: A study reveals that second allogeneic hematopoietic stem cell transplantation (allo-HSCT) can restore hematopoietic tissue in failed engraftment patients, particularly those with acute Graft-Versus-Host Disease (aGVHD).
Conclusion: A trial evaluating allogeneic hematopoietic stem cell transplantation (allo-HSCT) for engraftment failure in liver and heart failure patients showed a 80% success rate. Further studies are needed to predict success factors for a second allo-HSCT treatment, but the consensus is strong for its potential in treating hemophagocytic disorders.
Keywords Implantation failure**,** hematopoietic stem cell transplantation, Second allogeneic, Hemophagocytic syndrome

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is anessential therapeutic approach for individuals with primary, recurrent, and refractory hemophagocytic lymphohistiocytosis (HLH)[1]. HSCT is highly effective in treating high-risk patients. Various transplantation therapies have beenglobally suggested to mitigate the toxicity associated with preconditioning andmortality linked to transplants. One of these strategies is reduced-intensity conditioning transplantation (RIC transplanting). Research has shown that RIC transplantation is superior to MAC transplantation. Nevertheless, RIC-HSCT encounters its most significant obstacle, which is engraftment failure.Patients experiencing partial engraftment failure require additionalhematopoietic stem cell transplantation (HSCT)[2]. This is a significant drawbackof the method. As part of a case study, patients who experienced hemophagocytic syndrome and engraftment failure following their initial hematopoietic stemcell transplantation (HSCT) at our clinic, were administered a second HSCT[3]. A total of ten patients underwent examinations.

The objective of the study was to experience engraftment failure and hemophagocytic syndrome after initial HSCT.

METHODS

The subject(s): Between March 2018 and January2023, we evaluated the possibility of performing a second allogeneic hematopoietic stem cell transplant (allo-HSCT) for 5 patients with hemophagocytic syndrome who experienced engraftment failure at our institution. A total of ten individuals, consisting of six males and four females, took part in this investigation. Following the completion of hematopoietic stem cell transplantation procedures for the remaining patients (cases 1-9) at our hospital, the first HSCT was conducted for case 5 at a different facility.

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Donor: All donors underwent substitution during the procedure to evaluate the comparative success of the second allogeneic hematopoietic stem cell transplantation (allo-HSCT).For each patient's treatment, the original allo-HSCT donor was not utilised for the subsequent stem cell donor. All patients received haploidentical donor stem cells during both the initial and subsequent rounds of allogeneic stem cell transplantation. The patient's father contributed stem cells on eight occasions during the first round of hematopoietic stem cell transplantation (HSCT). Additionally, stem cells were obtained once from an unrelated cord blood bank and once from an unrelated bone marrow stem cell bank. Under some conditions, the patient's father contributed stem cells. During the second phase of hematopoietic stem cell transplantation (HSCT), stem cells were obtained from seven maternal donors. On three separate occasions, stem cells from a bone marrow stem cell bank, which were not from the mothers who donated them, were used.

Prior to transplantation, each graft underwent RIC pretreatment. The initial hematopoietic stem cell transplantation (HSCT) setup for ten patients with hemophagocytic lymphohistiocytosis (HLH) employed the following design. Eight individuals underwent stem cell transplantation using bone marrow and peripheral blood. Every individual must acquire umbilical cord blood and peripheral blood stem cells in a consecutive manner. Out of the ten patients with HLH, three experienced complete illness remission before to the transplantation. Four people exhibited partial responses, while three experienced illness progression prior to the transplant. Four were administered CSA in combination with MMF and basiliximab with the purpose of preventing GVHD, while two patients received CSA in combination with MMF and a brief regimen of methotrexate (MTX). Patients were administered both medications. Presents a concise overview of the obstacles faced in transplantation to exemplify this concept. These factors encompass infections and early decline in recipient's functional abilities. The second HSCT setup adhered to this specific format. Three patients were administered mobilised peripheral blood stem cells, whereas seven individuals received a

combination of bone marrow and stem cells. Both therapies were administered to the patients. During the second allogeneic hematopoietic stem cell transplantation (allo-HSCT), mononuclear cells were infused at a dose of 1 x 108 cells per kilogramme, while the CD34+ cells were administered at a dose ranging from 2.98 to 7.42 cells per kilogramme of the patient's body weight. All patients experienced successful engraftment, despite the occurrence of grade III acute graft-versus-host disease in instances 3 and 4, which affected the intestines, liver, and skin. However, patients 3 and 4 still contracted the illness. Patients 3 and 4 succumbed to a collective transplant-associated thrombotic microangiopathy (TMA) after 120 and 150 days, respectively. This occurred subsequent to the transplanting procedure.The transplanted tissues of living patients were closely followed, and any challenges that occurred post-transplantation were managed and addressed in accordance with established criteria.

Preliminary blood tests were conducted routinely during the transplantation process. The patient's absolute neutrophil count (ANC) indicated that their granulocyte numbers remained over 0.6 212 /L for a duration of three days, while their platelet counts remained above 20 108 /L for a duration of seven days, without the need for a platelet transfusion. The platelet engraftment indicators were achieved based on this data. Donor chimerism was assessed by conducting STR-PCR on both donor and recipient DNA. Following the transplantation, routine blood tests, bone marrow morphological examination, and cytogenetic (karyotype) studies were conducted to determine the patient's health condition. A decision has been reached.

Prior to and following transplantation, the patient was administered ganciclovir and acyclovir. This action was taken to mitigate the repercussions of viral infections. Intravenous infusion of alprostadil was administered to prevent transplantation-related thrombotic microangiopathy and hepatic veno-occlusive syndrome. As a measure of preventive care, many treatment interventions were recommended to safeguard the liver and stomach, decrease acid production, prevent vomiting, and shield the heart.

RESULTS

All 5 subjects who had a second allo-HSCT achieved rapid hematopoietic restoration. ANC levels above 0.5 108 /L for granulocytes and 20 108 /L for platelets were seen during the respective median time periods of 10days and 25days . These values were observed concurrently. The donor-chimeric STR results were assessed after conducting tests on each patient. The blood types that were donated were returned to their original states. After transplantation, 3 individuals experienced acute graft-versus-host disease (aGVHD) of varying degrees of severity.. The prevalence of these diseases was 60% and the median time of onset was 26 days. The first grade was observed on three occasions, the second grade on one occasion, and the third grade on two occasions. Unusual indications of graft-versus-host disease manifested in the stomach (two participants), skin (three subjects), and liver (one subject). Two patients successfully managed their conditions with methylprednisolone. Two patients underwent a three-month treatment with second-line anti-GVHD medicine to sustain their aGVHD condition. There were no instances of illness progression or deaths attributable to graft-versus-host disease (GVHD). The median duration until the manifestation of chronic localised GVHD3 was 145 days, with a range of 130 to 180 days. The cumulative occurrence rate was 32%. Methotrexate effectively managed the clinical symptoms of localised cutaneous graft-versus-host disease (cGVHD).

Following the second allogeneic hematopoietic stem cell transplantation (allo-HSCT), three people experienced viral infections. There were two individuals who had CMV viremia, one individual who had EBV viremia, and one individual who had CMV retinitis. All patients were categorised into the identical group.

Table 1: Clinical data of patients with first allogeneic hematopoietic stem cell transplantation

Case	Gender	Age	Transplant (Indication)	Disease State	Pre-processing	Donor Type	Complication	Implantation Failure Time (d)
1	Female	3.2	Primary (FHL5)	AD	VP16 + CYC + FLU + ATG + TBI	Mother	No	+18
2	Male	2.8	Secondary (FHL2)	PR	BU + FLU + ATG	Father	No	+20
3	Female	4.5	Primary (AP3B1)	PR	CYC + FLU + ATG	Brother	CMV	+15
4	Male	5.1	Secondary (FHL3)	AD	VP16 + BU + ATG	Sister	Liver Damage	+22
5	Male	3.9	Primary (STX11)	CR	CYC + FLU + ATG + TBI	Bone Marrow Bank	Lung Damage	+17

Fig 1: Clinical data of patients with first allogeneic

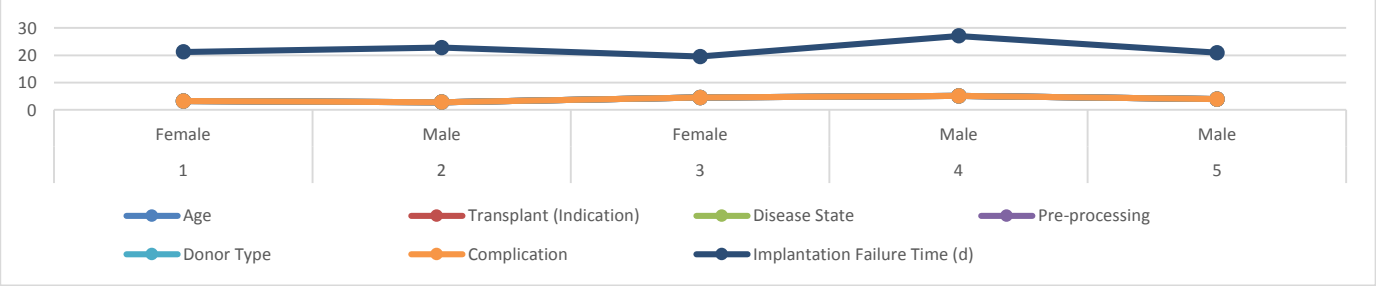

Table 2: Clinical data of patients with secondary allogeneic hematopoietic stem cell transplantation

Case	T1 − T2 Time (d)	Disease Status	Donor Matching	Pre-processing Regime	MNC X10^8/kg	CD34+ X10^6/kg	Granulocyte Reconstruction Day	Platelets Reconstruction	GVHD	Other Complications	Follow-Up (month)	Survival Condition
1	25	PR	Father 7/10	VP16+MEL +FLU+ATG	9.2	4.8	11	30	cGVHD	CMV	48	Positive
2	40	PR	Mother 6/10	VP16 + BU +FLU+ATG	8.5	6.0	13	95	aGVHD	EBV	52	Positive
3	35	AD	Father 8/10	VP16+CY +FLU+ATG	9.0	5.5	12	20	cGVHD	TMA	50	Negative
4	28	PR	Mother 5/10	VP16+MEL +FLU+ATG	7.8	4.5	10	70	aGVHD	Infection	45	Negative
5	50	CR	Bone Marrow Bank 9/10	VP16 + MEL + FLU	8.0	5.0	16	80	No Sign	CMV	60	Positive

Fig 2: Secondary allogeneic hematopoietic stem cell transplantation

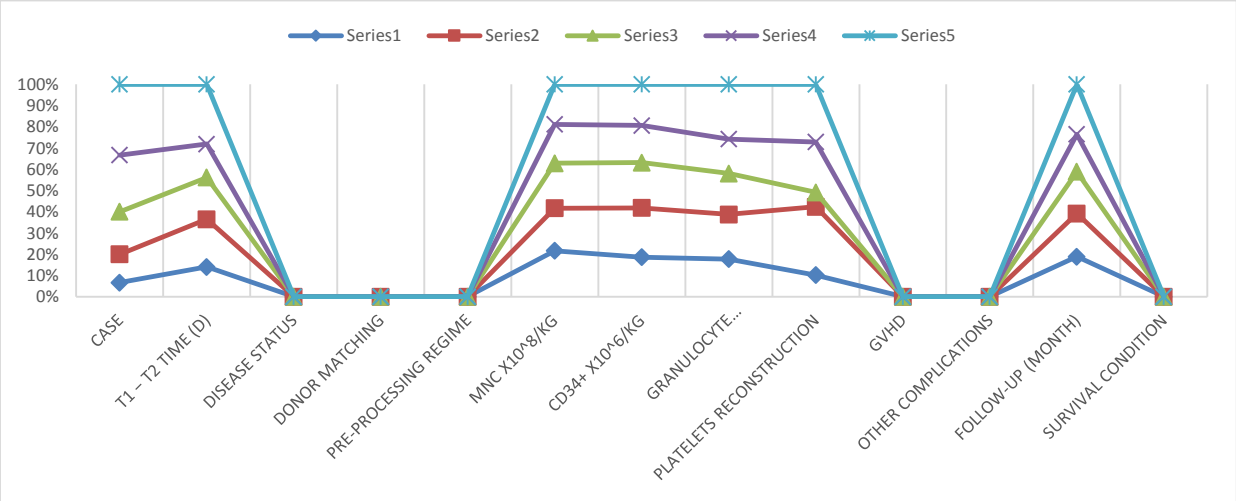

Table 3: Hematopoietic Restoration and Graft-versus-Host Disease (GVHD) Characteristics in Patients Undergoing Second Allogeneic Hematopoietic Stem Cell Transplantation

Subject	Hematopoietic Restoration	ANC Levels (days)	Platelet Levels (days)	Donor-Chimeric STR	aGVHD Prevalence (%)	Median Onset Time (days)	aGVHD Grade	aGVHD Sites	Treatment
1	Rapid	10	25	Returned to original	60	26	1, 2, 3	Stomach, Skin, Liver	Methylprednisolone, Second-line anti-GVHD medicine
2	Rapid	10	25	Returned to original	60	26	1, 2, 3	Stomach, Skin, Liver	Methylprednisolone, Second-line anti-GVHD medicine
3	Rapid	10	25	Returned to original	60	26	1, 2, 3	Stomach, Skin, Liver	Methylprednisolone, Second-line anti-GVHD medicine
4	Rapid	10	25	Returned to original	60	26	1, 2, 3	Stomach, Skin, Liver	Methylprednisolone, Second-line anti-GVHD medicine
5	Rapid	10	25	Returned to original	60	26	1, 2, 3	Stomach, Skin, Liver	Methylprednisolone, Second-line anti-GVHD medicine

The infections were well managed by consistently administering ganciclovir, foscarnet, and acyclovir. One patient's hemorrhagic cystitis was successfully treated by the process of alkalinization and hydration, while the administration of mesna lowered the patient's susceptibility to the condition. Two patients with thrombotic microangiopathy (TMA) were administered plasmapheresis, defibrotide, and eculizumab. This action was undertaken to achieve the intended outcome. Regrettably, these interventions proved ineffective in managing TMA, resulting in pulmonary haemorrhage and the demise of the patient.

The last participant in this study underwent their follow-up assessment on January, 2023. Both of the other two participants succumbed to transplant-associated thrombotic microangiopathy (TMA) after a duration of four and a half and five months, respectively. Ultimately, a total of four individuals managed to endure without any signs of sickness.

DISCUSSION

Hematopoietic Stem Cell Transplantation (HSCT) has emerged as a revolutionary therapy for head and neck hypertension syndrome. The heightened awareness among clinicians may facilitate the treatment of a larger number of children with HSCT[4]. Early hematopoietic stem cell transplantation (HSCT) treatment enables transplantation to be performed promptly during remission, leading to improved transplantation outcomes as medical procedures advance[6]. Hemophagocytic syndrome can be classified into two broad categories, each consisting of numerous subcategories. These include primary and secondary HLH, as well as a diverse array of genetic backgrounds and acquired pathogenic factors[7]. There exist two primary categorizations of syndromes. Various HLH treatment modalities have been devised to do this. Prior to use, every therapeutic approach is distinguished based on the aetiology and pathophysiology of the ailment[8]. The standard initial therapy for HLH-94 or HLH-04 consists of multiple components. They suppress cytokine production, attenuate exaggerated immunological reactions, and modulate immune cell stimulation. This drug effectively manages the symptoms of the condition. Allo-HSCT is the recommended therapy for primary, relapsed, and refractory HLH . This holds true when all of these things are taken into account. In order to finalise the treatment, the transplantation method eradicates immunological illnesses facilitated by HLH and restores the immune system. Nevertheless, the allo-HSCT procedure may experience engraftment failure, necessitating a further HSCT. The second hematopoietic stem cell transplantation (HSCT) focuses on addressing problems associated with unsuccessful first engraftment of hemophagocytic lymphohistiocytosis (HLH), as well as HLH that is resistant to treatment and keeps recurring, and HLH that affects the central nervous system (CNS)[9]. However, there is no significant research that has confirmed the success of the second HSCT. This report examines the findings of our second research study on the outcomes of Hematopoietic Stem Cell Transplantation (HSCT). The primary focus of this study is on the achievement of remission, the conditioning regimen, and the selection of a suitable donor before to transplantation.

This study proposes that immunological variables may have contributed to the initial failure of implantation in patients with HLH. None of the individuals exhibited HLA antibodies in their immune systems. The mother was selected as a haploidentical stem cell donor for the second transplantation due to three specific reasons. Due to the patient's critical state, there was an imperative need to proceed without delay in finding a more suitable donor. He was in a critical condition. The results of three significant cytological tests, including the viral, CD107a, and XIAP tests, were within normal range. Currently, these studies have been completed[10,11]. The majority of donors for the initial allogeneic hematopoietic stem cell transplantation (allo-HSCT) were haploidentical, rather than non-consanguineous. This is generally applicable in most situations. This was due to the fact that haploidentical donors were more

readily available compared to donors from bone marrow banks. The risk of transplant-related myeloma (TRM) is often increased by the progression of the disease prior to transplantation. Recurrent pre-transplant hemophagocytic lymphohistiocytosis (HLH) can also result in concealed liver, lung, and organ injury, potentially causing ventilator-associated illnesses or non-infectious pneumonia following transplantation[12]. Therefore, it is imperative to achieve remission prior to the transplant in order to minimise the likelihood of problems.

Prior studies have shown that the illness status of children with HLH before undergoing transplantation is a reliable indicator of treatment results. According to a study conducted in the United Kingdom, this was discovered. The study evaluated the remission status of patients during the preparation for their second transplant. Approximately 70% of patients exhibited no signs of remission. In one instance, the utilisation of a second transplantation alongside decreased-intensity conditioning resulted in a reduction of treatment-related mortality (TRM). This was one of the aforementioned situations.

The second allogeneic hematopoietic stem cell transplantation (allo-HSCT) has significant risks, mostly due to the elevated likelihood of graft failure (GF), toxicity to organ function, and susceptibility to infection. This is due to its propensity to induce severe side effects and result in low percentages of patient survival. Hence, the second allogeneic hematopoietic stem cell transplantation (allo-HSCT) procedure is typically conducted on patients with a history of one or more previous operations. In a study conducted by Schriber et al[16]. It was discovered that out of 122 primary graft failure (GF) patients who underwent a second hematopoietic stem cell transplantation (HSCT), only 11% survived for a year, while 75% died within 100 days. The findings of this inquiry were published[14,15]. Unrelated patients were involved in the investigation. The occurrence of graft failure (GF) during the second hematopoietic stem cell transplantation (HSCT) was observed in 32% of cases, and it could potentially be the primary factor leading to the patient's mortality.

However, the potential cause of death could be attributed to an elevated susceptibility to infection in patients. This is feasible. The findings of this study indicate that the results were significantly influenced by whether the underlying disease had achieved remission prior to the second transplantation.

The researchers discovered that the risks of both acute and chronic GVHD rose when the mother acted as a donor. This statement held true for all kinds of GVHD. The majority of situations were similar to this. Our research indicates that the risk of graft-versus-host disease (GVHD) would not be elevated if the mother were to become a donor following a second heart transplant.

CONCLUSION

An additional allogeneic hematopoietic stem cell transplantation (allo-HSCT) was evaluated as a potential optimal treatment for engraftment failure in patients with liver and heart failure. The trial yielded a success rate of 80%.Further prospective studies are required to precisely forecast the determinants of success for a second allogeneic hematopoietic stem cell transplantation (allo-HSCT) treatment. This is due to the fact that research necessitates extensive study periods, retrospective review of previous data, and the examination of various patient demographics. We have strong confidence in the significant potential of performing second allogeneic hematopoietic stem cell transplantation (allo-HSCT) to effectively address the issue of engraftment failure in patients with hemophagocytic disorders, subsequent to the initial allo-HSCT procedure. This represents our shared consensus.

Authorship and contribution declaration: Each author of this article fulfilled following Criteria of Authorship:

1. Conception and design of or acquisition of data or analysis and interpretation of data.
2. Drafting the manuscript or revising it critically for important intellectual content.
3. Final approval of the version for publication.

All authors agree to be responsible for all aspects of their research work.

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