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Case Report

Eltrombopag post autologous hematopoietic stem cell transplant - an emerging indication in younger pediatric patients

Aditya Kumar Gupta[1], Prasanth Srinivasan[1], Gargi Das[1], Jagdish Prasad Meena[1], Pranay Tanwar[2], Rachna Seth[1]

[1]*Division of Pediatric Oncology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110029, India;* [2]*Laboratory Oncology Unit, Dr. B. R. A. Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India*

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Abstract: Background: Engraftment of neutrophils and platelets after hematopoietic stem cell transplant (HSCT) is imperative for optimal outcomes. Eltrombopag has been used in adults after HSCT to boost platelet production. Its use in pediatric post HSCT patients has been limited. Methods: The clinical and laboratory details of a post autologous HSCT patient were fetched by a retrospective review of the records. Results: A 5-year old male child had primary thrombocytopenia post autologous HSCT for refractory Hodgkin lymphoma. Although the stem cell dose infused was adequate, the child had a delay in the engraftment of platelets. After ruling out the causes of post HSCT thrombocytopenia, eltrombopag was started for the child. With the use of eltrombopag, normal thrombopoiesis was restored in the child. Conclusion: Eltrombopag was effective and safe in overcoming post-HSCT primary thrombocytopenia in our patient.

Keywords: Eltrombopag, pediatric, autologous HSCT

Introduction

Engraftment of neutrophils and platelets after hematopoietic stem cell transplant (HSCT) is imperative for optimal outcomes. Neutrophil engraftment after hematopoietic stem cell transplant (HSCT) is defined as an unsupported absolute neutrophil count (ANC) exceeding 500/mm^3 for 3 consecutive days. Platelet engraftment is defined as platelet count exceeding 20,000/mm^3 without transfusion support for three consecutive days. The first day is considered the day of engraftment [1].

Delayed engraftment after autologous HSCT can be multifactorial. The conditioning regimen used, stem cell dose, nutritional status of the patient, drugs, and concomitant complications are some of the factors that may influence engraftment [2]. Granulocyte-colony stimulating factor (G-CSF) is used in the post-transplant period to facilitate neutrophil engraftment. Eltrombopag, a thrombopoietin receptor agonist (TPO-RA), has been used in pediatric disorders like chronic immune thrombocytopenia (ITP) and aplastic anemia. Its interaction with the thrombopoietin receptor stimulates proliferation and maturation of megakaryocytes, increasing the platelet count [3]. Eltrombopag has been used for the management of post-HSCT thrombocytopenia, but mainly in allogenic HSCT and in adults. There is little pediatric data to support the use of TRO-RA for post autologous HSCT thrombocytopenia. Here we report a child who had undergone autologous HSCT for refractory Hodgkin lymphoma and had delayed platelet engraftment. With the use of eltrombopag, the patient achieved a normal platelet count. This, to our knowledge, is the first report where eltrombopag has been used under the age of 10 years for this indication.

Case report

A 5-year old male child was diagnosed with Hodgkin lymphoma (stage III B + S + bulky).

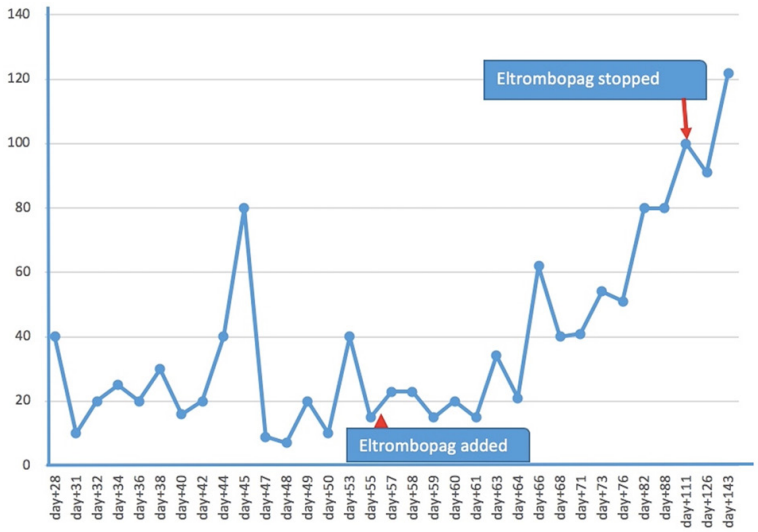

Figure 1. Trend of platelet counts post autologous hematopoietic stem cell transplant in the patient and response to the addition of eltrombopag (X-axis: day post-transplant; Y-axis: platelet counts $\times 10^3$/cumm).

Baseline blood investigations were: hemoglobin-7.4 gm/dl, total leukocyte counts-14500/mm^3, platelet counts-249/mm^3, and LDH-703 U/L. The child received six cycles of ABVD protocol, and he also received involved-field radiotherapy [(IFRT) with Waldeyer's ring-face and neck by AP-PA fields by Co-60 under 780-C, 30 Gy/15#/3 weeks]. Post-chemo-radiotherapy, the child achieved a partial response. Subsequently, he was treated with 2 cycles of ICE protocol (ifosfamide, carboplatin, and etoposide) and 3 cycles of DHAP (dexamethasone, cytarabine, and cisplatin). Even after the above three lines of chemotherapy, his disease was not in complete remission. So he was started on IGEV protocol (ifosfamide, gemcitabine, vinorelbine, and prednisolone), and after three cycles of IGEV, he achieved a complete metabolic response. He needed four times packed red blood cell (PRBC) transfusion during the salvage chemotherapy and four times platelets transfusion.

Because of refractory disease, he was taken up for consolidation with an autologous HSCT after achieving remission. He underwent peripheral blood stem cell harvesting with GCSF at 10 ug/kg/day for 8 days and pre-harvest plerixafor for stem cell mobilization. The child underwent conditioning with busulfan, melphalan, and gemcitabine for his HSCT. The CD34+ stem cell was infused with a dose of 4.5 million/kg. Due to the failure of the neutrophils to rise after day+20, a possibility of engraftment failure was considered, and bone marrow (BM) examination was performed. The BM examination showed a hypocellular marrow. Supportive management was continued, and on day+34, the child showed a rise in the ANC, and the G-CSF was stopped. After three days of unsupported ANC>500/mm^3, the day of engraftment for neutrophils was considered day+35.

The child had persistent thrombocytopenia and intermittently required platelet transfusions. Co-cotrimoxazole prophylaxis, which is otherwise a standard of care, was withheld for this child as he had persistent cytopenia. The child was investigated for common causes of post HSCT thrombocytopenia. The peripheral smear done on day+52 revealed adequate neutrophils, reduced platelets, and there were no schistocytes. The serum vitamin B12 levels (57.9 pmol/L), serum folate levels (3.6 ng/ml), and serum lactate dehydrogenase (LDH) levels were normal. The cytomegalovirus-polymerase chain reaction (CMV-PCR) values were non-significant. Multiple blood cultures were documented to be negative. The fungal culture was also negative. Chest x-ray and ultrasound of the abdomen were normal.

The provisional diagnosis of post HSCT delayed primary platelet engraftment was considered in this child. Immune thrombocytopenia was less likely as the bone marrow examination done on day+20 had shown a hypocellular marrow.

On day+56, the child was started on oral eltrombopag at a dose of 25 mg per day, considering a diagnosis of post-HSCT primary thrombocytopenia due to delayed engraftment. Following eltrombopag administration, there was a gradual platelet recovery, and the transfusion requirement for platelets decreased. The eltrombopag was stopped on day+110 (**Figure 1**). There was a transient fall in platelets after stopping eltrombopag. The platelets subsequently normalized. The child was discharged, and he is presently in good health 16

months post-HSCT. The current platelet counts are normal.

Discussion

Successful HSCT requires rapid and durable engraftment, with neutrophil (>500/mm^3) and platelet (>20,000/mm^3) reconstitution. Goncalves et al, showed that in 21 patients with lymphomas, after autologous HSCT, engraftment of neutrophils occurred at a median of 10 days and platelets at a median of 13 days [4].

The causes of delayed engraftment can be multifactorial. Contributing factors can be disease type, pre-transplant treatment, remission status of the disease before transplant, conditioning regimen used, the dose of CD34+ stem cells infused, infections such as CMV, the occurrence of veno-occlusive disease (VOD), and use of myelosuppressive drugs. Pre-transplant platelet counts are also known to influence platelet recovery post-HSCT [2, 5].

Before HSCT, patients with damage to the marrow compartments or marrow fibrosis have a slower platelet recovery and higher platelet requirement post-HSCT. The maturation of megakaryoblasts is dependent on the secretion of growth factors and maturation factors from the bone marrow epithelial cells and perivascular cells. Increased platelet destruction and turnover can be seen in cases of graft versus host disease (GVHD) related to immune dysregulation (for allogenic transplants), VOD, thrombotic microangiopathy (TMA), etc. Platelet refractoriness can be a manifestation due to immune and non-immune causes. Immune causes are due to ABO-mismatched transfusions, human leucocyte antigen (HLA), and platelet specific antibodies, and immune thrombocytopenia. Common non-immune causes of post-HSCT platelet refractoriness are infections, medications, and disseminated intravascular coagulation (DIC) [6].

Although the dose of CD34+ stem cell dose infused in our patient was adequate, he had a prolonged thrombocytopenia post-HSCT. The recovery of the neutrophil counts post-HSCT was also delayed. It is possible that the lineage-specific stem cell dose was less even with the adequate total stem cell dose. Further, the high doses of chemotherapy and radiotherapy pre-HSCT could have caused damage to the bone marrow microenvironment.

The use of eltrombopag in this child helped the patient to tide over the period of thrombocytopenia and decreased the platelet transfusion requirement for this child. Eltrombopag is a non-peptide, oral agonist of the thrombopoietin receptor. It interacts with the transmembrane domain of the receptor protein complex, initiating downstream signal transduction, involving both the Janus kinase/signaling transducers and activators of transcription (JAK/STAT) and mitogen-activated protein kinase (MAP-K) signal transduction pathways causing cell differentiation and proliferation [7].

Raut et al, in 12 adult patients after HSCT (10 were autologous HSCT), showed a response in all patients to eltrombopag (25-50 mg/day) for post-HSCT primary isolated thrombocytopenia [8]. In a retrospective series of adult patients post-allogeneic HSCT, Tanaka et al showed that eltrombopag was able to achieve transfusion independence in two-thirds of patients at a dose of 12.5-25 mg per day [9]. The response to eltrombopag was durable even after its stoppage. Vasudevan Nampoothiri et al recently published a review on the role of eltrombopag in post-HSCT thrombocytopenia and shown that a response rate of 62 to 100% has been documented in the five published studies that they collated [7].

Mahat et al in a systematic review, concluded that TPO-RA had a favorable response rate in post-HSCT primary isolated thrombocytopenia and secondary thrombocytopenia with a reasonable safety profile. However, due to the lack of control groups in the studies reviewed, heterogeneity, and the potential publication bias, they concluded that the interpretation should be with caution. The number of pediatric patients in the review was few, and all were older than 10 years of age. Our study details the safe use of eltrombopag in a very young pediatric patient post-HSCT [10].

Eltrombopag is approved to treat children aged ≥ one year with chronic ITP refractory to other therapies [3]. In adults, eltrombopag is also indicated in aplastic anemia and chronic hepatitis-C associated thrombocytopenia.

Conclusion

In our patient with primary thrombocytopenia post autologous HSCT, eltrombopag use led to a favorable response sustained even after its

discontinuation. The drug was well tolerated in this child, who was five years old. Its use should be further explored in trials in the setting of post-HSCT thrombocytopenia in pediatric patients. Eltrombopag can be used in young children to tide over post-HSCT primary thrombocytopenia.

Disclosure of conflict of interest

None.

Abbreviations

ANC, Absolute neutrophil count; BM, Bone marrow; CD, Cluster differentiation; CMV, Cytomegalovirus; G-CSF, Granulocyte-colony stimulating factor; HLA, Human leukocyte antigen; HSCT, Hematopoietic stem cell transplant; ITP, Immune thrombocytopenia; JAK-STAT, Janus kinase/signaling transducers and activators of transcription; MAP, Mitogen-activated protein; PCR, Polymerase chain reaction; TMA, Thrombotic microangiopathy; TPO-RA, Thrombopoietin receptor agonist; VOD, Veno occlusive disease.

Address correspondence to: Dr. Jagdish Prasad Meena, Division of Pediatric Oncology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110029, India. Tel: +91-01126593619; E-mail: drjpmeena@yahoo.com

References

[1] Chang YJ, Xu LP, Liu DH, Liu KY, Han W, Chen YH, Yu-Wang, Chen H, Wang JZ, Zhang XH, Zhao XY and Huang XJ. Platelet engraftment in patients with hematologic malignancies following unmanipulated haploidentical blood and marrow transplantation: effects of CD34+ cell dose and disease status. Biol Blood Marrow Transplant 2009; 15: 632-638.

[2] Lutfi F, Skelton WP, Wang Y, Rosenau E, Farhadfar N, Murthy H, Cogle CR, Brown R, Hiemenz J, Wingard JR and Norkin M. Clinical predictors of delayed engraftment in autologous hematopoietic cell transplant recipients. Hematol Oncol Stem Cell Ther 2020; 13: 23-31.

[3] Giordano P, Lassandro G, Barone A, Cesaro S, Fotzi I, Giona F, Ladogana S, Miano M, Marzollo A, Nardi M, Notarangelo LD, Pession A, Ruggiero A, Russo G, Saracco P, Spinelli M, Tolva A, Tornesello A, Palladino V and Del Vecchio GC. Use of eltrombopag in children with chronic immune thrombocytopenia (ITP): a real life retrospective multicenter experience of the Italian association of pediatric hematology and oncology (AIEOP). Front Med (Lausanne) 2020; 7: 1-7.

[4] Goncalves TL, Benvegnu DM and Bonfanti G. Specific factors influence the success of autologous and allogeneic hematopoietic stem cell transplantation. Oxid Med Cell Longev 2009; 2: 82-87.

[5] Woo KS, Goh RY, Kim SH, Kwon HC, Kim HJ, Lee YH and Han JY. Number of megakaryocytic progenitors and adhesion molecule expression of stem cells predict platelet engraftment after allogeneic hematopoietic stem cell transplantation. Cytotherapy 2007; 9: 555-561.

[6] Chavan P, Chauhan B, Joshi A, Ojha S and Bhat V. Differential diagnosis of thrombocytopenia in hematopoietic stem cell transplant patients. J Hematol Thromboembolic Dis 2014; 2: 1-5.

[7] Vasudevan Nampoothiri R and Kumar R. Eltrombopag: role in cytopenias following hematopoietic stem cell transplantation. Indian J Hematol Blood Transfus 2020; 36: 238-245.

[8] Raut SS, Shah SA, Sharanangat VV, Shah KM, Patel KA, Anand AS, Talati SS, Panchal HP, Patel AA, Parikh SK and Shukla SN. Safety and efficacy of eltrombopag in post-Hematopoietic Stem Cell Transplantation (HSCT) thrombocytopenia. Indian J Hematol Blood Transfus 2015; 31: 413-415.

[9] Tanaka T, Inamoto Y, Yamashita T, Fuji S, Okinaka K, Kurosawa S, Kim SW, Tanosaki R and Fukuda T. Eltrombopag for treatment of thrombocytopenia after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2016; 22: 919-924.

[10] Mahat U, Rotz SJ and Hanna R. Use of thrombopoietin receptor agonists in prolonged thrombocytopenia after hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2020; 26: e65-e73.