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McGill University
Health Centre

**Technology Assessment Unit of the
McGill University Health Centre
(MUHC)**

**PLERIXAFOR AS FIRST-LINE CHOICE FOR STEM
CELL MOBILIZATION IN NON-HODGKIN'S
LYMPHOMA AND MULTIPLE MYELOMA
PATIENTS**

Report number: 81

DATE: July 17, 2017

**Report prepared for the Technology
Assessment Unit (TAU) of the McGill
University Health Centre (MUHC)**

by

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Suggested citation

Almeida N., Saab L., Dendukuri N. Plerixafor as first-line choice for
stem cell mobilization in Non-Hodgkin's Lymphoma and Multiple
Myeloma patients. Montreal (Canada): Technology Assessment Unit
(TAU) of the McGill University Health Centre (MUHC); July 17, 2017.

Report no. 81. 65 pages

Report available from <http://www.mcgill.ca/tau>

ACKNOWLEDGEMENTS

The expert assistance of the following individuals is gratefully acknowledged:

- Andre Bonnici, Pharmacist-in-chief, Department of Pharmacy, McGill University Health Centre
- Celine Dupont, Pharmacist, Department of Pharmacy, McGill University Health Centre
- Felipe Forero, Technology Assessment Unit, McGill University Health Centre, for his expert input on the economic analysis.
- Guy Gagne, Pharmacist, Stem Cell Transplant Program, McGill University Health Centre
- Gizelle Popradi, Director, Stem Cell Transplant Program, McGill University Health Centre
- Yannie Racicot, Quality Assurance Officer and Data Manager, Stem Cell Transplant Program, McGill University Health Centre
- Nicolas Robert, Associate Director of Finance, Budget and Financial Performance, McGill University Health Centre

REPORT REQUESTOR

This report was requested by Celine Dupont, Assistant to Pharmacist-in-Chief on January 21, 2016. The final report will be presented to Celine Dupont, and to Dr. Gizelle Popradi, Director of the Stem Cell Transplant Program at the MUHC.

The date of the review was at the TAU Policy Committee meeting held on Wednesday, May 10, 2017.

TYPES OF RECOMMENDATIONS ISSUED BY TAU

Type of recommendation	Explanation
Approval	<ul style="list-style-type: none">• Evidence of efficacy, safety, and cost is sufficiently strong to justify a recommendation that the technology be accepted, used and funded through the institutional operating budget.
Approved for evaluation	<ul style="list-style-type: none">• There is a <i>high probability</i> that the technology is effective but the evidence is not yet sufficiently strong to support a recommendation for permanent approval;• The evidence is sufficiently strong to recommend a <i>temporary</i> evaluation funded through the institutional operating budget;• Other context-specific factors are favourable such as MUHC experience, feasibility, improved efficiency, and availability of alternatives.
Not approved	<ul style="list-style-type: none">• There is lack of evidence or conflicting evidence, and real uncertainty (equipose) of efficacy. The costs of such a study should not normally be carried by the institutional budget.

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ABSTRACT

- Autologous transplantation of hematopoietic stem cells is now a well-established treatment option for multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL). In this procedure, hematopoietic stem cells from the patient's peripheral blood are mobilized with a mobilizing agent, collected via apheresis, and subsequently transfused back into the patient, with the aim of restoring normal blood cell production.
- There are two conventional stem cell mobilization regimens: i) cytokine-based regimens which use growth factors such as granulocyte colony-stimulating factor (G-CSF); and ii) chemo-mobilization regimens, which use chemotherapeutic agents such as cyclophosphamide, in conjunction with growth factors such as G-CSF. Chemo-based regimens generally result in higher stem cell yields, fewer collection days, and lower mobilization failure rates than cytokine-based regimens. However, chemo-based regimens are associated with longer treatment time, greater unpredictability in scheduling apheresis sessions, and higher rates of severe complications requiring hospitalization.
- A third mobilization regimen, using plerixafor (Mozobil®, Genzyme, Cambridge, MA, USA), was approved by Health Canada in 2011 for use in combination with G-CSF to mobilize stem cells in patients with NHL and MM. Plerixafor is a novel agent that has high effectiveness in stem cell mobilization without the adverse effects of chemo-mobilization, but whose widespread adoption has been hindered by its high cost. In June 2015, the MUHC switched from a mobilization regimen of cyclophosphamide plus G-CSF to one using upfront plerixafor.
- To mitigate the high costs of plerixafor while harnessing its benefits, some institutions have developed risk-based algorithms, where all patients receive one of the standard regimens of either G-CSF alone, or cyclophosphamide plus G-CSF, with plerixafor added to the regimen only in those patients with a demonstrated risk of failure to mobilize (poor mobilizers). Such pre-emptive plerixafor regimens would be less expensive than upfront plerixafor regimens in which *all* patients receive plerixafor in combination with G-CSF.
- This report evaluates the effectiveness, safety, and cost of upfront or pre-emptive plerixafor regimens vs. conventional regimens using either G-CSF alone, or cyclophosphamide plus G-CSF.

- The effectiveness of a mobilization regimen is measured by the percentage of patients achieving a sufficient number of stem cells to proceed to autologous transplantation. We performed a cost minimization analysis to identify the regimen associated with the lowest cost per patient among 3 regimens with comparable effectiveness.
- Our systematic review identified 12 comparative studies (including two randomized controlled trials) evaluating the effectiveness, safety or cost of plerixafor. Either upfront or pre-emptive use of plerixafor was more effective than G-CSF alone or cyclophosphamide plus G-CSF in mobilizing a sufficient number of stem cells to proceed to transplantation. A single study that compared upfront plerixafor with a pre-emptive plerixafor regimen found no clinically significant difference in number of patients achieving the minimum target yield.
- Studies of plerixafor-based regimens reported no difference in the occurrence of serious adverse events versus G-CSF-only regimens, and fewer mobilization-related hospitalizations versus cyclophosphamide-based regimens.
- Studies that have compared the cost impact of upfront plerixafor with alternative regimens have generally concluded that upfront plerixafor regimens are more expensive, even after factoring in costs of mobilization-related hospitalizations and remobilizations.
- An analysis of MUHC data comparing 24 patients treated with upfront plerixafor from June to December 2015 with 20 patients who underwent chemo-mobilization with cyclophosphamide found no difference in mobilization or failure rates. However, more patients suffered adverse events requiring hospitalization in the chemo-based regimen versus the upfront plerixafor regimen (26% vs 5%). The cost per patient of the upfront plerixafor and chemo-mobilization regimens were \$19,898 and \$1,661, respectively.
- The projected total cost of mobilizing 40 patients at the MUHC for the purpose of autologous stem cell transplants would be lower if we were to follow a pre-emptive plerixafor regimen where plerixafor is administered only in those who mobilize poorly. Assuming that 10% of patients mobilized with cyclophosphamide, and 50% of patients mobilized with G-CSF alone, will require plerixafor due to poor mobilization, projected costs for these pre-emptive plerixafor regimens would be \$143,352 and \$406,320, respectively, versus \$785,871 for an upfront plerixafor regimen.

RÉSUMÉ

- L'autogreffe de cellules souches hématopoïétiques est maintenant un traitement reconnu chez les patients atteints de myélome multiple (MM) et de lymphome non hodgkinien (LNH). Lors de cette procédure, les cellules souches hématopoïétiques du sang périphérique du patient sont mobilisées à l'aide d'un agent mobilisateur, recueillies via l'aphérèse et retransfusées par la suite au patient dans le but de rétablir la production normale de cellules sanguines.
- Il existe deux protocoles conventionnels de mobilisation des cellules souches : i) les protocoles à base de cytokines, utilisant des facteurs de croissance tels que le facteur stimulant les colonies de granulocytes (GCS-F), et ii) les protocoles chimiomobilisateurs qui utilisent des agents de chimiothérapie tel que la cyclophosphamide, conjointement avec des facteurs de croissance comme le GCS-F. Les protocoles basés sur la chimiothérapie se traduisent généralement par des taux de cellules souches plus élevés, moins de journées de collecte et des taux plus faibles d'échec de mobilisation que ceux des protocoles basés sur les cytokines. Cependant, les protocoles basés sur la chimiothérapie sont associés à des traitements plus longs, une plus grande imprévisibilité dans la planification des sessions d'aphérèse ainsi qu'à des risques plus élevés de complications sévères nécessitant l'hospitalisation.
- Un troisième protocole utilisant le plerixafor (Mozobil[®], Genzyme, Cambridge, MA, USA) fut approuvé par Santé Canada en 2011 pour une utilisation conjointe avec le GCS-F pour la mobilisation des cellules souches chez les patients avec de LNH et de MM. Le plerixafor est un nouvel agent qui est très efficace pour la mobilisation des cellules souches sans les effets indésirables de la chimiomobilisation, mais dont l'adoption à grande échelle fut entravée par son coût élevé. Au mois de juin 2015, le CUSM délaissa le protocole de mobilisation basé sur la cyclophosphamide + le GCS-F, pour un protocole utilisant d'emblée le plerixafor (traitement de première ligne).
- Pour réduire les coûts élevés du plerixafor tout en tirant le meilleur parti de ses bénéfices, certains établissements ont développé des algorithmes basés sur les risques où tous les patients reçoivent un des traitements standards, soit le GCS-F seul ou la cyclophosphamide + le GCS-F, avec ajout du plerixafor seulement chez les patients démontrant un risque d'échec de mobilisation (faibles mobilisateurs). De tels protocoles préventifs (plerixafor utilisé en deuxième ligne) seraient moins

onéreux que les protocoles impliquant d'emblée le plerixafor, où *tous* les patients reçoivent à la fois le plerixafor et le GCS-F.

- Ce rapport évalue l'efficacité, l'innocuité et les coûts des protocoles impliquant l'utilisation d'emblée ou de façon préventive du plerixafor vs les protocoles conventionnels utilisant le GCS-F, seul, ou la cyclophosphamide + le GCS-F.
- L'efficacité d'un protocole de mobilisation se mesure par le pourcentage des patients atteignant un nombre suffisant de cellules souches, permettant ainsi une autogreffe. Nous avons effectué une analyse de minimisation des coûts pour identifier le protocole correspondant au coût par patient le plus faible parmi trois protocoles montrant une efficacité comparable.
- Notre revue systématique a identifié 12 études comparatives (incluant deux études randomisées) évaluant l'efficacité, l'innocuité et le coût du plerixafor. Que ce soit l'utilisation d'emblée ou préventive du plerixafor, celle-ci était plus efficace que le GCS-F, seul, ou la cyclophosphamide + le GCS-F, pour mobiliser un nombre suffisant de cellules souches afin de procéder à une transplantation. Une seule étude comparait le protocole avec plerixafor d'emblée au protocole préventif avec plerixafor et ne trouva aucune différence significative parmi les patients atteignant le taux minimum de cellules souches visé.
- Les études des protocoles basés sur le plerixafor n'ont rapporté aucune différence au niveau des effets indésirables importants versus les protocoles avec le GCS-F, seul, et moins d'hospitalisations liées à la mobilisation versus les protocoles basés sur la cyclophosphamide.
- Les études qui ont comparé l'impact financier du protocole avec plerixafor d'emblée versus les protocoles alternatifs ont conclu, de façon générale, que les protocoles avec plerixafor d'emblée sont plus onéreux, même après avoir pris en compte les coûts d'hospitalisation liés aux mobilisations, et les coûts de remobilisations.
- Une analyse des données du CUSM comparant 24 patients traités d'emblée avec le plerixafor, du mois de juin au mois de décembre 2015, avec 20 patients qui ont subi une chimio-mobilisation avec la cyclophosphamide, ne trouva aucune différence au niveau de la mobilisation ou des taux d'échecs. Par contre, un plus grand nombre de patients traités suivant le protocole basé sur la chimiothérapie subissent des effets indésirables nécessitant une hospitalisation, comparativement aux patients traités d'emblée avec le plerixafor (26% vs 5%). Le coût d'un patient

traité d'emblée avec le plerixafor et celui traité par chimiomobilisation étaient de 19 898 \$ et 1 661 \$, respectivement.

- Au CUSM, le coût total estimé pour un traitement de mobilisation chez 40 patients dans le but de réaliser une autogreffe de cellules souches serait moins onéreux si nous pouvions suivre un protocole préventif avec plerixafor, uniquement chez les patients où la mobilisation est difficile. En supposant que 10% des patients subissant un traitement de mobilisation avec la cyclophosphamide et que 50% des patients subissant le même traitement avec le GCS-F, seul, nécessitaient un traitement avec le plerixafor dû à une faible mobilisation, les coûts estimés pour ces protocoles préventifs au plerixafor seraient de 143 352 \$ et 406 320 \$, respectivement, versus 785 871 \$ pour le protocole avec plerixafor d'emblée.

LIST OF ABBREVIATIONS

aHSCT	Autologous hematopoietic stem cell transplant
CI	Confidence interval
G-CSF	Granulocyte colony-stimulating factor
HSC	Hematopoietic stem cells
HTA	Health technology assessment
INESSS	Institut National d'Excellence en Santé et en Service Sociaux
MM	Multiple myeloma
MUHC	McGill University Health Centre
NHL	Non-Hodgkin's lymphoma
NICE	National Institutes for Health and Clinical Excellence
RCT	Randomized controlled trial
RR	Risk ratio
SCTP	Stem cell transplant program
TAU	MUHC Technology Assessment Unit

EXECUTIVE SUMMARY

Background

Multiple myeloma and non-Hodgkin's lymphoma are hematopoietic cancers that are often treated with autologous hematopoietic stem cell transplants (aHSCT). Traditionally, regimens used to mobilize stem cells from the peripheral blood for aHSCT include growth factors such as G-CSF, with or without chemotherapeutic drugs like cyclophosphamide. Although cyclophosphamide is considered to be more effective than G-CSF in mobilizing stem cells, it is associated with greater complications rates, longer treatment duration, and greater unpredictability in scheduling apheresis sessions, placing a higher burden on resource use. Plerixafor is a novel agent that has high effectiveness in stem cell mobilization without the adverse effects of chemo-mobilization, and was approved by Health Canada in 2011 for use in conjunction with G-CSF as a stem cell mobilization agent in MM and NHL patients. The high cost of plerixafor has hindered its widespread adoption as first-line treatment, wherein all patients are administered plerixafor upfront. In an attempt to contain costs, several institutions have developed algorithms to add plerixafor to the standard regimen only in those patients with a demonstrated risk of failure to mobilize (poor mobilizers). In June 2015, the MUHC switched from a mobilization regimen of cyclophosphamide plus G-CSF to an upfront plerixafor regimen.

Objectives

The objectives of this report are to evaluate the effectiveness, safety and cost impact of using plerixafor as a stem cell mobilizer in multiple myeloma or non-Hodgkin's lymphoma patients requiring autologous stem cell transplants. We evaluated two regimens using plerixafor: (1) a regimen where plerixafor is used as first-line initialization i.e. upfront use of plerixafor; and (2) a regimen where plerixafor is used as immediate rescue treatment due to ineffective stem cell mobilization during the mobilization process with other agents i.e. pre-emptive use of plerixafor (also known as *on demand* or *just-in-time* use of plerixafor). The comparator regimens of interest used G-CSF alone or cyclophosphamide plus G-CSF.

Methods

We carried out a systematic literature search including randomized controlled trials and observational studies evaluating the effectiveness, safety and cost impact of regimens using plerixafor, either in an upfront or pre-emptive fashion, in comparison with regimens using G-CSF alone or in conjunction with cyclophosphamide. We summarized the recent

MUHC experience with an upfront plerixafor regimen versus the previous regimen of cyclophosphamide plus G-CSF. We performed a cost-minimization analysis comparing three different regimens with comparable effectiveness to identify the regimen with the lowest cost per patient.

Results: Literature review

We identified 12 studies that evaluated the use of plerixafor to mobilize stem cells for patients requiring autologous stem cell transplants: 7 were studies of upfront plerixafor use, 4 evaluated pre-emptive use of plerixafor, and 1 study evaluated both regimens. Two of the upfront studies were randomized controlled trials and the remaining 10 studies had a non-randomized design.

Effectiveness: The effectiveness of a mobilization regimen was measured as the percentage of patients achieving a sufficient number of stem cells to proceed to autologous transplantation. Downstream outcomes such as transplantation outcome and survival were not always assessed in these studies. Either upfront or pre-emptive use of plerixafor was more effective than G-CSF alone or cyclophosphamide plus G-CSF in mobilizing a sufficient number of stem cells to proceed to transplantation.

- **Upfront plerixafor plus G-CSF vs G-CSF alone:** A Cochrane meta-analysis of the only two RCTs evaluating plerixafor showed that upfront plerixafor was superior to G-CSF alone in collecting the target stem cell yield (RR 2.42; 95% CI: 1.98 to 2.96).
- **Upfront plerixafor plus G-CSF vs cyclophosphamide plus G-CSF:** Observational studies found that upfront plerixafor was more effective (RRs ranged from 1.13 to 1.36) than upfront cyclophosphamide + G-CSF in achieving the target yield.
- **Pre-emptive plerixafor regimens:** In the four identified studies, the percentage of patients requiring addition of plerixafor to the standard regimen due to poor mobilization ranged from 14% to 66%. Over 95% of patients in the pre-emptive arms of the studies reviewed collected the minimum number of stem cells to proceed to transplantation versus 77% - 93% of patients in the standard regimens.

Safety: The two RCTs reported no difference in the occurrence of serious adverse events between plerixafor and the G-CSF-only regimens, with only mild adverse events occurring in both groups. However, in comparison with cyclophosphamide regimens, 4 studies reported that plerixafor regimens resulted in fewer mobilization-related hospitalizations. Cyclophosphamide regimens were associated with more frequent hospitalizations for febrile neutropenia.

Cost impact: Unbiased cost comparisons between regimens must consider not only direct drug costs but also costs of hospitalizations, side effects and re-mobilizations. Studies factoring in these costs found divergent results when comparing upfront plerixafor use with cyclophosphamide plus G-CSF regimens, with one reporting an increased cost with upfront plerixafor use of USD 6,843 per patient, and the other a decrease in cost of USD 1,815 per patient. These differences could be due to the relatively fewer hospitalizations and remobilizations in the cyclophosphamide arm of the former study in comparison with that of the latter, underscoring the cost impact of a high rate of hospitalizations and remobilizations. A study comparing pre-emptive plerixafor use with a cyclophosphamide plus G-CSF regimen found the two regimens to be equivalent. A single study compared upfront plerixafor use with pre-emptive use and found the upfront plerixafor regimen to be more expensive by USD 3,900 per patient.

Experience at the MUHC

Until recently, patients at the Stem Cell Transplant Program (SCTP) of the MUHC were mobilized using cyclophosphamide plus G-CSF. Since June 2015, the SCTP has switched to a regimen of upfront plerixafor wherein patients are mobilized with G-CSF for 4 days, and administered plerixafor on the evening of the 4th day.

24 patients were treated with upfront plerixafor from June to December 2015, and their outcomes were compared with a historical cohort of 20 consecutive patients who underwent chemo-mobilization with cyclophosphamide plus G-CSF between October 2014 and October 2015. 79% in the upfront plerixafor group and 80% of patients in the cyclophosphamide cohort reached the target yield. However, patients in the chemo group had a greater proportion of mobilization-related hospitalizations (26%) compared with the plerixafor group (4%). The length of mobilization treatment was shorter in the plerixafor group vs the chemo group (mean length: 5.8 days vs 12.7 days). The transplant team also reported a lower burden on resource use since the switch to upfront plerixafor as a result of better predictability in scheduling apheresis sessions (60% of chemo-mobilized patients had to be rescheduled vs. 0% of plerixafor-mobilized patients), and the freeing up of space in the oncology day clinic due to patients no longer needing chemotherapy for mobilization.

Costs

The total cost of mobilizing 24 patients with plerixafor, including cost of drugs, nursing time, laboratory tests, and hospitalizations was \$477,555 vs \$33,208 for the 20 patients mobilized with cyclophosphamide plus G-CSF, which represents an average cost per

patient of \$19,898 and \$1,661, respectively. The cost of plerixafor (\$463,295 for the 24 patients treated between June and December 2015) accounted for 97% of the total plerixafor-mobilization costs.

The projected budget impact for treating 40 patients under three different regimens: (i) upfront plerixafor + G-CSF in all patients (the current regimen at the MUHC); (ii) pre-emptive plerixafor in poor mobilizers (10%) following upfront cyclophosphamide + G-CSF in all patients, and (iii) pre-emptive plerixafor in poor mobilizers (50%) following upfront G-CSF alone in all patients was \$785,871, \$143,352 and \$406,320, respectively.

CONCLUSIONS

- Plerixafor is a novel mobilization agent that has considerable advantages over the alternatives. It is more effective than either G-CSF alone or cyclophosphamide plus G-CSF in mobilizing sufficient stem cells for transplantation, and it is not associated with the severe complications and unpredictability of cyclophosphamide mobilization.
- The main disadvantage of plerixafor is its high cost. Published studies and an evaluation of our local MUHC experience have found upfront plerixafor regimens to be more expensive than other mobilization regimens, mainly due to the high cost of the drug.
- In order to mitigate these high costs, some institutions have developed risk-adapted algorithms for the use of plerixafor only in those patients at risk of poor mobilization. Studies that evaluated such pre-emptive plerixafor regimens versus G-CSF only or cyclophosphamide plus G-CSF have reported good mobilization rates.
- Furthermore, our analysis of local data found that projected costs associated with pre-emptive plerixafor regimens using either G-CSF alone, or cyclophosphamide plus G-CSF, were considerably lower than that of an upfront plerixafor mobilization regimen, making the adoption of such regimens a more attractive option at the MUHC.

RECOMMENDATIONS

- Given the superiority of plerixafor over other regimens in mobilizing stem cells, we recommend:
 - [Approval](#) of a pre-emptive plerixafor regimen wherein all patients are mobilized with G-CSF, and only the subset of poor mobilizers receive plerixafor. This regimen is not associated with the severe complications and unpredictability of chemo-mobilization, but may result in higher costs due to more frequent use of plerixafor needed to salvage poor mobilizers.
 - [Approval](#) of a pre-emptive plerixafor regimen wherein all patients are mobilized with cyclophosphamide + G-CSF, and only the subset of poor mobilizers receive plerixafor. This regimen is associated with a greater risk of complications, but may result in lower costs due to the higher mobilization rates of cyclophosphamide versus G-CSF alone.
 - [Non-approval](#) of routine use of upfront plerixafor as first-line treatment in NHL and MM patients undergoing autologous stem cell transplantation, due to the high costs associated with upfront plerixafor use. This recommendation may be re-evaluated in light of new evidence, or a drop in the drug price of plerixafor.
- We recommend that the Stem Cell Transplant Program develop a protocol for the choice of which pre-emptive plerixafor regimen is best suited to which patient.
- We recommend that the Stem Cell Transplant Program continue to systematically document treatment regimens, complications, and outcomes in patients mobilized from autologous stem cell transplants to allow for retrospective evaluation of the time to mobilization and the percentage of patients requiring plerixafor.
- We recommend that appropriate measures be undertaken to resolve discrepancies in the number of plerixafor vials dispensed by the department of Pharmacy and reported number used by the Stem Cell Transplant Program.
- Given that an ancillary benefit of upfront plerixafor use is a reduction in the wait list for stem cell collection, there is a need to evaluate the current infrastructure (number of apheresis beds, access to apheresis facilities) at the MUHC such that the non-use of upfront plerixafor does not hinder timely access to care for stem cell transplant patients.

SOMMAIRE

Contexte

Les myélomes multiples ainsi que les lymphomes non-hodgkiniens sont des cancers hématopoïétiques souvent traités par des autogreffes de cellules souches hématopoïétiques (ACSH). Traditionnellement, les protocoles utilisés pour mobiliser les cellules souches du sang périphérique pour une ACSH, incluent des facteurs de croissance tel que le GCS-F (facteur stimulant les colonies de granulocytes), avec ou sans agents de chimiothérapie tel que la cyclophosphamide. Même si l'on considère que la cyclophosphamide est plus efficace que le GCS-F pour mobiliser les cellules souches, celle-ci comporte un taux de complications plus élevé, des traitements plus longs et une plus grande imprévisibilité dans la planification des sessions d'aphérèse, entraînant ainsi une pression supplémentaire sur l'utilisation des ressources. Le plerixafor est un nouvel agent possédant une grande efficacité pour la mobilisation des cellules souches, sans les effets indésirables de la chimiomobilisation, et approuvé par Santé Canada en 2011 pour une utilisation conjointe avec le GCS-F pour la mobilisation des cellules souches chez les patients avec myélome multiple (MM) et lymphome non hodgkinien (LNH). Le coût élevé du plerixafor a entravé son adoption à grande échelle comme traitement de première ligne où tous les patients reçoivent d'emblée du plerixafor. Pour minimiser les coûts, plusieurs établissements ont développé des algorithmes pour ajouter le plerixafor aux protocoles existants, seulement chez les patients présentant un risque d'échec lors de la mobilisation (faibles mobilisateurs). Au mois de juin 2015, le CUSM délaissa le protocole basé sur la cyclophosphamide + le GCS-F pour un protocole utilisant d'emblée le plerixafor.

Objectifs

Les objectifs de ce rapport sont d'évaluer l'efficacité, l'innocuité et l'impact financier de l'utilisation du plerixafor comme mobilisateur de cellules souches chez les patients avec de myélome multiple ou de lymphome non hodgkinien, nécessitant des autogreffes de cellules souches. Nous avons évalué deux protocoles utilisant le plerixafor: 1) un protocole où le plerixafor est utilisé en première ligne, i.e. d'emblée; et 2) un protocole où le plerixafor est utilisé comme traitement d'aide immédiat, dû à une mobilisation inefficace des cellules souches lors du procédé de mobilisation avec d'autres agents, i.e. une utilisation préventive du plerixafor (aussi connue sous l'appellation *utilisation sur demande* ou *utilisation "just-in-time"*). Les protocoles comparateurs d'intérêt comprenaient le GCS-F, seul, ou la cyclophosphamide + le GCS-F.

Méthodologie

Nous avons fait une recherche systématique de la littérature comprenant les études randomisées et observationnelles évaluant l'efficacité, l'innocuité et l'impact financier des protocoles utilisant le plerixafor, soit d'emblée ou soit de façon préventive, par comparaison avec les protocoles utilisant le GCS-F, seul, ou conjointement avec la cyclophosphamide. Nous avons aussi résumé l'expérience récente du CUSM où le protocole avec plerixafor est utilisé d'emblée, versus le protocole précédent impliquant la cyclophosphamide + le GCS-F. Enfin, nous avons effectué une analyse de minimisation des coûts comparant trois différents protocoles avec une efficacité comparable, pour identifier le protocole avec le coût par patient le plus faible.

Résultats : Revue de la littérature

Nous avons identifié 12 études qui évaluaient l'utilisation du plerixafor pour mobiliser les cellules souches pour les patients nécessitant une autogreffe de ces cellules : 7 études concernaient l'utilisation du plerixafor d'emblée, 4 études évaluaient l'utilisation préventive du plerixafor et 1 étude évaluait ces deux protocoles. Deux des études portant sur l'utilisation du plerixafor d'emblée étaient des études randomisées tandis que les 10 autres études n'étaient pas randomisées.

Efficacité : L'efficacité d'un protocole de mobilisation était mesurée selon le pourcentage des patients obtenant un nombre suffisant de cellules souches, permettant une autogreffe. Les résultats en aval, tels que les résultats des transplantations et la survie, n'étaient pas toujours évalués dans ces études. L'utilisation d'emblée ou préventive du plerixafor était plus efficace que le GCS-F, seul, ou la cyclophosphamide + le GCS-F, pour mobiliser un nombre suffisant de cellules souches permettant de procéder à la transplantation.

- **L'utilisation d'emblée du plerixafor avec le GCS-F vs le GCS-F, seul** : Une méta-analyse Cochrane des deux seules études randomisées évaluant le plerixafor montra que l'utilisation d'emblée du plerixafor était supérieure au GCS-F, seul, pour atteindre le taux de cellules souches visés (RR 2.42; 95% CI : 1.98 à 2.96).
- **Le protocole avec le plerixafor d'emblée + le GCS-F vs le protocole avec la cyclophosphamide + le GCS-F** : Les études d'observation montrèrent que l'utilisation d'emblée du plerixafor était plus efficace (RR variait de 1.13 à 1.36) que l'utilisation d'emblée de la cyclophosphamide + le GCS-F, pour atteindre le taux visé.

- **Les protocoles préventifs avec le plerixafor** : Parmi les quatre études identifiées, le pourcentage des patients nécessitant l'ajout de plerixafor au protocole standard, dû à une faible mobilisation, variait de 14% à 66%. Plus de 95% des patients situés dans la branche préventive des études ont colligé le nombre minimum de cellules souches pour procéder à une transplantation, versus 77% à 93% des patients traités par des protocoles standards.

Innocuité : Les deux études randomisées ne montrèrent aucune différence au niveau de l'occurrence d'événements indésirables graves entre les protocoles avec le plerixafor et les protocoles avec uniquement le GCS-F, notant seulement quelques événements indésirables peu importants dans les deux groupes. Cependant, par comparaison avec les protocoles avec la cyclophosphamide, 4 études rapportèrent que les protocoles avec le plerixafor impliquaient moins d'hospitalisations reliées à la mobilisation. Les protocoles avec la cyclophosphamide étaient associés à des hospitalisations plus fréquentes pour neutropénie fébrile.

Impact financier : Les comparaisons non biaisées des coûts entre les différents protocoles doivent considérer, non seulement le coût des médicaments, mais aussi les coûts des hospitalisations, des effets secondaires et des remobilisations. Les études portant sur ces coûts trouvèrent des résultats divergents en comparant l'utilisation d'emblée du plerixafor avec les protocoles impliquant la cyclophosphamide + le GCS-F; ainsi, une étude rapportait une augmentation des coûts de 6 843 \$ USD par patient avec l'utilisation d'emblée du plerixafor, tandis qu'une autre mentionnait une diminution des coûts de 1 815 \$ USD par patient. Ces différences pourraient être dues au faible nombre d'hospitalisations et de remobilisations dans la branche cyclophosphamide de l'étude antérieure, par comparaison à la dernière étude, qui met en évidence l'impact financier d'un taux élevé d'hospitalisations et de remobilisations. Une étude comparant l'utilisation préventive du plerixafor à un protocole impliquant la cyclophosphamide + le GCS-F, souligna que les deux protocoles étaient équivalents. Enfin, une seule étude compara l'utilisation d'emblée du plerixafor à son utilisation préventive et montra que le protocole avec l'utilisation d'emblée coûtait 3 900 \$ USD de plus par patient.

L'expérience au CUSM

Jusqu'à récemment, les patients du "Stem Cell Transplant Program" (SCTP) du CUSM étaient mobilisés à l'aide de la cyclophosphamide + le GCS-F. Depuis le mois de juin 2015, le SCTP a adopté un protocole avec le plerixafor d'emblée où les patients sont mobilisés avec le GCS-F pendant 4 jours, pour recevoir par la suite le plerixafor le soir du 4^e jour.

Vingt-quatre patients ont ainsi été traités d'emblée avec le plerixafor, de juin à décembre 2015, et leurs résultats furent comparés à une cohorte historique de 20 patients consécutifs ayant subi une chimiomobilisation avec la cyclophosphamide + le GCS-F entre les mois d'octobre 2014 et octobre 2015. Ainsi, 79% des patients du groupe plerixafor et 80% des patients de la cohorte cyclophosphamide, ont atteint le taux de cellules souches visé. Cependant, les patients du groupe chimiothérapie ont eu un taux plus élevé d'hospitalisations (26%), par comparaison au groupe plerixafor (4%). La durée de traitement de mobilisation était plus courte chez le groupe plerixafor vs le groupe chimiothérapie (durée moyenne : 5.8 jrs vs 12.7 jrs). L'équipe de transplantation rapporta aussi une pression plus faible sur les ressources depuis l'adoption du protocole avec le plerixafor d'emblée, suite à une meilleure prévisibilité dans la planification des sessions d'aphérèse (60% des patients du groupe chimiothérapie ont dû être replanifiés vs 0% des patients du groupe plerixafor) et la libération d'espaces lors des cliniques d'oncologie, les patients ne nécessitant plus de chimiothérapie pour une mobilisation.

Coûts

Le coût total pour la mobilisation de 24 patients sous protocole avec le plerixafor, incluant le coût des médicaments, du temps infirmier, des tests de laboratoire et d'hospitalisation, était de 477 555 \$ vs 33 208 \$ pour 20 patients mobilisés avec la cyclophosphamide + le GCS-F, ce qui se traduit par un coût moyen par patient de 19 898 \$ et 1 661 \$, respectivement. Le coût du plerixafor (463 295 \$ pour les 24 patients traités entre les mois de juin et de décembre 2015) représentait 97% des coûts totaux pour la mobilisation avec le plerixafor.

L'impact budgétaire estimé pour traiter 40 patients sous trois différents protocoles, soit i) le plerixafor donné d'emblée + le GCS-F à tous les patients (le protocole actuel au CUSM), ii) le plerixafor donné de façon préventive aux faibles mobilisateurs (10%), suite à la cyclophosphamide + le GCS-F donnés d'emblée à tous les patients, et iii) le plerixafor donné de façon préventive aux faibles mobilisateurs (50%) suite au GCS-F, seul, donné d'emblée à tous les patients, était de 785 871 \$, 143 352 \$ et 406 320 \$, respectivement.

CONCLUSIONS

- Le plerixafor est un nouvel agent mobilisateur qui possède des avantages considérables par rapport aux protocoles alternatifs. Il est plus efficace que le GCS-F, seul, ou la cyclophosphamide + le GCS-F pour mobiliser le nombre suffisant de cellules souches pour la transplantation, et n'entraîne pas les complications sévères et l'imprévisibilité de la mobilisation avec la cyclophosphamide.

- Le désavantage majeur du plerixafor est son coût élevé. Les études publiées et l'évaluation de notre expérience au CUSM ont souligné que les protocoles basés sur le plerixafor d'emblée sont plus onéreux que les autres protocoles de mobilisation, principalement en raison du coût élevé du médicament.
- De façon à minimiser ces coûts élevés, certains établissements ont développé des algorithmes basés sur les risques pour l'utilisation du plerixafor, seulement chez les patients démontrant un risque d'une faible mobilisation. Les études qui ont évalué de tels protocoles préventifs avec plerixafor versus les protocoles basés sur le GCS-F, seul, ou sur la cyclophosphamide + le GCS-F, ont rapporté de bons taux de mobilisation.
- Par ailleurs, l'analyse de nos propres données a révélé que les coûts estimés correspondant aux protocoles préventifs avec plerixafor et avec le GCS-F, seul, ou avec la cyclophosphamide + le GCS-F, étaient considérablement plus faibles que le protocole de mobilisation avec le plerixafor d'emblée, rendant l'adoption de tels protocoles une option plus attrayante pour le CUSM.

RECOMMANDATIONS

- Étant donné la supériorité du plerixafor par rapport aux autres protocoles de mobilisation des cellules souches, nous recommandons :
 - [L'approbation](#) d'un protocole préventif basé sur le plerixafor où tous les patients sont mobilisés avec le GCS-F et où seulement le sous-ensemble des faibles mobilisateurs reçoit le plerixafor. Ce protocole n'est pas associé aux complications sévères et à l'imprévisibilité de la mobilisation par chimiothérapie, mais peut entraîner des coûts plus élevés dû à une utilisation plus fréquente du plerixafor nécessaire pour aider les faibles mobilisateurs.
 - [L'approbation](#) d'un protocole préventif basé sur le plerixafor où tous les patients sont mobilisés avec la cyclophosphamide + le GCS-F et où seulement le sous-ensemble des faibles mobilisateurs reçoit le plerixafor. Ce protocole est associé à un risque plus élevé de complications mais peut se traduire par des coûts plus faibles dû à des taux de mobilisation plus élevés avec la cyclophosphamide versus le GCS-F, seul.
 - [La non-approbation](#) de l'utilisation de routine du plerixafor donné d'emblée comme traitement de première ligne chez les patients avec de LNH et de MM

subissant une autogreffe de cellules souches, dû aux coûts élevés liés à l'utilisation du plerixafor donné d'emblée. Cette recommandation peut être réévaluée à la lumière de nouvelles preuves ou advenant une baisse du prix du plerixafor.

- Nous recommandons que le programme SCTP développe un protocole permettant le choix d'un protocole préventif basé sur le plerixafor, le mieux adapté pour un patient donné.
- Nous recommandons que le programme SCTP continue de documenter systématiquement les protocoles de traitement, les complications et les résultats des patients mobilisés pour une autogreffe de cellules souches, pour permettre une évaluation rétrospective des délais jusqu'à la mobilisation et du pourcentage des patients nécessitant le plerixafor.
- Nous recommandons que des mesures appropriées soient entreprises pour résoudre les divergences dans le nombre de flacons de plerixafor distribués par le département de la pharmacie et celui rapporté par le programme SCTP comme ayant été utilisé.
- Étant donné qu'un bénéfice secondaire découlant de l'utilisation d'emblée du plerixafor est une diminution de la liste d'attente pour la collecte des cellules souches, il est nécessaire d'évaluer l'infrastructure actuelle (nombre de lits d'aphérèse, accessibilité aux facilités d'aphérèse) au CUSM de sorte que la non utilisation d'emblée du plerixafor n'entrave pas l'accès aux soins des patients devant recevoir une transplantation de cellules souches en temps opportun.

PLERIXAFOR AS FIRST-LINE CHOICE FOR STEM CELL MOBILIZATION IN NON-HODGKIN'S LYMPHOMA AND MULTIPLE MYELOMA PATIENTS

1. BACKGROUND

[Multiple myeloma](#) (MM) and Non-Hodgkin's [lymphoma](#) (NHL) are cancers of the immune system, affecting specific types of white blood cells i.e. plasma cells and lymphocytes, respectively. Myeloma has an incidence of 4 per 100,000 in industrialized countries, and a 5-year survival rate of approximately 50%. The incidence rate for NHL is about 20 per 100,000, with a 5-year survival of 70%.

Autologous transplantation of [hematopoietic stem cells](#) (HSC), the precursors of all blood cells, including plasma cells and lymphocytes, is now a well-established treatment option for these malignancies. In this procedure, hematopoietic stem cells from the peripheral blood are mobilized and collected by [apheresis](#), and then transfused back into the patient after [conditioning chemotherapy](#), with the aim of replacing destroyed tissue and restoring normal blood cell production (hematopoiesis). Autologous hematopoietic stem cell transplantation (aHSCT) is now considered standard of care for MM patients,¹ and for relapsed chemosensitive NHL patients.

Figure 1 illustrates four types of mobilization regimens used to collect stem cells from peripheral blood. Conventionally, two types of mobilization regimens have been used: cytokine-based regimens which use growth factors such as granulocyte colony-stimulating factor (G-CSF) ([Figure 1A](#)); and chemo-mobilization regimens, which use chemotherapeutic agents such as cyclophosphamide or other cytostatic drugs, in conjunction with growth factors such as G-CSF ([Figure 1B](#)). Studies generally report that in comparison with cytokine-only regimens, chemo-mobilization regimens result in higher stem cell yields, fewer collection days, and lower mobilization failure rates; however, chemo-based regimens have far higher rates of severe complications, such as febrile neutropenia (**Table 1**), and are associated with greater unpredictability in scheduling apheresis sessions, resulting in higher resource burden.²

Recently, regimens using a novel mobilization agent, [Plerixafor](#) (Mozobil®, Genzyme, Cambridge, MA, USA), have proven particularly promising because they combine the advantages of the cytokine- and chemo-based regimens, resulting in a high stem cell yield

but without adverse events (**Table 1**). Plerixafor stimulates the release of stem cells from the bone marrow by inhibiting their binding to the bone marrow stromal cells, and was approved by Health Canada in December, 2011 for use in combination with G-CSF to mobilize stem cells from the peripheral blood of patients with NHL and MM.

Although studies have demonstrated that plerixafor is effective and safe to use in mobilizing stem cells for transplantation, its widespread adoption as first-line treatment, wherein all patients are administered plerixafor upfront ([Figure 1C](#)), has been hampered by its high cost. A pharmacoeconomic analysis by Quebec's Institut national d'excellence en santé et en service sociaux (INESSS) concluded that due to the high cost of plerixafor, it is indicated for use as a pre-emptive mobilizing agent i.e. as rescue treatment in patients who ineffectively mobilize with other agents (poor mobilizers), or as a re-mobilizing agent in patients who failed a previous attempt of mobilization with or without chemotherapy. Several institutions have developed such pre-emptive plerixafor regimens ([Figure 1D](#)) to contain costs, wherein only patients who mobilize insufficient cells according to pre-specified algorithms are administered plerixafor, with the remainder receiving the standard cytokine- or chemo-based regimens.

2. CONTEXT

Until recently at the MUHC, MM and NHL patients eligible for aHSCT were mobilized with [cyclophosphamide and G-CSF](#); plerixafor was only used as salvage treatment in patients who mobilized ineffectively, or who failed a previous mobilization attempt. However, use of the upfront cyclophosphamide regimen resulted in a number of accessibility issues and a long wait list due to:

- the longer treatment time of the cyclophosphamide regimen, and subsequent longer time to apheresis, as seen in [Figure 1B](#);
- the less reliable stem cell mobilization kinetics of cyclophosphamide, resulting in unpredictability of scheduling apheresis sessions. Hence, only 1 apheresis session could be scheduled per week;
- the limited number of apheresis beds available (4 beds).

As a result, the Stem Cell Transplant Program adopted a regimen of [upfront use of plerixafor](#) in June 2015. After its adoption, the program reported a reduction in the wait time for mobilization, from 2-3 months to less than 4 weeks (Dr. Gizelle Popradi, personal

communication). This was attributed to the reduction in the median number of collections days from 2 to 1, and to the greater ease of stem cell collection due to the predictable cell kinetics associated with plerixafor, enabling the scheduling of 2 patients for collection per week.

Although the use of upfront plerixafor was key in improving access to care, it also greatly increased costs. The TAU was hence commissioned to review the effectiveness, safety, and cost-effectiveness of upfront plerixafor use in comparison with alternative regimens, including regimens that use plerixafor pre-emptively ([Figure 1D](#)).

3. OBJECTIVES

The objectives of this report are to evaluate the effectiveness, safety and cost of using plerixafor as a stem cell mobilizer in multiple myeloma or non-Hodgkin's lymphoma patients requiring autologous stem cell transplants. The outcome of interest is the proportion of patients mobilizing a sufficient number of stem cells to proceed to autologous transplantation. Specifically, the objectives are to:

- Evaluate the effectiveness, safety and cost of an [upfront plerixafor](#) regimen, where all patients receive plerixafor, in comparison with mobilization regimens where all patients are mobilized with either [G-CSF alone](#), or [cyclophosphamide plus G-CSF](#);
- Evaluate the effectiveness, safety and cost of a [pre-emptive plerixafor regimen](#), where plerixafor is administered only in patients poorly mobilizing with G-CSF or cyclophosphamide plus G-CSF, versus regimens where all patients are mobilized with either [G-CSF alone](#), or [cyclophosphamide plus G-CSF](#).
- Estimate the cost and budget impact of using an [upfront plerixafor](#) regimen at the MUHC, versus two [pre-emptive plerixafor](#) regimens where plerixafor is administered only in patients poorly mobilizing with G-CSF, and cyclophosphamide plus G-CSF, respectively.

4. METHODS

4.1 Literature search and quality assessment

We conducted a literature search for relevant randomized controlled trials (RCT), observational studies, health technology assessment (HTA) reports, and systematic reviews evaluating plerixafor use in patients eligible for [aHSCT](#). We searched Pubmed, the Cochrane library and the health technology assessment (HTA) database of the Centre for Reviews and Dissemination. The most recent search was conducted on 22 April 2016.

Our literature search was limited to comparative studies evaluating the efficacy, safety and cost-effectiveness of upfront or pre-emptive plerixafor regimens versus other mobilization regimens. Definitions of the four mobilization regimes evaluated in this report are provided in [section 4.2](#).

We also identified relevant HTAs and clinical guidelines assessing the use of plerixafor.

4.2 Definitions of the four mobilization regimens

A. G-CSF only regimen

In the G-CSF only regimen, patients are administered G-CSF for four days, with apheresis starting on the 5th day, and continued G-CSF administration for every apheresis session ([Figure 1A](#)). The number of days of G-CSF administration is based on the literature, which has documented that peripheral blood CD34+ cell counts rise on the 4th day following the start of G-CSF treatment, and decrease after peaking on the 6th day.³

B. Cyclophosphamide plus G-CSF regimen

In the upfront cyclophosphamide regimen, patients receive 1.5-5g/m² of cyclophosphamide on day 1, with G-CSF generally administered the following day to enhance stem cell mobilization, and continued until the end of apheresis ([Figure 1B](#)). Apheresis is started on or after day 10 following cyclophosphamide treatment because it has been shown that peripheral blood CD34+ cell counts peak approximately 10 days after cyclophosphamide administration.⁴ Thus, patients in this regimen receive G-CSF for a longer duration (10-14 days) compared with patients mobilized with G-CSF only or plerixafor + G-CSF regimens (5-8 days).

C. Upfront plerixafor regimen

Patients mobilized with upfront plerixafor typically receive G-CSF (10ug/kg) subcutaneously for 4 days, with plerixafor (0.24 mg/kg) administered subcutaneously on the evening of the 4th day ([Figure 1C](#)). Apheresis is started on the 5th day, with additional apheresis sessions and doses of G-CSF and plerixafor continued until the target yield of CD34⁺ cells is reached, up to a maximum of 4 apheresis sessions.

D. Pre-emptive plerixafor regimens

In pre-emptive plerixafor regimens, all patients receive one of the standard regimens of either G-CSF alone, or cyclophosphamide plus G-CSF, with plerixafor added to the regimen only in those patients with a demonstrated risk of failure to mobilize (poor mobilizers) [[Figure 1D](#)]. Institution-specific algorithms are developed to define poor mobilizers, generally those patients whose peripheral blood CD34⁺ cell count on the first collection day is <10-15 cells/ μ l.

4.3 MUHC experience

We describe the current treatment regimen for multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) patients eligible for autologous stem cell transplantation at the Stem Cell Transplant Program (STCP) of the MUHC. We also describe the experience of the STCP in using plerixafor as first-line treatment and the previous regimen using cyclophosphamide + G-CSF by analysing two cohorts followed by Dr. Popradi with 24 and 20 patients, respectively, who were treated at the MUHC.

4.4 Cost analysis

We estimated the cost per patient in the two cohorts previously treated at the MUHC, i.e. for the 20 patients who received upfront cyclophosphamide, and the 24 patients who received upfront plerixafor. As there was a discrepancy in the reported number of plerixafor vials dispensed by Pharmacy and those reported used by the Stem Cell Transplant program, we report the cost using both numbers.

We also compared the projected cost per patient and total cost for treating 40 patients under three different regimens: (i) upfront plerixafor + G-CSF in all patients (the current regimen at the MUHC); (ii) pre-emptive plerixafor in poor mobilizers (assumed to be 10% of treated patients) following upfront cyclophosphamide + G-CSF in all patients, and (iii)

pre-emptive plerixafor in poor mobilizers (assumed to be 50%) following upfront G-CSF alone in all patients. The effectiveness of the different regimens is comparable in terms of the percentage of patients who reach the target stem cell yield (**Figure 2**). Therefore, interest lies in a cost minimization analysis, i.e. identifying the regimen associated with the lowest cost per patient. For this analysis, we used the number of plerixafor vials reported by Pharmacy because these numbers are based on purchasing data and reflect the budget impact on the department affected by the increased use in plerixafor i.e., the department of Pharmacy.

The cost analysis was carried out from the perspective of the MUHC. We considered all direct medical costs associated with the mobilization and apheresis procedures, including mobilization-related hospitalizations. Thus, costs included drug, procedure, nursing, and hospitalization costs. Though we estimated the cost of G-CSF under each regimen it was not included in our estimate of the total cost as it is not borne by the MUHC. Due to the short time horizon (14 treatment days), no discounting was applied. We estimated the average number of lab tests and ambulatory visits needed under each regimen using data from patients previously treated at the MUHC. We assumed that one additional lab test would be required under the two pre-emptive regimens to identify the poor mobilizers. We estimated values for the percentage of poor mobilizers requiring plerixafor, the number of apheresis days, the number of days of treatment with G-CSF, and the number of hospitalizations based on both our literature review and on the MUHC data. Numbers were rounded off to the nearest integer value for convenience. Data on the quantity of drugs dispensed under the different regimens were obtained from Mr. André Bonnici, Director of Pharmacy at the MUHC. Data on costs were obtained from Mr. Nicolas Robert, Director of Finance at the MUHC. Data on use of MUHC services (out-patient procedures and hospitalization) were obtained from the OACIS electronic database.

We did not consider indirect costs or quality of life, and did not attempt to quantify opportunity costs, e.g. increase in efficiency.

5. LITERATURE REVIEW

We identified 12 studies that evaluated the use of plerixafor to mobilize stem cells for patients requiring autologous stem cell transplants: 7 were studies of upfront plerixafor use, 4 evaluated pre-emptive use of plerixafor, and 1 study evaluated both regimens. Two of the upfront studies were randomized controlled trials and the remaining 10 studies had a non-randomized design.

5.1 Effectiveness

Effectiveness was assessed by comparing intervention and control groups in terms of the percentage of patients achieving a sufficient collection of [CD34⁺](#) cells/kg to proceed to transplantation.

5.1.1 Upfront use of plerixafor (Figure 1C)

We identified two randomized controlled trials (RCT) and five observational studies evaluating the upfront use of plerixafor, and results are summarized in **Table 2** and **Table 3**.

A. [Upfront plerixafor](#) vs. [G-CSF alone](#)

To date, only two RCTs have been conducted to assess the efficacy and safety of upfront use of Plerixafor. DiPersio et al. evaluated plerixafor plus G-CSF versus placebo plus G-CSF in two trials of patients with MM and NHL, respectively.^{5,6}

- Between 2005 and 2006, **DiPersio** et al. conducted a double blind, controlled, multi-centre trial (US, Canada, Germany) in MM patients, where all participants received G-CSF for four days, after which 154 were randomized to receive upfront plerixafor while 148 received placebo (median age 58 years, majority were males with stage III MM, and with prior chemotherapy).⁶ 72% of patients in the plerixafor arm reached the primary endpoint of collecting at least 6×10^6 CD34⁺ cells/kg within 2 apheresis days, versus 34% in the placebo arm (relative risk (RR) 2.12 (95% confidence interval (CI) 1.66, 2.71)) [Table 2]. 5% in the plerixafor group versus 12% of placebo patients failed to collect the minimum number of cells within 4 apheresis sessions to proceed to transplantation (RR of failure to mobilize: 0.40 (0.17, 0.94)).
- **DiPersio** et al. conducted another multi-centre trial (32 sites) between 2005 and 2006 in NHL patients, 150 of whom were randomized to receive upfront plerixafor and 148 received placebo, after 4 days of treatment with G-CSF.⁵ 59% of patients in the plerixafor arm achieved the primary endpoint of collecting at least 5×10^6 CD34⁺ cells/kg within 4 apheresis days, compared with only 20% in the placebo arm [RR 2.93 (95% CI 2.07, 4.14)] [Table 2]. 13% versus 53% failed to collect the minimum number of cells to proceed to transplantation in the plerixafor and placebo arms, respectively [RR 0.16 (95% CI 0.16, 0.37)].

- A Cochrane meta-analysis that only included these two RCTs showed that the plerixafor + G-CSF group was superior to placebo + G-CSF group in collecting the target stem cell yield (RR 2.42; 95% CI: 1.98 to 2.96; $p < 0.00001$).⁷

The Cochrane risk of bias assessment is shown in Appendix **Table A-1**. The authors did not provide information on random sequence generation and allocation concealment, and thus the studies may be at risk for selection bias. In particular, the high failure rate observed in the G-CSF only arm for NHL patients (53%) is higher than the failure rates expected from earlier studies (5-38%)² and the observational studies discussed below. Both trials were funded by Genzyme, the manufacturer of plerixafor.

B. Upfront plerixafor vs. Cyclophosphamide + G-CSF

We identified four observational studies comparing [upfront plerixafor](#) ([Figure 1C](#)) with upfront [cyclophosphamide + G-CSF](#) ([Figure 1B](#)) to mobilize stem cells ([Table 3](#)). No RCTs comparing these regimens have been conducted to date.

- **Afifi** et al. conducted a retrospective data analysis of patients treated at the Memorial Sloan Kettering Cancer Centre in New York between 2008 and 2012, where two mobilization regimens were in use: upfront use of cyclophosphamide, and upfront use of plerixafor.⁸ 112 patients were mobilized with plerixafor using the standard regimen as described earlier ([Figure 1C](#)). 111 patients were chemomobilized with 3 g/m² of cyclophosphamide followed by 10 days of G-CSF, with apheresis scheduled to start on day 12, based on peripheral CD34⁺ cell counts >5 cells/ μ l ([Figure 1B](#)). 94% versus 83% achieved the target yield of 5x10⁶ CD34⁺ cells/kg within 4 apheresis days in the plerixafor and chemo arms, respectively [RR 1.13 (95% CI 1.03, 1.25)]. 4% and 18% failed to sufficiently mobilize to proceed to transplant in the plerixafor and chemo groups, respectively [[Table 3](#)].
- **Shaughnessy** et al. performed a retrospective analysis of consecutive patients undergoing stem cell mobilization at two transplant centres in the US between 2008 and 2009.⁹ 33 patients who received [upfront plerixafor](#) according to the standard regimen were matched with patients who received 3-5 g/m² of [cyclophosphamide](#) followed by G-CSF for 9 days, with apheresis starting on day 10 based on a peripheral blood CD34⁺ cell count ≥ 10 cells/ μ l. 94% of participants in the plerixafor group reached the target yield of 5-6x10⁶ CD34⁺ cells/kg within 4 apheresis days, versus 76% in the cyclophosphamide group [RR 1.16 (95% CI 0.96, 1.41)] ([Table 3](#)). Failure rates could not be assessed because only patients who progressed to transplant were included in the study.

- **Chaudhary et al.** report the results of a retrospective analysis of 107 consecutive MM patients undergoing stem cell mobilization in a US centre between 2003 and 2012.¹⁰ 33 patients received [upfront plerixafor](#) ([Figure 1C](#)), and 74 patients were treated with 1.5 g/m² of intravenous [cyclophosphamide](#), followed by G-CSF started on day 8 and continued until end of apheresis. Apheresis was started on day 12 based on a peripheral blood CD34⁺ cell count ≥ 10 cells/ μ l. 94% versus 69% reached the minimum target yield of 5×10^6 CD34⁺ cells/kg [RR 1.36 (95% CI 1.14, 1.63)], and 0 vs. 8% failed to proceed to transplantation in the plerixafor and chemo groups, respectively.
- **Martin et al.** compared 98 prospectively followed recipients of [upfront plerixafor](#) with a historical cohort of 140 patient who received [cyclophosphamide](#).¹¹ 72% vs. 56% achieved the minimum target yield of 4×10^6 CD34⁺ cells/kg [RR 1.30 (95% CI 1.07, 1.58)], and 4% vs. 17% failed to proceed to transplantation in the plerixafor and chemo groups, respectively.

Summary of effectiveness results for use of an upfront plerixafor regimen

[Upfront plerixafor](#) was consistently more effective than either [G-CSF alone](#) or upfront [cyclophosphamide plus G-CSF](#) in mobilizing sufficient stem cells for transplantation across both randomized and non-randomized studies. Fewer patients who received upfront plerixafor failed to proceed to transplantation when compared to G-CSF alone or cyclophosphamide + G-CSF.

5.1.2 Pre-emptive use of plerixafor

Several institutions have developed algorithms to identify those patients likely to fail mobilization, thus limiting plerixafor use to only a subset of patients and containing costs ([Figure 1D](#)). We identified four studies that evaluated the effectiveness of algorithms for [pre-emptive use of plerixafor](#) compared to conventional regimens, and the subsequent cost impact of these methods ([Table 3](#)).

A. [Pre-emptive plerixafor](#) vs. [G-CSF alone](#)

- **Micallef et al.** compared 278 patients undergoing the conventional mobilization regimen using [G-CSF alone](#) with 98 patients receiving a risk-adapted approach between 2008 and 2010 at the Mayo Clinic.¹² In their risk-adapted algorithm, patients received G-CSF for 4 days after which apheresis was commenced if peripheral blood CD34⁺ cell count was ≥ 10 cells/ μ l. In patients with a CD34⁺ cell

count on day 4 of <10 cells/ μ l, plerixafor was administered in the evening, and apheresis started the following day; 59% of patients required plerixafor according to this criterion. 93% in the pre-emptive plerixafor vs. 72% in the routine G-CSF group reached the target yield of 4×10^6 CD34+ cells/kg [RR 1.28 (95% CI: 1.17, 1.41)], and 1% vs. 19% failed to mobilize [RR 0.05 (95% CI: 0.01, 38.9)], respectively (**Table 3**).

- In a retrospective analysis by Li et al., 148 patients received G-CSF or G-CSF + chemo, while 188 patients received the risk-adapted algorithm, where those with fewer than 15 CD34+ cells/ μ L blood and white blood cell (WBC) count of more than $10 \times 10^9/L$ after at least 5 days of G-CSF received plerixafor.¹³ 36% of the 188 patients qualified for plerixafor administration according to these criteria. 64% vs. 61% reached the target yield of 4×10^6 CD34+ cells/kg [RR 1.05 (95% CI 0.89, 1.24)], and 2% vs. 7% [RR 0.39 (95% CI 0.14, 1.13)] failed to mobilize in the pre-emptive plerixafor vs. G-CSF groups, respectively. Strikingly, when comparing poor mobilizers (defined based on pre-apheresis blood count) between the pre-emptive and routine groups, 93% of patients who received pre-emptive plerixafor vs. 72% in the G-CSF group reached the minimum transplant yield of 2×10^6 CD34+ cells/kg.

B. [Pre-emptive plerixafor](#) vs. [upfront cyclophosphamide + G-CSF](#)

- **Costa** et al. evaluated the effectiveness of two regimens: one in which 81 patients were mobilized with $2\text{gm}/\text{m}^2$ of [cyclophosphamide followed by G-CSF](#); and the other in which 50 patients received G-CSF for 4 days, and based on target-specific peripheral blood CD34+ cell counts, apheresis was started or plerixafor was added to the regimen and apheresis commenced the following day.¹⁴ 94% vs. 78% achieved the target collection yield [RR 1.23 (95% CI 1.07, 1.41)] and 2% vs. 23% failed to proceed to transplantation in the risk-adapted and chemo groups, respectively [RR 0.09 (95% CI 0.01, 0.65)] (**Table 3**). In addition, 2% in the plerixafor group vs. 30% of chemo-mobilized patients were hospitalized for mobilization-related complications.
- In a European study, **Milone** et al. compared a prospective group of 102 patients who followed the [pre-emptive plerixafor](#) algorithm, with a historical cohort of 228 patients who were mobilized with $4\text{gm}/\text{m}^2$ of cyclophosphamide alone.¹⁵ Patients in the pre-emptive plerixafor arm received $4\text{gm}/\text{m}^2$ of cyclophosphamide and were

administered plerixafor if peripheral blood CD34⁺ cell count was <10 cells/ μ l on day 13 (14% of these patients required plerixafor). 80% of patients in the pre-emptive plerixafor reached the target yield, and 4% failed to mobilized, compared to a 17% failure rate in the chemo group [RR 0.22 (95% CI 0.08, 0.61)].

Summary of effectiveness results for a pre-emptive plerixafor regimen

Administering plerixafor only in a subset of patients at risk of poor mobilization based on pre-apheresis peripheral blood CD34⁺ cell counts was effective in mobilizing sufficient stem cells required for transplantation in more than 80% of cases in most studies reviewed. The percentage of patients requiring pre-emptive plerixafor ranged from 14% to 66%.

5.1.3 Upfront plerixafor vs. pre-emptive plerixafor

Only one study compared upfront plerixafor with pre-emptive plerixafor use (**Table 3**).

Veltri et al. conducted a retrospective analysis of MM and NHL patients at their institution, comparing 76 patients who were mobilized with G-CSF + plerixafor (**Table 3**) with 60 patients who received a risk-adapted pre-emptive plerixafor regimen.¹⁶ According to the risk-adapted algorithm, all patients received G-CSF for 5 days, with plerixafor only administered to those at high risk of mobilization failure according to the following criteria: (i) CD34⁺ cell count <10 cells/ μ l on day 4; (ii) day 1 collection yield < 1 x10⁶ CD34⁺ cells/kg; or (iii) day 1+2 collection yield < 1.5x10⁶ CD34⁺ cells/kg.

There was no clinically significant difference in mobilization failure rates (5% vs. 3% for upfront and pre-emptive groups, respectively; [RR 0.63 (95% CI 0.12, 3.34)]), or in achieving the minimum collection yield (2x10⁶ CD34⁺ cells/kg) on apheresis day one (p=0.09). The authors report a significant difference between the two groups in achieving the target collection yield (5x10⁶ CD34⁺ cells/kg) on apheresis day one (66% for upfront vs. 36% for pre-emptive; p<0.001). However, total number of apheresis sessions needed was similar between the two groups (p=0.06).

5.2 Safety

5.2.1 Plerixafor vs. G-CSF

In the RCTs conducted by DiPersio et al., there were no differences in adverse events between the plerixafor and G-CSF arms. Only mild or moderate adverse events occurred, ranging from injection site reactions to gastrointestinal disorders.

In addition, the Cochrane meta-analysis of these two RCTS reported no difference between the plerixafor and placebo groups with respect to adverse events during stem cell mobilization and collection (RR 1.02; 95% CI 0.99 to 1.06; $p=0.19$).⁷

5.2.2 Plerixafor vs. chemo-mobilization

Hospitalization rates due to mobilization-related complications were significantly higher in the chemo-mobilized patients (9%-30%) compared with the plerixafor mobilized patients (0-3%) in all 4 studies that reported them [Table 3]. The most common complication in chemo-mobilized patients was [febrile neutropenia](#), a Grade 3-4 complication according to the Common Terminology for Adverse Events (CTCAE), i.e. one that is medically significant and potentially life threatening necessitating urgent intervention.¹⁷

5.3 Cost impact analyses of plerixafor

Two RCTs and several observational studies have reported that plerixafor is as effective as or superior to G-CSF or cyclophosphamide + G-CSF regimens in mobilizing stem cells, and that plerixafor is associated with significantly lower complication rates in comparison with chemo-mobilization (Table 3). Based on these promising results and given the high cost of plerixafor, several studies have attempted to calculate the cost impact of upfront or pre-emptive plerixafor use, versus standard regimens without plerixafor.

Below, we summarize the results of eight such studies that compare plerixafor with cyclophosphamide, as this is the most relevant comparison for our institution (Table 3).

Plerixafor vs. chemo-mobilization

Upfront plerixafor

- Four studies compared [upfront plerixafor](#) use with [cyclophosphamide](#) (doses ranged from 1.5 to 5gm/m²) [Table 3].⁸⁻¹¹ All but one were conducted in the US and used Medicare reimbursement rates. Studies also differed by type of costs included in the calculations; not all included costs of remobilization and hospitalizations, which could affect the final cost because hospitalizations rates are significantly higher in the chemo group.
- All but one study found that [upfront plerixafor](#) use was more expensive than the [cyclophosphamide](#) regimen (range: -USD1,815 to +USD6,843). Two studies that included remobilization and hospitalization costs, and used Medicare reimbursement rates, reported divergent results: Chaudhary et al. reported an increased cost with upfront plerixafor use of USD 6,843 per patient, while Afifi et al. found a decrease in cost of USD 1,815 per patient.^{8,10} These cost differences could be due to the lower rates of hospitalizations (9%) and remobilizations (8%) in the cyclophosphamide arm of the study by Chaudhary et al. in comparison with rates of hospitalization (12%) and remobilization (18%) in the cyclophosphamide arm reported by Afifi et al. In the latter study, costs of the cyclophosphamide regimen were lower than that of the plerixafor regimen when only drug and procedure costs were accounted for, underscoring the cost impact of high hospitalization and remobilization rates.

Pre-emptive plerixafor

- Three studies compared [pre-emptive plerixafor](#) use with [cyclophosphamide](#) (doses ranged from 2 to 4 gm/m²).¹³⁻¹⁵ All three studies used a different regimen for the pre-emptive arm: one used G-CSF alone before pre-emptive plerixafor was administered in a subset of patients; another used cyclophosphamide, and the third used either G-CSF alone or in combination with cyclophosphamide. Two studies were conducted in the US, and only one included hospitalization costs.
- The studies found that pre-emptive plerixafor use was equivalent to or more expensive than the cyclophosphamide regimen (range: +USD531 to +USD2,747). The study that included mobilization-related hospitalization costs reported that pre-emptive plerixafor use cost USD500 more per patient than the cyclophosphamide regimen,¹⁴ the study that did not include hospitalization costs

found pre-emptive plerixafor to cost USD2,742 more per patient than the cyclophosphamide regimen.¹³

5.3.1 Upfront plerixafor vs. pre-emptive plerixafor

- **Veltri** et al. compared [upfront plerixafor](#) with [pre-emptive plerixafor](#) use (**Table 3**).¹⁶ In the pre-emptive regimen, patients received G-CSF for 5 days, with plerixafor administered only to those at risk of mobilization failure based on a risk-adapted algorithm. This study was conducted in the US, and used Medicare reimbursement rates.
- The study found that the upfront regimen cost USD3,916 more than the pre-emptive regimen. This analysis did not account for remobilization costs, but failure to mobilize rates were similar in both groups (5% vs. 3%). Hospitalization costs were also not included, but as plerixafor is not associated with increased rates of hospitalization relative to G-CSF, exclusion of hospitalization costs would not have a significant impact on the cost analysis.

Summary of results

- Since patients treated with cyclophosphamide have a greater number of hospitalizations and remobilizations in comparison with treatment with plerixafor and G-CSF, failure to factor in these costs would bias costs for the cyclophosphamide arm.
- When comparing upfront plerixafor use with the cyclophosphamide plus G-CSF regimen, the two studies that did account for remobilization and hospitalization costs had conflicting results. One study concluded that upfront use was more expensive by almost USD 7,000 per patient, while a more recent study found that upfront plerixafor use decreased costs by approximately USD 2,000 in their institution when compared with the cyclophosphamide regimen. These cost differences could be due to differences in hospitalization and remobilization rates between the cyclophosphamide arms of the studies. The study that reported a decrease in costs with upfront plerixafor versus the cyclophosphamide regimen, also reported a higher rate of hospitalizations and remobilizations in the cyclophosphamide arm, increasing costs for the cyclophosphamide regimen.
- When comparing pre-emptive plerixafor use with cyclophosphamide, only one study included hospitalization costs, and it found costs of pre-emptive plerixafor to be equivalent to those of cyclophosphamide.

- One study comparing upfront plerixafor use with pre-emptive plerixafor found upfront use to be more expensive.

5.4 Guidelines or HTAs

Our literature search identified two recent health technology assessment documents.

5.4.1 INESSS

A health technology assessment report written by INESSS in 2012 concluded that plerixafor plus G-CSF satisfied the criteria of therapeutic value from a clinical perspective as a stem cell mobilizing agent in NHL and MM patients eligible for stem cell transplantation.¹⁸ Nevertheless, from a pharmacoeconomic perspective, the report concluded that mobilization with [upfront plerixafor](#) was not cost-effective when compared with mobilization with [cyclophosphamide plus G-CSF](#), or with [G-CSF alone](#).

The final INESSS recommendation for plerixafor use is as a pre-emptive mobilizing agent in NHL and MM patients who mobilize poorly following treatment with G-CSF or chemotherapy plus G-CSF, or as a re-mobilizing agent in patients who failed a previous attempt of mobilization with G-CSF or chemotherapy plus G-CSF. Patients must have received at least 4 days of treatment with G-CSF before being administered plerixafor, and may only receive a maximum of 4 doses of plerixafor.

5.4.2 Cancer Care Ontario

In 2015, the **Program in Evidence-Based Care (PEBC) of Cancer Care Ontario (CCO)** reviewed the efficacy of a plerixafor-based mobilization regimen as compared with either a G-CSF-only regimen or a chemotherapy-based regimen. Cost effectiveness was not reviewed in this report.¹⁹

- The main recommendations were to consider upfront use of plerixafor as an option (and not as routine use) when chemotherapy cannot be used and only G-CSF is available for stem cell mobilization.
- Plerixafor is recommended to be added to the mobilization regimens as pre-emptive therapy in poor mobilizers (patients with low pre-apheresis CD34+ cell counts of <10 cells/ μ L), or as salvage therapy after failing to collect an adequate CD34+ amount after the first day of apheresis. In those scenarios, the objective to

add plerixafor to the mobilization regimen is to maximize stem cell collection and avoid the need for remobilization.

- Plerixafor is recommended for use as a re-mobilization agent (with or without chemotherapy) in patients who have failed a previous mobilization attempt.

6. PLERIXAFOR AT THE MUHC

6.1 Current treatment policy

Until recently, patients at the Stem Cell Transplant Program (SCTP) of the MUHC were mobilized using chemotherapy. Patients were administered 2g/m² of cyclophosphamide on day 1, followed by 9 days of G-CSF (10ug/kg) administered subcutaneously in the outpatient setting ([Figure 1B](#)). Apheresis was scheduled to start on day 10, based on peripheral CD34⁺ cell counts of >10 cells/μl.

Since June 2015, the SCTP has adopted a regimen of [upfront plerixafor](#) wherein patients are mobilized with G-CSF (10ug/kg) subcutaneously for 4 days, and administered plerixafor (0.24 mg/kg) on the evening of the 4th day. Apheresis is commenced on the following day, with additional doses of plerixafor and G-CSF, up to a maximum of 4 apheresis days ([Figure 1C](#)).

6.2 MUHC experience with upfront plerixafor use

24 patients have been treated with upfront plerixafor from June to December 2015, and their outcomes were compared with a historical cohort of 20 consecutive patients who underwent chemo-mobilization with cyclophosphamide between October 2014 and October 2015.

64% of patients had multiple myeloma, and the remainder had lymphoma (Hodgkin's disease or NHL). Mobilization outcomes were similar in the two groups: 79% patients in the plerixafor group and 80% in the chemo group achieved the target collection yield, and 96% vs. 94% reached the minimum yield necessary to proceed to transplantation (**Table 4**). The remaining 1 patient in each group did not receive further re-mobilization treatment. The median number of collection days in the upfront plerixafor group was 1 day vs 2 days in the chemo-mobilized group. Patients in the chemo group had a greater proportion of mobilization-related hospitalizations (26%) compared with the plerixafor group (4%).

Table 5 lists the average usage of drugs, outpatient procedures and hospitalization per patient. We can see that the average number of days of hospitalization and the number of ambulatory visits and laboratory tests was greater in the cohort treated with cyclophosphamide. We estimated that the cost per patient under the two regimens was \$1,661 under the cyclophosphamide regimen and \$19,898 under the plerixafor regimen. It should be noted that whereas the cost of G-CSF is not borne by the MUHC, it is borne by the health care system. Taking this additional cost into account, the average cost per patient to the Quebec health care system is \$8,251 for the cyclophosphamide regimen, and \$23,294 for the upfront plerixafor regimen.

The length of mobilization treatment was shorter in the plerixafor group vs the chemo-mobilized group (mean length: 5.8 days vs 12.7 days). The Stem Cell Transplant team reported that use of upfront plerixafor resulted in better predictability in scheduling apheresis sessions in comparison with chemo-mobilization, thus placing a lower burden on resource use (60% of chemo-mobilized patients had to be rescheduled vs. 0% of plerixafor-mobilized patients). The better predictability also enabled the team to schedule 2 collection sessions per week, as opposed to 1 session per week with the chemo-mobilization regimen. They also report a decrease in the wait list for aHSCT as a result of shorter treatment times with plerixafor, the better predictability of scheduling apheresis sessions, the reduced number of collection days, and freeing up of space in the oncology day clinic due to patients no longer needing chemotherapy for mobilization. The number of plerixafor vials dispensed as reported by Pharmacy was on average 2.5 vials per patient compared to an average of 1.9 vials per patient as recorded by the SCTP.

6.3 Cost analysis

Table 6 lists the cost per patient and budget impact for treating 40 patients under three different regimens: (i) upfront plerixafor + G-CSF in all patients (the current regimen at the MUHC); (ii) pre-emptive plerixafor in 10% of patients (poor mobilizers) following an upfront cyclophosphamide + G-CSF regimen in all patients, and (iii) pre-emptive plerixafor in 50% of patients (poor mobilizers) following upfront G-CSF alone in all patients.

The total cost of the upfront plerixafor regimen in 40 patients was estimated to be \$785,871. The estimated total cost was considerably lower under the two regimens where plerixafor was used as a pre-emptive treatment. It was \$143,352 following the regimen that used upfront cyclophosphamide and \$406,320 following the regimen where patients

received only G-CSF upfront. It is interesting to note that under the upfront plerixafor regimen, the cost of plerixafor accounts for 97% of the total cost to the MUHC. Although the cost of G-CSF was not included in our analysis, it was \$134,890 for the upfront plerixafor regimen, and for the pre-emptive plerixafor + G-CSF regimen, and \$247,298 for the pre-emptive plerixafor + cyclophosphamide regimen.

This analysis used the number of plerixafor vials reported by Pharmacy. If the number of vials reported by the SCTP are used instead, the projected cost of the upfront plerixafor regimen would be reduced considerably by \$180,000 to \$603,591. However, it would remain the most expensive regimen.

7. DISCUSSION

7.1 Summary of the effectiveness and safety of plerixafor

Based on the results from two RCTs, plerixafor is more effective than G-CSF in mobilizing sufficient stem cells for multiple myeloma and non-Hodgkin's lymphoma patients to proceed to autologous hematopoietic stem cell transplants. These trials also found plerixafor to be as safe as G-CSF during the mobilization procedure.

No RCTs have been conducted to date comparing plerixafor with cyclophosphamide. Prior to the introduction of plerixafor, cyclophosphamide had been adopted as the preferred regimen by several institutions because of its greater effectiveness in stem cell mobilization relative to G-CSF alone. However, the use of cyclophosphamide has several disadvantages including longer treatment time, lower predictability for scheduling apheresis sessions, and higher rates of adverse events associated with chemotoxicity requiring hospitalization.

Several observational studies have found that plerixafor is as effective as or superior to cyclophosphamide in mobilizing stem cells. Some have argued that [upfront use of plerixafor](#) allows for the same (or higher) effectiveness in stem cell mobilization as cyclophosphamide while avoiding its disadvantages. However, the main obstacle in the universal adoption of plerixafor as first-line treatment has been its high cost.

In an effort to mitigate these high costs, several institutions have developed algorithms wherein plerixafor is only used in patients who mobilize poorly with G-CSF or cyclophosphamide. Four studies that evaluated these [pre-emptive approaches](#) versus [G-CSF](#) or [cyclophosphamide plus G-CSF](#) found them to be effective in achieving the target

stem cell yield. The single study that compared upfront plerixafor use with a pre-emptive regimen wherein all patients received G-CSF, and were only given plerixafor in case of poor mobilization, reported no difference in mobilization failure rates, in the number of patients achieving the minimum target yield, and in the number of apheresis sessions between the two groups.

7.2 Cost impact of plerixafor

Several studies have evaluated the cost impact of plerixafor relative to other mobilization regimens. The variability in institution-specific costs considered in each analysis (e.g. hospitalization costs, re-mobilization costs) reduce the ability to compare results across these studies. In general, most studies found upfront plerixafor to be more expensive than other mobilization regimens.

7.3 Feasibility of using an upfront plerixafor regimen at the MUHC

Several studies and our own analysis of local data suggest that plerixafor is more expensive than other mobilization regimens. A potential solution that would ensure high mobilization rates while keeping costs low is a risk-adapted approach, where all patients are mobilized with G-CSF or G-CSF and cyclophosphamide upfront, and only the subset of poor mobilizers receive plerixafor. Our projected total cost for treating 40 patients with a pre-emptive plerixafor regimen was \$406,320 when patients received G-CSF alone upfront (assuming 50% poor mobilizers) vs. \$143,352 when patients received G-CSF and cyclophosphamide upfront (10% poor mobilizers). In comparison, the estimated total cost of an upfront plerixafor regimen was \$785,871.

The use of cyclophosphamide within a pre-emptive plerixafor regimen has several disadvantages, including the higher risk of adverse events arising from chemo-toxicity, and the longer treatment duration. Although the use of G-CSF in a pre-emptive plerixafor regimen would have none of these disadvantages, the lower mobilization rates of G-CSF would result in more frequent use of plerixafor, thus raising costs. Under a pre-emptive plerixafor regimen, apheresis could be scheduled in a predictable fashion, e.g. on day 5 following G-CSF administration or day 10 following G-CSF with cyclophosphamide. Thus, to adapt the current upfront plerixafor regimen in use at the MUHC to a pre-emptive plerixafor regimen, an additional blood test would be required on a pre-scheduled day, prior to the start of apheresis, to assess the potential mobilization failure.

8. CONCLUSIONS

- Plerixafor is a novel mobilization agent that has considerable advantages over the alternatives. It is more effective than either G-CSF alone or cyclophosphamide plus G-CSF in mobilizing sufficient stem cells for transplantation, and it is not associated with the severe complications and unpredictability of cyclophosphamide mobilization.
- The main disadvantage of plerixafor is its high cost. Published studies and an evaluation of our local MUHC experience have found upfront plerixafor regimens to be more expensive than other mobilization regimens, mainly due to the high cost of the drug.
- In order to mitigate these high costs, some institutions have developed risk-adapted algorithms for the use of plerixafor only in those patients at risk of poor mobilization. Studies that evaluated such pre-emptive plerixafor regimens versus G-CSF only or cyclophosphamide plus G-CSF have reported good mobilization rates.
- Furthermore, our analysis of local data found that projected costs associated with pre-emptive plerixafor regimens using either G-CSF alone, or cyclophosphamide plus G-CSF, were considerably lower than that of an upfront plerixafor mobilization regimen, making the adoption of such regimens a more attractive option at the MUHC.

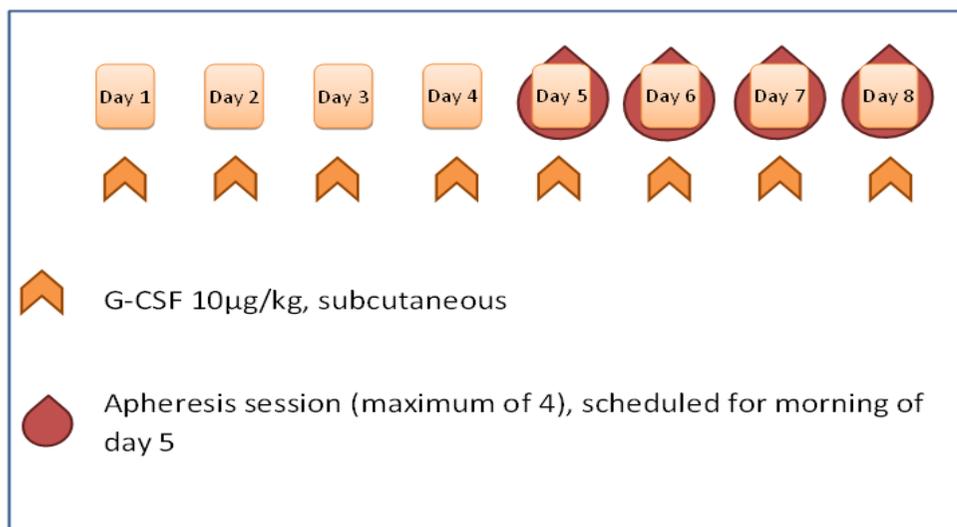
9. RECOMMENDATIONS

- Given the superiority of plerixafor over other regimens in mobilizing stem cells, we recommend:
 - [Approval](#) of a pre-emptive plerixafor regimen wherein all patients are mobilized with G-CSF, and only the subset of poor mobilizers receive plerixafor. This regimen is not associated with the severe complications and unpredictability of chemo-mobilization, but may result in higher costs due to more frequent use of plerixafor needed to salvage poor mobilizers.
 - [Approval](#) of a pre-emptive plerixafor regimen wherein all patients are mobilized with cyclophosphamide + G-CSF, and only the subset of poor mobilizers receive plerixafor. This regimen is associated with a greater risk

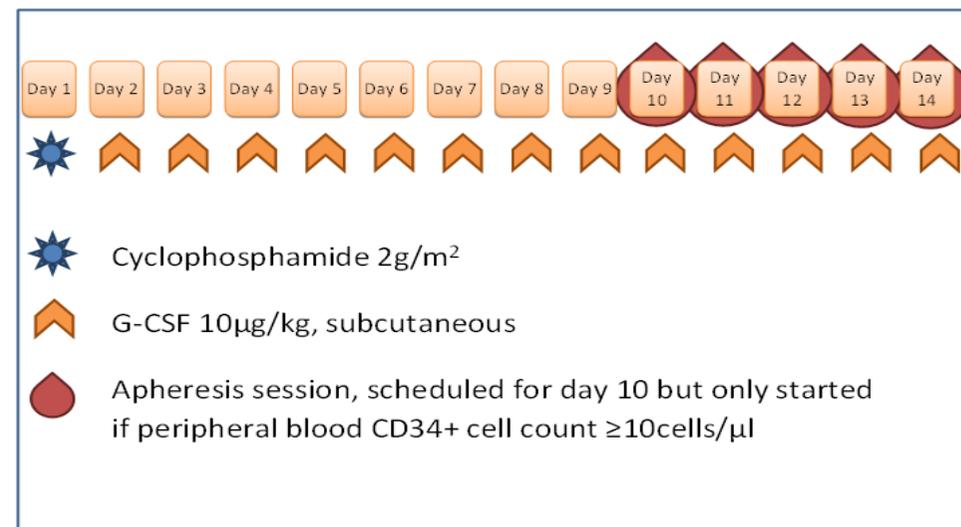
of complications, but may result in lower costs due to the higher mobilization rates of cyclophosphamide versus G-CSF alone.

- [Non-approval](#) of routine use of upfront plerixafor as first-line treatment in NHL and MM patients undergoing autologous stem cell transplantation, due to the high costs associated with upfront plerixafor use. This recommendation may be re-evaluated in light of new evidence, or a drop in the drug price of plerixafor.
- We recommend that the Stem Cell Transplant Program develop a protocol for the choice of which pre-emptive plerixafor regimen is best suited to which patient.
- We recommend that the Stem Cell Transplant Program continue to systematically document treatment regimens, complications, and outcomes in patients mobilized from autologous stem cell transplants to allow for retrospective evaluation of the time to mobilization and the percentage of patients requiring plerixafor.
- We recommend that appropriate measures be undertaken to resolve discrepancies in the number of plerixafor vials dispensed by the department of Pharmacy and reported number used by the Stem Cell Transplant Program.
- Given that an ancillary benefit of upfront plerixafor use is a reduction in the wait list for stem cell collection, there is a need to evaluate the current infrastructure (number of apheresis beds, access to apheresis facilities) at the MUHC such that the non-use of upfront plerixafor does not hinder timely access to care for stem cell transplant patients.

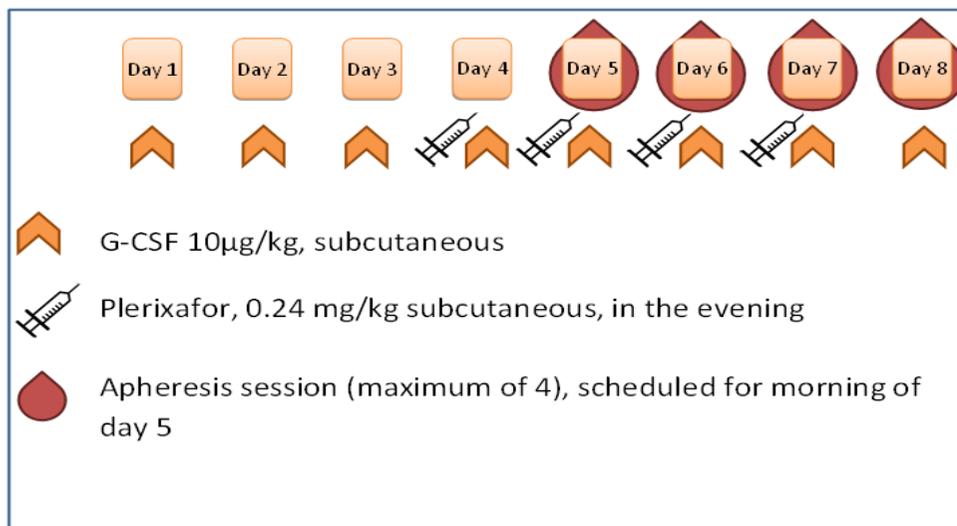
FIGURES



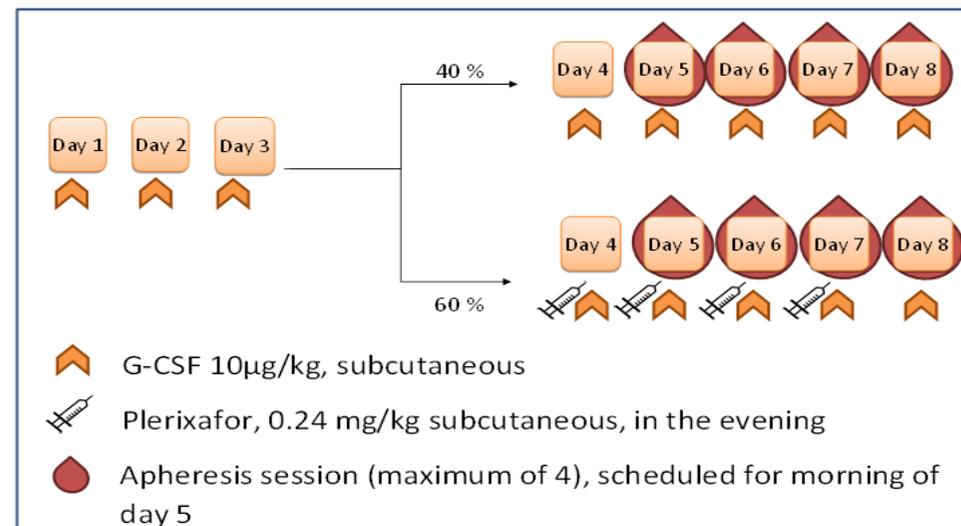
A. Regimen with G-CSF alone



B. Regimen with Cyclophosphamide + G-CSF



C. Regimen with Upfront Plerixafor



D. Regimen with Pre-emptive Plerixafor

Figure 1. Different mobilization regimens for stem cell transplant patients

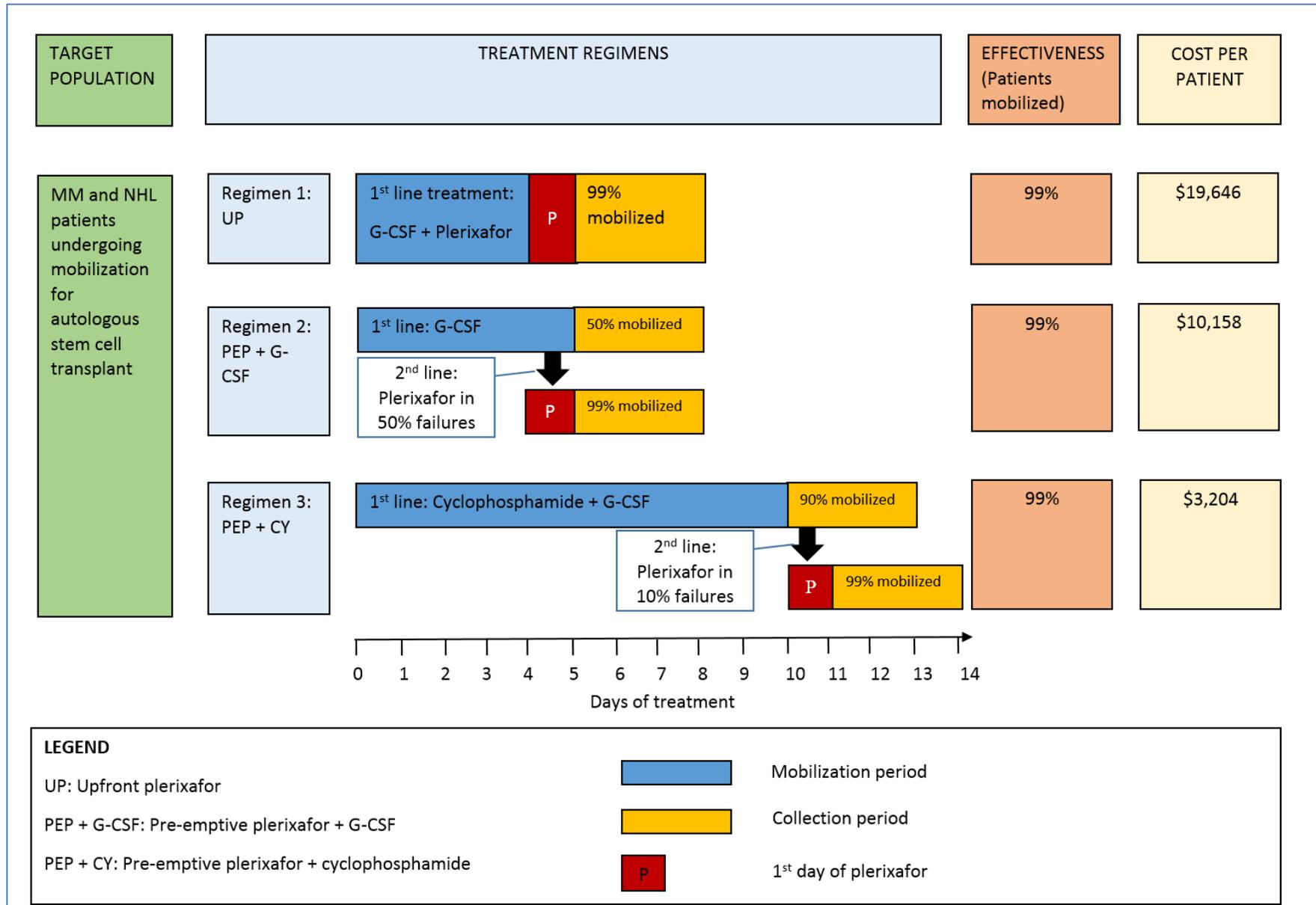


Figure 2. Cost-minimization analysis schematic

18 TABLES

Table 1: Comparison of the three common stem cell mobilization regimens

Mobilization regimen	Advantages	Disadvantages
Cytokine alone	<ul style="list-style-type: none"> • Outpatient administration • Predictable mobilization, permitting ease of scheduling apheresis sessions • Shorter time from administration to collection (~4 days) • Few severe adverse events due to low toxicity 	<ul style="list-style-type: none"> • Lower stem cell yield
Chemo + cytokines	<ul style="list-style-type: none"> • Higher stem cell yield vs. cytokine alone • Requires fewer collection sessions than cytokine alone 	<ul style="list-style-type: none"> • Less predictable mobilization, causing higher burden on resource use • Longer time from administration to collection (~10 days) • Severe complications (febrile neutropenia requiring hospitalization) due to toxicity • May impair future mobilization attempts
Plerixafor	<ul style="list-style-type: none"> • Outpatient administration • Higher yield requiring fewer apheresis sessions • Predictable mobilization, permitting ease of scheduling apheresis sessions • Shorter time from administration to collection (~4 days) • Few severe adverse events due to low toxicity 	<ul style="list-style-type: none"> • High cost of drug

Table 2. Randomized controlled trials assessing the effectiveness of upfront use of plerixafor for stem cell mobilization in multiple myeloma and non-Hodgkin's lymphoma patients

Study (design)	Patient population	Groups	N	Target CD34 ⁺ yield (cells/kg)	Patients collecting target yield N (%)	Failed to sufficiently mobilize **N (%)	Median no. of apheresis days to achieve target yield (range)
DiPersio 2009 (RCT) ⁶	MM	G-CSF + placebo	154	6x10 ⁶	52 (34)	18 (12)	4
		G-CSF + plerixafor (0.24 mg/kg)	148	6x10 ⁶	106 (72)	7 (5)	1
DiPersio 2009 (RCT) ⁵	NHL	G-CSF + placebo	148	5x10 ⁶	30 (20)	78 (53)	Only 24% had reached target after 4 days
		G-CSF + plerixafor (0.24 mg/kg)	150	5x10 ⁶	89 (59)	20 (13)	3

** Failed to achieve 2x10⁶ cells/kg within 4 days of apheresis

Table 3: Observational studies assessing the effectiveness, safety, and cost of regimens comparing upfront or pre-emptive plerixafor to other mobilization regimens

Study (design)	Country	Groups	N	Target CD34 ⁺ yield (cells/kg)	Patients collecting target yield N (%)	Failed to proceed to transplant (<2 x10 ⁶ cells/kg) N (%)	Median apheresis days	No. of hospitalizations	Costs included in analysis	Cost per patient	Difference (Plerixafor vs other)
UPFRONT PLERIXAFOR[‡]											
Afifi 2016		CY (3 gm/m ²) + G-CSF	111		92 (83)	20 (18)	2.3*	13 (12)	Drugs Procedure costs	Institution cost: \$72,138	
	US	Upfront Plerixafor +G-CSF	112	5 x10 ⁶	105 (94)*	5 (4)	2.6* (Mean)	0	Hospitalization costs Remobilization costs	Medicare: \$22,959 Institution cost: \$52,200 Medicare: \$21,144	-1,815
Shaughnessy 2011		CY (3-5g/m ²) + G-CSF	33		25 (76)	0 [†]	1	19 (53)	Drugs Procedure costs	\$19,173	
	US	Upfront Plerixafor +G-CSF	33	MM: 6x10 ⁶ NHL: 5x10 ⁶	31 (94)*	0 [†]	1	0	Hospitalization costs	\$20,298	+1,125

Table continued on next page

Study (design)	Country	Groups	N	Target CD34 ⁺ yield (cells/kg)	Patients collecting target yield N (%)	Failed to proceed to transplant (<2 x10 ⁶ cells/kg) N (%)	Median apheresis days	No. of hospitalizations	Costs included in analysis	Cost per patient	Difference (Plerixafor vs other)
UPFRONT PLERIXAFOR CONTINUED											
Martin 2015	UK	CY + G-CSF	140	4x10 ⁶	78 (56)	24 (17)	NR		Drugs	£11,182	
		Upfront Plerixafor + G-CSF	98		71 (72)	4 (4)	NR	NR	Procedure costs		
									Remobilization costs	£12,679	+1,497
Chaudhary 2013	US	CY (1.5 gm/m ²) + G-CSF	74	5-10x10 ⁶	51 (69)	6 (8)	2	7 (9)	Drugs	\$22,137	
		Upfront Plerixafor +G-CSF	33		31 (94)	0 (0)	2	1 (3)	Procedure costs		
									Hospitalization costs	\$28,980	+6,843
									Remobilization costs		
Kim 2014	US	G-CSF	25	5-10 x10 ⁶	19 (76)	6 (24)	3	NR	Drugs	\$105,279	
		Upfront Plerixafor + G-CSF	25		23 (92)	2 (8)	2	NR	Procedure costs		
										\$119,371	14,092

Table continued on next page

Study (design)	Country	Groups	N	Target CD34 ⁺ yield (cells/kg)	Patients collecting target yield N (%)	Failed to proceed to transplant (<2 x10 ⁶ cells/kg) N (%)	Median apheresis days	No. of hospitalizations	Costs included in analysis	Cost per patient	Difference (Plerixafor vs other)
PRE-EMPTIVE PLERIXAFOR											
Micallef 2013	US	G-CSF (10% received chemo)	278	4x10 ⁶	201 (72)*	52 (19)	2	NR	Drug costs	\$17,150	+3,467
		Pre-emptive Plerixafor (2% chemo)+ G-CSF	98 [59% required P]	4x10 ⁶	91 (93)	1 (1)	1	NR	Equipment costs Remobilization costs	\$20,617	
Li 2011 (retrospective)	US	G-CSF or chemo + G-CSF (49%)	148	Lymphoma : 5 x10 ⁶ MM: 10 x10 ⁶	90 (61)	10 (7)	NR	NR	Only drug and procedure costs after starting apheresis	\$16,234	+2,747
		Pre-emptive Plerixafor + G-CSF or chemo+G-CSF (38%)	188 [36% required P]		120 (64)	5 (2)	NR	NR		\$18,981	
Costa 2011	US	CY (2 gm/m ²) + G-CSF	81	3 x10 ⁶	62 (78)	18 (23)	1	24 (30)	Drugs	\$22,885	+531
		Pre-emptive Plerixafor + G-CSF	50 [66% required P]		47 (94)	1(2)	1	1(2)	Physician and equipment costs Hospitalization costs	\$23,416	

Study (design)	Country	Groups	N	Target CD34 ⁺ yield (cells/kg)	Patients collecting target yield N (%)	Failed to proceed to transplant (<2 x10 ⁶ cells/kg) N (%)	Median apheresis days	No. of hospitalizations	Costs included in analysis	Cost per patient	Difference (Plerixafor vs other)
PRE-EMPTIVE PLERIXAFOR CONTINUED											
Milone 2013	Europe	CY (4 gm/m ²) + G-CSF	228	Lymphoma : 3 x10 ⁶ MM: 4 x10 ⁶	NR	40 (17)	1.6 (mean)	NR	Drugs Remobilization costs	€4656	-412
		Pre-emptive Plerixafor + CY + G-CSF	102 (14% required P)		82 (80)	4 (4)	1.4 (mean)	NR	€4244		
Veltri 2015	US	Upfront Plerixafor + G-CSF	76	Lymphoma : 5 x10 ⁶ MM: 10 x10 ⁶	NR	4 (5)	2	0	Drugs Procedure costs	\$27,513	+3,917
		Pre-emptive Plerixafor + G-CSF	60 (60% required P)		NR	2(3)	2	0	\$23,597		

* Significant difference

† This study only included patients who proceeded to transplant.

‡ Plerixafor dose in all studies was 0.24 mg/kg.

Table 4: Outcomes in patients treated with upfront plerixafor versus a historical cohort of chemo-mobilized patients at the MUHC

Outcomes	Regimen 1: Cyclophosphamide (October 2014-2015) N=20	Regimen 2: Upfront plerixafor (June 2015 – December 2015) N= 24
No. of days of G-CSF treatment, median (range)	11 (9-15)	5 (5-7)
No. of days of plerixafor treatment, median (range)	NA	1 (1-4)
No. of apheresis days, median (range)	2 (1-3)	1 (1-4)
CD34+cells/kg collected, median (range)	8.0 (3.6-26.3)	7.9 (0.11-11.9)
Reached target yield, % (N)	80 % (16)	79% (19)
Achieved minimum number of stem cells to proceed to transplant, % (N)	95% (19)	96% (23)
Proceeded to transplant, % (N)	85% (17)	88% (21)
Neutrophil engraftment among those who proceeded to transplant, % (N)	100 % (17)	100% (21)
Collection efficiency (% yield)	113	105
Adverse events related to mobilization regimen, % (N)	26% (5)	25% (6)
Grade 3-4 adverse events, % (N)	26% (5)	4% (1)
Hospitalizations related to mobilization regimen, % (N)	26% (5)	4% (1)

Table 5: Cost analysis comparing the average use of resources and costs in two cohorts treated at the MUHC

Drugs	Regimen 1: Cyclophosphamide (October 2014-2015) (20 patients)		Regimen 2: Upfront plerixafor (June 2015 – December 2015) (24 patients)			
	Average use	Cost	Including wastage ^a		Excluding wastage ^b	
			Average use	Cost	Average use	Cost
Cyclophosphamide	2.9 vials for 1 day	\$3,662.12 ^c				
Plerixafor		\$0	2.5 vials	\$463,295.00	1.9 vials	\$356,965.00
G-CSF	2.1 vials for 11.2 days	\$0 ^d	2.1 vials for 5.7 days	\$0 ^d	2.1 vials for 5.7 days	\$0 ^d
MESNA	5.8 vials	3,739.32 ^c				
Procedures						
Cyclophosphamide administration	1 day	\$5,847.80				
Apheresis sessions	1.9 days	\$8,325.00	1.8 days	\$9,675.00	1.8 days	\$9,675.00
Lab tests	4.2 tests	\$413.34	1.8 tests	\$214.14	1.8 tests	\$214.14
Ambulatory costs	7.0 visits	\$4,900.00	3.8 visits	\$3,185.00	3.8 visits	\$3,185.00
Hospitalization	3.2 days	\$6,326.56	1.0 days	\$1,186.23	1.0 days	\$1,186.23
Total		\$33,214.14		\$477,555.37		\$371,225.37
Cost per patient		\$1,660.71		\$19,898.14		\$15,467.72

^a Costs calculated using number of plerixafor vials per patient dispensed by Pharmacy.

^b Costs calculated using number of plerixafor vials used per patient reported by the Stem Cell Transplant Program.

^c 3 patients received a type of chemotherapy other than cyclophosphamide. We assumed the cost of these regimens was the same as that of cyclophosphamide.

^d Cost of G-CSF (\$131,798.34 for the cyclophosphamide regimen, and \$81,495.80 for the upfront plerixafor regimen) is not assumed by the MUHC

Table 6. Cost analysis comparing total cost of treating 40 patients with three different regimens

	Unit cost	Scenario 1: Pre-emptive plerixafor – upfront cyclophosphamide			Scenario 2: Upfront plerixafor			Scenario 3: Pre-emptive plerixafor – upfront G-CSF alone		
		Resource use	No. of patients	Cost	Resource use	No. of patients	Cost	Resource use	No. of patients	Cost
	a	b	c	a x b x c	e	f	a x e x f	g	h	a x g x h
Drug costs										
Cyclophosphamide	\$63.14/vial	3 vials for 1 day	40	\$7,576.80						
Plerixafor	\$7595.00/vial	2.5 vials	4	\$75,950.00	2.5 vials	40	\$759,500.00	2.5 vials	20	\$379,750.00
G-CSF	\$281.02/ vial	2 vials for 11 days	40	\$0.00	2 vials for 6 days	40	\$0.00	2 vials for 6 days	40	\$0.00
MESNA	\$31.96/vial	6 vials	40	\$7,670.40			\$0.00			\$0.00
Procedure costs										
Cyclophosphamide administration	\$292.39/patient day	1 day	40	\$11,695.60			\$0.00			\$0.00
Apheresis sessions	\$225.00/patient day	2 days	40	\$18,000.00	2 days	40	\$18,000.00	2 days	40	\$18,000.00
Lab tests	\$4.98/test	4 tests	40	\$796.80	2 tests	40	\$398.40	3 tests	40	\$597.60
Ambulatory costs	\$35.00/visit	7.0 visits	40	\$9,800.00	4 visits	40	\$5,600.00	4 visits	40	\$5,600.00
Hospitalization costs	\$395.41/ day	3 days	10	\$11,862.30	1 days	6	\$2,372.46	1 days	6	\$2,372.46
Total cost				\$143,351.90			\$785,870.86			\$406,320.06
Cost per patient				\$3,583.80			\$19,646.77			\$10,158.00

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APPENDICES

APPENDIX A: RISK OF BIAS ASSESSMENT

Table A-1: Cochrane assessment of bias of the two randomized trials of plerixafor

Judgement	DiPersio et al (MM)	DiPersio et al (NHL)
Selection bias		
Random sequence generation		
Allocation concealment		
Performance bias		
Blinding of participants and personnel		
Detection bias		
Blinding of outcome assessment		
Attrition bias		
Incomplete outcome data addressed		
Funding source	Genzyme Corporation	Genzyme Corporation
Low risk High risk Unclear (not reported) risk of bias		

APPENDIX B: GLOSSARY OF TERMS

Autologous stem cell transplant process

Mobilization: Patients eligible for autologous stem cell transplant undergo mobilization with either (i) cytokine (G-CSF or GM-CSF) alone; (ii) chemotherapy and cytokine; or (iii) plerixafor and cytokine or chemotherapy. White blood cell and CD34+ cell counts are monitored to determine the appropriate time to start apheresis. Most protocols require a CD34+ cell count threshold of between 5-20 cells/ μ l before initiating apheresis.

Apheresis: Apheresis is the process to collect stem cells that have been mobilized into the peripheral blood. In regimens not requiring chemotherapy, apheresis may start as early as 4 days after administration of the mobilization agent. If chemotherapy is used, apheresis is started 10-12 days after mobilization initiation. Patients are connected to an apheresis machine which separates the stem cells from the rest of the blood, which is returned to the patient. Each apheresis session lasts 2-5 hours, during which 6 times the average blood volume may be processed. Most institutions process 3 blood volumes per session. Patients may require up to 4 apheresis sessions to reach the target stem cell collection. Apheresis is generally a safe procedure, but is associated with some adverse events including citrate toxicity, thrombocytopenia, hypovolemia, catheter malfunction, and infection.

Conditioning chemotherapy: After harvesting of stem cells, patients are treated with additional chemotherapy, for e.g. with melphalan, to ensure all diseased cells are destroyed before undergoing transplantation.

Transplantation: Successful engraftment is measured by rising counts of neutrophils and platelets, 2 to 4 weeks after transplantation.

CD34+

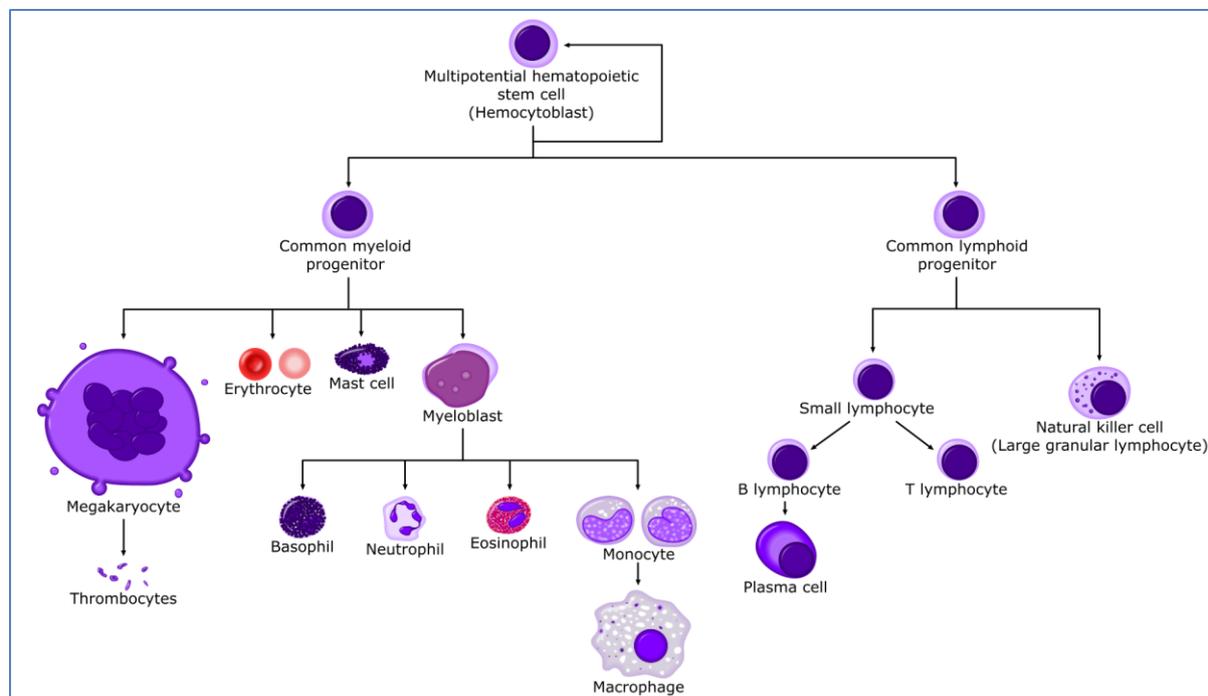
A cell surface marker antigen expressed by stem cells, and is used as an indicator of stem cell collection yields.

Febrile neutropenia

Febrile neutropenia is defined as the development of a fever (an oral temperature $>38.5^{\circ}\text{C}$) in patients with an abnormally low neutrophil count ($<0.5 \times 10^9/\text{l}$). It remains a major complication of chemotherapy. It is generally treated with antibiotics until the neutrophil count has recovered and the fever has subsided. Prognosis is worse in the elderly or patients with proven bacteremia (bacteria in the blood stream).

Hematopoietic stem cells

All blood cells are derived from progenitor cells known as hematopoietic stem cells. These cells are pluripotent because they have the ability to differentiate into all the different types of blood cells.



Appendix Figure 1. Differentiation of hematopoietic stem cells into blood cells

Image from Wikipedia https://en.wikipedia.org/wiki/Hematopoietic_stem_cell

Lymphoma

Lymphomas, such as Hodgkin's lymphoma and Non-Hodgkin's lymphoma, are hematopoietic neoplasms (blood cell tumours), affecting lymphocytes, which are derived from hematopoietic stem cells. 90% of lymphomas are non-Hodgkin's lymphoma.²⁰ Other types of lymphoma include diffuse large B-cell lymphoma (DLBL), mantle cell lymphoma (MCL), and follicular lymphoma (FL).

Treatment: Depending on the subtype and stage, NHL may be treated with a variety of options: radiation therapy, chemotherapy, targeted therapy, antibiotic therapy, plasmapheresis, surgery, and stem cell transplant. aHSCT is the recommended approach in patients with relapsed or refractory disease.

Multiple myeloma

A hematopoietic neoplasm, affecting blood cells arising in the bone marrow known as plasma cells. Plasma cells are matured B cells, a type of lymphocyte derived from the hematopoietic stem cell precursors. Myeloma results in extensive bone lesions. Most

patients have multi-focal disease (known as multiple myeloma), which has poor prognosis.²¹

Treatment: Patients <65 years are considered eligible for aHSCT, and approximately 50% of MM patients may be eligible. Transplant-eligible patients undergo induction chemotherapy with lenalidomide, thalidomide, bortezomib or a combination of these drugs along with dexamethasone. Following 3-4 months of induction therapy, stem cells are mobilized for harvest using cytokine- or chemo-based mobilization regimens. MM patients usually collect enough stem cells for two transplants (tandem transplant). Those patients without complete response or very good partial response after transplantation undergo a second transplantation. aHSCT is not curative, but may prolong progression-free survival and overall survival. Patients are stratified into standard, intermediate, or high risk. Patients with standard risk have a median overall survival of 6-7 years, while those with high risk MM have a median survival of 2-3 years, even after treatment with tandem aHSCT.²¹

Plerixafor

Plerixafor is an antagonist of the chemokine receptor CXCR4, expressed by stem cells and which anchors them to the bone marrow stroma.²² By blocking this receptor, plerixafor accelerates the release of stem cells from the bone marrow into the peripheral blood.