

CASE REPORT

Plerixafor as a salvage mobilization strategy for haploidentical peripheral blood allogeneic stem cell transplantation

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Introduction

Currently, granulocyte colony-stimulating factor (G-CSF) is the standard agent used for mobilization of Peripheral Blood Stem Cells (PBSCs) for Stem Cell Transplant (SCT), in both the autologous and allogeneic setting [2]. G-CSF is a growth factor that stimulates proliferation of progenitor cells. It is also thought to inhibit the activity of neutrophil elastase, which is involved in the production of stromal-cell-derived factor 1 (SDF-1), a chemokine that anchors stem cells to the bone marrow. G-CSF induces the activation of proteases within the bone marrow to degrade adhesive interactions, stimulating release of stem cells into circulation [3]. The recommended dose of G-CSF is 10 $\mu\text{g}/\text{kg}$ daily as a subcutaneous injection and continued until target CD34⁺ counts are achieved [2].

Other options for mobilization include Plerixafor, a reversible bicyclam chemokine receptor 4 (CXCR4) inhibitor. Plerixafor competes with SDF-1 for binding to CXCR4, thus releasing anchored stem cells into the periphery [3]. Plerixafor is FDA approved for use in combination with G-CSF for mobilization in autologous SCT

Key Clinical Message

In allogeneic stem cell mobilization, peripheral blood stem cell mobilization with filgrastim can be considered standard of care. Poor mobilizers may be at risk for inadequate stem cell collection during apheresis. Here we present a successful case of salvage plerixafor use with filgrastim in a haploidentical identical transplant patient.

Keywords

CLL, mobilization, plerixafor, stem cell transplant.

for patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) [4]. Higher stem cell yields are achieved when plerixafor is used with G-CSF, compared to single agent G-CSF or single-agent plerixafor. The use of plerixafor upfront however, is often reserved for patients at high risk for poor mobilization, given the cost implications for use of plerixafor for all patient subsets [2, 5]. In autologous stem cell collection trials, when plerixafor is added to G-CSF on day 4 of mobilization, the combination therapy yields higher cell counts per leukapheresis session compared to G-CSF alone, with fewer apheresis sessions to reach target CD34⁺ counts and early and stable engraftment [6]. The optimal role of plerixafor in disease states beyond NHL and MM and for healthy donors for allogeneic SCT continues to be investigated. Initial clinical trials demonstrated high stem cell yields with use of plerixafor for mobilization as a single-agent and as combination therapy with G-CSF in healthy volunteers [7]. The use of plerixafor has also been evaluated for use in mobilization of HLA-matched sibling donors for allogeneic SCT. Nine donors received plerixafor and leukapheresis with a 1-week washout, at which point they

received a second mobilization with single-agent G-CSF. Eight patients achieved target CD34⁺ cells defined as 2.0×10^6 CD34⁺ cells/kg following treatment with plerixafor, which was comparable to the CD34⁺ cell counts achieved in the G-CSF mobilized allografts. Subsequently, seven patients were successfully transplanted with the plerixafor mobilized stem cells with rates of graft-versus-host disease comparable to the G-CSF mobilized allografts [8]. Current literature also cites reports using Plerixafor as a salvage mobilization strategy for allogeneic SCT in healthy donors failing to mobilize with single-agent G-CSF [9].

The failure rate for mobilization with single-agent G-CSF ranges between 5% and 30%. The addition of plerixafor to G-CSF-based regimens improves mobilization rates to 60% for autologous SCT [3]. Further studies are needed to determine the efficacy of plerixafor as a salvage mobilization strategy for allogeneic SCT.

Clinical History

We report a case of a 57-year-old female who was selected as a sibling haplodonor for PBSCs for allogeneic SCT. Her brother was initially diagnosed with early stage chronic lymphocytic leukemia (CLL) when he was noted to have lympholeukocytosis during routine prectoscopy blood work. His initial Rai stage was unknown, with a high-risk presentation of unmutated *IgVH*. Following his initial diagnosis, he was managed with watchful waiting. On disease progression, he received six cycles of fludarabine, cyclophosphamide, and rituximab (FCR). One year after completing his last cycle of FCR, he was noted to have evidence of recurrent CLL and subsequently received six cycles of bendamustine and rituximab. The patient achieved a partial remission with this combination. Given this response, and the high-risk features of his CLL, the patient was scheduled for allogeneic SCT. Prior to transplant,

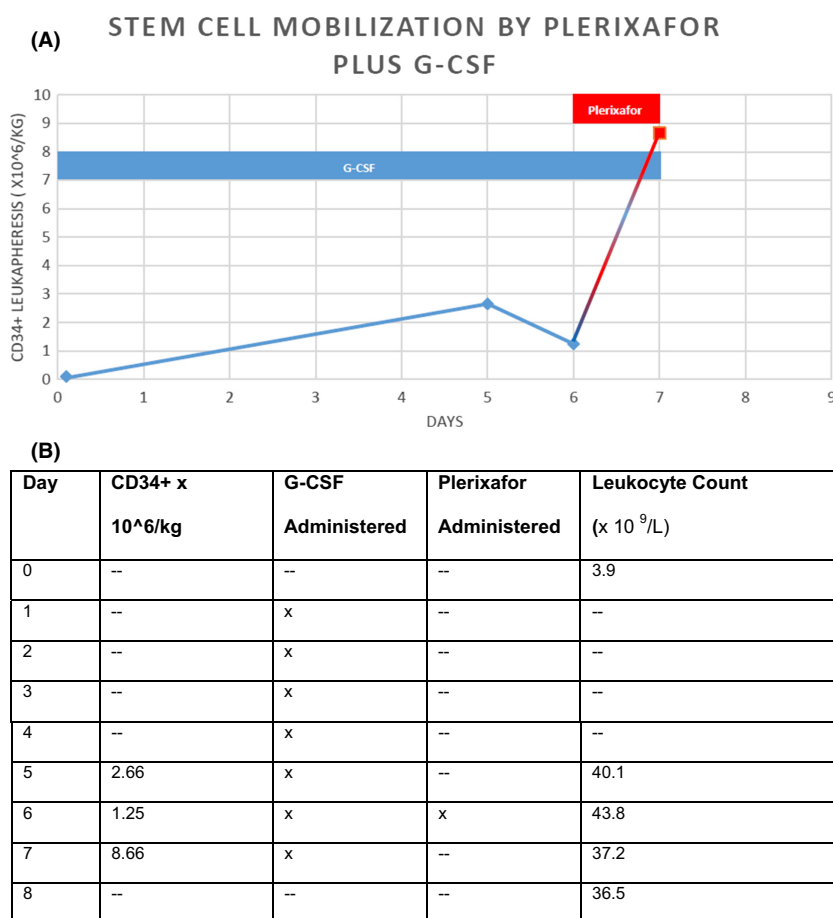


Figure 1. Schematic of patient's current mobilization for haploidentical transplant. (A) Administration schedule of filgrastim and plerixafor during mobilization versus CD34⁺ counts. (B) Outcomes with sequential CD34⁺ count and leukocyte count during mobilization with growth factor mobilization and plerixafor. Patient was administered plerixafor on day 6 with successful apheresis on day 7 for collection.

busulfan, melphalan, and alemtuzumab were as used as a reduced-intensity preparative regimen.

The donor search for an allogeneic transplant was unsuccessful in identifying an HLA-matched unrelated donor. However, one of his two healthy sisters qualified as a haploidentical donor with 7/12 HLA match and a 3/6 match at HLA-A, -B, and -DRB1.

Following pretransplant evaluation, mobilization of the donor was initiated with G-CSF 10 $\mu\text{g}/\text{kg}$ daily, 5 days before leukapheresis. The first leukapheresis session yielded $2.66 \times 10^6/\text{kg}$ cells $\text{CD}34^+$ stem cells, and continued G-CSF administration yielded $1.25 \times 10^6/\text{kg}$ $\text{CD}34^+$ stem cells on day 2. Given insufficient mobilization, plerixafor was added to the regimen in an attempt to increase stem cell yield. The donor received one dose of plerixafor 240 $\mu\text{g}/\text{kg}$ the evening prior to the third planned leukapheresis session. Addition of plerixafor led to a significant increased yield 8.63×10^6 $\text{CD}34^+$ stem cells.

The patient received three consecutive days of haplo-identical PBSC infusions for a total $\text{CD}34^+$ cell dose of $12.54 \times 10^6/\text{kg}$ (Fig. 1). Posttransplant GVHD prophylaxis consisted of cyclosporine and mycophenolate mofetil. His posttransplant course was notable for chemotherapy-associated nausea, mucositis, and neutropenic fever, treated with empiric antibiotics. Day +28 bone marrow studies showed no evidence of CLL and peripheral blood chimerisms on day +30 showed 100% donor DNA. He was discharged on day +31 and thereafter, followed as an outpatient in the clinic. Peripheral blood chimerisms on day +66 continued to show 100% donor DNA. Both the 6-month and 1-year posttransplant evaluation continued to show no progression of disease, no evidence of disease in the bone marrow, and 100% donor DNA chimerisms in the bone marrow.

Discussion

Our report contributes to the increasing, yet limited, support for using plerixafor in combination with G-CSF for satisfactory mobilization of donor stem cells for allogeneic SCTs. We show here a marked increase in mobilization after plerixafor usage, followed by successful patient recovery up to 1 year posttransplant. This increased efficacy, coupled with findings that suggest stem cells mobilized by plerixafor may be more protective against GVHD [10], suggest the utility of conducting larger clinical trials investigating the use of plerixafor in conjunction with G-CSF for stem cell mobilization in the allogeneic transplant setting, while also observing any effects on relapse rate and GVHD incidence.

Conflict of Interest

None declared.

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