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Case Report
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Immune Thrombocytopenia after Allogeneic Stem Cell Transplantation: Case Report and Brief Overview of Treatment Strategies

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ABSTRACT

Immune thrombocytopenia (ITP) is a rare but well-recognized post-allogeneic hematopoietic stem cell transplant (HSCT) autoimmune complication for which a standard treatment approach is lacking. Herein we report on an adult patient affected by high-risk acute myeloid leukemia (AML) who developed a post-HSCT ITP. Due to the refractoriness to first-line therapies the patient underwent the thrombopoietin (TPO) mimetic Eltrombopag obtaining the ITP resolution. We also discuss the clinical course of ITP in post-HSCT setting and pros and cons of different therapeutic strategies, focusing on the emerging role of TPO mimetics.

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Introduction

Hematological autoimmune complications can occur, although infrequently, after autologous and allogeneic hematopoietic stem cell transplantation (HSCT). Immune thrombocytopenia (ITP) is a rare but well recognized post-autologous HSCT complication, whose underlying pathogenetic mechanisms include imbalances in CD4/CD8 T cell subsets, abnormal expression of self antigens as a result of damage induced by radiotherapy or chemotherapy, and viral infections that can occur during the post-transplant period[1]. After allogeneic HSCT, isolated thrombocytopenia can result from poor (or loss of) engraftment, infectious events, graft versus host disease (GVHD), impending relapse of the underlying hematologic disease or, in the absence of any of these conditions, immune dysregulation. To our knowledge, there are few data about the incidence of post-allogeneic HSCT ITP because they are usually described in case reports or brief case series whereas large clinical studies often include other types of post-HSCT thrombocytopenia. Indeed post-allogeneic HSCT ITP pathogenesis is far from been elucidated and a consensus for treatment lacks too[2]. In fact first line therapies such as steroid and intravenous gamma globulins (IVIG) tend to be ineffective in most cases[2], whereas second line treatments may prove more toxic than we observe in general ITP population. Thrombopoietin (TPO) mimetic agents Romiplostim and Eltrombopag have recently appeared in the landscape of ITP treatment but their efficacy and safety in post transplantation setting have not been extensively evaluated yet[6-12]. Herein we describe the clinical course of an adult patient affected by post-allogeneic HSCT ITP refractory to prednisolone, IVIG and Rituximab who was treated with Eltrombopag because of the high risk of side effects associated with other second line therapies.

Case Report

In December 2013 a 55-years old man was diagnosed with de novo FLT3-ITD and NPM1-mutated acute myelogenous leukaemia (AML), FAB M5a. Between December 2013 and April 2014 the patient received standard induction chemotherapy with cytarabine, etoposide and mitoxantrone, obtaining complete remission, and two consolidation cycles with high-dose cytarabine. Because of the high biological risk of the disease, in June 2014 the patient underwent an HSCT from an HLA-matched unrelated donor. The myeloablative conditioning included cyclophosphamide and total body irradiation, while GVHD prophylaxis consisted of short-course methotrexate and cyclosporine. The immediate post-transplantation course was unremarkable, and no infectious complications or GVHD were observed. The engraftment was obtained on day 15, and a full-donor chimerism was documented on day 21; cyclosporine was gradually tapered off and discontinued by day 185.

In January 2015, on day 230 after HSCT, the patient developed bilateral lower limb petechiae. At that time the platelet count was 8000/μl, whereas haemoglobin levels and white blood cell count remained within the normal range. Platelet transfusions were no effective. A bone marrow aspirate revealed a normocellular marrow with 2-3 megacaryocytes per low-magnification field without dysplastic aspects. No cytomegalovirus, Epstein-Barr virus, and herpes simplex virus 1-2-6-8 DNA copies were detected in bone marrow. A full-donor chimerism was confirmed.

A diagnosis of ITP was therefore made. The patient was initially treated with IVIG at the dosage of 0.4 g/Kg for 5 days without success; oral prednisone (1 mg/Kg per day) was then administered for 3 weeks with no results. Given the high surgical (the platelet count never rose above 10 000/ml) and infectious risks of splenectomy, in March 2015 the patient underwent a further pharmacological treatment (Rituximab 375 mg/sqm for four-weekly doses) without any improvement in platelet count. Although data about the post-HSCT use

of TPO-receptor agonists were scanty, starting from May 2015 the patient received Eltrombopag 50 mg per day, escalated to 75 mg per day 2 weeks later. After 6 weeks of treatment the platelet count rose stably above 10 000/ml reaching 50 000/µl after 3 months (Figure 1); the treatment was well tolerated and caused just a grade 1 transaminitis. Unfortunately, in October 2015, 5 months after Eltrombopag beginning and 16 months after HSCT, the patient developed red-purplish skin nodules; punch biopsy taken from a left arm skin lesion confirmed AML relapse. At that time bone marrow examination showed no increase in blast cells, however one month later a bone marrow relapse also occurred and the patient died of septic shock during reinduction chemotherapy.

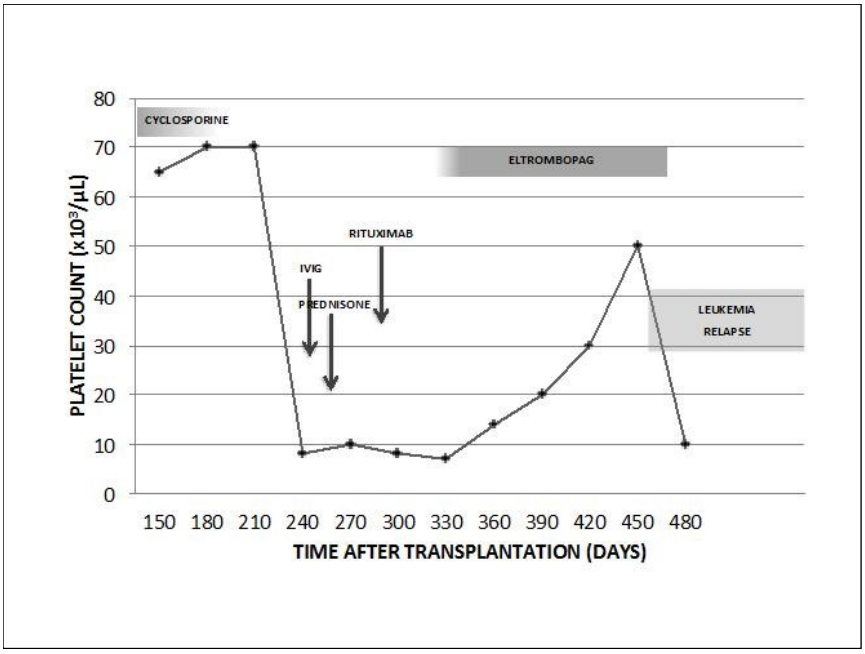

Figure 1. Course of platelet count and its correlation with therapeutical interventions and days after transplantation.

Discussion

ITP is a rare but well-recognized post-HSCT hematologic autoimmune complication. Although reduced conditioning regimens and matched unrelated donors have been suggested as risk factors[2], donor haematological background should also be considered. Indeed ITP transmission from donor to recipient, especially in T-replete transplantation platforms, has been previously described[3].

As occurred in our case and according to the literature, post-HSCT ITP is frequently refractory to first line therapies such as steroids and IVIG[2] thus representing a clinical challenge. Different strategies have been reported to manage refractory post-HSCT ITP (Table 1). Gergis U *et al* treated successfully a refractory post-HSCT ITP patient resuming immunosuppression with tacrolimus, which had been tapered off and stopped 3 months before[4]. Although the patient obtained prompt platelet recovery, this approach may not be advisable in some malignant disease, such as high-risk AML, in which prolonged immunosuppression may reduce graft versus leukaemia effect and increase relapse risk. Splenectomy was reported as a treatment option for severe post-transplant hematologic autoimmune diseases, but serious infectious complications are a major concern and limit its use in this setting[5]. Rituximab was also reported as an effective treatment for post-HSCT ITP. Raj K *et al* treated successfully two post-HSCT ITP patients with Rituximab without significant toxicity[2]; Faraci M *et al*

Table 1. Treatment of refractory post-allogeneic HSCT ITP

Author	No. Refractory Post-HSCT ITP patients	Treatment	Platelet recovery >50.000/mmc	Follow-up (months)	Toxicity	Reference
Gergis	1	Tacrolimus	1/1	2	no	4
Proleznik	2	Splenectomy	2/2	12	1 patient died of septic shock	5
Raj	2	Rituximab	2/2	6-13	no	2
Faraci	6	Rituximab (3 out of 6 patients)	2/3	34-43	no	6
Poon	1	Romiplostim	1/1	24	no	9
Beck	1	Romiplostim	1/1	2	no	10
Battipaglia*	3	Romiplostim	3/3	5-10	no	11
Tanaka*	7	Eltrombopag	6/7	2-8	no	13

* Patients included in these studies had post-transplant thrombocytopenia defined as secondary failure of platelet recovery (SFPR).

demonstrated that Rituximab is a good option for children affected by post-HSCT hematologic autoimmune complications, but among 10 post-HSCT ITP patients only 3 received Rituximab, with 2 of them showing a successful response[6]. As for our case we cannot completely exclude that a delayed effect of Rituximab contributed to the response.

The TPO mimetics Romiplostim and Eltrombopag are now widely used in relapsed/refractory ITP patients, with a response rate from 60% to 90%[7,8], as well as in other conditions such as aplastic anemia and chronic HCV infection, but their use in the post-HSCT setting is not extensively investigated yet. In addition most studies include post-HSCT ITP along with post-HSCT thrombocytopenia secondary to other causes. Therefore prospective studies specifically focused on post-HSCT ITP are lacking. Poon LM *et al* reported 3 cases of severe post-HSCT thrombocytopenia (1 post-HSCT ITP and 2 thrombocytopenias secondary to graft failure) successfully treated with Romiplostim. Worthy of note those patients did not relapse of their haematological disease nor developed marrow fibrosis[9]. Other groups argue in favour of using Romiplostim in post-transplant setting, both in children and adults[10,11]. However, if we consider that Romiplostim is reported to increase the leukemic evolution of patients affected by myelodisplastic syndromes[12], there may be a concern in its use in patients with underlying high risk myeloid malignancy, as in our case.

Eltrombopag is a nonpeptide orally active TPO-receptor agonist. A series of 12 patients affected by post-transplant immune or not immune thrombocytopenia treated with Eltrombopag has been recently reported by Tanaka T *et al*[13]; the response rate was 72%, with no significant increase in risk of marrow fibrosis, disease relapse or worsening of pre-existing GVHD. *In vitro* and *in vivo* studies show conflicting results about the direct effects of Eltrombopag on AML cells and on stromal supportive microenvironment[14,15], thus making this topic an interesting research area. Although in our case disease relapse occurred 5 months after Eltrombopag beginning, it seems more likely that it was favoured by the high biological risk of FLT3-ITD AML rather than by the Eltrombopag possible stimulating effect on leukaemia cells. Moreover, we assumed that the risk of fatal bleeding exceeded the risk of leukaemia relapse. Anyway, caution is advisable in using Eltrombopag in this specific setting until more data will be available and

strategies to reduce bone marrow exposure to this agent – such as using it as a bridge to splenectomy or other treatment platforms – could be investigated in the near future.

In summary we present a case of refractory post -allogeneic HSCT ITP - not associated with GVHD or infectious events - successfully treated with Eltrombopag. According to our experience TPO-mimetics could represent a reasonable treatment option in HSCT patients. However prospective studies are needed in order to evaluate their efficacy and safety in HSCT settings.

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