Biol Blood Marrow Transplant 19 (2013) 1301–1309

Pharmacoeconomics of Hematopoietic Stem Cell Mobilization: An Overview of Current Evidence and Gaps in the Literature

Paul Shaughnessy [1,*], Nelson Chao [2], Jamie Shapiro [3], Kent Walters [4], John McCarty [5], Sunil Abhyankar [6], Sepideh Shayani [7], Pieter Helmons [8], Helen Leather [9], Amy Pazzalia [9], Simon Pickard [10]

[1] *Texas Transplant Institute, San Antonio, Texas*
[2] *Duke University Medical Center, Durham, North Carolina*
[3] *Moffit University, Tampa, Florida*
[4] *University of Texas MD Anderson Cancer Center, Houston, Texas*
[5] *BMT Program VCU, Richmond, Virginia*
[6] *University of Kansas Medical Center, Westwood, Kansas*
[7] *City of Hope, Stanford, California*
[8] *University Medical Center Groningen, Apeldoorn, Netherlands*
[9] *University of Florida, Gainesville, Florida*
[10] *Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, Illinois*

Article history:
Received 26 November 2012
Accepted 8 May 2013

Key Words:
Pharmacoeconomics
Mobilization
Autologous
Plerixafor
Costs
Failure to mobilize

A B S T R A C T

Adequate hematopoietic stem cell (HSC) mobilization and collection is required prior to proceeding with high dose chemotherapy and autologous hematopoietic stem cell transplant. Cytokines such as G-CSF, GM-CSF, and peg-filgrastim, alone or in combination with plerixafor, and after chemotherapy have been used to mobilize HSCs. Studies have shown that the efficiency of HSC mobilization and collection may vary when different methods of mobilization are used. No studies have shown that survival is significantly affected by the method of mobilization, but some studies have suggested that cost and resource utilization may be different between different mobilization techniques. After the FDA approval of plerixafor with G-CSF to mobilize HSCs many transplant centers became concerned about the cost of HSC mobilization. A panel of experts was convened ant this paper reviews the current literature on the pharmacoeconomics of HSC mobilization.

INTRODUCTION

High-dose chemotherapy followed by hematopoietic stem cell rescue is a frequently used strategy in the treatment of hematological malignancies. Autologous hematopoietic stem cell transplantation (aHSCT) is used routinely in the treatment of relapsed non-Hodgkin lymphoma (NHL) and Hodgkin's lymphoma [1-3], and it has been shown to improve both depth of response and overall survival in patients with multiple myeloma (MM) [4-11]. The ability to improve patient outcomes with aHSCT is directly dependent, however, on successful mobilization and collection of stem cells. Historically, stem cell mobilization options have been limited to either growth factors alone or chemotherapy in combination with growth factors [12]. Granulocyte colony-stimulating factor (filgrastim, G-CSF) and granulocyte macrophage colony-stimulating factor (sargramostim, GM-CSF) are US Food and Drug Administration (FDA)-approved for hematopoietic stem cell (HSC) mobilization [12]. Chemomobilization (CM) regimens often include agents, such as cyclophosphamide, etoposide, or cytarabine, and may incorporate rituximab for lymphoma patients. A CM strategy may be chosen over growth factors alone in an effort to produce higher stem cell yield or reduce tumor burden and possible tumor contamination of the stem cell product [13,14].

In this paper, we review the current literature on the pharmacoeconomics of mobilization in HSCT. Our goals are to summarize economic evaluations to date with an emphasis on the issues that are somewhat unique to outcomes studies of HSCT and to better understand the value of recent developments in HSCT, particularly plerixafor. First, we provide an overview of the literature on the clinical and economic outcomes associated with traditional mobilization strategies. Second, we examine the pharmacoeconomic evidence on novel mobilization approaches, focusing on the novel agent plerixafor. This is accompanied by a general overview of methods used in economic evaluations of healthcare interventions, followed by a discussion of the limitations of the current literature and suggestions for future studies.

Standard Mobilization Costs

The costs and consequences associated with traditional mobilization strategies vary. Over the past 15 years, reported costs of mobilization with growth factors alone have ranged from approximately $6000 up to $20,000 per patient [15-18]. When CM is used as a stand-alone cycle apart from standard induction or salvage therapy, this results in additional expenses for chemotherapy, hospitalization for chemotherapy administration, and management of chemotherapy-related complications, including febrile neutropenia. Costs with this approach are therefore higher, with reports ranging

Financial disclosure: See Acknowledgments on page 1307.

* Correspondence and reprint requests: Paul Shaughnessy, MD, Texas Transplant Physician Group, Adult Blood and Bone Marrow Hospital Clinic, 4410 Medical Drive Suite 410, San Antonio, TX 78229.
E-mail address: Paul.Shaughnessy@MHShealth.com (P. Shaughnessy).

1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.05.008

from $11,000 up to $52,000 per patient, depending on the regimen [19-21]. CM readmission rates at some centers have been reported to be 20% to 26%, and the additional hospitalization generates $7000 to $10,000 in increased costs [19,20,22]. A recent cost analysis of CM demonstrated that this approach is associated with an 80% chance of a nonideal outcome (ie, collections below target, additional apheresis sessions, and complications), which was, in turn, associated with higher mobilization costs [19]. Other disadvantages of CM include the unpredictability of the apheresis schedule, increased costs to patients and caregivers by missed work, frequent clinic visits and admissions, and housing costs [23,24]. Much of these increased costs associated with CM are abrogated by mobilizing stem cells after a planned cycle of chemotherapy rather than administering CM as a standalone regimen, although this approach will not eliminate unpredictable apheresis scheduling. One multicenter retrospective review found that, in addition to an increase in apheresis costs of nearly $3000 per patient, CM resulted in increased weekend apheresis, with 12.6% of patients beginning apheresis on a Thursday or Friday, and 13.3% beginning on a weekend [24].

The advantages of CM include providing standard salvage therapy for relapsed NHL or Hodgkin's Disease patients and greater $CD34^+$ cell collections compared to cytokine-only mobilization. However, no studies to date have shown any difference between CM and cytokine-only mobilization in the amount of tumor contamination of the stem cell product and transplantation outcomes, such as engraftment and survival.

Costs Associated with Poor Mobilization/Failure to Mobilize

Various patient-related and disease-related characteristics have been identified as having a negative impact on mobilization success rates. These include advanced age [25-27]; diagnosis of NHL [25]; prior radiation therapy, extensive prior chemotherapy, or prior treatment with lenalidomide or purine analogs [26-38]; a hypocellular marrow, marrow involvement at diagnosis, low platelet count, and refractory disease [25]; and prior mobilization failure. Historical failure rates with traditional mobilization approaches have been reported to be as high as 18% to 38% [18,39-42], although more recent studies consistently show mobilization failure rates to be below 15% in patients with up-front–treated MM [43-45] and below 10% when CM is incorporated into planned chemotherapy cycles for patients with NHL [46-48]. For those patients who do fail initial mobilization attempts, however, remobilization failures reach 77% [39].

In addition to being potentially unsuccessful, remobilization attempts are expensive. Standard remobilization strategies include dose-escalated G-CSF [49-51], G-CSF plus GM-CSF (G + GM) [52-54], and CM [27]. In 2004, G + GM remobilization was estimated to cost $5900 per patient, whereas remobilization with G-CSF alone averaged $9000 per patient [55]. A recent cost assessment of CM remobilization of MM patients with hyper-cyclophosphamide, vincristine, adiamycin, and dexamethasone chemotherapy followed by G-CSF was shown to be $45,000 per patient, with 37.5% of those incurring an additional $13,000 in charges for hospital readmissions [20]. Poor mobilization is associated not only with an increase in cost, but also escalated resource consumption, including increased growth factor, antibiotic, and transfusion support; more frequent hospitalization; more apheresis procedures; and delayed engraftment [19,42]. Table 1 summarizes the costs and consequences of poor mobilization.

Options are limited for those patients who fail to collect sufficient stem cells for transplantation on multiple mobilization attempts. Bone marrow harvest and subsequent autologous bone marrow transplantation (BMT) add considerable cost and are associated with more complications than peripheral blood stem cell transplantation (PBSCT). The cost of the harvest procedure itself ranges from nearly $5000 to $8500 [15,56,57], and early comparisons of autologous BMT to PBSCT showed an average 20% to 30% increase in total transplantation costs with BMT [15,56,58]. BMT has also been associated with poorer engraftment and reduced quality of life (QoL) when compared with PBSCT [58]. Allogeneic stem cell transplantation may be an option in select patients who fail multiple mobilization attempts, but it is associated with increased morbidity and mortality and is not available to all patients because of lack of a suitable donor. For these patients, further treatment options become limited to salvage or maintenance chemotherapy without transplantation, which may be associated with increased risk of relapse.

Novel Mobilization Approaches

In 2008, the novel agent plerixafor, a CXCR4 chemokine receptor antagonist, was approved for use by the FDA in the United States. Plerixafor is indicated for first-line mobilization of hematopoietic stem cells into the peripheral blood for collection and subsequent autologous transplantation in patients with NHL and MM. Several studies, including the initial phase III trials of plerixafor and G-CSF compared with G-CSF and placebo, have demonstrated that plerixafor can overcome some of the known risk factors for poor stem cell mobilization [26,43,59-61], and may reduce overall mobilization failure rates from as high as 30% to <10% [16,21,62-68]. Unfortunately, the acquisition cost of plerixafor has limited its use in up-front mobilization despite the FDA indication, as expensive agents within institutions are often restricted because of budget constraints. In such situations, pharmacoeconomic (PE) analysis methods are essential to determine if the superior effectiveness warrants the higher price.

Table 1
Costs and Consequences of Suboptimal Mobilization [25,44]

Consequence	Outcome
Failure to mobilize a sufficient number of $CD34^+$ cells	• Ineligibility for transplantation and subsequent relapse • Increased apheresis days • Need for bone marrow harvest • Added cost of remobilization attempts • Increased resource utilization
Transplantation with suboptimal apheresis product	• Delayed, partial, or failed engraftment • Prolonged hospitalization and increased hospitalization costs • Increased infections • Increased bleeding or need for transfusions
Unmeasured costs to patient/caregiver	• Transportation to/from apheresis center • Cost of housing/sustenance • Psychological strain • Missed work time
Unmeasured costs to center	• Weekend apheresis • Delay in treatment • Disruption of patient flow • Inability to proceed to transplantation