Stem Cell Transplantation in Glanzmann's Thrombasthenia: A Report of Two Adult Patients

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ABSTRACT

Glanzmann's thrombasthenia (GT) is an autosomal recessive bleeding disorder characterised by mucocutaneous bleeding. At molecular level, defect in platelet receptor glycoprotein (GP) IIb/IIIa leads to defective platelet aggregation. Anti-fibrinolytic agents, platelet transfusions, and factor rVIIa are used for prophylaxis before invasive procedures and treatment of bleeding events. Allogeneic stem cell transplant is the only curative option. Here, we report cases of two adult male patients who underwent matched sibling donor stem cell transplantation for GT with recurrent bleeding requiring platelet and red cell transfusions. Both showed marked improvement in quality of life. To conclude, stem cell transplant is a viable treatment option for severe, difficult-to-control cases of GT.

Key Words: *Platelet disorders, Hematopoietic stem cell transplantation, Thrombasthenia.*

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INTRODUCTION

Glanzmann's Thrombasthenia (GT) is a rare congenital bleeding disorder caused by a defect in the platelet surface receptor glycoprotein (GP) IIb/IIIa complex (ITG αIIbβIIIa). It is characterised by mucocutaneous bleeding, a normal platelet count and prolonged bleeding time.[1] Intracerebral haemorrhage is relatively rare but potentially life-threatening complication.[2] Diagnosis is made by demonstration of abnormal platelet aggregation.[3] Treatment in the form of anti-fibrinolytic therapy, platelet transfusions and rVIIa is needed for surgical and non-surgical bleeding events.[1] Recurrent severe bleeding requiring platelet and red cell transfusions and platelet alloimmunization are the major management complexities. Stem cell transplant is the only curative treatment option.[4] There are 19 reported cases of transplants in GT internationally with a median patient age of 5 years. Here, we present, for the first time, reports of two adult patients who underwent stem cell transplants for GT.

CASE 1:

An 18-year male was referred to our institute for evaluation of bleeding since birth. He first presented at the age of 1 year with heavy per rectal bleeding. Since then, recurrent episodes of epistaxis and gum bleeding occurred leading to transfusion-dependent anaemia. Red cells were transfused almost once every month.

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Since platelet count and coagulation profile were normal, he was investigated for platelet function defects and was found to have GT. When taken to transplant, he had received more than 40 units of red cell concentrates and more than 250 units of platelets. He was fully HLA-matched with his younger sister (age 16 years). Both patient and donor had the same ABO blood group but Rh incompatibility was present (the recipient was Rh positive and the donor was Rh negative).

During pretransplant workup, he was incidentally found to have situs inversus and dextrocardia. His general condition was good, with Karnofsky Performance score of 90% and haematopoietic stem cell transplant comorbidity index (HCT-CI) score of zero (0). Both donor and recipient tested positive for CMV and EBV IgG antibodies.

After conditioning chemotherapy with busulfan, 14 mg/m^2, cyclophosphamide, 120 mg/m^2, and ATG 10 mg/kg ($BU^{14}CY^{120}ATG^{10}$), he received stem cells collected *via* bone marrow harvest and peripheral blood apheresis (PBSC) with CD34 dose of 5.6×10^6/kg. He received graft *vs*. host disease (GvHD) prophylaxis with twice daily dosing of Cyclosporine (CSA) starting from Day -1 and IV Methotrexate (MTX) 10 mg/m^2 on day +1, and 8 mg/m^2 on day +3 and +6. Standard prophylaxis for herpes zoster and pneumocystis jirovecii was also given. The posttransplant period was complicated by febrile neutropenia starting on day +6, which responded to broad-spectrum antibiotics. Grade 2 mucositis occurred after the second dose of MTX. However, he managed his oral feed and did not require parenteral nutrition.

Neutrophil engraftment was achieved on day +13 and platelet engraftment on day+19. Currently, the patient is 100 days post

transplant. He is asymptomatic with stable blood counts (platelet counts 110×10^9/l; haemoglobin (Hb), 14.9 g/dl; total leucocyte count (TLC), 4.5×10^9/l). Donor chimerism is more than 95% and there is no evidence of GvHD.

CASE 2:

A 23-year male presented to the outpatient department in 2015, with history of epistaxis and recurrent gum bleeding from childhood. Regular red cell transfusions were required (~2 red cell concentrates per month) to maintain Hb of around 7-8 g/dl. The diagnosis of GT was confirmed on platelet aggregation studies and, given the severity of his disease, the option of allogeneic stem cell transplant was explored. Fortunately, he had an HLA-matched sister available with no ABO mismatch. Myeloablative conditioning chemotherapy with busulfan, 12.8 mg/m^2, cyclophosphamide 120 mg/m^2 and ATG 15 mg/kg (BU $^{12.8}$ CY ^{120} and ATG ^{15}) was given, followed by infusion of bone marrow harvested stem cells (CD34+ dose 6.9×10^6 cells/kg). Posttransplant GvHD prophylaxis was with cyclosporine and methotrexate. Neutropenic fever occurred in an immediate posttransplant period which settled with broad-spectrum antibiotics and anti-fungal agents. Neutrophil engraftment occurred on day +14 and platelet engraftment on day +19.

A month posttransplant (day +28), his renal functions deteriorated with creatinine rising to 886 umol/l and urea 27.2 mmol/l. Cyclosporine was withheld and replaced with methylprednisolone. Renal functions improved gradually on cessation of nephrotoxic medication. This was followed by the development of CMV reactivation which was managed with IV ganciclovir initially and oral valganciclovir, later on.

On day +81, he developed poor graft function with donor chimerism dropping to 60%. A stem cell boost was planned but the patient and family declined. Immune suppression was optimised with low-dose cyclosporine and mycophenolate mofetil (MMF). The patient was followed closely for graft function, which improved over time. At 1-year posttransplant, whole blood donor chimerism improved to 85%. Lineage-specific chimerism was 75% for T-cells and CD15 (myeloid) 85% percent at 18 months.

Currently, he is 23 months posttransplant, off immunosuppression and without GvHD. Short Tandem Repeats (STRs) for donor chimerism show stable mixed chimerism (85%). He is living a good quality life with normal blood counts, and no bleeding or transfusion requirement.

DISCUSSION

Data reported till date regarding hematopoietic stem cell transplant in GT is limited to case reports and series and includes transplants carried out in children and young adults with serious bleeding symptoms, both with and without antiplatelet antibodies, using bone marrow, umbilical cord, or peripheral blood stem cells.[5] To our knowledge, patients presented here are the first ever reported cases from Pakistan.

GT is an autosomal recessive bleeding disorder, with prevalence of 1 per million worldwide. In certain ethnic groups, with increased incidence of consanguinity, prevalence rate of 1 in 200,000 have been reported.[1] The true burden of the disease is not known in Pakistan; however, a study from Karachi showed GT in 9.6% (n=27) of patients who presented with bleeding history, making it the third most common disorder after von Willebrand disease and fibrinogen deficiency in autosomal recessive bleeding disorders (ARBDs).[6] In another study from Lahore, the incidence was reported to be 20.4%.[2] The male-to-female ratio was 1.2:1. Mean age at diagnosis was 7 ±2.5 years ranging from 3 months to 35 years. Consanguinity was observed in 65% patients.[2]

Treatment options in response to surgical, traumatic or spontaneous bleeding include anti-fibrinolytic therapy and platelet transfusion. Repeated platelet transfusions carry the risk of development of platelet alloimmunisation, in addition to the risks of transfusion-transmitted infections, transfusion-associated lung injury and volume overload common to all blood products. Antibody formation has been reported to occur in 25-70% of patients.[1,3] Apart from anti-HLA antibodies, antibodies against missing platelet glycoproteins are also formed, which is of particular concern in women of child-bearing age as these antibodies may cross the placenta causing severe foetal thrombocytopenia.[1] Transfusing HLA-matched and leukocyte-depleted platelets reduce but do not eliminate the risk of antibody formation. These processes, while recommended, may not be feasible in many clinical settings. Recombinant factor VIIa is approved both for prophylaxis before invasive procedures and treatment of bleeding episodes, especially in platelet refractory cases.[3]

Despite tremendous advances in understanding the molecular nature of the disease, satisfactory treatment of GT remains a challenge. Recurrent spontaneous bleeding and persistently high haemorrhagic risk impair the quality of life significantly. Apart from allogeneic stem cell transplant, the other treatment options mentioned above are non-curative. Indications for stem cell transplant in GT are not clearly defined but include recurrent, severe bleeding episodes, platelet refractoriness and red cell transfusion dependency due to recurrent blood loss.[7] So far, 19 cases of stem cell transplant in GT have been reported.[4] The median age of patients was 5 years. At a median follow-up of 25 months, all patients were alive. Busulfan plus cyclophosphamide was the most common conditioning regimen used.[7-9] The outcome of stem cell transplant is compromised by various complications including conditioning toxicity, infectious complications and GvHD. While data in GT is limited, fully matched sibling donors, reduced conditioning regimens and well-optimised GvHD prophylaxis strategies improve transplant outcomes in hematologic disorders in general. In Pakistan, the large average family size and high prevalence of consanguinity make it possible to find matched sibling donors. In 70% of cases, a matched family donor is identified.[10] In our case, the recurring requirement of red cell concentrates and platelet transfusion in face of inadequate transfusion facilities was the main indication for stem cell transplantation. Both of our patients had fully

matched sibling donors available and received ATG in addition to busulfan and cyclophosphamide in conditioning regimen. Both are doing well with adequate graft function, have not experienced bleeding symptoms posttransplant and are transfusion-independent.

With gene therapy still in the experimental phase, haematopoietic stem cell transplant remains the only curative option.[5] It is indicated in cases with recurrent life-threatening bleeding complications, particularly if patients are refractory to platelet transfusions. Transplant is usually considered in younger population with probably lower risks of associated complications mainly GvHD and platelet refractoriness.

In adults, haematopoietic stem cell transplant should be assessed on an individual basis and the risk of transplantation complications should be balanced against the risk of bleeding problems of GT and the ability to control bleeding with the available therapy.

COMPETING INTEREST:
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JR: Collected data and prepared initial draft.
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NS: Proofread and collected data.
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