Use of Eltrombopag in Improving Poor Graft Function after Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract
Eltrombopag is a thrombopoietin agonist and has been used in aplastic anemia and post-transplantation thrombocytopenia. The c-MPL receptor is present on hematopoietic stem cells. There are no reports of eltrombopag utilization for improving poor graft function in the post-transplant setting. Here we report a case of a young female with post-transplant poor graft function as evident from the low absolute neutrophil count, anemia, and thrombocytopenia on day 60. Eltrombopag was started on day 72 and resulted in improvement in all 3 cell lines. The counts continued to be stable even after eltrombopag was discontinued. The patient tolerated the drug without significant side effects for 1 year.
Introduction

Eltrombopag is a c-MPL receptor agonist drug [1–3]. Murine studies have shown that the thrombopoietin (TPO)/c-MPL receptor system is present in early hematopoiesis and hematopoietic stem cells (HSCs) [4]. There are few case reports of TPO agonist use in post-transplantation thrombocytopenia. Also, TPO agonist use has been suggested in the management of severe aplastic anemia. Here we report a case of eltrombopag utilization in the treatment of trilineage graft failure.

Case Report

A 26-year-old female with acute myeloid leukemia developed marrow hypoplasia after 1 cycle of consolidation with high-dose cytarabine. This resulted in severe pancytopenia causing transfusion dependence for both red blood cells and platelets. Following persistence of pancytopenia for almost 5 months, she underwent a matched related (brother) allogeneic hematopoietic stem cell transplant using fludarabine/melphalan conditioning and alemtuzumab/tacrolimus as graft versus host disease prophylaxis. The patient had delayed engraftment as the absolute neutrophil count stayed below 1,000/µL (with granulocyte colony-stimulating factor support), hemoglobin was less than 8 g/dL, and the platelet count was less than 20,000/µL even at day 60. Bone marrow biopsy done on days 30 and 60 as well as at 1 year showed adequate cellularity, no evidence of relapse, and cytogenetics showed normal male karyotype. Chimerism studies showed 100% donor cells in myeloid lineage (CD33+) at days 30 and 60. Eltrombopag was started at 50 mg orally daily on day 72 to promote poor graft function. As shown in Figure 1, all 3 cell lines responded. The patient tolerated eltrombopag without any significant side effects. The patient was on eltrombopag for 1 year, and after that, it was stopped. Blood counts continued to be stable after discontinuing eltrombopag.

Discussion

Binding of TPO to the c-MPL receptor on megakaryocytes is the principal step that results in platelet maturation and release [1]. c-MPL is also expressed on the surface of HSCs [2–4]. Previous studies have shown that the addition of recombinant TPO leads to expansion of the pool of HSCs in culture [4]. In vitro models using knockout mice have shown that deficiency of c-MPL receptor [5, 6] or the TPO ligand leads to a reduced number of HSCs. Eventually, multilineage bone marrow failure develops [7]. These observations suggest that stimulation of c-MPL-signaling pathways may overcome depletion of HSCs and progenitor cells in aplastic anemia. Previous studies were done on cytokines like erythropoietin, and granulocyte colony-stimulating factor in aplastic anemia did not show a benefit because HSCs did not have receptors for these cytokines on them [8].

Romiplostim is a peptide TPO mimetic which activates the TPO receptor by binding to the distal hematopoietic receptor domain. Eltrombopag is a non-peptide TPO mimetic that activates the TPO receptor by binding to the transmembrane domain [9]. While romiplostim
is given subcutaneously, eltrombopag can be given orally [9]. While romiplostim is only FDA approved for immune thrombocytopenia [10], eltrombopag is FDA approved for immune thrombocytopenia, hepatitis C-related thrombocytopenia, and severe aplastic anemia [11].

Previous studies have shown that both are useful in post-transplantation thrombocytopenia anemia [12–14] and aplastic anemia [15, 16]. To our knowledge, this is the first case of eltrombopag use for the treatment of trilineage graft failure after allogeneic stem cell transplant [17]. Our case highlights the use of eltrombopag as a very effective medication with minimal side effects to promote poor graft function after allogeneic hematopoietic stem cell transplant. Repeat biopsy done after 1 year did not show any signs of myelodysplasia, recurrent acute myeloid leukemia, or myelofibrosis. Like previous studies on aplastic anemia [6], in our patient, the response continued even after eltrombopag was stopped.

There is evidence that eltrombopag might be stimulating hematopoiesis in noncompetitive activation of c-MPL. In immune thrombocytopenia, TPO levels are at the upper end of average, while in aplastic anemia they are significantly elevated [18]. Ertrombopag binds outside the ligand-binding pocket at the membrane, spanning a region of c-MPL. It activated signaling by JAK-STAT (Janus-associated kinase-signaling transducers and activators of transcription) and MAPK (mitogen-activated protein kinase) pathways [19].

Umbilical cord blood is emerging as a promising source of stem cells for allogeneic stem cell transplant, but it is challenged by low stem cell yield. In a previous study done on umbilical cord blood, eltrombopag enhanced expansion of HSCs in vivo and in vitro [5]. Also, eltrombopag favored earlier HSC populations which differed from recombinant TPO [20].

**Statement of Ethics**

The authors have no ethical conflicts to disclose.

**Disclosure Statement**

The authors have no conflicts of interest to declare.

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Fig. 1. Three graphs showing the response to eltrombopag. The x axis shows the days after transplant.