Use of Eltrombopag in Patients with Platelet Engraftment Failure Following Second Allogeneic Peripheral Stem Cell Transplantation

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ABSTRACT

Thrombocytopenia after peripheral stem cell transplantation (PSCT) is associated with morbidity and mortality. Eltrombopag, a thrombopoietin receptor agonist, is successfully used primarily in the treatment of chronic idiopathic thrombocytopenic purpura and other thrombocytopenias associated with aplastic anemia and myelodysplastic syndrome. Recently, the use of eltrombopag in the treatment of thrombocytopenia after allogeneic PSCT has shown promising results. The use of eltrombopag in three patients with hematologic malignancy who experienced graft failure after the first PSCT and developed platelet engraftment failure following the second bone marrow (BM) transplantation was presented retrospectively. The patients included two males and one female, with the mean age of 52 (45–57) years. The diagnoses were acute myeloid leukemia, non-hodgkin lymphoma (NHL), acute lymphocytic leukemia. All patients underwent allogeneic PSCT with the myeloablative regimen. Platelet engraftment failure was detected during the follow-up of the patients. Acute grade 3 skin graft versus host disease developed in the patient with NHL. Mycophenolate-mofetil, cyclosporin-A, steroid-based immunosuppression therapy was given. Graft versus host disease completely responded to this treatment in the first week of treatment. However, thrombocytopenia persisted. None of the patients had any viral infection or relapse. BM biopsies of patients were hypocellular, and the number of megakaryocytes were found to be decreased. Eltrombopag was initiated in three patients after 110 (60–144) days of transplantation. Responses were obtained in all of the patients; the platelet value was ≥30 × 10³/µL (30.000–247.000). The mean duration of response was 27 (20–35) days. Although engraftment failure is not a routine indication of the eltrombopag, it can be used safely and effectively in patients with platelet engraftment failure after PSCT.

Keywords: Allogeneic peripheral stem cell transplantation, eltrombopag, prolonged thrombocytopenia

INTRODUCTION

Thrombocytopenia after allogeneic peripheral stem cell transplantation is a very common complication (1). It may develop for several reasons. Some of these reasons include; reduced platelet production due to graft failure, viral infections, drug side effects and increased breakdown of platelets (1, 2). The treatment of thrombocytopenia is very important as thrombocytopenia may extend the duration of hospital stay, lead to transfusion dependence and fatal hemorrhage.

Rituximab, corticosteroids and intravenous immunoglobulin treatments have been used in immune-mediated thrombocytopenia (3). Donor leukocyte infusions and immunosuppressive agents can be used in the treatment of poor graft function (1). Yet, there is no standard treatment approach for the treatment of thrombocytopenia that develops after allogeneic peripheral stem cell transplantation (APSCT).

Eltrombopag and romiplostim are thrombopoietin receptor (TPO-R) agonists used for idiopathic thrombocytopenic purpura (4). There have been promising publications regarding their use in post-APSCT thrombocytopenia recently (5-7).

CASE PRESENTATIONS

Case 1: A 52-year old male patient presented to our clinic with weight loss and lethargy complaints and his examination showed: leukocyte: 43x10³ /µL (3.39- 8.86), hemoglobin: 6.7 g/dL, platelet: 143x10³/µL (158-374). Bone marrow aspiration, biopsy and flow cytometry were performed due to the pre-diagnosis of acute leukemia and the patient was then diagnosed with B-cell acute lymphoblastic leukemia (B-ALL). Conventional cytogenetics at the time of diagnosis was: 46; XY, normal karyotype. With the diagnosis of moderate risk B-ALL, Hoelzer Phase-I (Prednisolone, Daunorubicin, Vincristine, L-Asparaginase) was

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administered as remission induction treatment, Hoelzer Phase-II (Cyclophosphamide, Cytarabine, Methotrexate, 6-Mercapto-purine, central nervous system irradiation) was administered as consolidation treatment and Hoelzer Phase-III (Cytarabine, mi-toxantrone) chemotherapy protocol was applied. After complete remission, transplantation was performed from 65-year old fully HLA compatible sister donor with 7.1x10/kg CD34+ peripheral stem cell infusion using Bu12,8Flu180ATGf10 (Busulfan, Fludar-abin, Anti-Thymocyte globulin) preparation regimen. Neutrophil engraftment was achieved on day 19 and platelet engraftment on day 15. On post-transplant day 50, donor leukocyte infusion (DLI) was carried out. On post-transplant day 60: leukocyte was 870 (neutrophil: 20) /µL, hemoglobin: 8 g/dL, platelet: $8x10^3$/µL. The patient with hypocellular bone marrow was assessed as sec-ondary engraftment failure. The second transplantation was per-formed with 6.3x10/kg CD34+ peripheral stem cell (PSC) infusion from the same donor using ATGf10 preparation regimen. Neu-trophil engraftment (neutrophil: $2.1x10^3$/µL, hemoglobin: 11.3 g/dL) was achieved on day 21. On day 40 after the second trans-plantation, platelet level was around $9x10^3$/µL and the patient still had thrombocytopenia. The patient received nearly 2-3 units of platelet transfusion weekly. Patient did not respond despite the administration of methylprednisolone and intravenous im-munoglobulin and developed mucosal bleeding. It was assumed that the patient, who didn't have any signs of GVHD, viral infec-tions or relapse on day 60 and continued to exhibit thrombo-cytopenia, had isolated platelet engraftment failure. The patient was started on a weekly dose of 1x50 mg eltrombopag and the dose was increased to 2x50 mg after 14 days. Platelet level on day 7 during 100 mg/day eltrombopag treatment was $23x10^3$/µL. Platelet level was >$100x10^3$/µL on day 120 of eltrombopag treatment and increased up to the maximum level of $247x10^3$/µL. Chimerism results before and after eltrombopag treatment did not show any changes.

Case 2: A fifty seven-year old female patient presented to our clinic with malaise and dizziness complaints. Her examination showed leukocyte: $113x10^3$/µL (3.39- 8.86), hemoglobin: 6.8 g/dL, platelet: $21x10^3$/µL (158-374). Bone marrow aspiration, biopsy and flow cytometry were performed due to the pre-diagnosis of acute leukemia and the patient was then diagnosed with acute myeloid leukemia (AML). Conventional cytogenetics at the time of diagnosis was: 46; XY, normal karyotype, t(8;21) mutation was FLT-3/ITD negative. The patient was administered 3+7 (Idarubi-cin + Cytarabine) remission induction treatment and IDAC (Ida-rubicin + Cytarabine) chemotherapy as consolidation treatment due to moderate-risk AML. The patient had complete remission. Transplantation was performed from the 45-year old fully HLA compatible sister donor with 6.5x10/kg CD34+ PSC infusion us-ing Bu12,8Flu180ATG10 (Busulfan, Fludarabin, Anti-Thymocyte globulin) preparation regimen. On post-transplant day 60, the patient had no neutrophil and platelet engraftment. The patient with primary engraftment failure received the second transplant from the same donor with 6.5x10/kg CD34+ PSC infusion using ATGf10 preparation regimen. Neutrophil engraftment after the transplantation (neutrophil: $1.9x10^3$/µL, hemoglobin: 10.8 g/dL) was achieved on day 16. On the other hand, platelet engraftment (platelet: $7x10^3$/µL) did not occur. The patient received 1-2 units

of platelet transfusion weekly and bone marrow aspiration and biopsy performed on day 60 showed hypocellular bone marrow. The patient, who did not have any signs of GVHD, viral infections or relapse, was started on high-dose Eltrombopag (2x50 mg) treatment due to massive hematuria secondary to thrombocyto-penia on post-transplant day 75. The dose was increased to 2x75 mg/day after receiving no response 2 weeks after the initializa-tion of treatment. On day 71 of eltrombopag treatment and day 6 of 150 mg/day dose, platelet level increased to $26x10^3$/µL and to a maximum level of $43x10^3$/µL. The patient still receives 1x75 mg/day eltrombopag treatment.

Case 3: A 45 year-old male patient was administered 4 courses of CHOP (cyclophosphamide, adriamycin, vincristine, methyl pred-nisolone) treatment after being diagnosed with peripheral T cell lymphoma. The patient had primary refractory disease and was administered Hyper CVAD AB (Cyclophosphamide, Vincristine, dexamethasone, methotrexate, ARA-C) rescue therapy. Stem cell mobilization was performed using Hyper CVAD-2B. 8.5x10/kg CD34+ peripheral stem cells were collected. High-risk patient underwent autologous peripheral stem cell transplantation with 8.5x10/kg CD34+ PSC infusion using BEAM (carmustine, etopo-side, cytarabine, melphalan) preparation regimen in the first complete remission. Engraftment was achieved with $1.1x10^3$/µL neutrophils on post-transplant day 12. On day 60 after the trans-plantation, the platelet level was still low at $11x10^3$/µL. Bone mar-row biopsy revealed markedly hypocellular bone marrow and fewer megakaryocytes, therefore the patient was considered to have aplastic anemia. Transplantation was performed from the 50 year-old fully HLA compatible brother donor with 9x10/kg CD34+ PSC infusion using Bu6Fu180ATG10 preparation regimen. Neutrophil (neutrophil: $1.5x10^3$/µL, hemoglobin: 11.8 g/dL) en-graftment was achieved on post-transplant day 18. However, the patient did not have platelet engraftment and developed acute grade-3 skin GVHD. Patient exhibited full response to immuno-suppression therapy with mycophenolate-mofetil, cyclosporin-A and steroid in one week. Bone marrow biopsy of the patient with platelet engraftment failure revealed hypocellular bone marrow and few megakaryocytes on post-transplant day 100. The pa-tient was started on 1x50 mg eltrombopag on post-transplant day 126. The dose was increased (2x50 mg) due to no response. Response was observed on day 35 of treatment. The patient's platelet level increased to $32x10^3$/µL.

DISCUSSION

Persistent thrombocytopenia after PSCT is a common problem and an important cause of morbidity and mortality (8-10). Prolonged isolated thrombocytopenia is defined as recovery of other cell counts with continuous dependence on platelet transfusions for greater than 3 months after PSCT. It develops in approximately 2.6-37% of the patients who undergo PSCT and is strongly associated with transplant-related mortality and total survival (1, 11-13). For instance, it is generally accepted as a sign of engraftment failure and disease recurrence in autologous transplants (1).

Thrombocytopenia formation is usually multifactorial. Despite the fact that the main causes of prolonged thrombocytopenia after allogeneic transplantation are reduced platelet production

and accelerated peripheral degradation, the exact mechanism is still unclear (1, 11, 13).

There are publications in literature that state donor type, existence and degree of GVHD, CMV infection, number of transfused CD34+ cells and such factors are the predictors of prolonged post-transplant thrombocytopenia (1). Yamazaki et al. (14) reported that TPO status in patients with prolonged thrombocytopenia after APSCT had a similar pattern with aplastic anemia and this played an important role in impaired platelet production. Bielski et al. (12) reported that the bone marrow biopsy performed on 12 patients with prolonged thrombocytopenia after PSCT revealed the absolute number of megakaryocytes to be lower than normal; Zhang et al. (15) reported that there were significant shifts towards low-ploidy cells and that the number of immature megakaryocytes was higher in patients with prolonged thrombocytopenia after PSCT as compared to non-thrombocytopenic patients.

There is no standard treatment approach in order to accelerate platelet healing or ensure platelet engraftment in the post-transplantation period. In this period, the use of thrombopoietin-mimetics with this purpose is a logical approach. Among the second generation TPO agonists, eltrombopag was approved by FDA for the treatment of Chronic ITP in 2008, it is widely accepted for the treatment of chronic viral hepatitis C-associated thrombocytopenia and studies for including eltrombopag in immunosuppressive therapy in the treatment of aplastic anemia are still ongoing, and recently eltrombopag has been mentioned in the literature with promising studies on post-transplant thrombocytopenia treatment (4).

Raut et al. (16) reported an increase in the number of platelets with no side effects within 29 days on average by administering 25-50 mg/day eltrombopag to 12 patients with post-transplant primary thrombocytopenia, 2 patients allogeneic (AML, aplastic anemia), 10 patients autologous (MM, lymphoma, AML). Reid et al. (8) reported that platelet levels were within the safe interval and patients no longer needed platelet infusion after administering 50 mg/day eltrombopag to two patients, one of which underwent allogeneic PSCT and the other autologous PSCT. Fujimi et al. (11) used eltrombopag in one case diagnosed with follicular lymphoma and underwent allogeneic transplantation in the third remission and reported that eltrombopag could be a suitable choice in cases with prolonged thrombocytopenia after APSCT.

In our case series, bone marrow biopsies of patients showed, similar to the results of Bielski et al. (12), fewer number of megakaryocytes and hypocellularity, which imply reduced platelet production. The common characteristics of the three patients were that they all developed graft failure after the first PSCT and platelet engraftment failure after the second bone marrow transplantation. Eltrombopag treatment was initiated in 3 patients 110 days (60-144) after transplantation on average. Responses were obtained in all of the patients; the platelet value was ≥30×10³/μL (30.000-247.000). The mean response time was 27 days (20-35). There were no side effects associated with Eltrombopag.

TPO affects multilineage progenitors and eltrombopag is expected to do the same. Eltrombopag binds to thrombopoietin receptors and stimulates megakaryopoiesis and therefore enables platelet release from mature megakaryocytes. Although the increase in the number of platelets is more remarkable, it also provides some increase in erythroid and myeloid cell lines. It also facilitates treatment compliance as it can be administered orally and leads to fewer and low-degree drug-related adverse events (nausea, headache, nasopharyngitis, lethargy) in patients with ITP. In the post-transplant thrombocytopenic period, it can be recommended for use in order to prevent bleeding rather than to normalize the number of platelets.

CONCLUSION

We determined that the use of Eltrombopag in the treatment of thrombocytopenia after PSCT was safe and effective in all three cases in accordance with the literature. Although there is need for further studies, Eltrombopag treatment is promising in that it can be used safely and effectively in patients with platelet engraftment failure after PSCT.

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