



Improving Stem Cell Mobilization Results: --- A CaseBook™ Approach

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Faculty

Steven M. Devine, MD

The Ohio State University School of Medicine
Columbus, Ohio

Leona A. Holmberg, MD, PhD

Fred Hutchinson Cancer Research Center
Seattle, Washington

John M. McCarty, MD

VCU Medical Center
Richmond, Virginia

Peter A. McSweeney, MD

Rocky Mountain Blood and Marrow Transplant Program
Denver, Colorado

Ivana N.M. Micallef, MD, FRCP(C)

Mayo Clinic
Rochester, Minnesota

Jeffrey R. Schriber, MD, FRCP(C)

Banner Blood and Marrow Transplant Program
Phoenix, Arizona

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Educational Overview

Target Audience

The target audience for the program includes hematologists, hematologist-oncologists, medical oncologists, oncology specialty pharmacists, and stem cell collection personnel charged with the care of patients undergoing stem cell mobilization.

Learning Objectives

Upon completion of this educational activity, participants should be better able to:

- Discuss challenges and opportunities for improvement with currently available techniques for stem cell mobilization such as role of chemotherapy-based mobilization regimens and optimal stem cell collection yield
- Prospectively predict patients at high risk for poor stem cell mobilization and determine appropriate timing for incorporation of novel stem cell mobilization strategies
- Develop treatment algorithm for the management of patients at risk for poor mobilization
- Consider pharmacoeconomic issues associated with stem cell mobilization and recommend techniques for improving efficiencies

Statement of Need

A frequent approach to mobilizing stem cells for peripheral collection involves administering hematopoietic growth factors. Currently, granulocyte-colony-stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are used in the autologous setting, while G-CSF is predominately used in the allogeneic setting. Growth factors are generally administered for 4-6 days prior to cell collection to allow adequate time for CD34+ cell mobilization from bone marrow to peripheral circulation. Chemotherapy administration prior to growth factor is a common approach that may increase peripheral blood stem cells (PBSC) 5-15 fold, but also introduces the risk of chemotherapy toxicity. In current clinical practice, patients who do not mobilize enough CD34+ cells for collection following multiple attempts at apheresis may require bone marrow harvest. Novel methods for obtaining the optimal dose of stem cells in the most efficient manner for transplant represents a significant medical need in autologous SCT. Furthermore, continuing clinical investigation in the allogeneic setting may demonstrate improved convenience for normal donors, and pharmacoeconomic analysis may indicate health-system cost savings. Healthcare professionals caring for patients requiring stem cell mobilization prior to SCT need to understand the basis for emerging therapeutic options, and the preclinical and clinical data supporting the development and integration of novel mobilization regimens into clinical practice. This educational program will address optimal integration of emerging therapeutic strategies regarding stem cell mobilization, describe the means of optimizing stem cell mobilization while minimizing adverse events, and provide a perspective of directions in stem cell mobilization.

Media: Monograph

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Genzyme Corporation

John M. McCarty, MD
Grants/Research Support
Celgene Corporation, Genzyme Corporation,
Seattle Genetics

John M. McCarty, MD (Cont.)
Honorarium
Celgene Corporation, Genzyme Corporation

Speakers' Bureau
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Grants/Research Support, Honorarium
Genzyme Corporation

Ivana N.M. Micallef, MD, FRCP(C)
Grants/Research Support
Genzyme Corporation

Jeffrey R. Schriber, MD, FRCP(C)
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For further information, please contact:
Educational Concepts Group, LLC
1300 Parkwood Circle SE, Suite 325
Atlanta, Georgia 30339
Phone: 1.770.933.1681
Fax: 1.770.933.1692
www.educationalconcepts.net

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Faculty

Steven M. Devine, MD

Associate Professor of Medicine
Division of Hematology/Oncology
Director, Blood and Marrow Transplant Program
The Ohio State University Comprehensive Cancer Center
The Ohio State University School of Medicine
Columbus, Ohio

Steven M. Devine, MD is associate professor of medicine and director of the Blood and Marrow Transplant Program at The Ohio State University Comprehensive Cancer Center in Columbus, Ohio. Dr Devine received his medical degree from the University of Massachusetts Medical School in Worcester, Massachusetts. He did his residency at Michael Reese Medical Center in Chicago, Illinois and fellowships in hematology and oncology at Emory University Hospital in Atlanta, Georgia and the University of Chicago Hospital.

Dr Devine's research focuses on stem cell transplantation for patients with acute myeloid leukemia and the use of novel agents for the mobilization of stem cells in both patients and normal donors. Dr Devine currently serves as chair or co-chair of two multicenter NIH-supported clinical transplantation trials in AML, one led by the BMT CTN and the other with the CALGB.

Dr Devine is a member of the CALGB Transplant Committee and serves on the board of directors of the American Society of Blood and Marrow Transplantation. Dr Devine has been primary or coauthor of over 90 peer-reviewed publications and more than 200 abstracts, as well as several reviews and book chapters in the field of stem cell transplantation and hematology.

Leona A. Holmberg, MD, PhD

Associate Professor
Department of Medicine and Oncology
University of Washington
Associate Member
Clinical Research Division
Fred Hutchinson Cancer Research Center
Seattle, Washington

Leona A. Holmberg, MD, PhD is associate professor in the department of medicine and oncology at the University of Washington and associate member in the clinical research division at Fred Hutchinson Cancer Research Center in Seattle, Washington. Dr Holmberg earned her medical degree from the University of Miami School of Medicine in Miami, Florida and her PhD in immunology from Harvard University in Cambridge, Massachusetts.

Dr Holmberg's current clinical research interests have been focused on attempting to augment the immune system and use of maintenance therapy after an autologous transplant. She is an investigator for the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI).

Dr Holmberg is a member of several professional organizations, including the American Society of Blood and Marrow Transplantation, American Society of Oncology, American Society of Hematology, and the Southwest Oncology Group. She is a member of the editorial board of *Transplantation Proceedings*. Dr Holmberg also serves as reviewer for several industry publications, including *Blood*, *Respiration*, and the *British Journal of Cancer*, and is the author or coauthor of more than 50 journal manuscripts and several book chapters.

John M. McCarty, MD

Medical Director, Bone Marrow Transplantation Program
Member, Massey Cancer Center
VCU Medical Center
Richmond, Virginia

John M. McCarty, MD is the medical director for the Bone Marrow Transplantation Program at VCU Medical Center and a member of the Massey Cancer Center's Hematologic Malignancy Multidisciplinary Group in Richmond, Virginia. Dr McCarty received his medical degree from the Mount Sinai School of Medicine in New York, New York. He completed his residency at Tufts-New England Medical Center in Boston, Massachusetts, and then went on to complete his fellowship in hematology and bone marrow transplantation at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle, Washington.

Dr McCarty's clinical research focuses on reduced intensity hematopoietic stem cell transplantation and immunotherapeutic approaches to malignant and non-malignant disorders. Other areas of interest include transplant strategies in myelodysplasia and myeloproliferative syndromes and supportive measures in transplantation, including cellular immunotherapy for graft-versus-host disease. Dr McCarty is principal or co-investigator for a number of ongoing clinical protocols.

Dr McCarty is a member of the Wellpoint Center Hematopoietic Stem Cell Transplant Excellence Review Committee and the Blood Disorders and Myeloproliferative Diseases Committee for the congressionally directed peer-reviewed medical research program. In addition, he is a reviewer for a number of journals and has published numerous peer-reviewed manuscripts, review articles, editorials, and research abstracts in journals such as *Blood*, *New England Journal of Medicine*, *Seminars of Hematology*, *PNAS*, and *Journal of Immunology and Experimental Hematology*. Dr McCarty has presented his research at the American Society of Hematology, the Tandem Bone Marrow Transplantation Meetings, and at the European Bone Marrow Transplantation meetings, as well as numerous invited professorships and grand rounds throughout the country.

Peter A. McSweeney, MD

Scientific Director and Director of Long-Term Follow-Up
Rocky Mountain Blood and Marrow Transplant Program
Associate Clinical Professor of Medicine
University of Colorado School of Medicine
Denver, Colorado

Peter A. McSweeney, MD is scientific director and director of long-term follow-up at Rocky Mountain Blood and Marrow Transplant Program and associate clinical professor of medicine at the University of Colorado School of Medicine in Denver, Colorado. Dr McSweeney earned his medical degree at the University of Otago Medical School in Dunedin, New Zealand. He also completed his internal medicine residency and fellowships in oncology/hematology and clinical hematology and hematopathology in New Zealand. He then came to the United States for additional training at the Fred Hutchinson Cancer Research Center in Seattle, Washington where he became a consultant physician and researcher for 10 years. He was director of allogeneic transplantation at the University of Colorado between 1999 and 2003 prior to assuming his current position.

Dr McSweeney's research has focused on marrow transplant biology and developing new treatments in myeloma, lymphoma, and leukemia. His research efforts have been highlighted in more than 100 publications.

Ivana N.M. Micallef, MD, FRCP(C)

Associate Professor of Medicine, Mayo Clinic College of Medicine
Consultant – Division of Hematology/Blood & Marrow Transplantation
Department of Internal Medicine
Medical Director, Infusion Therapy Center
Mayo Clinic
Rochester, Minnesota

Ivana N.M. Micallef, MD, FRCP(C) is associate professor of medicine at the Mayo Clinic College of Medicine, medical director of the Infusion Therapy Center, and a consultant in the Division of Hematology, Department of Internal Medicine at the Mayo Clinic in Rochester, Minnesota. Dr Micallef earned her medical degree from the University of British Columbia in Vancouver, British Columbia. She completed her internship at St. Joseph's Health Centre in Toronto, Ontario, Canada and internal medicine residency at the University of British Columbia, Vancouver, Canada. This was followed by fellowships in hematology and leukemia and bone marrow transplantation at the University of British Columbia. She subsequently served as a senior registrar and a Imperial Cancer Research Fellow in hematological malignancies at St. Bartholomew's Hospital in London, United Kingdom.

Dr Micallef is principal investigator or co-investigator on numerous ongoing clinical trials. Her research interests include therapy for lymphoma, stem cell transplantation for malignant lymphoma, and stem cell mobilization in autologous stem cell transplantation. Dr Micallef is a member of the Lymphoma Disease-Oriented Group in the Department of Internal Medicine, Division of Hematology, and the Blood and Marrow Transplant Program at the William J von Liebig Transplant Center at the Mayo Clinic, Rochester, Minnesota. She is the author or coauthor of more than 100 peer-reviewed manuscripts and editorials and has lectured extensively, nationally and internationally.

Jeffrey R. Schriber, MD, FRCP(C)

Medical Director, Bone Marrow Transplantation
Banner Blood and Marrow Transplant Program
Phoenix, Arizona

Jeffrey R. Schriber, MD, FRCP(C) is the medical director for the Banner Bone Marrow Transplantation Unit. Dr Schriber received his medical degree from the University of Toronto in Toronto, Canada. He completed fellowships in internal medicine and hematology at the Royal College of Physicians and Surgeons in Canada and a transplant fellowship at Stanford University School of Medicine in Stanford, California.

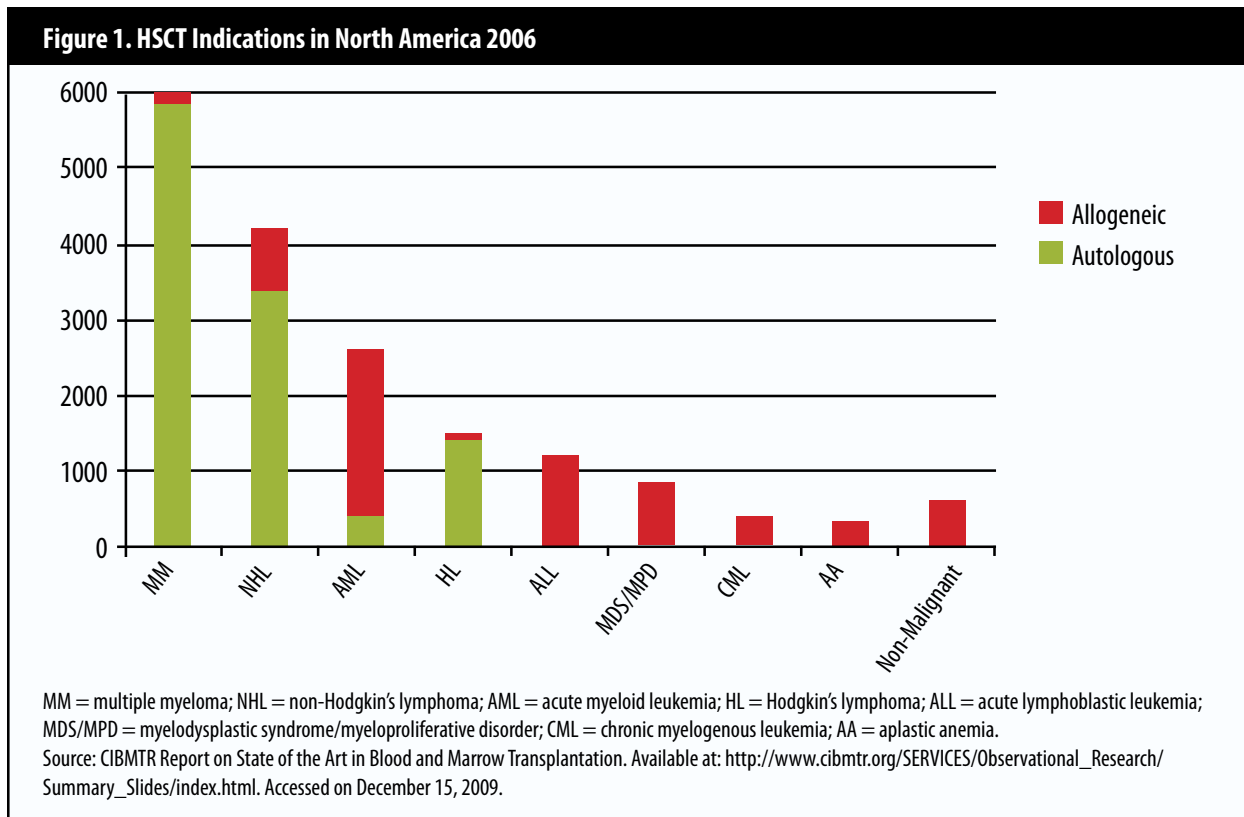
Dr Schriber serves as a member of the *National Comprehensive Cancer Network Multiple Myeloma* guidelines committee and is a board member of the American Society of Bone Marrow Transplantation. He has served as an examiner for the Malcolm Baldrige national quality award for the past three years and has an active interest in applying Baldrige Principles to improve the results in the field of transplantation. Dr Schriber has published numerous peer-reviewed manuscripts, review articles, text book chapters, and abstracts and has served as investigator for a number of clinical trials.

Introduction

The first successful hematopoietic stem cell transplant (HSCT) attempt was reported more than 50 years ago.¹ Today more than 50,000 autologous (auto-SCT) and allogeneic (allo-SCT) stem cell transplants are performed annually for both malignant and non-malignant hematological disease.²

Figure 1. In the decades since that first report, advances in scientific understanding and process improvements in the transplant maneuver have resulted in increased numbers of long-term survivors and decreased adverse events.

Modifications of the graft composeure and advances in how the product is obtained are among the many changes that have taken place. Current sources for HSCT grafts include bone marrow (BM), peripheral blood stem cells (PBSC), and cord blood. Today, more than 90% of auto-SCT and 70% of allo-SCT in adults utilize a mobilized PBSC product.³ The quality of the mobilized stem cell product, currently measured by the quantity of CD34+ cells collected, remains a critical factor for engraftment.⁴ Further optimization of the PBSC mobilization process may further improve patient outcomes.



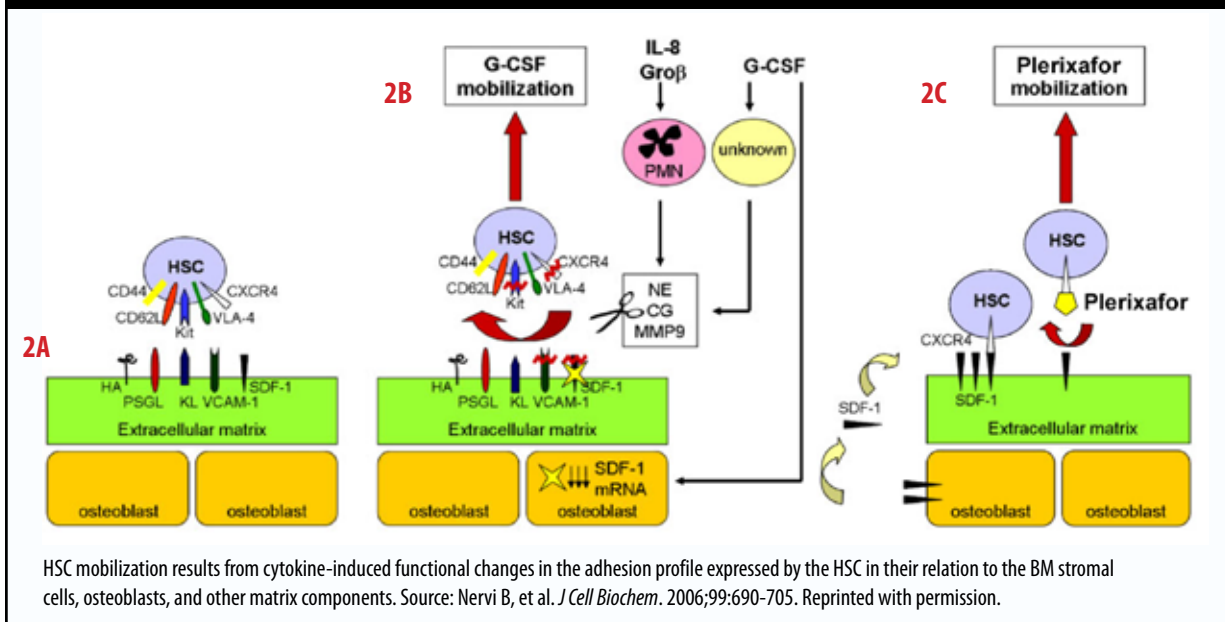
Unfortunately, the availability of quality data on current mobilization practices from randomized controlled trials are limited. Therefore, a great deal of knowledge is generated from clinical anecdotes, experiences, and impressions. This case-based educational tool will synthesize the scientific literature with expert commentary to help clinicians translate the latest scientific findings into practical patient care scenarios.

Biology of Hematopoietic Stem Cell Mobilization

The BM microenvironment is comprised of a complex mixture of cells (mesenchymal cells [eg, fibroblasts, adipocytes, and smooth muscle], osteoblasts, and monocyte/macrophages) and extracellular matrix components (collagens, fibronectins, and proteoglycans).^{5,6} Hematopoietic stem cells (HSC) reside in highly organized niches within the BM microenvironment and are anchored to the stroma by interactions between receptors and ligands expressed on the cell surface of HSC and stromal cells. **Figure 2A.**

The mechanisms governing hematopoietic progenitor cell mobilization are not fully understood. It has been discovered that adhesion molecules expressed by HSC include very late antigen-4 (VLA-4), the hyaluronan (HA) receptor, CD44, c-kit, the L-selectin CD62L, and the chemokine receptor CXCR4. Bone marrow stromal cells express ligands for these receptors such as vascular cell adhesion molecule-1 (VCAM-1), kit ligand, P-selectin glycoprotein ligand (PSGL), HA, and stromal cell derived factor-1 (SDF-1).^{4,7} Factors that alter the adhesion molecule expression profile change the HSC-stroma interaction and can result in HSC mobilization into peripheral blood circulation.⁸ **Figure 2B, 2C.**

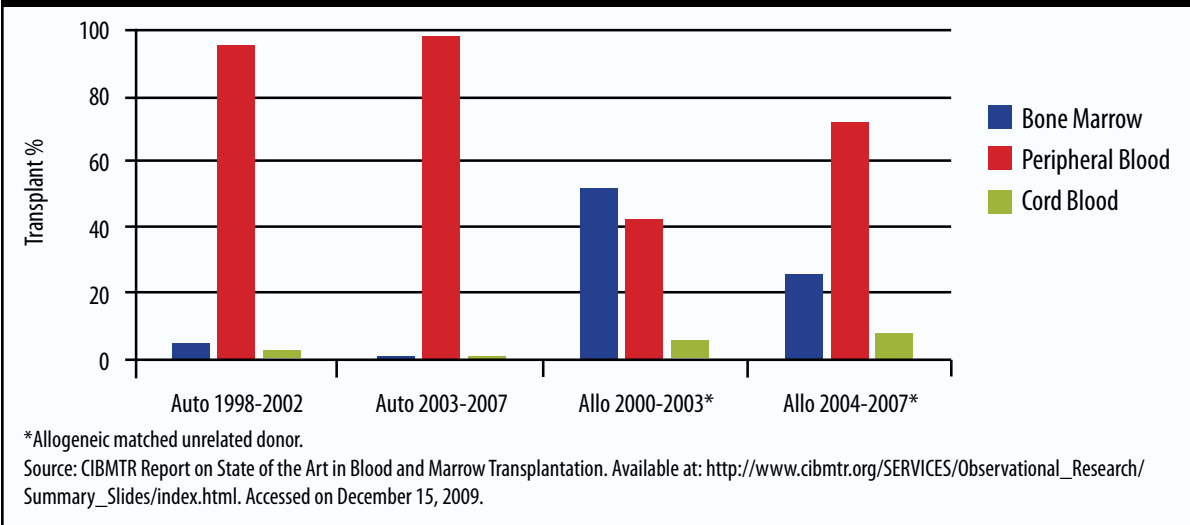
Figure 2A, 2B, 2C. HSC Mobilization



Mobilization Strategies

Various hematopoietic growth factors, some chemokines, and cytotoxic chemotherapeutic agents induce HSC mobilization. In the 1980s it was demonstrated that autologous mobilized PBSC reconstitute ablated bone marrow.⁹ Since then, the use of mobilized PBSC has been shown to result in higher CD34+ graft content, shorter hospital stays, shorter engraftment times for neutrophils and platelets, improved immune reconstitution, and reduced morbidity.^{4,10,11} Therefore, PBSC mobilization is attempted in nearly all adult auto-SCT and in the majority of allo-SCT. **Figure 3.**

Figure 3. Stem Cell Source in Patients ≥ 20 Years Old 1998-2007



Granulocyte Colony Stimulating Factor (G-CSF) is the most widely utilized mobilizing agent.⁴ G-CSF increases the number of granulocytes and granulocytic precursors in the microenvironment causing a release of neutrophil serine proteases, cathepsin G, neutrophil elastase, and matrix metalloproteinase-9 (MMP-9).¹² Increased concentration of these factors results in cleavage of VCAM-1, c-kit, CXCR4, and SDF-1. Compared to G-CSF, Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) is a less potent mobilizing agent. However, GM-CSF does act synergistically with G-CSF and the combination may be used as a salvage mobilization strategy.^{8,13} Stem cells are also commonly mobilized during hematopoietic recovery after treatment with myelosuppressive chemotherapy. Mobilization by chemotherapeutic agents is augmented by the addition of cytokines such as G-CSF and GM-CSF.^{8,14}

In 2008 the chemokine receptor inhibitor plerixafor (AMD 3100) in combination with G-CSF was FDA approved for autologous stem cell mobilization in patients with multiple myeloma (MM) and non-Hodgkin’s lymphoma (NHL).¹⁵ Plerixafor is a reversible antagonist of CXCR4 that disrupts the CXCR4-SDF-1 interaction and downstream signaling resulting in rapid HSC mobilization.^{16,17} The addition of plerixafor to the mobilization armamentarium has raised several intriguing questions regarding the optimal mobilization strategy.



Mobilization With Chemotherapy-Based Regimens

Leona A. Holmberg, MD, PhD

Selection of a Mobilization Regimen

There is not a standardized approach to stem cell mobilization. Current PB mobilization options for MM and NHL patients undergoing autologous HCST include use of hematopoietic growth factors alone, in conjunction with disease-specific chemotherapy regimens, or in combination with plerixafor.

Patient Case

A 59-year-old male presented to an outside physician with fatigue and bone pain. His only significant past medical history (PMH) was hypertension. Diagnostic work-up showed an elevated serum total protein 12.9 gm/dL, IgA lambda M-spike 6.62 gm/dL, albumin 2.4 gm/dL, beta-2 microglobulin 6.8 mg/L, creatinine 0.7 mg/dL, calcium (normal), and Hgb 7.7 gm/dL. Bone marrow had 75% plasma cells. Cytogenetics were normal by classic assessment and FISH evaluation for deletion 13, 17p, t(4;14), and t(14;16). Total IgG was 300 mg/dL, IgA 6700 mg/dL, IgM 30 mg/dL. A spot urine sample had monoclonal lambda protein. Osseous survey had lytic lesions: right femur (n = 1), left femur (n = 2), T12 compression fracture and diffuse osteopenic changes. International Staging System (ISS) stage III. Zoledronic acid was administered qmonth. First-line therapy with lenalidomide and dexamethasone x 6 cycles was given and the patient went into partial remission (PR), with plateauing of the M-spike at 0.75 gm/dL and resolution of bone pain. The patient was referred for transplant evaluation. Family history: 1 brother undergoing therapy for metastatic prostate cancer, mother died of breast cancer at 60 years old, and father died from a myocardial infarction at age 50. When presented with transplant options, the patient was not interested in any type of allogeneic transplant because of concerns about morbidity and mortality and quality of life issues with graft versus host disease.

Commentary

Even in the era of new novel agents, high-dose chemotherapy followed by autologous PBSC rescue remains the standard of care for treating MM. Although autologous PBSC transplants result in high complete response (CR) rates, the median duration of response after autologous transplant is only about 24-36 months. Patients with sensitive disease and those not heavily treated have historically had the best outcomes. In randomized studies with older chemotherapy regimens, the median progression-free survival rate (PFS) after transplant was prolonged in all studies. In the majority of the studies there was a higher CR rate and prolonged survival with transplant arm compared to standard therapy.¹⁻⁵

In the last few years there has been an attempt to increase the benefit from an auto-SCT. One of those ways was to offer tandem auto-SCT thus requiring enough autologous stem cell product to be collected to support recovery after 2 planned transplants.⁶ However, only a subset of patients; that is those who did not achieve a very good partial response (VGPR)/near complete response (nCR) or CR after the first auto-SCT, seem to benefit significantly from tandem autologous transplants.

The integration of newer therapeutic agents into the transplant setting has put more patients into CR/nCR/VGPR after first auto-SCT and thus decreased the need for the second planned transplant. In both the French and HOVON trials by adding bortezomib into the initial therapy for MM more patients achieved a ≥ CR/nCR/VGPR after a first auto-SCT.^{7,8} **Table 1.**

Table 1. Response to First Autologous Transplant

		VAD	Vel-DEX	PAD
Harousseau et al⁷ (ASH 2009)	CR/nCR %	18	35 <i>P</i> < 0.0001	-
	≥ VGPR %	50	-	80 <i>P</i> = 0.0019

VAD = vincristine, doxorubicin, and dexamethasone; Vel-DEX = bortezomib and dexamethasone; PAD = bortezomib, doxorubicin, and dexamethasone.

Lenalidomide/dexamethasone is a common, active, up-front regimen used to treat newly diagnosed MM patients and was given to the patient by his referring oncologist prior to coming to our transplant center.⁹

The optimal means to collect PBSC has not been identified. Neither the dose nor type of chemotherapy or growth factor is standardized for mobilization. The usual apheresis collection goal is 5 x 10⁶ CD34+ cells/kg per transplant.^{10,11} The success of autologous transplant is well established to be associated with the number of CD34+ cells/kg infused in MM and NHL patients. Higher CD34+ cells/kg product is associated with faster engraftment of platelets and neutrophils and reduction in need for blood product transfusions and administration of antibiotics.¹⁰⁻¹⁸

For years it was appreciated that the type of initial therapy used to treat myeloma impacted the ability to mobilize autologous PBSC. The use of alkylating agents such as melphalan was known to impair stem cell reserve and adversely impacted on the collection of PBSC depending both on duration of exposure to melphalan as well as dose.^{19,20} Thus patients who were considered potential autologous transplant candidates are not historically offered melphalan containing regimens prior to stem cell collection. Since lenalidomide affects the stromal environment and causes cytopenia (especially neutropenia), there was concern that its use would also impact detrimentally on mobilization of autologous PBSC. A number of groups have reported such a detrimental effect after lenalidomide exposure on the ability to mobilize autologous PBSC.²¹⁻²⁵ Kumar et al showed that after G-CSF (alone) mobilization there was a significant decrease in the number of CD34+ cells collected (*P* < 0.0001), an increase in the number of required apheresis days (*P* < 0.0001), and a decrease in average daily apheresis collection (*P* < 0.0001).²¹ **Table 2.**

Table 2. Median Yield of Autologous PBSC Collection After Cyclophosphamide/G-CSF or G-CSF Alone²¹

	Total CD34+ x 10 ⁶ cells/kg	Number of collections	Average Daily Collection CD34+ x 10 ⁶ cells/kg	Day 1 CD34+ x 10 ⁶ cells/kg	Days 1-2 CD34+ x 10 ⁶ cells/kg	Days 1-3 CD34+ x 10 ⁶ cells/kg
G-CSF	9.6	4	2.5	2.5	5.2	7.5
Cyclophosphamide/ G-CSF	12.7	2	7.9	8.3	11.6	12.7
P Value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

More recently, a retrospective review by Popat et al showed that as little as 3 cycles of lenalidomide may have profound impact on the ability to mobilize autologous PBSC with 25% of lenalidomide treated patients failing to mobilize with G-CSF alone vs 4% of patients who had not received previous lenalidomide therapy, $P < 0.01$.²⁴ Eighty-six percent of patients who failed to mobilize with G-CSF alone were able to be mobilized successfully using chemotherapy plus growth factor as a rescue remobilization attempt.

A number of authors showed similar benefit in higher number of CD34+ cells collected after chemotherapy and growth factor vs growth factor alone.²⁶⁻²⁸ The most common chemotherapy regimen used in myeloma patients to mobilize autologous PBSC has included cyclophosphamide 2-4 gm/m² and G-CSF. It should be noted that chemotherapy including cyclophosphamide with growth factor mobilization has its disadvantages. There has been reported a 1-1.5% mortality rate. Chemotherapy and growth factor mobilization also cause greater utilization of resources with increased risk for hospitalization and need for blood product transfusions and antibiotics.²⁹⁻³³ Time to recover after chemotherapy to starting collection of CD34+ cells is variable and thus individualized for patients. In addition there may be impact on engraftment. Gertz et al compared the use of G-CSF alone vs chemotherapy with G-CSF in a retrospective study.³⁴ They reported slower engraftment of platelets and neutrophils in patients who got cyclophosphamide/G-CSF mobilized stem cells. Seventy-five percent of patients who received mobilized stem cells < 30 days after collection, did not achieve a platelet count > 50 x 10⁹ cells/L until day +39 post transplant. Patients who received mobilized cells > 30 days after collection all achieved platelet engraftment by day +29. If the cells were collected by growth factor alone the engraftment time for platelets was day +18 post-transplant.

Chemotherapy and growth factor apheresis products also have been noted to be less likely to be tumor contaminated. It is not obvious in myeloma whether that translates into a better outcome for patients. Borurihis et al showed no difference in relapse rates in the group of patients who received autologous PBSC without detectable tumor contamination vs the group who received tumor-contaminated stem cell product. This observation argues that endogenous myeloma cells that are not eradicated by the myeloablative conditioning regimen may play a greater role in determining relapse.³⁵

In 2008, the novel growth factor plerixafor was FDA approved. In MM patients, the combination of G-CSF and plerixafor has been used to mobilize more effectively autologous PBSC than G-CSF alone.³⁶ To date, the impact of the combination on patients previously treated with lenalidomide has not been well studied. At the BMT Tandem Meetings in 2009, an abstract was presented looking in retrospective fashion at 40 patients previously treated with lenalidomide (median 4 cycles) that were mobilized with G-CSF plus plerixafor. The median number of stem cells collected was 4.9×10^6 CD34+ cells/kg.³⁷

Recommendation

Chemotherapy-based mobilization strategies produce higher stem cell yields, which is especially important in this patient heavily pretreated with lenalidomide. Since the patient still had evidence of disease and could be a candidate for planned tandem auto-SCT, he was mobilized with cyclophosphamide (4 gm/m²) and G-CSF. The apheresis collection goal for this patient was 10×10^6 CD34+ cells/kg.

Outcome

The patient mobilized 10.5×10^6 CD34+ cells/kg in 3 large volume apheresis sessions. He underwent single autologous PBSC with melphalan 200 mg/m² followed by infusion of 5.25×10^6 CD34+ cells/kg and on restaging after first autologous transplant was in VGPR. He was then enrolled on clinical trial for maintenance therapy with bortezomib post-transplant. He remains in remission at 2 years post-transplant. The remaining autologous PBSC product remains cryopreserved.

Patient Case

A 58-year-old woman presents with frequent night sweats and growing axillary lymph nodes. Her PMH included asthma, hypertension, and social history of being an ex-smoker; 10 pack-years. Biopsy of axillary node was positive for aggressive CD20+ diffuse large B cell (DLBC) NHL. CT scans of chest, abdomen, and pelvis showed disease above and below diaphragm. Bone marrow was normal by pathology and flow. She received 6 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and went into CR.

Twenty-five months after initial diagnosis the patient had reoccurrence of night sweats. CT of the chest, abdomen, and pelvis had axillary, hilar, anterior mediastinum, portal hepatic and inguinal bulky adenopathy. Repeat biopsy of inguinal node was positive for recurrent CD20+ DLBC NHL. Bone marrow was positive by 10% on pathology review for NHL disease. Peripheral blood by flow had 0.1% circulating abnormal lymphoma cells.

The patient was evaluated to determine the next treatment course. Of note on review of family history, the patient was adopted.

Commentary

Although 40-50% of patients with aggressive DLBC NHL are cured by initial chemotherapy, at the time of reoccurrence, standard salvage therapy alone is not very effective in curing patients.³⁸ High-dose therapy with autologous stem cell rescue is the standard of care for chemosensitive relapsed patients based on evidence such as the Parma study.³⁹ In patients who achieve CR or PR with standard second-line chemotherapy, around 35-45% of patients remain in durable remission after auto-SCT. As expected, those in CR after second-line chemotherapy have the best outcome.⁴⁰

The toxicity of high-dose therapy followed by autologous stem cell rescue in lymphoma patients has decreased with most regimens over the years to around a 5% mortality rate. Relapse still remains the major reason for transplant failure. Relapses occur because of the inability to eradicate endogenous tumor cells or due to reinfusion of tumor cells in the autograft.^{41,42} Second-line salvage chemotherapy is routinely used to determine chemo-sensitivity and to reduce the tumor burden prior to auto-SCT. A number of strategies have been employed to do *in vivo* or *in vitro* purging of the autograft but one of the easiest and most practical ways is to use standard chemotherapy and growth factors to collect autologous stem cells from PB after recovery from hematological nadir.

Different chemotherapy regimens have been used for second-line therapy and in the past era of not using rituximab combined with chemotherapy, (regimens such as DHAP, ESHAP, MINIBEAM, ICE, etc) almost all had about 25-35% CR rates. Since rituximab became available and is known to enhance the sensitivity of NHL cells to chemotherapy, it has been included in most second-line chemotherapy regimens for CD20+ NHL. No one to date has demonstrated superiority of a second-line chemotherapy regimen compared to another in terms of disease control; however, toxicity profiles are different and do guide our choices.

One of the most common regimens used in the United States (US) is rituximab plus ifosfamide, carboplatin, and etoposide (R-ICE).⁴³ In the initial studies, R-ICE compared to ICE had higher CR rate of 53% vs 27%, $P = 0.01$ with a PR rate of 35%. Febrile neutropenia was the most common grade 3/4 non-hematological toxicity. The R-ICE regimen with G-CSF was successful in mobilizing autologous PBSC, median of 6.3×10^6 CD34+ cells/kg. A number of other reports have showed no detriment on collection of PBSC in the presence of rituximab therapy.^{44,45}

Historically, chemotherapy with G-CSF had been preferred for NHL mobilization for a number of reasons including: cleaner stem cell product, taking advantage of chemotherapy to debulk tumor burden, and collecting higher number of mobilized PBSC.^{46,47} It has been shown that chemotherapy with G-CSF is superior in its ability to mobilize an adequate number of PBSC to get good engraftment compared to G-CSF alone in terms of total number of CD34+ cells/kg collected.⁴⁸⁻⁵⁰ Many factors including the number of previous cycles of chemotherapy, underlying disease, BM status, radiation therapy, age > 60 years old, exposure to myelosuppressive drugs such as fludarabine (with failure rates of up to 60% reported), and weight have all been reported to have an impact on the number of PBSC collected.⁵¹⁻⁵⁵

The number of CD34+ cells contained in the apheresis product is important to ensure timely engraftment. There is also reported a high correlation with the CD34+ cell count of product and outcome for lymphoma patients.⁵⁶⁻⁵⁹ However, it is not obvious that chemotherapy plus growth factor is superior to growth factor alone for collecting stem cells in the total lymphoma population. Micallef et al reported 35% of lymphoma patients failed to collect an adequate number of CD34+ cells/kg with G-CSF alone.⁵² Pusic et al reported the Washington University experience in lymphoma patients.⁶⁰ The rates for suboptimal mobilization with first attempt to collect were similar after G-CSF alone or chemotherapy plus G-CSF for NHL patients. Approximately 27% failed to collect after G-CSF and 23% after chemotherapy plus G-CSF, respectively. Similar failure rates were seen in Hodgkin's Lymphoma: 26.4% with G-CSF alone and 25% with chemotherapy plus G-CSF.

Compared to MM patients, NHL patients historically have had higher failure rates for initial mobilization. In addition, patients able to collect with G-CSF alone have been reported to have improved PFS and overall survival (OS) after auto-SCT compared to patients who achieved adequate collection only after chemotherapy plus growth factor mobilization.⁶¹ Similar to myeloma patients, chemotherapy plus growth factor mobilization in lymphoma patients is associated with increased risk for infections, febrile neutropenia, and increased utilization of resources.⁶²⁻⁶⁵

Less data have been generated on clinical significance of getting a purged PBSC stem cell product. Most data were generated on BM that showed purging was associated with better outcome especially in the follicular NHL setting.⁶⁶⁻⁶⁷ Indirect evidence does come from registry data where stem cell purging for follicular NHL was an independent predictor for PFS and OS.⁶⁸ A controlled study comparing outcome after syngeneic transplants also showed a lower relapse rate with syngeneic transplant than purged auto-SCT, which had lower relapse rate than unpurged auto-SCT.⁶⁹ Rituximab is most commonly used today as a purging agent and is effective in eliminating CD20+ NHL cells in a significant proportion of cell harvests. Magni et al showed that 93% of patients who received rituximab with chemotherapy had PCR-negative stem cell product vs 40% of control cases.⁷⁰ As none of these studies included a randomized control group, the ability to achieve a tumor-free stem cell product may only be a surrogate marker for chemosensitivity of NHL to salvage therapy. Apostolidis et al showed that achieving a minimal tumor burden in the patient rather than purging prior to transplant is the most important factor to determine long-term outcome.⁷¹

Once a patient is in CR, if already hematopoietically recovered from chemotherapy, one could consider G-CSF alone or the combination of G-CSF and plerixafor for mobilization. In a randomized study comparing G-CSF plus plerixafor vs G-CSF alone for mobilizing autologous PBSC the primary endpoint of the study was to achieve $\geq 5 \times 10^6$ CD34+ cells/kg in ≥ 4 apheresis sessions.⁷² In NHL patients, 59% of the G-CSF plus plerixafor treated patients met the goal vs 20% in G-CSF plus placebo group ($P < 0.001$; HR = 3.64). Eighty-eight percent of patients treated with G-CSF plus plerixafor collected $> 2 \times 10^6$ CD34+ cells/kg in 4 apheresis days vs 47% in control group, $P < 0.0001$. Median time to engraftment post-transplant was the same in both arms.

Recommendation

Since this patient required second-line chemotherapy to treat the relapsed diffuse NHL we elected to utilize R-ICE plus G-CSF 10 mcg/kg/day to get tumor debulking as well as to collect autologous PBSC after recovery. The goal collection for this patient was 5×10^6 CD34+ cells/kg.

Outcome

The patient had dramatic response to R-ICE and after 1 cycle blood was normal by flow assessment and on physical exam disease was dramatically shrunk. 4.5×10^6 CD34+ cells/kg were collected off R-ICE and G-CSF in 2 large-volume apheresis sessions. She was placed into CR by R-ICE before undergoing auto-SCT with carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning. The patient subsequently engrafted in a timely fashion and remains in CR at 2 years post-autologous transplant.



PBSC Collection for Optimal Results

Peter A. McSweeney, MD

Stem Cell Collection Success

The goal of PB mobilization is to produce a sufficient number of hematopoietic stem cells to achieve prompt and durable hematopoietic reconstitution with the least amount of overall toxicity and financial costs.

Patient Case

The patient is a 51-year-old male who had MM diagnosed in April 2008 after presenting with back pain. Initial treatment included 3000 cGy radiation to the thoracic spine followed by first-line therapy with lenalidomide and dexamethasone for 6 cycles. He had an incomplete response but declined an early auto-SCT attempt. The patient was subsequently hospitalized in October 2008 with hypercalcemia and renal failure. He was then treated with bortezomib and dexamethasone with a very good response after 8 cycles. He presented to our transplant center for autologous transplant. Psychosocial issues of note in this patient are that the patient is a single father of 2 children, the primary source of family income, with minimal extended family support. In addition, the patient suffers from morbid obesity (weight 274 lb at start of procedure, body surface area 2.44 m², body mass index 41.7).

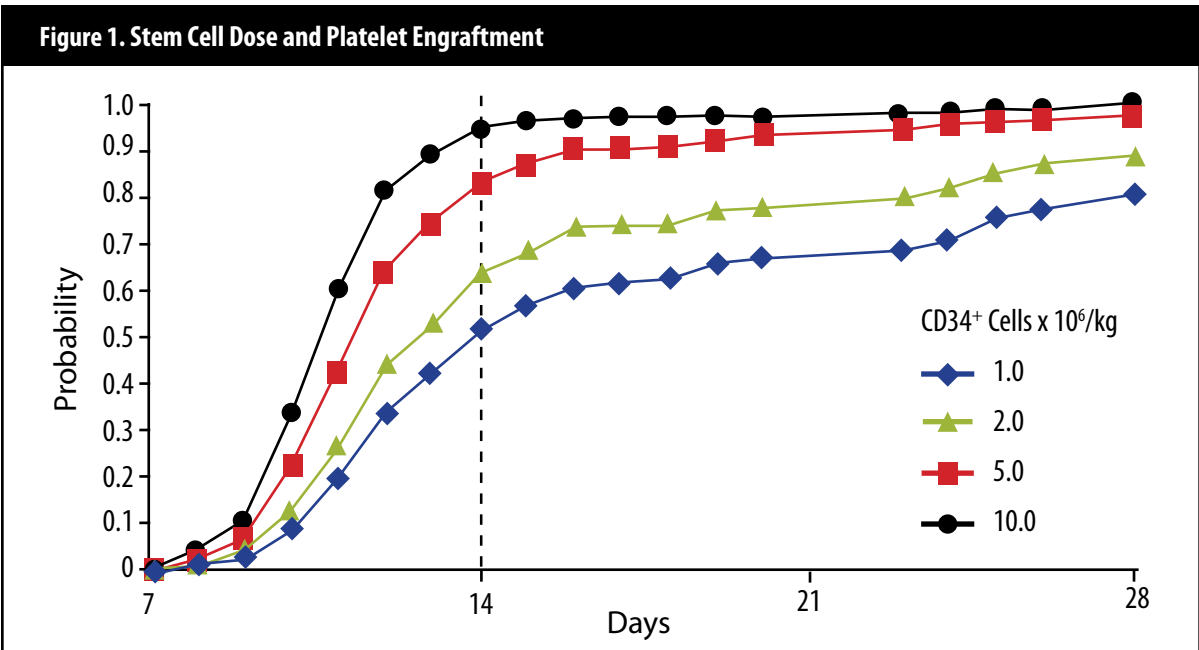
Commentary

The goal of mobilization was to overcome any myelosuppressive effects of prior therapy, maximize apheresis yield, and minimize days out-of-work required for the mobilization and collection process for this patient. Current protocols use CD34+ as a surrogate marker for hematopoietic stem and other progenitor cells and define adequate engraftment as recovery of the absolute neutrophil count (ANC) to ≥ 500 cells/mm³ in 10-14 days and platelet count to more than 20×10^9 /L in 15-30 days post transplant with durable hematologic and immune system recovery. There is no clear consensus on the minimum CD34+ cell dose needed for successful auto-SCT. In the US, the average number of infused CD34+ cells/kg is approximately $3-5 \times 10^6$ cells/kg. When patients are given 2×10^6 CD34+ cells/kg, 60% recover platelets by day +14. However, when 10×10^6 CD34+ cells/kg are given, 90% of patients recover platelets by that time. **Figure 1.**

For this patient, a target dose of $> 10 \times 10^6$ CD34+ cells/kg was the goal in order to provide maximum flexibility for future treatment including at a minimum 2 autologous transplant procedures. Ideally these cells could be collected in 1-2 apheresis sessions. Self administration of G-CSF is possible for some patients and can help patient convenience.

Recommendation

Minimizing time off from work was important to this patient's home circumstances and thus a shorter mobilization procedure was desired. Mobilization was undertaken with plerixafor and G-CSF 10 mcg/kg/dose in order to overcome any mobilization resistance due to prior radiation and chemotherapy exposure. Dosing of plerixafor used adjusted ideal body weight and G-CSF actual body weight. The package insert for plerixafor recommends dosing of plerixafor at 0.24 mg/kg actual body weight (not to exceed 40 mg/day if CrCl > 50 mL/min). However an alternative dosing strategy was used as there are no published studies that specifically address the issue of dosing these agents together in morbidly obese patients.



Cox proportional hazards analysis for probability of platelet engraftment to 20×10^9 platelets/L by CD34+ cell dose (n = 212). Glaspy EJ, Shpall CF, LeMaistre CF, et al. Peripheral blood progenitor cell mobilization using stem cell factor in combination with filgrastim in breast cancer patients. *Blood*. 1997;90(8):2939-2951. Reprinted with permission.

Outcome

Autologous stem cells were collected in 1 apheresis session and a total of 15.9×10^6 CD34+ cells/kg were stored. The patient proceeded to high-dose chemotherapy (melphalan 200 mg/m^2) and auto-SCT. The transplant was uncomplicated and hematological recovery including platelets, neutrophils, and red cells was complete. Neutrophil recovery to $> 500 \text{ cells/mm}^3$ occurred on day +12 and platelets to $> 20 \times 10^9/\text{L}$ without transfusions on day +22. The patient is currently 3 months post-transplant with an excellent response without detectable disease by serum protein markers and back at work full-time. There is no plan for a second transplant at this time and stored autologous progenitors are available for possible future transplant.

Patient Case

The patient is a 40-year-old male diagnosed with stage IV mantle cell lymphoma in 2008. Disease was found in the conjunctiva and BM at diagnosis. He was treated initially with hyperfractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone alternating with high-dose methotrexate and cytarabine (hyper-CVAD) and rituximab. He received 4 cycles of chemotherapy, the last of which was complicated by influenza pneumonia. According to standard practice the patient was offered auto-SCT to consolidate his chemotherapy. Mobilization was attempted with a combination of cyclophosphamide and peg-filgrastim supplemented by 4 doses of G-CSF when mobilization of CD34+ cells was not detected. The maximum PB CD34+ level reached on this mobilization attempt was $< 5 \text{ cells}/\mu\text{L}$.

Commentary

Failure to mobilize a sufficient number of CD34+ cells may result in prolonged apheresis sessions, place additional strain on patient and facility resources, or even result in ineligibility for transplantation. Options for patients after a failed mobilization attempt include repeat mobilization with G-CSF, use of alternative cytokine regimens (increased dosing of G-CSF or combining G-CSF and GM-CSF), addition of chemotherapeutic agents if not used previously, BM collection via a traditional marrow harvest, or the addition of plerixafor. **Table 1.**

All options are associated with additional costs. In addition, repeat mobilization with G-CSF has high associated failure rates.² Alternative cytokine regimens and the addition of chemotherapy is associated with added toxicity and the efficacy rates are generally low. For BM harvest, the patients must be put under general anesthesia, collections are painful, and only provide enough cells for a single transplant.

Successful re-mobilization with G-CSF plus plerixafor after failed chemotherapy or cytokine mobilization was reported to be greater than 70% in one study.³ However, the plerixafor-induced grafts differ in composition, the significance of which is not fully understood and long-term studies yet to be performed.⁴

Table 1. Re-Mobilization Strategies

Strategy	Potential Complication
Repeat First Mobilization Regimen	Repeat failure
Employ Alternative Cytokine Regimen (Higher Dose or in Combination)	Additional toxicity risk Additional costs
Addition of Chemotherapy	Additional toxicity risk (including risk of neutropenic fever, which may require hospital admission)

Recommendation

After a 2-week rest period, re-mobilization was attempted with G-CSF and plerixafor.

Outcome

Mobilization was successful and 6.93×10^6 CD34+ cells/kg were collected from 2 apheresis sessions. He went on to have an uncomplicated outpatient auto-SCT after conditioning with BEAM chemotherapy. Hematopoietic recovery was initially slow but by 3 months post-transplant his PB counts were normal, Karnofsky performance status was 100%, and there was no sign of recurrent disease.



Poor Mobilization Prediction

Ivana N.M. Micallef, MD, FRCP(C)

Can risk of mobilization failure be predicted?

Approximately 5-30% of patients undergoing stem cell mobilization are unable to mobilize sufficient CD34+ cells to support administration of high-dose chemotherapy. Various factors have been associated with poor mobilization including increased age, female gender, increased cycles and regimens of chemotherapy, prior treatment

with specific chemotherapeutics such as purine analogs or platinum-based chemotherapy, prior myelosuppressive therapy such as lenalidomide, prior radiation to the bone marrow, low pre-mobilization platelet count, and low PB CD34+ count.

Patient Case

A 73-year-old female was diagnosed with MM in December 2007 after presenting with an impending left hip pathologic fracture. She underwent hemiarthroplasty followed by radiotherapy (35 Gy) to the left hip and femur. She received first-line treatment with lenalidomide and dexamethasone x 3 cycles to a PR. The decision was then made to proceed with autologous HSCT. She was mobilized with G-CSF alone at an initial dose of 10 mcg/kg/day. On day 4 of G-CSF, PB CD34+ was < 10 cells/μL and a decision regarding the mobilization course was required to be made.

Commentary

Overall, in patients with lymphoma, 20-30% of patients fail to collect adequate numbers of stem cells to proceed with transplantation ($\leq 2 \times 10^6$ CD34+ cells/kg) and up to 50% of patients fail to collect the optimal goal of $\geq 5 \times 10^6$ CD34+ cells/kg. In MM the failure rate is lower. However, there have been recent reports of difficulty mobilizing stem cells in patients previously treated with myelosuppressive agents including thalidomide and lenalidomide, which have now become standard therapy for most myeloma patients. Duration of lenalidomide beyond 3 cycles and age > 65 years has been associated with poor mobilization in MM patients.¹

Gertz et al recently reported on a review of stem cell mobilization in over 1700 patients; results of stem cell mobilization were divided between "successful" CD34+ collections ($\geq 5 \times 10^6$ CD34+ cells/kg) in 53% of patients, "low" CD34+ collections ($2-5 \times 10^6$ CD 34+ cells/kg) in 25% of patients, "poor" CD34+ collections ($< 2 \times 10^6$ CD34+ cells/kg) in 10%, and "failed" (apheresis not performed due to low circulating PB CD34+ cells/μL) in 12%.² Thus 47% of patients had a less than optimal collection ($< 5 \times 10^6$ CD34+ cells/kg). Pusic et al showed that the failure rate ($< 2 \times 10^6$ CD34+ cells/kg) was similar between cytokine mobilization and chemotherapy mobilization (19% in both groups). The main difference was that the addition of chemotherapy to the mobilization regimen allowed successful collectors to collect better, but did not diminish the rate of poor or failed collection ($< 2 \times 10^6$ CD34+ cells/kg).³ Gertz et al reported that patients who received chemotherapy for stem cell mobilization required parenteral antibiotics in 24% of cases and hence increased resource utilization including increased hospitalizations, transfusion support, and antibiotic use.²

Until recently, re-mobilization strategies using G-CSF plus GM-CSF or G-CSF plus chemotherapy, in general, have been unsuccessful. In the study by Pusic et al only 23% of patients undergoing re-mobilization were able to collect $\geq 2 \times 10^6$ CD34+ cells/kg. The success rate with G-CSF alone

or G-CSF plus GM-CSF was 18% and with G-CSF plus chemotherapy was 26%. Bone marrow harvest has also been used in the past. Patients who fail to mobilize sufficient CD34+ cells to the PB for collection who then undergo BM harvest may have up to a 30% incidence of platelet non-engraftment. Plerixafor, a CXCR4 receptor antagonist, in combination with G-CSF has been shown to mobilize more CD34+ cells/kg compared to G-CSF alone in 2 randomized phase III studies in NHL and MM.^{4,5} Combination G-CSF plus plerixafor in patients who have previously failed to mobilize was also shown to have a high success rate of approximately 60-70% in the compassionate use program.⁶

Poor mobilization has been noted to be associated with a low PB CD34+ count during G-CSF mobilization. Recent reports have shown that patients who have a PB CD34+ of < 10 cells/ μ L on day 4 have a low likelihood of successfully collecting an adequate number of stem cells. In a retrospective review of stem cell mobilization, PB CD34+ < 10 cells/ μ L on day 4 and day 5 was associated with a 25% and 48% failure to collect at least 2×10^6 CD34+ cells/kg, respectively.⁷ Post ad hoc analysis of the 2 phase III plerixafor studies also looked at using a PB CD34+ cutoff of 10 cells/ μ L as a predictor. In this analysis, if the PB CD34+ was < 10 cells/ μ L on day 4 only 34% of patients collected more than 2×10^6 CD34+ cells/kg in 4 days and only 22% were able to achieve a goal of 5×10^6 CD34+ cells/kg, which is the optimal goal in NHL.⁸

Recommendation

It was initially recommended to increase G-CSF to 16 mcg/kg bid. After multiple days of high-dose G-CSF, the PB CD34+ did not increase and the mobilization attempt was aborted. After a 1-week rest period, the patient was re-mobilized on the compassionate use protocol utilizing G-CSF plus plerixafor. G-CSF was given at 10 mcg/kg/day x 4 days and plerixafor 0.24 mg/kg administered starting the evening of day 4; both G-CSF and plerixafor continued daily until apheresis was completed.

Outcome

On day 4 PB CD34+ was < 1 cells/ μ L; the morning of day 5 PB CD34+ measured 20 cells/ μ L (a 22-fold increase). The apheresis yield on day 1 was 2.7×10^6 CD34+ cells/kg and on day 2 was 4.3×10^6 CD34+ cells/kg, for a total of 7.0×10^6 CD34+ cells/kg. She then went on to auto-SCT with melphalan conditioning (200 mg/m^2) followed by stem cell re-infusion. The patient received 3.51×10^6 CD34+ cells/kg and the other half remains in storage for a possible future second transplant. The post-transplant course was relatively uncomplicated. She experienced neutrophil engraftment at day +17 and platelet engraftment to $50 \times 10^9/\text{L}$ at day +20. At 1-year post transplant she remains in remission with no evidence of progression and with a normal CBC.

Patient Case

A 59-year-old female patient was diagnosed with mantle cell lymphoma in December 2008, stage IIIA. The initial treatment recommendation was to proceed with R-CHOP x 6 cycles chemotherapy followed by auto-SCT in first remission. Evaluation by CT after 2 cycles showed an excellent response. She obtained a first CR and returned to proceed with autologous HSCT in June 2009. Pre-transplant testing confirmed a first CR, negative bone marrow, and platelet count of $281 \times 10^9/\text{L}$. She was mobilized with G-CSF at 10 mcg/kg/day. On day 4, PB CD34+ was measured at 3 cells/ μ L; on day 5 of G-CSF it was 7 cells/ μ L.

Commentary

Peripheral blood CD34+ of < 10 cells/ μ L has been shown to be a risk factor for poor mobilization. We have recently implemented a risk-adapted mobilization strategy whereby patients who are ineffectively mobilizing with G-CSF alone have plerixafor added to their mobilization regimen. In this algorithm, if the PB CD34+ is < 10 cells/ μ L then plerixafor is added. These results were reported at the American Society of Hematology 51st Annual Meeting and Exposition in 2009. Out of 147 mobilization attempts, 37 patients had ineffective mobilization as measured by low PB CD34+ (< 10 cells/ μ L on day 4 and day 5). In this group of patients, plerixafor (0.24 mg/kg/day) was added in the evening of day 5 and then patients underwent apheresis the following morning. G-CSF continued in the mornings and plerixafor in the evenings until apheresis was complete. If the daily yield was $< 0.5 \times 10^6$ CD34+ cells/kg on 2 consecutive days then mobilization was aborted. Using this algorithm, the median apheresis yield obtained was 4.4×10^6 CD34+ cells/kg (range 0.1 - 12.7×10^6 CD34+ cells/kg) in this group of patients. Number of apheresis days was a median of 3 (range 1-7). The failure rate ($< 2 \times 10^6$ CD34+ cells/kg) was 5% compared to a rate of 22% prior to this risk-adapted algorithm.⁹

Recommendation

This patient had a PB CD34+ < 10 cells/ μ L on day 4 and day 5, therefore plerixafor was added on the evening of day 5 and apheresis was initiated the following morning.

Outcome

Daily apheresis collections were as follows: Day 1, 1.54×10^6 CD34+ cells/kg; day 2, 2.39×10^6 CD34+ cells/kg; day 3, 1.81×10^6 CD34+ cells/kg for a total of 5.74×10^6 CD34+ cells/kg. The patient then proceeded with BEAM conditioning followed by stem cell re-infusion of all collected cells. Neutrophils engrafted at day +12 and platelets to 50×10^9 /L on day +17. At day +100 follow-up, she remained in CR by CT and PET scan, with a normal CBC.



Stem Cell Mobilization Following Myelosuppressive Agents

Jeffrey R. Schriber, MD, FRCP(C)

Does prior myelosuppressive therapy influence mobilization regimen selection?

Patients who fail initial mobilization require additional strategies if they are to proceed successfully to transplantation. This may cause delays in therapy, increase costs as well as the resources used by both the patient and the transplant center. While it remains unknown precisely why some patients mobilize poorly, several factors have been identified that influence stem cell collection. One such identified factor includes prior myelosuppressive therapy.

Patient Case

A 48-year-old previously healthy male presents with non-specific bone discomfort over the right fourth rib and occasional numbness in his feet. He was found to be anemic with a Hgb of 11.5 gm/dL. A gastrointestinal work-up was negative. Additional laboratory workup reveals a total protein of 12 gm/dL, SPEP 5.4 gm/dL, IgA of 4800 mg/dL, creatinine 0.9 mg/dL, calcium 7.8 mg/dL, and beta-2 microglobulin 3.5 mg/L. Multiple bony lesions are noted on X-ray but no impending fractures are noted. Bone marrow aspirate shows 60% plasma cells (with atypical forms noted), normal cytogenetics and FISH.

The patient was started on lenalidomide and dexamethasone as first-line therapy. After 4 cycles, IgA decreased to 2800 mg/dL. After 6 cycles IgA was 2200 mg/dL and marrow showed 15% plasma cells. Post 8 cycles of therapy, IgA dropped to 1200 mg/dL, and marrow showed 3% plasma cells. The patient was then referred for auto-SCT evaluation and HSC collection planned.

Commentary

For patients with MM, increased age, prior exposure to radiotherapy, and certain therapeutic agents such as melphalan or lenalidomide have been shown to negatively impact the ability to collect adequate numbers of stem cells. As transplant became more popular in myeloma, the upfront use of melphalan and radiation to major marrow producing areas has dropped dramatically. However, initial therapy with immunomodulators such as lenalidomide remains a common practice. In this patient this regimen may have been chosen in part because of the pre-existing neuropathy, which could potentially be exacerbated by the use of bortezomib.

Several groups have reported that extended exposure of patients to lenalidomide decreases the number of PB CD34+ cells obtained.¹⁻⁴ Kumar et al showed a decrease in total CD34+ cells collected, day 1 collection and average daily collections, and an increase in the number of apheresis sessions needed to achieve collection goals in patients treated with longer durations of lenalidomide.¹ The authors went on to suggest patients should be collected within 6 months of therapy initiation to minimize the risk of future mobilization failure. Paripati et al showed a 100% mobilization failure rate in patients who had received > 10 cycles of lenalidomide.² Mazumder et al also reported lower stem cell yields after lenalidomide induction though 6/12 (50%) patients who had a failed mobilization attempt received ≤ 5 cycles.

One possible method to overcome this difficulty is to collect stem cells following chemotherapy plus growth factors. Mark et al treated 28 treatment-naïve myeloma patients with a clarithromycin, lenalidomide, and dexamethasone (BiRD) regimen to maximum response. Patients were then mobilized with either G-CSF or 3 gm/m² cyclophosphamide plus 10 mcg/kg G-CSF. Sufficient stem cells for 2 auto-SCT were collected from all patients mobilized with cyclophosphamide plus G-CSF, versus 33% mobilized with G-CSF alone ($P < 0.0001$).⁵ Popat et al reported mobilization failure in 25% of MM patients who had previously received lenalidomide compared with 4% of patients who had not received lenalidomide ($P < 0.001$).⁴ Twenty-one of 26 patients who failed initial mobilization with G-CSF alone underwent remobilization with chemotherapy and G-CSF and in 18/21(86%) patients, this combination successfully mobilized a median of 7×10^6 CD34+ cells/kg.

In the past it was common to use cyclophosphamide not only to collect stem cells but also to further reduce the myeloma burden. With the addition of the newer agents for primary therapy more patients have demonstrated an excellent clinical response and there may no longer be a need for additional chemotherapy for cytoreduction. This would mean that the sole purpose of chemotherapy would be to allow the collection of sufficient stem cells. Cyclophosphamide mobilization however is not without risks including the potential for febrile neutropenia, the need for transfusional support, hemorrhagic cystitis, and approximately 20% of patients may require hospitalization.⁶ At most centers now this risk for patients who already have a good clinical response is not acceptable and the majority of centers do not choose chemotherapy and would utilize other options instead.

Mobilization in Myeloma IMWG Consensus Perspective¹¹

Among patients receiving initial therapy with lenalidomide regimens failing to collect with G-CSF alone, there are 3 options for the subsequent attempt:

1. Cyclophosphamide priming and G-CSF
2. Use of plerixafor in combination with G-CSF
3. Combination G-CSF and GM-CSF

Recommendation

For such a patient it is difficult to see how a strategy with growth factors alone will be successful. Given the excellent pre-mobilization disease status we would not feel justified in treating the patient with additional cytotoxic therapy solely for collection purposes as our first choice. We began therapy with G-CSF 10 mcg/kg/day and measured CD34+ counts on the fourth day of G-CSF. With a count of 4 cells/ μ L, we gave 1 further day and the count remained at 4 cells/ μ L. He was then given plerixafor that evening and the next morning underwent high volume stem cell apheresis. A total of 2.2×10^6 CD34+ cells/kg were collected. One additional day of therapy allowed a total collection of 5.6×10^6 CD34+ cells/kg and the patient went on to transplant.

Outcome

Following collection the patient underwent auto-SCT using melphalan 200 mg/m² conditioning as an outpatient. The patient was admitted on transplant day +9 with febrile neutropenia and engrafted to an ANC of 500 cells/mm³ by day +11. The patient was discharged from hospital on day +12. On day +100 post-transplant the marrow showed 2% plasma cells, IgA was 650 mg/dL with a beta-2 microglobulin of 1.8 mg/L. Immunoelectrophoresis was negative. Follow up 1 year later showed no evidence of disease and normal blood counts.

Patient Case

A 52-year-old female presents with abdominal bloating, weight loss, fatigue, and change in bowel habits. Laboratory work-up revealed a mild anemia with a Hgb of 10.8 gm/dL. Physical exam revealed palpable bilateral axillary lymph nodes. CT scan showed multiple enlarged lymph nodes and PET scan confirms these findings. Biopsy of the axilla shows follicular NHL, grade 2. There was 10% bone marrow involvement. The patient was started on fludarabine, cyclophosphamide, and rituximab (FCR) for 4 cycles and repeat PET showed a 50% improvement. She completed FCR and achieved a CR. Two years later she returns having developed a palpable node in her left axilla. Repeat scans show multiple small nodes, axilla SUV 11.5 (pre-biopsy). Biopsy pathology reads DLBC NHL. Bone marrow was not involved. She was given 2 cycles of etoposide, methylprednisolone, cytarabine, and cisplatin (ESHAP) and the follow-up PET scan was negative. She was referred for transplant consultation at this time.

Commentary

In general, mobilizing patients with NHL is more difficult despite the need for fewer total CD34+ stem cells as compared to MM. It is also more challenging to predict who might fail standard methods of collection. A number of factors including prior therapies, fludarabine exposure, and platelet count have been correlated with poor collections in patients with NHL.⁷ Purine analogues such as fludarabine are frequently used for initial and salvage treatment of low grade NHL.⁸ In

one study, as many as 60% of patients in this population failed to mobilize with conventional mobilization regimens such as G-CSF +/- chemotherapy.⁹ Despite advances in our knowledge, there remains a need for more effective and predictable PBSC mobilization strategies for this patient population.

A recent retrospective analysis was performed on the subgroup of patients who participated in the G-CSF plus plerixafor compassionate use program (CUP) who had received fludarabine prior to attempted stem cell collection.¹⁰ By definition, all of these patients had failed prior attempts to collect stem cells. A subgroup of 48 patients (12% of the initial population) was identified who received plerixafor plus G-CSF as part of this trial. Complete data was available for 33 patients. The median number of fludarabine cycles prior to mobilization was 5 (range 1-50).

The combination of G-CSF plus plerixafor resulted in a median collection of 2.8×10^6 CD34+ cells/kg (range $0.3-6.6 \times 10^6$ CD34+ cells/kg). **Table 1.** The majority (64%) collected $\geq 2 \times 10^6$ CD34+ cells/kg in a median of 2 apheresis sessions (range 1-6 days). Of the patients who attempted the salvage mobilization regimen, 27/33 (82%) proceeded to transplant. Importantly, there was no apparent difference in the median number of stem cells collected or the percentage who successfully completed a minimum collection between the patients who had received fludarabine vs those with no prior exposure. Following transplantation median engraftment times for neutrophils and platelets were 12 and 22 days in the patients with prior fludarabine exposure, similar to patients who had not received fludarabine.

Table 1. Outcome of G-CSF Plus Plerixafor in Patients With and Without Prior Fludarabine Exposure

	Prior Fludarabine n = 33	No Prior Fludarabine n = 297
Median Number of CD34+ cells/kg	2.8×10^6	2.5×10^6
Patients Collecting $\geq 2 \times 10^6$ CD34+ cells/kg	64%	64%

These preliminary data suggest that the majority of NHL patients pretreated with fludarabine who have failed a previous mobilization regimen can be successfully mobilized using a combination of G-CSF plus plerixafor.

The majority of NHL patients are initially mobilized with a combination of chemotherapy and growth factors to take advantage of the cytoreductive properties of chemotherapy as well as the proliferative rebound of stem cells demonstrated with the use of chemotherapy and growth factors in this setting. There are less data on how to incorporate plerixafor into these regimens although this is the subject of intensive investigation.

Recommendation

The patient was to be collected post the next cycle of ESHAP with G-CSF 10 mcg/kg/day started on day 5 of the regimen. The collection target goal for this patient was 2×10^6 CD34+ cells/kg.

Outcome

The WBC peaked at 60×10^3 cells/ μL and the maximum CD34+ count documented was 5 cells/ μL and after 15 days of G-CSF. Collection attempts were discontinued and growth factors were stopped. After a 1-week rest period, G-CSF 10 mcg/kg/day plus plerixafor .24 mg/kg/day (starting day 4) was initiated. After 2 apheresis sessions, 3×10^6 CD34+ cells/kg were collected. The patient proceeded to transplantation with a conditioning regimen of BCNU/etoposide/cyclophosphamide and engrafted WBC on day +12 and platelets on day +15 post transplant. Day +100 work-up showed no evidence of disease.

Follow-Up Question and Response

In retrospect would you attempt mobilization with up-front G-CSF plus plerixafor post-chemotherapy?

Data using plerixafor and G-CSF post chemotherapy are still in their infancy. As we learn more we may well incorporate directly into the mobilization regimen as is often practiced now with growth factors alone. At present we would typically base the decision to use chemotherapy on the underlying disease state. For those patients who do not require additional chemotherapy we would consider G-CSF plus plerixafor as outlined in the previous case. In those patients who require chemotherapy for disease control, at this time, we would attempt to collect using growth factors alone as we did in this patient. We currently reserve the use of plerixafor for those patients, like this one, who fail our initial attempts. One advantage to early use of plerixafor is that you minimize the exposure to additional chemotherapy when it is not clinically indicated and by collecting rapidly you ensure that the patient can proceed to transplant without significant delays following chemotherapy.



Pharmacoeconomic Considerations/Efficiency

John M. McCarty, MD

Is there a method of stem cell mobilization which optimizes resource utilization?

As compared to harvesting BM, PBSC collection in the outpatient setting requires careful coordination between multiple healthcare teams including the transplant clinic, apheresis center, cellular therapy processing lab, flow cytometry lab, and most importantly, patients and families. Any unexpected delays in the stem cell mobilization or apheresis process may lead to inefficient and ineffective resource utilization including prolonged apheresis machine time or overtime and weekend staffing for the apheresis and stem cell laboratories. In addition, delays complicate planning for transplant admissions and challenge adequate scheduling of nursing staff. Any process that can lead to enhanced predictability of successful stem cell collection would have a wide-ranging impact on the entire multi-disciplinary transplant team and the financial impact of stem cell acquisition costs. Furthermore, reduction in the resources used to acquire a successful stem cell dose will allow for cost reduction and improved stewardship of healthcare dollars; an important consideration in light of the current healthcare debate in the US.

Patient Cases

Patient “Salvage” is a 47-year-old male with MM who after multiple treatment courses with lenalidomide was found to have minimal disease response. He was next treated with a pegylated liposomal doxorubicin-bortezomib-dexamethasone (DVD) regimen for 4 cycles with a similar result. Following 6 cycles of dexamethasone, cyclophosphamide, etoposide, cisplatin, and thalidomide (DCEP-T), he achieved a PR. However, his chemotherapy course was complicated by asthenia, fatigue, and neutropenic fevers. As a result of his demonstrated poor response to initial cytoreductive therapy, he was considered for tandem autologous PBSCT with high-dose melphalan. His target PBSC collection goal was $8-10 \times 10^6$ CD34+ cells/kg. Stem cell mobilization was undertaken with G-CSF at 10 mcg/kg/day. On day 4, he was noted to have 13 CD34+ cells/ μ L in the PB, and collected approximately 750,000 CD34+ cells/kg on that day. Subsequent days showed both a decreasing peripheral blood CD34+ count and diminishing apheresis yield. At the end of 5 days of apheresis, only 2.16×10^6 CD34+ cells/kg had been collected. According to institutional guidelines active at the time a 1-week washout period was initiated, he then again started G-CSF at 10 mcg/kg/day followed by plerixafor on the evening of day 4. The following morning, his PB CD34+ count was 58 cells/ μ L, and he collected 6.85×10^6 CD34+ cells/kg in 2 days of apheresis. Combined with the previous collection attempt, he proceeded to transplant with a total of 9.01×10^6 CD34+ cells/kg.

Patient “EPI 1” is a 62-year-old female with MM documented at diagnosis to carry a mutation of 13q. She successfully underwent initial cytoreductive therapy with DVD and achieved a PR in her disease. She elected to undergo stem cell mobilization with G-CSF at 10 mcg/kg/day, with a target collection goal of $8-10 \times 10^6$ CD34+ cells/kg to support high-dose melphalan followed by tandem autologous transplants. On the 4th day, while her total WBC count had risen to 20,000, her peripheral blood CD34+ count was 2 cells/ μ L. According to our “Early Plerixafor Intervention” (EPI) protocol, apheresis was not attempted on day 4. She received plerixafor the evening of day 4, and the next morning’s peripheral blood CD34+ count was 71 cells/ μ L. She underwent a total of 2 days apheresis and collected 9.11×10^6 CD34+ cells/kg.

Patient “EPI 2” is a 54-year-old male with stage III recurrent DLBC NHL. Originally treated to CR1 with R-CHOP 2 years prior to relapse, he was re-induced to a near CR2 by PET-CT criteria using R-ICE chemotherapy for 4 cycles. His pre-transplant testing showed him to be a candidate for high-dose BEAM chemotherapy followed by PBSCT. Because of his excellent response to R-ICE, it was felt that additional chemotherapy was not indicated, and he was referred for stem cell mobilization using G-CSF with a target collection goal of $4-5 \times 10^6$ CD34+ cells/kg. On the 4th day of G-CSF at 10 mcg/kg, his peripheral blood CD34+ count was noted to be 8 cells/ μ L and in accordance with our EPI protocol apheresis was not attempted on day 4; he received plerixafor that evening. The next morning’s PB CD34+ count was measured at 25 cells/ μ L. He proceeded to collect a total of 4.57×10^6 CD34+ cells/kg in 1 day of apheresis.

Commentary

The economic environment for autologous transplantation in the US is different than the typical fee-for-service approach and different cost-saving strategies may have differing economic impacts on either the individual patient, transplant program provider, insurer, or the healthcare delivery system as a whole. Most transplants are done in transplant centers under a case-rate

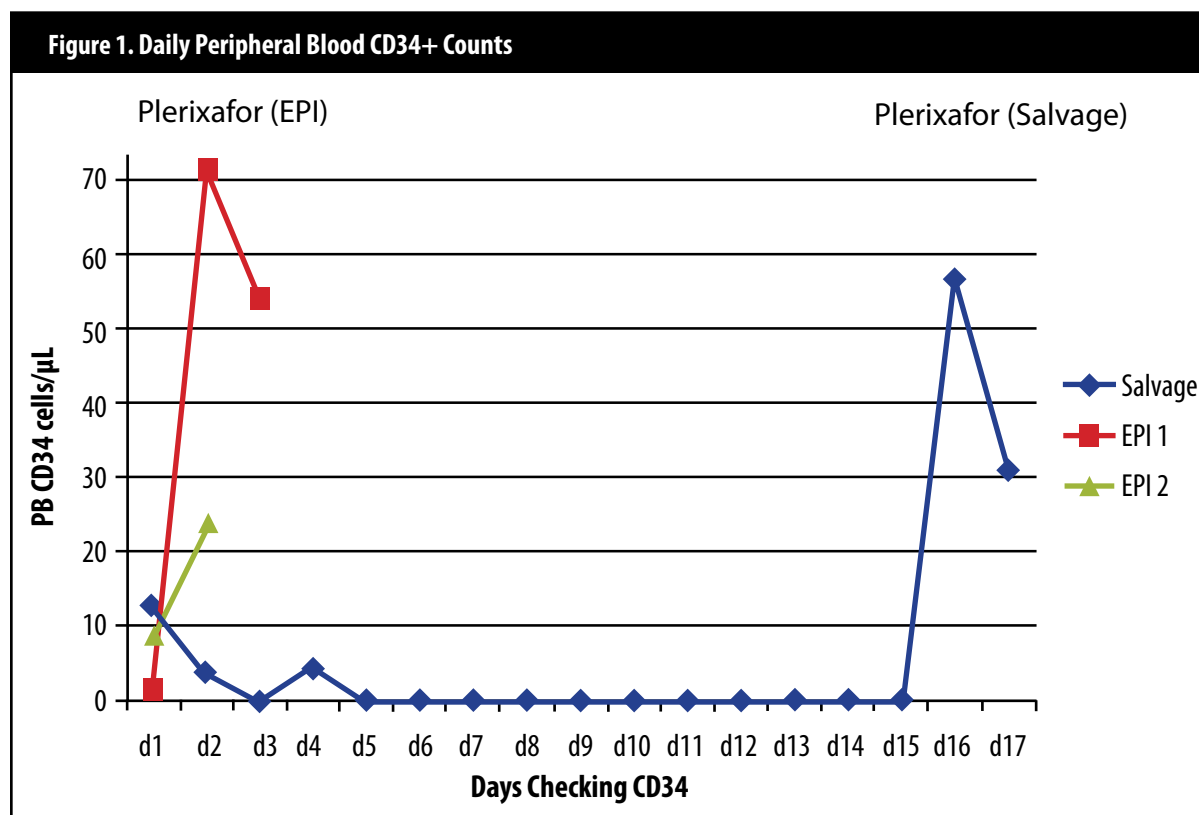
contract. Therefore, strategies that have lower total costs for optimal stem cell acquisition, hospitalization, and post-transplant care per patient are “better” for the center given the fixed fee contract, and would drive greater interest in a more cost effective approach. Likewise, strategies that allow for more rational, efficient, and predictable use of specialized resources, such as apheresis time, stem cell processing, freezer space, and bone marrow transplant clinic visit time can be valued as a cost savings in personnel and capital expenditures. From the patient and societal perspective, a slightly different endpoint is relevant: patient “success” is being able to undergo transplantation with fewer potential short- and long-term complications with a minimum of delays to allow an early return to productivity.

Three strategies are currently available as initial selection for mobilizing PBSC: chemotherapy plus growth factors (eg, using ICE, cyclophosphamide, or ESHAP), G-CSF alone, or G-CSF plus plerixafor. There is considerable variation among centers in the US and around the world regarding the optimal method to obtain PBSC, as well as to the definition of sufficient and optimal cell collection targets. Often institutional practice has guided both the method and the decision tree paradigm by which stem cell targets are set and met. Prior to the advent of plerixafor, these parameters have been often guided by what is possible or tolerable, rather than what is optimal. Recent studies investigating plerixafor in the salvage and up-front setting have shown that a substantial number of patients may now be expected to mobilize and collect an optimal number of CD34+ cells, often in < 5 days. While these studies have shown the efficacy and safety of both plerixafor plus G-CSF strategies, what will most likely influence the decision to incorporate the use of plerixafor into current institutional practices, and which will inform centers as to its best use as either a salvage or initial agent is a combined economic and outcome comparison of these strategies when a consistent set of mobilization targets and definitions of success and failure have been implemented. Wider use of plerixafor would be justified if it can be shown to represent the most reliable and reproducible mobilization method with the least impact on financial and resource assets.

One strategy to optimize the predictability of stem cell mobilization and subsequent mobilization is to use plerixafor in all patients with NHL and MM. The logistics of obtaining sufficient plerixafor means that in accordance with the FDA-approved administration method, 4 vials of the drug would have to be available for each patient, through their pharmacy insurance benefit requiring advance ordering. Using the phase III upfront NHL and myeloma trials as a guideline, this would result in an optimal stem cell collection in 4 days for nearly 60% of NHL patients and over 71% of myeloma patients. A successful collection of a minimal 2×10^6 CD34+ cells/kg collection could be obtained in nearly 88% of lymphoma patients and over 76% of myeloma patients. Furthermore, 23% of lymphoma patients would be expected to save up to 3 days of apheresis in an attempt to collect an optimal cell dose; 35% of patients could expect to save up to 2 days apheresis. Over 37% of myeloma patients would save up to 3 days and 43% up to 2 days of apheresis with upfront use of plerixafor. However, blanket use of this agent would also mean that a significant number of patients would have purchased more plerixafor than required for obtaining an optimal or minimal stem cell dose, unnecessarily raising both transplant center and societal healthcare costs, as well as resulting in a significant co-pay burden on the part of the patient.

While the transplant literature is well populated with studies attempting to predict patients likely to fail standard mobilization methods, it remains difficult to accurately predict the majority of patients who will fail to collect an optimal cell dose. With the availability of plerixafor, some

centers have adopted a strategy of using plerixafor for up-front mobilization in NHL patients and as salvage in myeloma patients, but this strategy both overestimates the failure rate in NHL, and underestimates the failure rate in myeloma. This is due to a rising prevalence of lenalidomide therapy prior to transplant, a therapeutic change in the standard of care not fully reflected in the most recent phase II and phase III trials of plerixafor in the salvage and upfront use settings. Several manuscripts have reported the high degrees of successful collection of at least a minimum CD34+ collection when plerixafor is used in salvage of failed standard stem cell mobilization attempts. Calandra et al showed that 60% of patients with NHL, 76% of patients with Hodgkin's Lymphoma, and 71% of patients with myeloma successfully collected at least 2×10^6 CD34+ cells/kg.¹ However, routinely relegating plerixafor to a strictly salvage role increases the unpredictability of resource use, and extends both time and cost of the stem cell mobilization process when the historically required washout period is implemented between initial and salvage attempts. This is illustrated in **Figure 1**, the peripheral blood CD34+ plot of patient "Salvage" in whom the 7-day washout period not only added additional days of waiting time before effective treatment could begin, but also represents another course of G-CSF, laboratory and clinic costs, and additional apheresis and stem cell processing time and costs.



From a logistics standpoint, it means a feast-or-famine approach to utilization of the apheresis chair and transplant bed resources in which the unpredictable failure of a patient means they are underutilized in the planned week and over-scheduled during the salvage week. Thus, apheresis stem cell lab, flow cytometry lab, and transplant center staffing is difficult to predict, resulting in increased overtime, scheduling conflicts. Even if combined with products obtained with the earlier

apheresis attempt to reduce the time required for salvage, the additional daily products processed need to be stored, requiring more capital expenditures in freezer storage capacity and stem cell laboratory needs. Further, this strategy often commits the patient and transplant pharmacy to 4 doses of drug, all of which may or may not be used in the subsequent re-mobilization attempt.

Recently, there have been anecdotal reports of using plerixafor immediately proximate to objective data suggesting a patient's failure to mobilize or collect, such as was illustrated in the "EPI 1 and EPI 2" patients seen in **Figure 1**. In this approach, plerixafor is used to boost a flagging or failing stem cell mobilization or collection attempt while it is underway, without a G-CSF washout period prior to the mobilization re-attempt as stipulated in the plerixafor salvage and upfront use study protocols. This novel approach has merit in that only patients who objectively demonstrate mobilization or collection failure will receive plerixafor without an intervening wait for the salvage attempt. The logistics of this "Early Plerixafor Intervention", or EPI salvage method, however, require close coordination between clinicians who monitor the patient's progress, the pharmacy who must acquire and deliver the drug within less than 12 hours, and the stem cell apheresis and processing labs. It also points to the importance and value in predicting collection success or failure based on mobilized PB CD34+ counts. There is a further advantage of the transplant center and pharmacy committing the patient to each daily dose of plerixafor only if and when it is needed, reducing excess dose waste and cost to the patient, pharmacy and healthcare delivery system. Preliminary data at this center incorporating this strategy demonstrate a 3-4 times increase in PB CD34+ cells after the plerixafor boost with subsequent successful apheresis collections for all patients in whom it has been attempted (15 as of this writing).

Recommendations

There is a large body of literature that has reported the efficacy of plerixafor in obtaining an optimal stem cell dose in the initial and salvage mobilization settings. The transplant community is now fortunate to have a highly effective agent in which it is reasonable to expect optimal as opposed to merely minimal stem cell doses to be collected. Several studies from centers experienced in the use of plerixafor are underway to help determine the optimal strategic use of and timing of this agent in stem cell mobilization and its impact on the economics of autologous SCT. While the results of these studies are still unpublished, individual transplant centers will need to analyze these results based on their own center characteristics with an eye to best understanding of the critical cost components of the stem cell acquisition process.

In our initial review of the use of plerixafor, the daily cost of apheresis and PB stem cell processing are comparable to the cost of 1 vial of plerixafor. Therefore, if we can save an equivalent number of day's apheresis and processing to vials of plerixafor used, we regard its use as cost neutral. If days of collection can be further reduced it provides additional savings against our case rate reimbursement.

While current methods of predicting the outcome of successful stem cell collection in individual patients are neither sufficiently sensitive nor specific, novel approaches under study, such as the EPI protocol show promise in applying this highly successful agent in the most effective, efficient, and appropriate manner. By demonstrating the impact of this and traditional strategies on not just overall costs, but on individual resources, which contribute to the cost of stem cell acquisition, individual transplant centers may better analyze the impact of plerixafor use on specific cost component shifts for their own unique program economies.



Effective Algorithms for Mobilization Agents

Steven M. Devine, MD

Development and Implementation of a Mobilization Algorithm

The development of standard operating procedures is a well established practice within BMT programs. Incorporation of treatment standards and practice algorithms may result in improved outcomes, increased safety, and overall patient and staff satisfaction.

Patient Case

A 62-year-old female initially presented in February 2007 with cervical lymphadenopathy. Imaging studies at that time showed supraclavicular, axillary, and periaortic lymphadenopathy. A PET scan also showed hypermetabolic activity within the spleen and an intense bone marrow signal. She underwent a cervical biopsy, which was consistent with a DLBC NHL. A BM aspirate and biopsy was positive for lymphoma. Her IPS score was 3 of 5. She was initiated on first-line therapy consisting of R-CHOP. PET scan following 3 cycles was consistent with a CR and the patient went on to receive a total of 8 cycles. First-line therapy was completed in September 2007 and she received routine follow-up care. She did well until June 2009 when she developed recurrent cervical lymphadenopathy. Biopsy was again consistent with DLBC NHL. PET scan at that time showed hypermetabolic activity in the cervical lymph node, left pterygoid muscle, pretracheal lymph nodes, and left axillary lymph nodes. She proceeded to salvage chemotherapy with R-ICE. She received 2 cycles and a PET/CT scan following the second cycle of salvage chemotherapy was consistent with a good PR. She was then referred for evaluation for autologous HSCT.

Her pre-transplant evaluation showed that she had an excellent performance status and other than for some mild fatigue was essentially asymptomatic. Physical examination did not reveal any significant abnormalities and she had no evidence of palpable lymphadenopathy. Biochemical evaluation was unremarkable, and a CBC revealed a WBC of $4.6 \times 10^9/L$, ANC 2500 cells/mm³, Hgb 8.9 gm/dL with MCV of 89 fl, and a platelet count of $366 \times 10^9/L$. A BM aspirate and biopsy performed at the time of pre-transplant evaluation revealed an overall cellularity of 30%, with trilineage hematopoiesis and no evidence of myelodysplasia. A cytogenetic analysis revealed a normal female karyotype.

Commentary

Per our program standards, she was considered at high-risk for mobilization failure with G-CSF alone given the fact that she was over 60 years of age, and had more than 9 cycles of prior chemotherapy. As a result, the high-risk algorithm was followed. **Figure 1A, 1B.** A plan was made to obtain prior approval for the use of an up-front plerixafor plus G-CSF mobilization regimen.

Outcome

Per our institution-specific mobilization algorithm, she received G-CSF at 10 mcg/kg/day for 4 days. On the fourth day of G-CSF based mobilization, her PB CD34+ count was 6 cells/ μL . She received plerixafor .24 mg/kg at approximately 6 PM the evening before planned leukapheresis. On the morning of day 5, just prior to leukapheresis, her PB CD34+ count was 20 cells/ μL . She underwent a total of 2 days of leukapheresis and received a total of 2 doses of plerixafor and 6 doses of G-CSF. She achieved a total dose of 2.5×10^6 CD34+ cells/kg and based on program standards was able to proceed to high dose chemotherapy.

Figure 1A. Ohio State University Autologous Mobilization Algorithm: Plerixafor Up-front

High Risk for Mobilization Failure*

Note: Plerixafor is only approved for use in Multiple Myeloma (MM) and Non-Hodgkin's Lymphoma (NHL). All MM and NHL patients should be pre-certified for use of plerixafor.

NHL – risks for mobilization failure:

1. Age greater than 59 years old.
2. Any prior radiation therapy.
3. Greater than 9 cycles of prior chemotherapy.
4. Bone marrow involvement at BMT work-up.

MM – risks for mobilization failure:

1. Greater than 6 cycles of lenalidomide.
2. Greater than 6 cycles of lenalidomide and greater than 10% plasma cell involvement of bone marrow at BMT work-up.
3. Greater than or equal to 2 episodes of any prior radiation therapy.
4. Greater than or equal to 4 months of melphalan.

*Risk for mobilization failure based on anecdotal evidence, BMT Program historical data, and literature review.

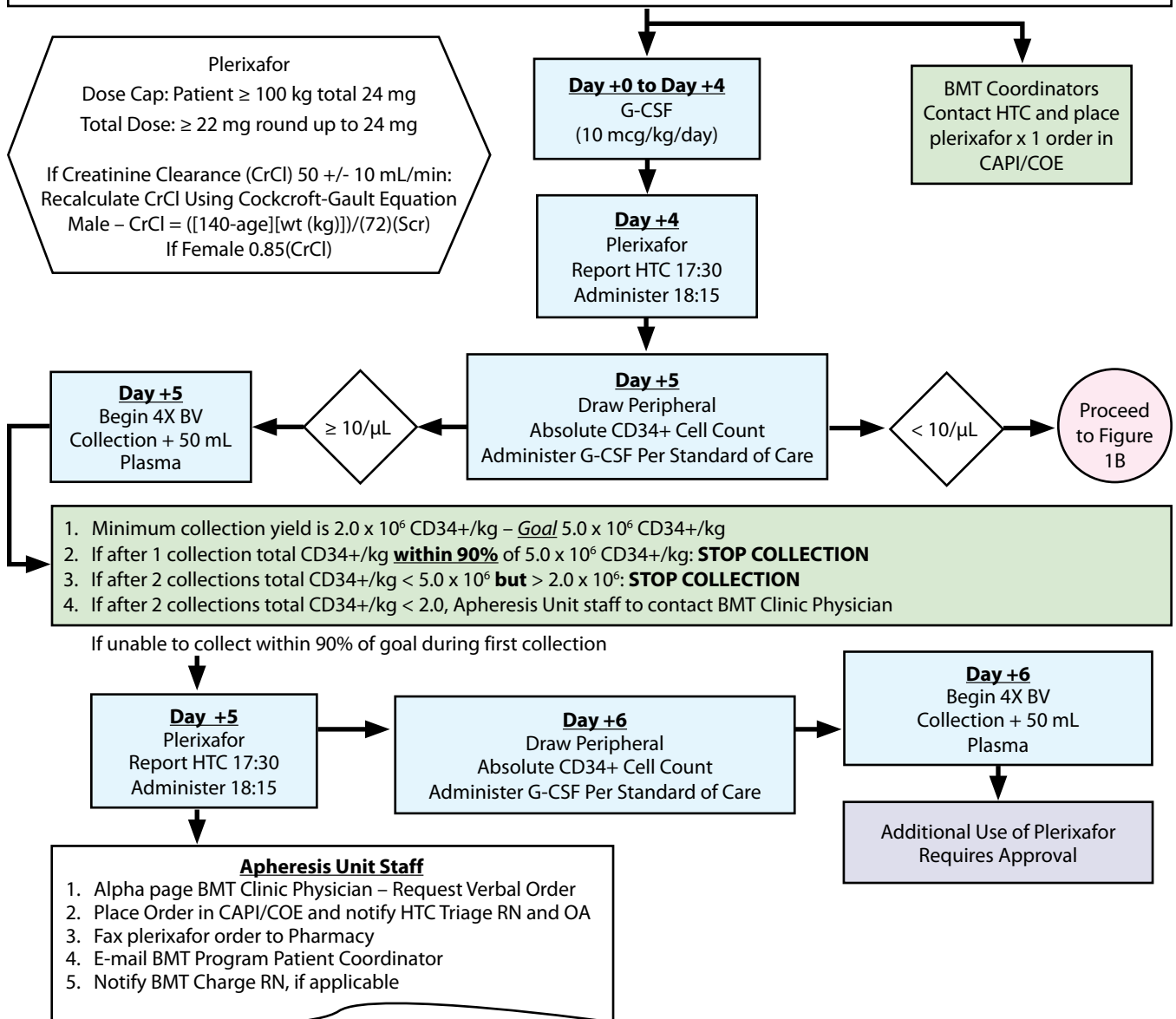
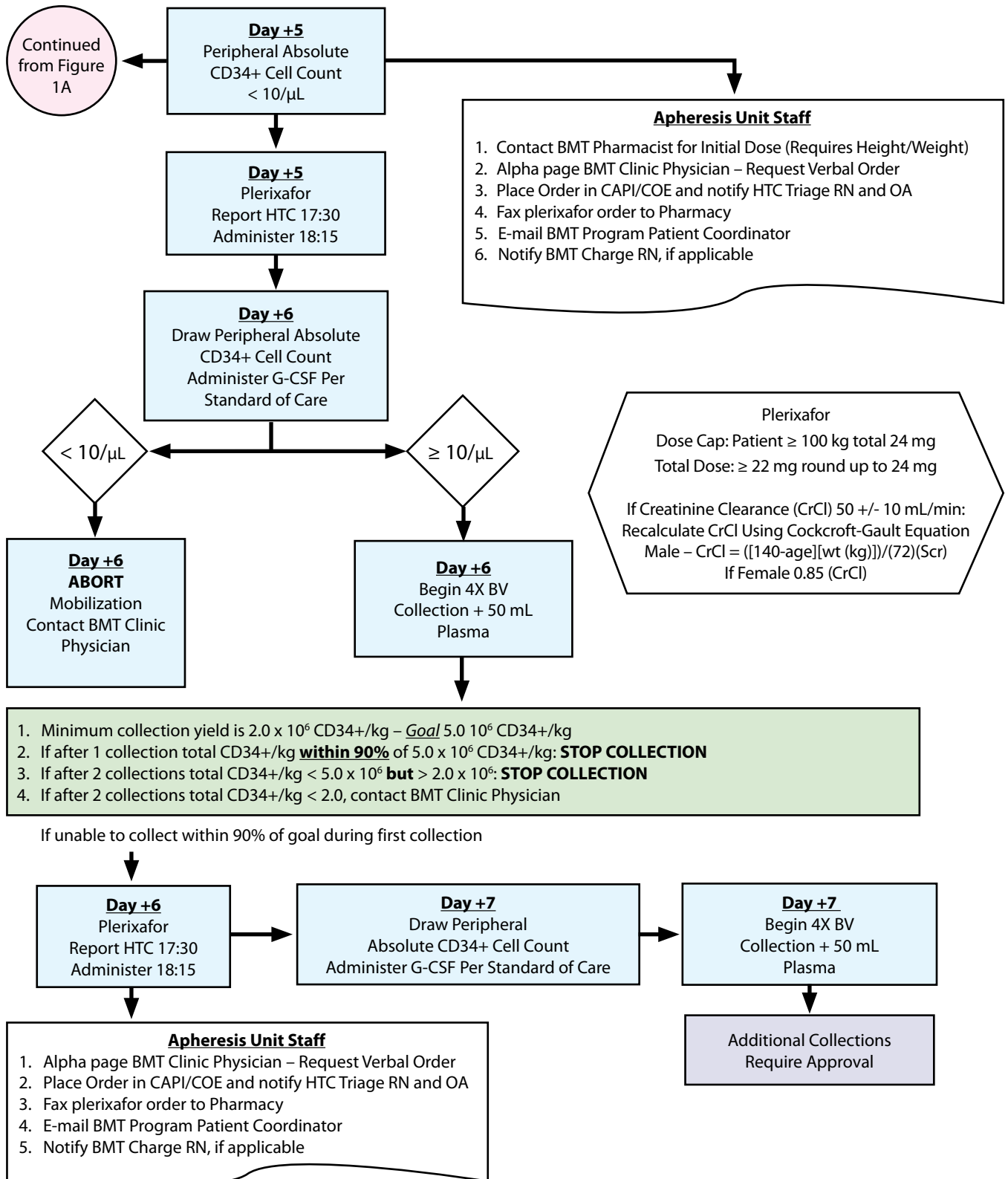


Figure 1B. Autologous Mobilization Plerixafor Rescue (MM and NHL Only)



Approximately 1-week following stem cell collection, she was admitted for high-dose chemotherapy using the BEAM conditioning regimen. She tolerated this relatively well but did develop, as anticipated, profound pancytopenia, mucositis, and febrile neutropenia requiring supportive care and antibiotics. By day +10 post-transplant, her ANC had risen above 500 cells/mm³ and by day +13, she was platelet transfusion free. Within 20 days post transplant, her platelet count was 134,000. By day +30 post-transplant she had a Karnofsky performance status of 90%, was feeling much improved, and was considered for a phase II clinical trial evaluating a new monoclonal antibody designed to prevent disease recurrence post-transplant.

Follow-Up Question and Response

Anecdotally, how successful has your high-risk mobilization algorithm been in achieving goal collections?

Prior to use of G-CSF plus plerixafor, roughly 30% of our NHL patients failed G-CSF (alone) mobilization. Now, with the use of G-CSF plus plerixafor, our failure rate is less than 15%.

How has the development of the algorithm impacted the staff and patient experience? Was the adoption and implementation of the algorithm well accepted?

The institution of the new algorithm has been well accepted by our staff for 2 main reasons. First, the staff like to have a “roadmap” that outlines how we will proceed under specified circumstances, so it helps them be more efficient and to better educate the patients and their families. Second, since we participated in the plerixafor clinical trials and compassionate use program prior to FDA approval, our staff had become familiar with the drug and were enthusiastic since it was relatively safe and quite effective in our experience.

What challenges did a 6 PM dose administration time pose on both the patient and BMT staff? In your experience what is a reasonable plerixafor “window of administration”?

This has been a challenge for the obvious logistical reasons with staffing so we have changed to a 5 PM administration time. I think any time within 15-18 hours of collection is likely to be effective, but this is just a guess and we do need to track this closely.

Have you ever been denied prior insurance approval for up-front plerixafor use?

We have never been denied, to date, for an FDA approved indication.

Patient Case

A 64-year-old man with a PMH of hypertension and hypercholesterolemia who had been complaining of progressively worsening lower back pain over the course of several months presented for evaluation. He underwent a lumbar spine film that revealed evidence of compression fracture in the L3 vertebral body. There was concern raised that this was a lytic lesion. He therefore underwent a full evaluation that included a biochemistry profile that revealed evidence of a total protein of 9.3 gm/dL and albumin of 3.2 gm/dL. A serum protein electrophoresis with immunofixation revealed the presence of an IgG lambda monoclonal protein of 2.4 gm/dL. A full skeletal survey revealed evidence of lytic lesions in his skull, multiple ribs, left humerus, and fourth thoracic and third lumbar vertebrae. The beta-2 microglobulin level was 3.5 mg/L. Calcium was within normal limits and Hgb was 13.5 gm/dL. A BM aspirate and

biopsy revealed evidence of sheets of lambda clonally restricted plasma cells expressing CD138, consistent with MM. A cytogenetic analysis and FISH evaluation revealed a normal karyotype.

With a diagnosis of symptomatic MM, he was begun on a combination of lenalidomide and low-dose dexamethasone. Within 2 months, his back pain had resolved and he was tolerating the lenalidomide relatively well. He received a total of 6 cycles of lenalidomide and dexamethasone and achieved a VGPR. At that time, he was referred for an evaluation for high-dose chemotherapy and autologous HSCT.

Upon evaluation, the patient was found to have a Karnofsky performance status of 90% and other than for some fatigue and constipation, was relatively asymptomatic. Physical examination was unremarkable. Biochemistry profile revealed evidence of a normal total protein, and albumin of 4.0 gm/dL, and an IgG kappa monoclonal protein of 240 mg/dL. A bone marrow aspirate and biopsy revealed an overall cellularity of 30%, with less than 5% monoclonal plasma cells. Cytogenetic and FISH analysis were unremarkable. The patient was then referred for transplant evaluation.

Commentary

The patient was considered an excellent candidate for high-dose chemotherapy and auto-SCT and underwent an initial stem cell mobilization attempt with G-CSF alone at 10 mcg/kg/day. The goal of collection for this patient was 5.0×10^6 CD34+ cells/kg for 1 transplant. We choose G-CSF alone to mobilize most of our myeloma patients since it is safer, easier, and less expensive compared to chemotherapy based mobilization and because in general we do not perform double autografts (instead we give maintenance chemotherapy). Also, the failure rates following G-CSF alone in MM patients are lower than in NHL patients. We have also found a lot of variability in the capacity to mobilize patients receiving prior lenalidomide and have successfully mobilized several patients having up to 6-8 months of lenalidomide either with G-CSF alone or G-CSF plus plerixafor. Since now we can see how well they are mobilizing after G-CSF alone and add plerixafor if the CD34+ cell count is low, we rarely need to mobilize myeloma patients with chemotherapy plus G-CSF.

Outcome

On day 5, the first day of planned leukapheresis, a PB CD34+ count was only 4 cells/ μ L and thus he did not undergo leukapheresis. Per program algorithm, we had obtained prior approval for the use of plerixafor and thus he returned in the evening of day 5 of mobilization and received plerixafor at .24 mg/kg. **Figure 1C, 1D**. On the morning of day 6 of mobilization, PB CD34+ count was 15 cells/ μ L, and he commenced leukapheresis. He received a total of 7 doses of G-CSF, and 2 doses of plerixafor, undergoing a total of 2 days of leukapheresis. He collected a total dose of 2.46×10^6 CD34+ cells/kg and 10 days later was admitted for high-dose chemotherapy using melphalan (200 mg/m²) conditioning.

He underwent re-infusion of G-CSF and plerixafor mobilized peripheral blood stem cells. He experienced the usual toxicities related to melphalan including mucositis, nausea, and vomiting requiring supportive care. He also developed febrile neutropenia, but by 9 days post-transplant his ANC was > 500 cells/mm³ and by day +14 he was platelet transfusion free. By day +45 post-transplant, he achieved a CR based on serum protein electrophoresis with immunofixation and a negative bone marrow aspirate and biopsy. He was considered for a phase I protocol of maintenance therapy evaluating the combination of lenalidomide with the histone deacetylase inhibitor vorinostat.

Figure 1C. Ohio State University Autologous Mobilization Algorithm: G-CSF

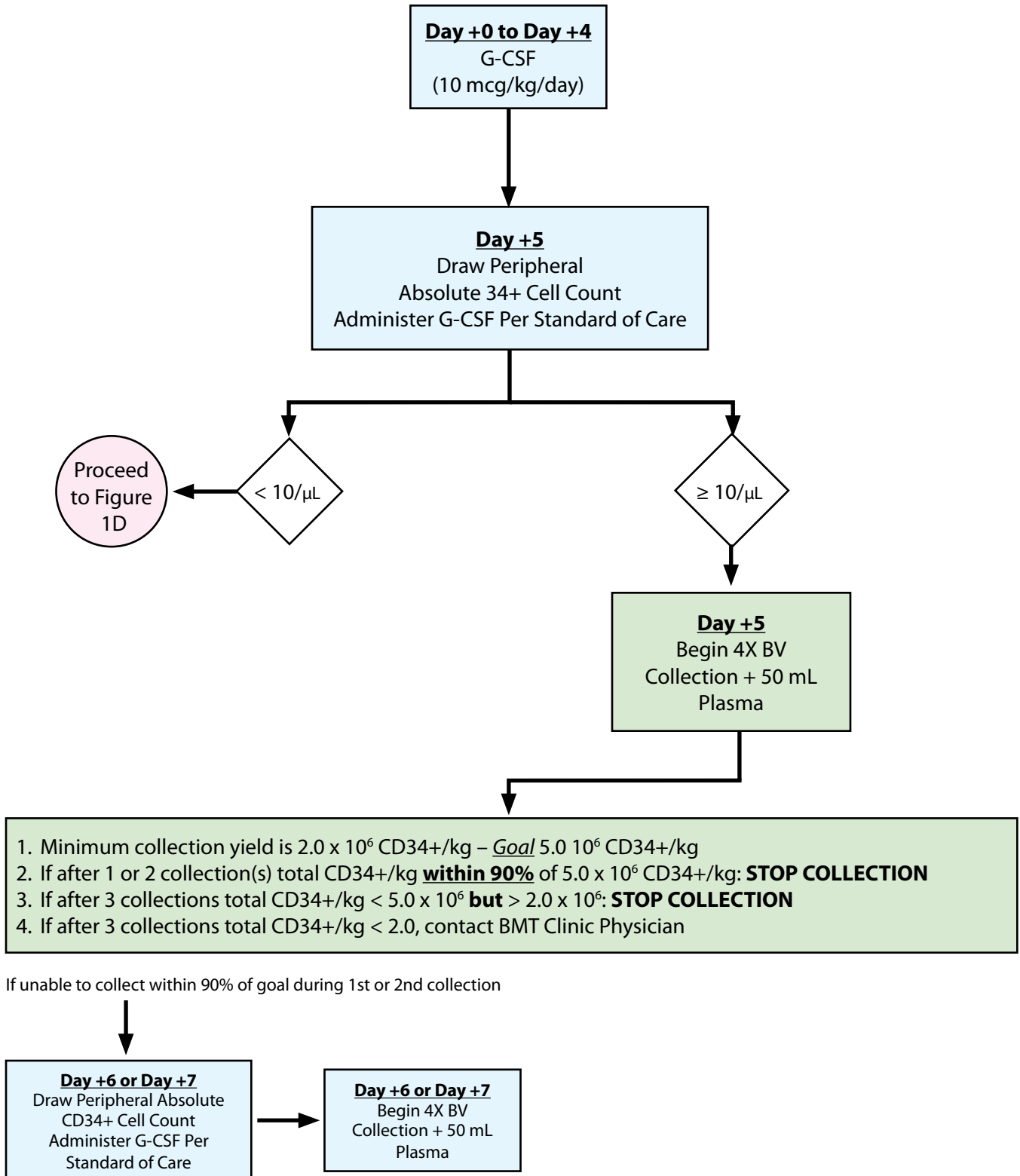
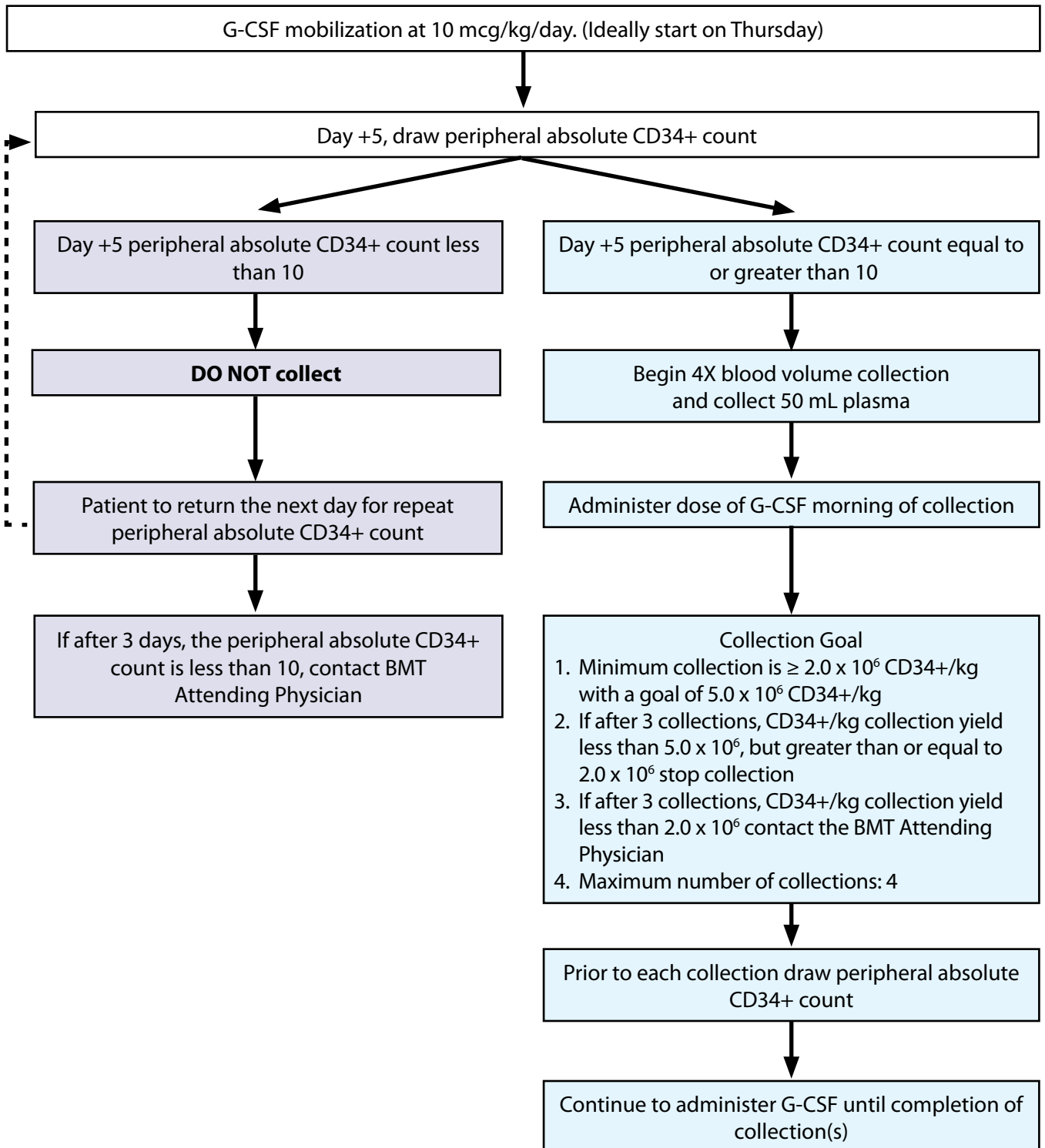


Figure 1D. Peripheral Blood Stem Cell Mobilization/G-CSF Autologous Donor*



*Excluding patients on research protocols.

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