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Case Report

Clinical Case: Successful Boost Infusion for Graft Hypofunction After Haploidentical Hematopoietic Stem Cell Transplantation in the Blast Phase of Primary Myelofibrosis

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ABSTRACT

Primary myelofibrosis is a myeloproliferative neoplasm characterized by progressive bone marrow fibrosis, splenomegaly, and cytopenic syndrome, leading to a decreased quality of life.

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only potentially curative method; however, it is associated with the risk of transplant-related complications, including graft hypofunction. This report presents a rare clinical case of graft hypofunction in a patient with primary myelofibrosis after haploidentical HSCT from a related donor (son).

Graft hypofunction is associated with high transplant-related mortality due to infectious complications and hemorrhagic syndrome.

Keywords: Primary Myelofibrosis; JAK2; HSCT; Boost-Infusion; Graft Hypofunction

Introduction

Primary myelofibrosis (PMF) is a chronic clonal myeloproliferative neoplasm characterized by the proliferation of atypical megakaryocytes and granulocyte lineage, progressive bone marrow fibrosis, extramedullary hematopoiesis, and the development of cytopenias. The disease belongs to the group of classic Ph-negative myeloproliferative neoplasms alongside polycythemia vera and essential thrombocythemia. The pathogenesis of PMF is closely associated with mutations in genes that regulate the JAK-STAT signaling pathway, the most common of which are JAK2V617F, CALR, and MPL mutations. These molecular disturbances lead to uncontrolled proliferation of hematopoietic cells and the production of pro-inflammatory cytokines, contributing to the development of bone marrow fibrosis and systemic symptoms. The clinical course of PMF exhibits significant heterogeneity, ranging from asymptomatic forms to aggressive disease with marked splenomegaly, anemia, and transformation into acute myeloid leukemia. The prognosis is determined by a combination of clinical, hematological, and molecular factors, as reflected in modern prognostic scales such as IPSS, DIPSS, and MIPSS. To date, the only potentially curative treatment method for PMF remains allogeneic hematopoietic stem cell transplantation (HSCT); however, its application is limited by the age of patients, comorbidities, and the risk of transplant-related complications. Data on haploidentical HSCT in patients with PMF are sparse, making it difficult to draw conclusions about this approach.

Clinical Case

A 40-year-old female patient presented with complaints of pain in the left hypochondrium. Laboratory evaluation revealed moderate anemia (hemoglobin 82 g/L, leukocytes 3.75 × 10^9/L, platelets 160 × 10^9/L) and splenomegaly with an area of 230 cm^2. Histological examination demonstrated marked hypoplasia, myelofibrosis (MF-3), and osteosclerosis. Bone marrow cellularity ranged from 5–10% in different areas. Molecular testing was negative for BCR/ABL, CALR, MPL and JAK2 mutations.Based on these findings, a diagnosis of primary myelofibrosis, JAK2-negative was established. Risk stratification using IPSS and DIPSS+ classified the patient as high-risk. The patient was started on the Janus kinase inhibitor ruxolitinib at a dose of 30 mg/day. After 3 months, imaging showed a reduction in splenomegaly from 230 cm^2 to 123 cm^2, indicating a positive response. However, hematologic toxicity developed, including transfusion dependence and worsening cytopenias (leukocytes 2.6 × 10^9/L, platelets 58 × 10^9/L, hemoglobin 58 g/L). Due to toxicity, the ruxolitinib dose was reduced to 15 mg/day; however, splenomegaly progressed to 276 cm^2. Treatment was switched to interferon. Interferon therapy was associated with adverse effects, including low-grade fever, chills, and musculoskeletal pain unresponsive to NSAIDs, as well as septic complications. The patient remained transfusion-dependent, and rapid spleen enlargement was observed within one month (from 230 cm^2 to 324 cm^2). Given the high-risk status and lack of response to therapy, hematopoietic stem cell transplantation (HSCT) was indicated. As no HLA-matched donor was available, a decision was made to proceed with haploidentical HSCT from her son (5/10 match). As part of pre-transplant preparation, splenectomy was performed. Three months post-splenectomy, the patient developed a blast phase, with 20% blasts in bone marrow, 4% blasts in peripheral blood, and leukocytosis (33 × 10^9/L). This was interpreted as disease progression; however, given the poor prognosis with delay and the potential benefit of transplantation, HSCT was pursued. Conditioning regimen: reduced-intensity conditioning (RIC) with busulfan 10 mg/kg and fludarabine 180 mg/m^2. After premedication, infusion of hematopoietic stem cells was performed (CD34+ dose: 9.3 × 10^6/kg; CD3+: 12.3%). Graft-versus-host disease (GVHD) prophylaxis included: Cyclophosphamide 50 mg/kg on days +3 and +4 (total 5000 mg), Uromitexan 100 mg/kg (total 10,000 mg), Tacrolimus 0.03 mg/kg starting from day +5 (per L. Luznik protocol), Mycophenolate mofetil 1800 mg/day orally from day −1 to +36. The post-transplant period was complicated by gram-negative sepsis (Klebsiella pneumoniae ESBL++++), which responded to combination antibiotic therapy (meropenem 6 g/day + colistimethate 9 million IU/day + tigecycline 100 mg/day). On day +20 after haplo-HSCT, the patient developed severe trilineage cytopenia despite G-CSF support (Zarxio 300 μg/day): leukocytes 0 × 10^9/L, platelets 11 × 10^9/L, hemoglobin 76 g/L, with transfusion dependence.

Mixed donor chimerism was 25.59%. This condition was diagnosed as poor graft function. A decision was made to perform a stem cell boost infusion from the same donor. Prior to this, immunosuppressive therapy with antithymocyte globulin (equine) at 75 mg/m^2/day for 2 days was administered. On day +35 post-transplant, a boost infusion was performed (CD34+ dose: 3.4 × 10^6/kg). On day +28 after the boost infusion, full donor chimerism (99.30%) was achieved.

However, persistent trilineage cytopenia with transfusion dependence remained, although no blasts were detected in the bone marrow. Post-transplant immunosuppression included tacrolimus (Prograf) along with supportive therapy. The course was complicated by acute GVHD with skin involvement, resistant to corticosteroids (methylprednisolone 1 mg/kg). Therefore, ruxolitinib 15 mg/day was added. Due to worsening thrombocytopenia, eltrombopag 100 mg/day was initiated to stimulate megakaryopoiesis. By day +152 after the boost infusion, clinical improvement was achieved: recovery of peripheral blood counts, transfusion independence, absence of GVHD, and sustained donor chimerism. Blood counts were: leukocytes 5.72 × 10^9/L, hemoglobin 71 g/L, platelets 114 × 10^9/L; donor chimerism 95.41%. One year after the boost infusion, the patient remained transfusion-independent, with complete donor chimerism, no detectable malignant cells in the bone marrow, and no histological evidence of myelofibrosis.

Discussion

Poor graft function and delayed hematopoietic recovery after hematopoietic stem cell transplantation (HSCT) remain major challenges in the treatment of primary myelofibrosis (PMF). In patients with myelofibrosis, due to bone marrow fibrosis, chronic inflammation, or splenomegaly, hematopoietic recovery often takes longer compared to patients with other hematologic malignancies [8]. Primary graft failure is defined as the failure to achieve adequate neutrophil recovery by day +28 and is usually associated with low or absent donor chimerism [9]. It has been reported to occur in approximately 14% of patients [10]. The use of alternative donor HSCT in patients with poor graft function is of critical importance. However, a second transplantation requires intensified immunosuppression and a new conditioning regimen to overcome HLA mismatch, which is associated with an increased risk of organ toxicity and infectious complications. According to recent data, haploidentical HSCT, particularly following reduced-intensity conditioning (RIC) regimens, can be performed safely and effectively in patients with poor graft function. However, most published data involve patients with acute and chronic leukemias, juvenile myelomonocytic leukemia, or myelodysplastic syndrome [11–17]. In the present case, given the patient's severe clinical condition, absence of hematopoiesis in the bone marrow at day +28 after haplo-HSCT, lack of an alternative donor, and persistent pancytopenia, a second HSCT with a conditioning regimen was not considered. Of particular interest is the observation that restoration of donor hematopoiesis in this patient was accompanied by regression of bone marrow fibrosis. This finding supports the concept that the severity of fibrosis is not an absolute barrier to successful transplantation in myelofibrosis but rather represents a dynamic process largely dependent on the bone marrow microenvironment.

Conclusion

This clinical case demonstrates that in high-risk primary myelofibrosis (PMF), in the absence of response to standard therapy, including ruxolitinib and interferon, hematopoietic stem cell transplantation (HSCT) remains the only potentially curative treatment option. The use of a haploidentical donor enabled timely transplantation in the absence of a fully matched donor, highlighting the importance of alternative donor strategies. A key element in this case was the administration of a stem cell boost infusion, which allowed achievement of full donor chimerism and restoration of hematopoiesis without the need for a second transplantation. The therapeutic goal was achieved: full donor chimerism, absence of blasts in the bone marrow, recovery of peripheral blood counts, and regression of morphological features of myelofibrosis.

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