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PRACTICE GUIDELINE

Plerixafor for autologous stem-cell mobilization and transplantation for patients in Ontario

C.T. Kouroukis MD MSc,* N.P. Varela PhD,† C. Bredeson MD MSc,‡ J. Kuruvilla MD,§ and A. Xenocostas MD||

ABSTRACT

Background High-dose chemotherapy with autologous stem-cell transplantation (ASCT) is an accepted part of standard therapy for patients with hematologic malignancies. Usually, stem-cell mobilization uses granulocyte colony–stimulating factor (G-CSF); however, some patients are not able to be mobilized with chemotherapy and G-CSF, and such patients could be at higher risk of failing mobilization. Plerixafor is a novel mobilization agent that is absorbed quickly after subcutaneous injection and, at the recommended dose of 0.24 mg/kg, provides a sustained increase in circulating CD34+ cells for 10–18 hours. The main purpose of the present report was to evaluate the most current evidence on the efficacy of plerixafor in enhancing hematopoietic stem-cell mobilization and collection before ASCT for patients in Ontario so as to make recommendations for clinical practice and to assist Cancer Care Ontario in decision-making with respect to this intervention.

Methods The MEDLINE and EMBASE databases were systematically searched for evidence from January 1996 to March 2015, and the best available evidence was used to draft recommendations relevant to the efficacy of plerixafor in enhancing hematopoietic stem-cell mobilization and collection before ASCT. Final approval of this practice guideline report was obtained from both the Stem Cell Transplant Steering Committee and the Report Approval Panel of the Program in Evidence-Based Care.

Recommendations These recommendations apply to adult patients considered for ASCT:

- Adding plerixafor to G-CSF is an option for initial mobilization in patients with non-Hodgkin lymphoma or multiple myeloma who are eligible for ASCT when chemotherapy cannot be used and only G-CSF mobilization is available.
- For patients with a low peripheral blood CD34+ cell count (for example, <10/μL) at the time of anticipated stem-cell harvesting, or with an inadequate first-day apheresis collection, it is recommended that plerixafor be added to the mobilization regimen to maximize stem-cell collection and to prevent the need for remobilization.
- It is recommended that patients who have failed a previous mobilization attempt undergo remobilization with G-CSF and plerixafor, with or without chemotherapy.

Key Words Plerixafor, autologous stem-cell transplantation, mobilization, remobilization, collection, Hodgkin lymphoma, non-Hodgkin lymphoma, CD34+ cell count

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BACKGROUND

High-dose chemotherapy with autologous stem-cell transplantation (ASCT) is an accepted part of standard therapy for a variety of hematologic malignancies, including non-Hodgkin (NHL) and Hodgkin lymphoma (HL), multiple myeloma (MM), and germ-cell tumours. The benefits of transplantation include improvement in disease control and can include an improved overall survival rate. In some situations, ASCT is potentially curative.

A necessary step in the process of treating patients with high-dose chemotherapy is the ability to mobilize, collect, and cryopreserve autologous stem cells. Although a variety of protocols are available, stem-cell mobilization is usually performed using granulocyte colony–stimulating factor (G-CSF), often with the addition of chemotherapy (for

Correspondence to: Norma P. Varela, Cancer Care Ontario, Program in Evidence-Based Care, 60(G) Wing, 2nd Floor, McMaster University, Henderson Site, 711 Concession Street, Hamilton, Ontario L8S 4L8.
E-mail: Varela@mcmaster.ca **DOI:** http://dx.doi.org/10.3747/co.23.3137

example, high-dose cyclophosphamide). In some clinical scenarios, patients are not able to undergo mobilization with chemotherapy and G-CSF, and such patients can be at higher risk of failing mobilization. Other risk factors for failing mobilization include prior treatment with multiple lines of chemotherapy or purine analogues, radiation to bone marrow–containing areas, and patient age; however, those factors remain poorly defined for the most part and largely consensus-driven[1].

Plerixafor is a novel mobilization agent and a bicyclam derivative that binds with high affinity to the human C-X-C chemokine receptor type 4 receptor and disrupts interactions with its cognate ligand stromal cell–derived factor 1α. Interruption of that receptor–ligand interaction results in mobilization of CD34+ hematopoietic stem cells to the peripheral blood, where they can be collected via apheresis. Plerixafor is absorbed quickly after a subcutaneous injection and, at the recommended dose of 0.24 mg/kg, provides a sustained increase in circulating CD34+ cells for 10–18 hours. Dose adjustments are not needed for patients with hepatic or renal insufficiency, and in general, the agent is well tolerated. In December 2011, Health Canada approval was granted for the use of plerixafor with G-CSF in stem-cell mobilization for patients with NHL or myeloma. In Ontario, plerixafor is currently covered for use with G-CSF in patients with NHL or myeloma who have suboptimal peripheral blood CD34+ cell counts after at least 4 days of G-CSF (CD34+ count < 10/μL), or who have less than half the required CD34+ cells after 1 apheresis procedure, or who have failed a previous apheresis attempt.

To make recommendations for clinical practice and to assist Cancer Care Ontario in decision-making with respect to intervention with plerixafor, the Working Group of the Stem Cell Transplant Steering Committee developed the present recommendation report. Based on the objectives of the guideline, the members of the Working Group derived the research questions as outlined later in the report.

METHODS

This recommendation report, produced by the Program in Evidence-Based Care (PEBC) and approved by the Stem Cell Transplant Steering Committee of Cancer Care Ontario, was developed through a systematic review of the available evidence using the methods of the practice guidelines development cycle[2,3]. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

This evidence review was conducted in 3 planned stages, including a search for existing guidelines followed by a search for systematic reviews and primary literature.

Literature Search Strategy

Before any search for systematic reviews or primary literature, an electronic search for existing guidelines concerning the efficacy of plerixafor was conducted using the electronic databases MEDLINE (Ovid) and EMBASE (Ovid) and the Standards and Guidelines Evidence (SAGE) directory of cancer guidelines. The goal was to identify existing guidelines for adaptation or endorsement so as to avoid duplication of guideline development efforts across jurisdictions. Only guidelines published in English and after 2010 were considered and evaluated for quality using the AGREE II instrument[4]. In addition, the Cochrane Database of Systematic Reviews and the MEDLINE (Ovid) and EMBASE (Ovid) databases were searched from January 2009 to April 2014. Any systematic reviews identified were assessed for quality using AMSTAR[5]; the results of the AMSTAR assessment were used to determine the inclusion of existing systematic reviews as part of the evidence base.

Assuming that no existing guidelines or systematic reviews were identified, a systematic review of the primary literature was also planned. If a suitable guideline or systematic review had been found, a systematic review of the primary literature would be conducted from the date of the reported search, solely to update the evidence from the existing guidelines or systematic reviews.

In April 2014, the MEDLINE (Ovid; 1996 through 18 April 2014) and EMBASE (Ovid; 1996 through Week 16, 2014) databases were searched for primary literature; the search was updated in March 2015. The search strategy included a logical combination of terms for the condition (stem-cell transplantation), the intervention (plerixafor), and studies of interest (systematic reviews, clinical trials, nonrandomized studies with an appropriate control group). Relevant articles were reviewed by 2 reviewers (CTK, NPV), and the reference lists from those sources were searched for additional trials. A data audit procedure was conducted by an independent individual (Kristy Yiu) to verify the accuracy of the information obtained from the included studies.

RESULTS

Literature Search

Twenty-two studies assessing the efficacy and safety of plerixafor for autologous stem-cell mobilization and transplantation were retained: two randomized controlled trials (RCTs)[6,7], five nonrandomized controlled trials[8–12], three retrospective cohort studies with a contemporaneous control arm[13–15], and twelve single- arm studies[16–27].

Quality was assessed according to the criteria described in the Methods section. Table I provides details about patient selection criteria, peripheral blood stem-cell mobilization regimen, sample size, and reported outcomes.

The two RCTs reported by DiPersio *et al.*[6,7] were phase III, multicentre, double-blind trials with random allocation schemes and involved patients with NHL or MM. In the lymphoma study[6], patients were randomized 1:1, but other details were not reported. In the myeloma study[7], patients were stratified by study centre, baseline platelet count, and type of transplantation planned.

The five nonrandomized controlled trials[8–12] included fully described the inclusion and exclusion criteria, mobilization protocol, and outcomes of interest. Four of the studies compared outcomes with matched historical controls mobilized using a therapy that did not include plerixafor[8,9,11,12].

The twelve single-arm trials[16–27] were included in the review to inform recommendations both for patients failing mobilization before ASCT and for patients failing a prior mobilization attempt. In all those studies, the patients were fully described and were representative of

TABLE I Summary of the studies assessing efficacy of plerixafor in enhancing hematopoietic stem-cell mobilization and collection before autologous stem-cell transplantation (ASCT)

Reference (study years)	Treatment allocation	Pts (*n*)	Population	Peripheral blood stem-cell mobilization regimen	Outcome reported
Randomized controlled trials					
DiPersio *et al.*, 2009[6] (Jan 2005–Aug 2006)	G-CSF plus plerixafor	150	NHL	Before the 1st day of apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Plerixafor 240 μg/kg PM, day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis After 1st day of apheresis (day 5→): ■ Plerixafor (PM), G-CSF (AM), and apheresis daily for up to 3 days or until ≥5×10⁶/kg CD34+ cells collected	Successful mobilization criterion: ≥2×10⁶/kg CD34+ cells Patients not mobilized before: successful apheresis (primary and secondary endpoint of ≥5×10⁶/kg CD34+ cells and ≥2×10⁶/kg CD34+ cells respectively), number of apheresis days, CD34+ cell collection, ASCT, 12-month post-SCT survival rate Patients who failed prior mobilization regimen: successful apheresis (primary and secondary endpoint of ≥5×10⁶/kg CD34+ cells and ≥2×10⁶/kg CD34+ cells respectively), apheresis days, ASCT, 12-month post-SCT survival rate
	G-CSF plus placebo	148		Before 1st day of apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Placebo, day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis After 1st day of apheresis (day 5→): ■ Placebo, G-CSF, and apheresis daily for up to 3 days or until ≥5×10⁶/kg CD34+ cells collected	
DiPersio *et al.*, 2009[7] (Feb 2005–Jul 2006)	G-CSF plus plerixafor	148	MM	Pre-apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Plerixafor 240 μg/kg PM on day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis Post-apheresis (day 5→): ■ Plerixafor (PM), G-CSF (AM), and apheresis daily for up to 3 days or until ≥6×10⁶/kg CD34+ cells collected	Successful mobilization criterion: ≥2×10⁶/kg CD34+ cells Patients not mobilized before: successful apheresis, apheresis days, CD34+ cell collection, ASCT, 12-month post-SCT survival rate Patients who failed prior mobilization regimen: successful apheresis, apheresis days, ASCT, 12-month post-SCT survival rate
	G-CSF plus placebo	154		Before 1st day of apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Placebo on day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis After 1st day of apheresis (day 5→): ■ Placebo, G-CSF, and apheresis daily for up to 3 days or until ≥6×10⁶/kg CD34+ cells collected	

TABLE I Continued

Reference (study years)	Treatment allocation	Pts (*n*)	Population	Peripheral blood stem-cell mobilization regimen	Outcome reported
Nonrandomized trials, historical control group					
Cashen *et al.*, 2008[8] (1998–2003)	G-CSF plus plerixafor	22	Relapsed or refractory Hodgkin lymphoma	Pre-apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Plerixafor 240 μg/kg PM on day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis after G-CSF Post-apheresis (day 5→): ■ Plerixafor (PM), G-CSF (AM), and apheresis daily for up to 5 consecutive days or until ≥5×10^6/kg CD34+ cells collected	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients not mobilized before: successful apheresis, apheresis days, CD34+ cell collection, ASCT, 12-month post-SCT survival rate
	G-CSF[a]	98	Hodgkin lymphoma	Not reported	
Shaughnessy *et al.*, 2011[12] (Jul 2008–Jan 2009)	G-CSF plus plerixafor	33	NHL, MM, relapsed HD	Before the 1st day of apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Plerixafor 240 μg/kg PM on day 4 After 1st day of apheresis (day 5): ■ G-CSF 10 μg/kg AM for 5 days ■ Plerixafor 240 μg/kg PM for4 days or until ≥5×10^6/kg CD34+ cells collected (NHL or HD) and ≥6×10^6/kg CD34+ cells collected (MM)	Patients not mobilized before: successful apheresis, apheresis days, CD34+ cell collection, ASCT
	Chemotherapy plus G-CSF[a]	33		Before 1st day of apheresis: ■ Cyclophosphamide chemotherapy 3–5 g/m^2 on day 1 ■ G-CSF 10 μg/kg on days 2–9 After 1st day of apheresis (day 10): ■ G-CSF 10 μg/kg AM for 6 days	
Chaudhary *et al.*, 2013[9] (Apr 2010–Sep 2012) (Jan 2003–Mar 2010)	G-CSF plus plerixafor	33	MM	Pre-apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Plerixafor 240 μg/kg PM on day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis after G-CSF Post-apheresis (day 5→): ■ Plerixafor (PM), G-CSF (AM), and apheresis daily for up to 3 additional apheresis sessions	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients not mobilized before: successful apheresis, apheresis days, CD34+ cell collection
	Chemotherapy plus G-CSF[a]	74		■ Cyclophosphamide chemotherapy 1.5 g/m^2 on day 1 ■ G-CSF 10 μg/kg on day 8 until completion of apheresis	

TABLE I Continued

Reference (study years)	Treatment allocation	Pts (*n*)	Population	Peripheral blood stem-cell mobilization regimen	Outcome reported
Nonrandomized trials, historical control group					
Hundemer *et al.*, 2014[10] (2009–2010)	Chemotherapy plus G-CSF plus plerixafor on demand	60	MM	■ Chemotherapy[b] ■ G-CSF 10 μg/kg AM until the end of stem-cell collection ■ Plerixafor after the 1st apheresis session	Patients who seem to mobilize poorly to current regimens: CD34+ cell collection, apheresis days
	Chemotherapy plus G-CSF	45		■ Chemotherapy[b] ■ G-CSF 10 μg/kg AM until the end of stem-cell collection	
Milone *et al.*, 2014[11] (Apr 2012–May 2013)	Chemotherapy plus G-CSF plus plerixafor on demand	102	MM, lymphoma	■ Cyclophosphamide chemotherapy 4 g/m^2 or DHAP[c] ■ G-CSF 5–10 μg/kg on day 3 ■ Plerixafor 240 μg/kg[d] on demand	Patients not mobilized before: successful apheresis, apheresis days, CD34+ cell collection, ASCT Patients who seem to mobilize poorly to current regimens:
(Jan 2000–Jan 2009)	Chemotherapy plus G-CSF[a]	240		■ Cyclophosphamide chemotherapy 4 g/m^2 or DHAP[c] ■ G-CSF 10 μg/kg on day 3	successful apheresis, apheresis days
Retrospective cohort studies, contemporaneous control group					
Perkins *et al.*, 2012[15] (Nov 2000–Jul 2009)	G-CSF plus plerixafor	38	NHL, MM, Hodgkin lymphoma	■ G-CSF 10 μg/kg for 4 days ■ Plerixafor 240 μg/kg PM on day 4 ■ Apheresis, G-CSF, plerixafor on day 5 until completion of apheresis	Patients who seem to mobilize poorly to current regimens: successful apheresis, CD34+ cell collection, apheresis days, ASCT
	Chemotherapy plus G-CSF	15		■ Chemotherapy[e] plus G-CSF 5 μg/kg daily, starting on the day after the last chemotherapy dose and continued until completion of apheresis	
	G-CSF with or without GM-CSF	43		■ G-CSF 10–20 μg/kg with or without GM-CSF 10 μg/kg for 4 days ■ Apheresis plus G-CSF with or without GM-CSF on day 5 until completion of apheresis	
Kim *et al.*, 2014[14] (Jan 2008–Apr 2011)	G-CSF plus plerixafor	25	MM	■ G-CSF 10 μg/kg AM for 5 days ■ Plerixafor 0.24 mg/kg on day 4 for up to 4 days	Patients not mobilized before: apheresis days, CD34+ cell collection
	G-CSF	25		■ G-CSF 10 μg/kg AM for 5 days	
Cheng *et al.*, 2015[13] (2009–2012)	Chemotherapy plus G-CSF plus plerixafor	23	MM	■ Chemotherapy ■ G-CSF 5–10 μg/kg AM until end of stem-cell collection period ■ Plerixafor about 12 hours before the apheresis procedure	Patients who seem to mobilize poorly to current regimens and patients who failed prior mobilization: apheresis days, CD34+ cell collection, number of patients proceeding to ASCT
	Chemotherapy plus G-CSF	23		■ Chemotherapy[f] ■ G-CSF 5–10 μg/kg AM until end of stem-cell collection period	

TABLE I Continued

Reference (study years)	Treatment allocation	Pts (*n*)	Population	Peripheral blood stem-cell mobilization regimen	Outcome reported
Single-arm trials					
Calandra *et al.*, 2008[20]	G-CSF plus plerixafor[g]	115	NHL, MM, HD	Pre-apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Plerixafor 240 μg/kg PM on day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis after G-CSF Post-apheresis (day 5→): ■ Plerixafor (PM), G-CSF (AM), and apheresis daily until ≥2×10^6/kg CD34+ cells collected or mobilization failure as determined by the investigator	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients who failed prior mobilization regimen: successful apheresis, CD34+ cell collection, apheresis days, ASCT
Arcaini *et al.*, 2011[17] (2008–2009)	G-CSF plus plerixafor[g]	35	NHL, Hodgkin lymphoma	Pre-apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Plerixafor 240 μg/kg PM on day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis 1 hour after G-CSF Post-apheresis (day 5→): ■ Plerixafor (PM), G-CSF (AM), and apheresis daily until ≥2×10^6/kg CD34+ cells collected or mobilization failure as determined by the investigator	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients who failed prior mobilization regimen: successful apheresis, CD34+ cell collection, apheresis days, ASCT
Basak *et al.*, 2011[18]	G-CSF plus plerixafor[g]	76	MM	Pre-apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Plerixafor 240 μg/kg PM on day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis 1 hour after G-CSF Post-apheresis (day 5→): ■ Plerixafor (PM), G-CSF (AM), and apheresis daily until ≥2×10^6/kg CD34+ cells collected or mobilization failure diagnosed	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients who failed prior mobilization regimen: successful apheresis, CD34+ cell collection, apheresis days
Basak *et al.*, 2011[19]	G-CSF plus plerixafor[g]	61	NHL, MM, Hodgkin lymphoma	Pre-apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Plerixafor 240 μg/kg PM on day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis 1 hour after G-CSF Post-apheresis (day 5→): ■ Plerixafor (PM), G-CSF (AM), and apheresis (up to 3 days of plerixafor administration or until ≥20 CD34+ cells/μL collected)	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients who failed prior mobilization regimen: successful apheresis, CD34+ cell collection, apheresis days, ASCT

TABLE I Continued

Reference (study years)	Treatment allocation	Pts (*n*)	Population	Peripheral blood stem-cell mobilization regimen	Outcome reported
Single-arm trials					
Duarte *et al.*, 2011[21]	G-CSF plus plerixafor[g]	56	Lymphoma, MM	Pre-apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Plerixafor 240 μg/kg PM on day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis 1 hour after G-CSF Post-apheresis (day 5→): ■ Plerixafor (PM), G-CSF (AM), and apheresis daily until ≥2×10^6/kg CD34+ cells collected or mobilization failure as determined by the investigator	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients who failed prior mobilization regimen: successful apheresis, CD34+ cell collection, apheresis days, ASCT
Hübel *et al.*, 2011[23] (May 2008–Aug 2009)	G-CSF plus plerixafor[g]	60	NHL, Hodgkin lymphoma, MM, other diseases[h]	Pre-apheresis (days 1–4): ■ G-CSF 10 μg/kg AM for 4 days ■ Plerixafor 240 μg/kg PM on day 4 Apheresis day (day 5): ■ G-CSF 10 μg/kg AM ■ Apheresis 1 hour after G-CSF Post-apheresis (day 5→): ■ Plerixafor (PM), G-CSF (AM), and apheresis daily until ≥2×10^6/kg CD34+ cells collected or up to a maximum of 7 days of plerixafor injections	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients who failed prior mobilization regimen: successful apheresis, CD34+ cell collection, apheresis days, ASCT
Jantunen *et al.*, 2011[24] (Aug 2009–Oct 2010)	Chemotherapy plus G-CSF plus plerixafor	63	Lymphoma, MM, Hodgkin lymphoma	■ Chemotherapy ■ G-CSF ■ Plerixafor 12–24 mg per injection	Successful mobilization criteria: ≥2×10^6/kg CD34+ cells and ≥4×10^6 CD34+ cells for patients <65 years of age with MM Patients who seem to mobilize poorly to current regimens: successful apheresis, CD34+ cell collection, apheresis days
Abhyankar *et al.*, 2012[16] (Apr 2009 to Dec 2010)	G-CSF plus plerixafor on demand	159	MM (79), lymphoma (76), germ cell tumours (3), Ewing	Days 1–4: ■ G-CSF 10 μg/kg AM ■ CD34+ cell count (day 5) ■ G-CSF and plerixafor 240 μg/kg on demand daily until adequate number of CD34+ cells collected	Successful mobilization criterion: ≥2.5×10^6/kg CD34+ cells Patients who seem to mobilize poorly to current regimens: CD34+ cell collection, apheresis days

TABLE I Continued

Reference (study years)	Treatment allocation	Pts (*n*)	Population	Peripheral blood stem-cell mobilization regimen	Outcome reported
Single-arm trials					
Hübel *et al.*, 2012[22] (May 2008–Aug 2009)	G-CSF plus plerixafor[g]	580	NHL, Hodgkin lymphoma, MM	Pre-apheresis (days 1–4): ■ G-CSF 10 µg/kg AM for 4 days ■ Plerixafor 240 µg/kg PM on day 4 Apheresis day (day 5): ■ G-CSF 10 µg/kg AM ■ Apheresis 1 hour after G-CSF ■ Plerixafor (PM) Post-apheresis (day 6→): ■ G-CSF (AM), apheresis, and plerixafor (PM) daily until ≥2×10^6/kg CD34+ cells collected or up to a maximum of 7 days of plerixafor injections	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients who failed prior mobilization regimen: successful apheresis, CD34+ cell collection, apheresis days
Lor *et al.*, 2012[25] (Jan 2008–Dec 2009)	G-CSF plus plerixafor	33	NHL, MM	Pre-apheresis (days 1–4): ■ G-CSF (filgrastim) 10 µg/kg AM day 1 ■ Plerixafor 24 µg/kg PM on day 4 Apheresis day (day 5) Post-apheresis (day 5→): ■ Plerixafor (PM), filgrastim (AM), and apheresis until sufficient number of CD34+ cells attained or a certain number of days were elapsed ■ Patients who received more than 5 doses of plerixafor and who did not achieve the minimum CD34+ cell yield were allowed to receive another mobilization regimen of filgrastim plus plerixafor after a washout period of at least 11 days	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients who failed prior mobilization regimen: successful apheresis, CD34+ cell collection, apheresis days
Malard *et al.*, 2012[26] (Jun 2008 to Aug 2010)	G-CSF plus plerixafor[g]	83	NHL, MM	Pre-apheresis (days 1–4): ■ G-CSF 10 µg/kg AM for 4 days ■ Plerixafor 240 µg/kg PM on day 4 ■ Apheresis day (day 5): ■ G-CSF 10 µg/kg AM Apheresis 1 hour after G-CSF Post-apheresis (day 5→): ■ Plerixafor (PM), G-CSF (AM), and apheresis daily until ≥2×10^6/kg CD34+ cells collected or a maximum of 7 plerixafor injections	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients who failed prior mobilization regimen: successful apheresis, CD34+ cell collection, apheresis days

TABLE I Continued

Reference (study years)	Treatment allocation	Pts (*n*)	Population	Peripheral blood stem-cell mobilization regimen	Outcome reported
Single-arm trials					
Smith *et al.*, 2013[27] (Jan 2009–Mar 2011)	Chemotherapy plus G-CSF plus plerixafor	38	NHL, Hodgkin lymphoma, MM	■ G-CSF 10 μg/kg 24 hours after chemotherapy ■ Plerixafor 240 μg/kg 12±2 hours before apheresis ■ G-CSF was continued concurrently with plerixafor until apheresis complete	Successful mobilization criterion: ≥2×10^6/kg CD34+ cells Patients who seem to mobilize poorly to current regimens: successful apheresis, CD34+ cell collection, apheresis days, ASCT

[a] Historical control population.
[b] Cyclophosphamide 1 g/m^2 on day 1, doxorubicin 15 mg/m^2 on days 1–4, dexamethasone 40 mg on days 1–4 in 54 patients; high-dose cyclophosphamide 2 g/m^2 on days 1–2 in 2 patients; cyclophosphamide 1 g/m^2 and liposomal doxorubicin 48 mg/m^2 on day 1, dexamethasone 40 mg on days 1–4 in 1 patient with cardiac comorbidity; cyclophosphamide 1 g/m^2 on day 1, dexamethasone 40 mg on days 1–4 in 2 patients; or bortezomib 1.3 mg/m^2 on days 1 and 8, cyclophosphamide 900 mg/m^2 on day 1, dexamethasone 40 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 (8 doses) in 1 patient.
[c] Dexamethasone 40 mg for 4 days, cytarabine 2 g/m^2 on day 2, cisplatin 100 mg/m^2 or oxaliplatin 130 mg/m^2 on day 1.
[d] A 2nd and 3rd dose of plerixafor was administered only in patients demonstrating a good response (>0.01×10^9 CD34+ cells/L) to plerixafor and needing further apheresis to reach a total of 2×10^6/kg CD34+ cells.
[e] Regimens included cyclophosphamide 50 mg/kg for 2 days; cyclophosphamide 50 mg/kg for 2 days plus etoposide 300 mg/m^2 for 2 days; or etoposide 100 mg/m^2 on days 1–3, ifosfamide and MESNA 5 g/m^2 each on day 2 (followed by MESNA 10 g on day 3), and carboplatin AUC 5 on day 2.
[f] Regimens included cyclophosphamide 1000 mg/m^2 on day 1, doxorubicin 15 mg/m^2 daily on days 1–4, dexamethasone 40 mg daily on days 1–4), cyclophosphamide 200 mg/m^2 daily on days 1 and 2; bortezomib 3 mg/m^2 daily on days 1, 4, 8, and 11, cyclophosphamide 900 mg/m^2 on day 1, dexamethasone 40 mg daily on days 1, 2, 4, 5, 8, 9, 11, and 12; cyclophosphamide 1000 mg/m^2 on day 1, dexamethasone 40 mg daily on days 1–4; and lenalidomide 25 mg daily on days 1–21, dexamethasone 20 mg daily on days 1–4, 9–12, and 17–29.
[g] Centres participating in the compassionate use program for plerixafor were also able to combine chemotherapy with G-CSF and plerixafor for mobilization.
Pts = patients; G-CSF = granulocyte colony–stimulating factor; NHL = non-Hodgkin lymphoma; SCT = stem-cell transplantation; MM = multiple myeloma; HD = Hodgkin disease; AUC = area under the curve.

the population of interest. In all studies, the mobilization regimen was consistent with the regimen that would be used in Ontario clinical practice. Eight of the studies[17,18,20–23,26,28] included patients enrolled in a European compassionate-use program (CUP) for patients who had previously failed conventional mobilization attempts. The inclusion and exclusion criteria were fully described for all those studies. The remaining three trials were independent studies conducted in education centres in Finland[24] and the United States[25,27]. Selection of patients was based on low peripheral blood CD34+ cell count or poor yield in the 1st apheresis procedure. The mobilization regimens were well described, as were the outcomes of median collection, percentage of patients meeting the primary endpoint of achieving the CD34+ cell target, and number of apheresis procedures. The reported outcomes included the proportion of patients reaching at least 2×10^6 CD34+ cells per kilogram, median CD34+ cell collection and range, and number of apheresis procedures. Some studies reported the number and proportion of patients who proceeded to ASCT and who survived to the 12-month follow-up.

Overall, the quality assessment found all of the foregoing plerixafor trials to be of acceptable quality given the nature of their study designs.

Outcomes

Patients Not Previously Mobilized

Table II summarizes results in patients in whom mobilization had not previously been attempted.

CD34+ Cells Collected: The two RCTs reported by DiPersio *et al.*[6,7] detected a statistically significant difference in mobilization rates favouring regimens using plerixafor compared with conventional mobilization treatment, both for patients with NHL (59.3% vs. 19.6%, $p < 0.001$, and 86.7% vs. 47.3%, $p < 0.001$ for patients collecting ≥5×10^6 and ≥2×10^6 CD34+ cells respectively)[6] and for patients with MM (71.6% vs. 34.4%, $p < 0.001$ for patients collecting ≥6×10^6/kg CD34+ cells)[7]. Similarly, four nonrandomized trials using historical controls[8,9,11,12] reported a statistically significant increase in the proportion of patients collecting CD34+ cells in favour of mobilization therapies using plerixafor compared with conventional treatment (68%–94% vs. 15%–76% respectively). The two RCTs reported by DiPersio *et al.*[6,7] are the current best evidence from research concerning the safety and efficacy of plerixafor for autologous stem-cell mobilization and transplantation, given that RCTs are the most rigorous way of determining evidence of cause and effect.

Apheresis Procedures: One RCT reported by DiPersio *et al.*[7] and two trials with historical controls demonstrated the ability of regimens with plerixafor, compared with conventional mobilization therapies, to significantly reduce the number of apheresis procedures required to collect the target number of CD34+ cells (1 vs. 4, $p < 0.001$)[7], (1.61 vs. 1.43, $p = 0.04$)[11], and (3 vs. 2, $p < 0.0001$)[14]. Two trials with historical controls reported no differences between groups with respect to the time of collection[9,12].

TABLE II Summary of outcomes reported by studies assessing the efficacy of plerixafor in patients not previously mobilized

Reference	Treatment arms	Pts (*n*)	Diagnosis	Successful CD34+ harvest by apheresis demonstrated [*n* (%) patients]		Apheresis days [*n* (range)]	Median CD34+ collection [$\times 10^6$ cells/kg per days (range) of apheresis]	Proceeded to ASCT [*n* (%)]	12-Month post-SCT survival [*n* (%)]
				≥5×10^6 cells/kg	≥2×10^6 cells/kg				
Randomized controlled trials									
DiPersio *et al.*, 2009[6]	G-CSF plus plerixafor	150	NHL	89 (59.3)	130 (86.7)	Median[a]: 3	5.69 (0.03–29.22)	135 (90)	119 (88.1)
	G-CSF plus placebo	148		29 (19.6)	70 (47.3)	Median[b]: 1	1.98 (0.06–15.00)	82 (55.4)	71 (86.6)
				p<0.001	*p*<0.001	Median[c] Median[b]: 3		*p*<0.001	
DiPersio *et al.*, 2009[7]	G-CSF plus plerixafor	148	MM	106 (71.6)[d] 112 (75.7)[e]	Not reported	1.0[d]	10.96 (0.66–104.57)	142 (95.9)	141 (95.3)
	G-CSF plus placebo	154		53 (34.4)[d] 79 (51.3)[e]		4.0[e]	6.18 (0.11–42.66)	136 (88.3)	148 (96.1)
				p<0.001[d] *p*<0.001[e]		*p*<0.001	*p*<0.001		
Nonrandomized trials, historical control group									
Cashen *et al.*, 2008[8]	G-CSF plus plerixafor	22	Relapsed or refractory Hodgkin lymphoma	15 (68)	21 (95)	2.5	6.2 (0.6–10.4) per 1–2 days	21 (95)	21 (95)
	G-CSF	98		15 (15)	76 (78)	2.9	3.0 per 1–2 days		
				p<0.001	*p*=0.071	*p*=NS	*p*<0.001	Not reported	Not reported
Shaughnessy *et al.*, 2011[12]	G-CSF plus plerixafor	33	NHL, MM, relapsed Hodgkin lymphoma	31 (94)	33 (100)	1 (1–4)	10.7 (3.5–37.9)	33 (100)	Not reported
	Cyclophosphamide chemotherapy plus G-CSF	33		25 (76)	33 (100)	1 (1–4)	11.6 (2.1–69.3)	33 (100)	
				p=0.04	Not reported	*p*=0.45	*p*=0.5		
Chaudhary *et al.*, 2013[9]	G-CSF plus plerixafor	33	MM	31 (93.9)	31 (93.9)[f]	2 (1–4)	11.6 (3.0–26.8) 6.9 (1.0–26.8)[f]	Not reported	Not reported

TABLE II Continued

Reference	Treatment arms	Pts (*n*)	Diagnosis	Successful CD34+ harvest by apheresis demonstrated [*n* (%) patients]		Apheresis days [*n* (range)]	Median CD34+ collection [$\times 10^6$ cells/kg per days (range) of apheresis]	Proceeded to ASCT [*n* (%)]	12-Month post-SCT survival [*n* (%)]
				≥5×10^6 cells/kg	≥2×10^6 cells/kg				
Nonrandomized trials, historical control group									
Chaudhary *et al.*, 2013[9]	Chemotherapy plus G-CSF	74		51 (68.9)	42 (56.7)[f]	2 (1–5)	7.0 (0–18) 2.4 (0–15)[f]		
				p=0.01	*p*=0.001	*p*=0.17	*p*=0.001 *p*=0.001[f]		
Kim *et al.*, 2014[14]	G-CSF	25	MM	Not reported	Not reported	3 (1–5)	7.4 (2.3–21.2)	Not reported	Not reported
	G-CSF plus plerixafor	25				2 (1–4)	13.2 (4–43.4)		
						p=0.0001	*p*=0.0007		
Milone *et al.*, 2014[11]	Cyclophosphamide chemotherapy or DHAP plus G-CSF plus plerixafor on demand[g]	102	MM, lymphoma (L)	86% MM 80% L	98 (96) 70 (97) MM 28 (93) L	1.61	8.0 9.43 MM 7.0 L	52 (51)	Not reported
	G-CSF plus cyclophosphamide chemotherapy or DHAP	228			188 (83) 153 (85) MM 35 (73) L	1.43	6.65		
				Not reported	*p*=0.0008 *p*=0.006 MM *p*=0.02 L	*p*=0.04	*p*=0.03	Not reported	

[a] Collecting ≥5×10^6/kg CD34+ cells.
[b] Collecting ≥2×10^6/kg CD34+ cells.
[c] Median number of apheresis days required to achieve ≥5×10^6/kg CD34+ cells was not calculated because fewer than half the patients reached the target within 4 apheresis days.
[d] Collecting ≥6×10^6/kg CD34+ cells in 2 or fewer days of apheresis.
[e] Collecting ≥6×10^6/kg CD34+ cells in 4 or fewer days of apheresis.
[f] On day 1, $n\times10^6$/kg CD34+ cells collected.
[g] Plerixafor was given only to patients with fewer than 0.01×10^9/L peripheral blood CD34+ cells at day 13, because that level was judged to have high sensitivity for the identification of patients who would subsequently fail to mobilize (<0.02×10^9/L peripheral blood CD34+ cells).
Pts = patients; ASCT = autologous stem-cell transplantation; G-CSF = granulocyte colony–stimulating factor; NHL = non-Hodgkin lymphoma; MM = multiple myeloma; NS = nonsignificant); DHAP = dexamethasone–cytarabine–cisplatin.

Peripheral Blood CD34+ Cell Count: Five studies reported a statistically significant increase in the median number of CD34+ cells collected (given here as millions per kilogram body weight) after plerixafor mobilization than after conventional mobilization (10.96 vs. 6.18, $p < 0.001$[7]; 6.2 vs. 3.0, $p < 0.001$[8]; 8.0 vs. 6.65, $p = 0.03$[11]; 11.6 vs. 7.0, $p = 0.001$[9]; and 7.4 vs. 13.2, $p = 0.0007$[14]). Shaughnessy *et al.*[12] reported a nonsignificant difference between groups (10.7 for plerixafor vs. 11.6 for conventional therapy, $p = 0.5$). DiPersio *et al.*[6] reported a higher number of CD34+ cells associated with a plerixafor mobilization strategy (5.69 vs. 1.98), but statistical significance was not reported.

Proportion of Patients Who Proceed to ASCT: Only the RCT reported by DiPersio *et al.*[6] detected a statistically significant difference in the proportion of patients undergoing ASCT that favoured plerixafor regimens over mobilization therapy using G-CSF alone (90% vs. 55.4%, $p < 0.001$). None of the other comparative studies reported statistically significant differences between groups[7–9,11,12,29].

Survival Rate After ASCT: Only two studies, the RCTs reported by DiPersio *et al.*[6,7], reported the 12-month survival rate after ASCT for both groups (mobilization therapy using G-CSF alone, and with added plerixafor), but the statistical difference between the rates was not reported. None of the other studies reported this outcome[8,9,11,12,14,29].

Patients Who Seem to Mobilize Poorly to Current Regimens

Table III summarizes results in patients in whom mobilization had been attempted, but with poor response.

CD34+ Cells Collected: An "on demand" prospective study by Milone *et al.*[11] assessed the efficacy of plerixafor in patients who mobilize poorly. In patients predicted to fail harvest, those authors detected a statistically significant increase in CD34+ harvest rates associated with the use of plerixafor compared with no plerixafor (60% vs. 0%, $p = 0.01$). Similarly, a retrospective study comparing G-CSF (filgrastim) plus plerixafor with other regimens after primary mobilization failure[15] detected a statistically significant increase in favour of plerixafor in the number of CD34+ cells collected in 1 apheresis procedure after 2nd mobilization (37%, 0%, and 2% for G-CSF plus plerixafor, G-CSF plus chemotherapy, and G-CSF plus granulocyte–macrophage colony–stimulating factor respectively; $p < 0.0001$). Two single centres evaluated the efficacy of the pre-emptive use of plerixafor after chemomobilization with G-CSF in patients who seem to mobilize poorly and reported that the minimum CD34+ collection target was achieved by 80%[24] and 97%[27] of their patients.

Peripheral Blood CD34+ Cell Count and Number of Apheresis Procedures: Two comparative studies reported a statistically significant increase in the number of CD34+ cells collected (given here as millions per kilogram body weight) and in the median number of apheresis procedures for patients who received plerixafor compared with patients who received other regimens after primary mobilization failure[10,15]. In the retrospective comparative study reported by Perkins *et al.*[15], the median number of CD34+ cells collected was reported to be 2.1 in 1 apheresis procedure for G-CSF plus plerixafor, 1.19 in 2 apheresis procedures for G-CSF plus chemotherapy, and 1.44 in 2 apheresis procedures for G-CSF plus granulocyte–macrophage colony–stimulating factor ($p = 0.01$ for median number of CD34+ cells collected and $p = 0.04$ for median number of apheresis procedures). The study by Hundemer *et al.*[10], in which data were matched with a historical control group on the basis of poor stem-cell yield in the first apheresis session, reported a median CD34+ collection of 4.9 in 2 apheresis procedures with plerixafor and 3.7 in 4 apheresis procedures with G-CSF ($p = 0.01$). The comparative study reported by Cheng *et al.*[13] reported a median CD34+ collection of 8.5 for patients receiving plerixafor compared with 4.8 for patients not receiving plerixafor ($p = 0.003$), but the median number of apheresis procedures was not reported.

Three single-arm studies[16,24,27] reported median numbers of CD34+ cells of 2.9, 5.08, and 3.42 with a median number of apheresis procedures of 1 (range: 1–3), 5 (range: 1–10), and 2 (range: 1–4) respectively.

Proportion of Patients Who Proceed to ASCT: Only the comparative study reported by Perkins *et al.*[15] reported a statistically significant difference in the proportion of patients who underwent transplantation favouring plerixafor compared with other regimens after primary mobilization failure (84% for G-CSF plus plerixafor, 53% for G-CSF plus chemotherapy, and 84% for G-CSF plus granulocyte–macrophage colony–stimulating factor; $p = 0.03$). Cheng *et al.*[13] reported that all patients (100%) in the group receiving plerixafor and 83% of patients in the group not receiving plerixafor underwent transplantation, but statistical significance was not reported. The single-arm study by Smith *et al.*[27] reported that, among patients who seem to mobilize poorly and who received just-in-time rescue plerixafor plus chemotherapy and G-CSF, 95% proceeded to ASCT. No other studies reported that outcome.

Survival Rate After ASCT: None of the studies evaluating the efficacy of plerixafor in patients failing mobilization (those who seemed to mobilize poorly) reported on survival rate after ASCT.

Patients Who Failed a Prior Mobilization Regimen

Table IV summarizes results in patients who failed a prior mobilization attempt.

CD34+ Cells Collected: Eleven studies reported on the efficacy of plerixafor in patients who mobilize poorly. One comparative study reported by DiPersio *et al.*[6] reported that, among patients with NHL who failed prior mobilization regimens with G-CSF plus plerixafor and G-CSF plus placebo, 40% and 64% were able to achieve at least the minimum collection target. Those authors also reported that all patients with MM who failed previous mobilization attempts (7 of 7) were able to achieve the minimum collection target of 2×10^6/kg CD34+ cells[7]. An additional single-arm study reported by Lor *et al.*[25] assessed the efficacy of plerixafor plus G-CSF (filgrastim) as second-line therapy for patients who failed to respond to G-CSF (filgrastim) plus

TABLE III Summary of outcomes reported by studies assessing the efficacy of plerixafor in patients who seem to mobilize poorly to current regimens (low peripheral blood CD34+ collected before first apheresis procedure or inadequate first-day apheresis collection)

Reference	Mobilization				Efficacy of plerixafor					
	Initial therapy	Pts (*n*)	Criteria for failing (CD34+ cell count in peripheral blood)	Patients failing (*n*)	Remobilization protocol	CD34+ cells ≥2×10^6/kg [*n* (%)]	Median CD34+ cell collection [×10^6/kg (range)]	Median apheresis days [*n* (range)]	Proceed to ASCT [*n* (%)]	12- Month survival
Jantunen *et al.*, 2011[24]	Chemotherapy plus G-CSF	63	Peripheral blood: <10×10^6/L; or peripheral blood stem-cell collection: <1.0×10^6/kg	16 Total 12 NHL 1 HL 3 MM	Plerixafor	13 (80) 10 (77) NHL 0 (0) HL 3 (100) MM	2.9 (1.6–6.1)	1 (1–3)	Not reported	Not reported
Smith *et al.*, 2013[27]	Chemotherapy plus G-CSF		Peripheral blood: <10×10^9/L after chemotherapy; or peripheral blood stem-cell collection: <0.3×10^6/kg daily for 2 days	38 Total 27 NHL 3 HL 8 MM	Plerixafor	37 (97) 26 (96) NHL 3 (100) HL 8 (100) MM	5.08 Total (1.95–16.55) 4.93 NHL (1.95–10.89) 5.04 NHL+HL (1.95–10.89) 8.81 MM (2.86–16.55)	5 Total (1–10) 5 NHL (2–10) 5 HL (2–10) 7 MM (5–9)	36 (95)	Not reported
Abhyankar *et al.*, 2012[16]	G-CSF	159	Peripheral blood on day 5: <10[a] or 20[b]/μL; or peripheral blood stem-cell collection on day 1: less than one-half the total CD34+ dose needed (≥2.5[a] or ≥5[b]×10^6/kg)	55 Total 28 NHL, HL 26 MM 1 Other	Plerixafor		3.42 Total (0.11–12.49) 2.84 NHL, HL (0.38–6.50) 2.96 MM[c] (2.78–6.12) 6.46 MM[d] (0.62–12.49) 5.8 Other	2 (1–4) 2 (1–4) 1 (1–3) 2 (1–3) 2	Not reported	Not reported
Perkins *et al.*, 2012[15]	Not reported		Peripheral blood stem-cell collection: <2×10^6/kg in 1st mobilization attempt	96	G-CSF plus plerixafor (*n*=38) Chemotherapy plus G-CSF (*n*=15) G-CSF with or without GM-CSF (*n*=43)	22 (58) 14 (37)[e] 4 (27) 0[e] 17 (40) 1 (2)[e] *p*=0.08 *p*<0.0001[e]	2.10 (0.24–14.35) 1.19 (0–5.76) 1.44 (0–12.01) *p*=0.01	1 (1–4) 2 (1–3) 2 (1–3) *p*=0.04	32 (84) 8 (53) 36 (84) *p*=0.03	Not reported

TABLE III Continued

Reference	Mobilization				Efficacy of plerixafor					
	Initial therapy	Pts (*n*)	Criteria for failing (CD34+ cell count in peripheral blood)	Patients failing (*n*)	Remobilization protocol	CD34+ cells ≥2×10^6/kg [*n* (%)]	Median CD34+ cell collection [×10^6/kg (range)]	Median apheresis days [*n* (range)]	Proceed to ASCT [*n* (%)]	12- Month survival
Hundemer *et al.*, 2014[10]	Chemotherapy plus G-CSF		Peripheral blood stem-cell collection: <2×10^6 cells/kg	15/60 MM 45[f] MM	Plerixafor (*n*=15) G-CSF (*n*=45[g])	Not reported	4.92 (1.6–14.1) 3.7 (1.08–8.0) *p*=0.042	2 (2–3) 4 (2–9) *p*=0.001	Not reported	Not reported
Milone *et al.*, 2014[11]	Cyclophosphamide chemotherapy or DHAP plus G-CSF	102	Peripheral blood on day +13[h] or +15[i]: <0.02×10^9/L	16/102	Plerixafor (*n*=10) No plerixafor (*n*=6)	6/10 (60) 0/6 (0) *p*=0.01	1.4 (1–3)	Not reported	Not reported	
Cheng *et al.*, 2015[13]	G-CSF plus chemotherapy		Patients with CD34+ levels of 20×10^6/L or more in peripheral blood and a low CD34+ stem-cell yield in 1st apheresis session	24 MM	Plerixafor (*n*=12) No plerixafor (*n*=12)	Not reported	8.5 (5.5–16.4) 4.8 (2.2–10.0) *p*=0.003	Not reported	12 (100) 10 (83)	Not reported

[a] For 1 transplant.
[b] For >1 transplant.
[c] Target of 2.5×10^6/kg CD34+ cells.
[d] Target of 5.0×10^6/kg CD34+ cells.
[e] Collecting >2×10^6/kg CD34+ cells in 1 apheresis procedure only.
[f] Matched historical control group who also had a poor stem-cell yield in 1st apheresis session, but continued mobilization with G-CSF alone.
[g] Historical control group.
[h] For patients received mobilizing chemotherapy based on cyclophosphamide.
[i] For patients receiving the DHAP schedule.

Pts = patients; ASCT = autologous stem-cell transplantation; G-CSF = granulocyte colony-stimulating factor; NHL = non-Hodgkin lymphoma; HL = Hodgkin lymphoma; MM = multiple myeloma; GM-CSF = granulocyte–macrophage colony–stimulating factor; DHAP = dexamethasone–cytarabine–cisplatin.

TABLE IV Summary of outcomes reported by studies assessing the efficacy of plerixafor in patients who have failed a prior mobilization regimen ("poor mobilizers")

Reference (single-arm studies)	Mobilization				Efficacy of plerixafor					
	Initial therapy	Pts (*n*)	Criteria for poor response (CD34+ cell count $\times 10^6$/kg in peripheral blood)	Patients with poor response (*n*)	Remobilization protocol	CD34+ cells $\geq 2\times 10^6$/kg [*n* (%)]	Median CD34+ cell collection [$\times 10^6$/kg (range)]	Median apheresis days [*n* (range)]	Proceed to ASCT [*n* (%)]	12-Month survival
Calandra *et al.*, 2008[20,a]	Conventional regimen		Previously failed to proceed to apheresis because of low peripheral blood cell count (<10 before apheresis) or peripheral blood stem-cell count <2.0 after 7 apheresis procedures maximum	115 Total	G-CSF plus plerixafor	76 (66) 38 (60) NHL 25 (71) MM 13 (77) HD	Mean: 3.51±2.90 2.97±2.51 NHL 4.44±3.68 MM 4.54±4.22 HD	3 (0–7) 3 NHL (0–7) 4 MM (1–7) 3 HD (1–5)	87 (76) 45 (71) NHL 27 (77) MM 15 (88) HD	Not reported
DiPersio *et al.*, 2009[6]	G-CSF plus plerixafor G-CSF plus placebo	150 148	Peripheral blood stem-cell collection <0.8 or <2.0 within 2 and 4 apheresis days respectively	10/150 NHL 52/148 NHL	G-CSF plus plerixafor with or without chemotherapy	4/10 (40) 33/52 (64)	Not reported	≤4	52/62 (84)	53/62 (85.5)
DiPersio *et al.*, 2009[7]	G-CSF plus plerixafor G-CSF plus placebo	148 154	Peripheral blood stem-cell collection <0.8 or <2.0 within 2 and 4 apheresis days respectively, or patients planned for tandem transplantation with <4 within3 apheresis days	0/145 MM 7/154 MM	G-CSF plus plerixafor with or without chemotherapy	7/7	Not reported	4	7/7 (100)[b]	7/7 (100)
Arcaini *et al.*, 2011[17,a]	Chemotherapy plus G-CSF		Previously failed to proceed to apheresis because of low peripheral blood cell count (<10 before apheresis) or peripheral blood stem-cell collection <2.0 after 7 apheresis procedures maximum	35 Total 29 HL 6 NHL	G-CSF plus plerixafor	13 (37)	2.6 (0.7–5.7)	1 (1–4)	6 (17)	Not reported

TABLE IV Continued

Reference (single-arm studies)	Mobilization				Efficacy of plerixafor					
	Initial therapy	Pts (*n*)	Criteria for poor response (CD34+ cell count $\times 10^6$/kg in peripheral blood)	Patients with poor response (*n*)	Remobilization protocol	CD34+ cells $\geq 2\times 10^6$/kg [*n* (%)]	Median CD34+ cell collection [$\times 10^6$/kg (range)]	Median apheresis days [*n* (range)]	Proceed to ASCT [*n* (%)]	12-Month survival
Basak *et al.*, 2011[19,a]	G-CSF with or without chemotherapy		Previously failed to proceed to apheresis because of low peripheral blood CD34+ cell count (<10 before apheresis) or peripheral blood stem-cell count <2.0 after 7 apheresis procedures maximum	61[c] Total 23 MM 20 NHL 18 HL	G-CSF plus plerixafor	40[d] (66) 18 (78) MM 8 (40) NHL 14 (78) HL $p<0.05$	2.8 (0.94–5.4) 2.8 MM (0.6–5.5) 0.89 NHL (0–6.5) 2.8 HL (0–8.0) $p<0.05$	2 (0–4)	34 (56)	Not reported
Basak *et al.*, 2011[18,a]	G-CSF with or without chemotherapy		Previously failed to proceed to apheresis because of low peripheral blood CD34+ cell count (<10 before apheresis) or peripheral blood stem-cell count <2.0 after 7 apheresis procedures maximum	76[e] Total MM 30[f] MM 46[g] MM	G-CSF plus plerixafor	59 (78) 21 (70)[f] 38 (83)[g] p=NS	3.6 (0.6–14.2) 2.8[f] (0.6–8.3) 4.2[g] (0.6–14.2) $p<0.05$	2 (1–3) 2[f] (1–3) 2[g] (1–3) p=NS	Not reported	Not reported
Duarte *et al.*, 2011[21,a]	G-CSF with or without chemotherapy		Previously failed to proceed to apheresis because of low peripheral blood cell count (<10 before apheresis) or peripheral blood stem-cell collection <2.0 after 7 apheresis procedures maximum	56 Total 24 L 32 MM	G-CSF plus plerixafor	42 (75) Total 15 (63) L 27 (84) MM p=0.06	2.6 (0.4–10.6) 2.3 L (1.1–4.6) 2.8 MM (0.4–10.6)	2 (0–4) 2 (0–4) 2 (1–4)	35 (63)	Not reported

TABLE IV Continued

Reference (single-arm studies)	Mobilization				Efficacy of plerixafor					
	Initial therapy	Pts (*n*)	Criteria for poor response (CD34+ cell count ×10^6/kg in peripheral blood)	Patients with poor response (*n*)	Remobilization protocol	CD34+ cells ≥2×10^6/kg [*n* (%)]	Median CD34+ cell collection [×10^6/kg (range)]	Median apheresis days [*n* (range)]	Proceed to ASCT [*n* (%)]	12-Month survival
Hübel *et al.*, 2011[23,a]	Conventional regimen (G-CSF with or without chemotherapy)		Previously failed to proceed to apheresis because of low peripheral blood cell count (<10 before apheresis) or peripheral blood stem-cell collection <2.0 after 7 apheresis procedures maximum	60 Total 28 NHL 17 MM 2 HD 13 Others[h]	G-CSF plus plerixafor with or without chemotherapy	45 (75) 18 (64) NHL 15 (88) MM 2 (100) HD 10 (77) Others	3.35 (0–29.53) 2.21 NHL (0–8.77) 5.38 MM (0–10.98) 2.41 HD (2.01–2.8) 3.3 Others (0.89–29.5)	2 (0–5) 2 NHL (0–3) 2 MM (0–5) 2 HD (2–2) 2 Others (1–4)	40 (67) 16 (57) NHL 15 (88) MM 1 (50) HD 8 (62) Other	Not reported
Hübel *et al.*, 2012[22,a]	Conventional regimen		Previously failed to proceed to apheresis because of low peripheral blood cell count (<10 before apheresis) or peripheral blood stem-cell count <2.0 after 7 apheresis procedures maximum	580 Total 270 NHL 54 HL 256 MM	G-CSF plus plerixafor with or without chemotherapy	428 (74) 175(65) NHL 44 (82) HL 209 (82) MM NHL vs. MM: p<0.0001 NHL vs. HL: p=0.017	3.06 (0–32.6) 2.56 NHL (0–17.4) 3.14 HL (0–32.6) 3.60 MM (0–15.27) NHL vs. MM: p<0.0001 NHL vs. HL: p=0.013	2 (1–5) 2 NHL (1–4) 2 HL (1–4) 2 MM (1–5)	Not reported	Not reported
Lor *et al.*, 2012[25]	G-CSF plus cyclophosphamide chemotherapy	33	Peripheral blood stem-cell collection <2.0 in a median of 3 apheresis sessions	19 Total 10 MM 9 NHL	G-CSF plus plerixafor	16 (84) Total 10 (100) MM 6 (67) NHL	4.32 Total 7.84 MM (2–10.16) 2.45 NHL (0.39–6.45)	3 Total 3 MM (1–11) 3 NHL (1–10)	Not reported	Not reported

TABLE IV Continued

Reference (single-arm studies)	Mobilization				Efficacy of plerixafor					
	Initial therapy	Pts (*n*)	Criteria for poor response (CD34+ cell count $\times 10^6$/kg in peripheral blood)	Patients with poor response (*n*)	Remobilization protocol	CD34+ cells $\geq 2\times 10^6$/kg [*n* (%)]	Median CD34+ cell collection [$\times 10^6$/kg (range)]	Median apheresis days [*n* (range)]	Proceed to ASCT [*n* (%)]	12-Month survival
Malard *et al.*, 2012[26,a]	Fludarabine Lenalidomide	48 NHL 35 MM[i]	Previously failed to proceed to apheresis because of low peripheral blood cell count (<10 before apheresis) or peripheral blood stem-cell collection <2.0 after 7 apheresis procedures maximum	83 Total 48 NHL 35 MM	G-CSF plus plerixafor	— 28 (58) NHL 24 (69) MM	— 2.3 NHL (0.3–13.4) 3.4 MM (1.1–14.8)	— 2 NHL (1–3) 2 MM (1–4)	Not reported	Not reported
Cheng et *et al.*, 2015[13]	G-CSF plus chemotherapy		Peripheral blood cell count <20	22 MM	Plerixafor	Not reported	5.6 (2.3–9.4) 3.5 (2.1–9.2) p=0.282	Not reported	9 (81.8) 9 (81.8)	Not reported

[a] Plerixafor compassionate use programmes (CUPs) or named patient programs for patients having prior failed mobilization attempts (conventional therapies for hematopoietic stem-cell collection had failed; or peripheral blood CD34+ cell count was low after conventional mobilization therapy, and the physician did not think there was a reasonable chance of collecting enough cells).
[b] Of the 7, 4 underwent tandem transplantation.
[c] Includes 10 patients who were predicted to be poor mobilizers.
[d] Of these patients, 30 had already undergone stem-cell transplantation.
[e] Includes 24 patients who were predicted to be poor mobilizers and 52 patients who had failed a previous mobilization attempt (30 of 52 poor mobilizers had already undergone ASCT in the past, and about 16 of them were mobilized with plerixafor).
[f] Previously transplanted.
[g] Not previously transplanted.
[h] Includes 7 children with Wiskott–Aldrich syndrome and neuroblastoma, and 6 patients with other malignant diseases (1 each: seminoma, germ-cell tumour, thyroid carcinoma, testicular carcinoma, composite lymphoma, and chronic lymphocytic leukemia).
[i] Before salvage mobilization with plerixafor, 7 patients (20%) had received a prior autologous hematopoietic stem-cell transplant.

Pts = patients; ASCT = autologous stem-cell transplantation; G-CSF = granulocyte colony-stimulating factor; NHL = non-Hodgkin lymphoma; MM = multiple myeloma; HD = Hodgkin disease; HL = Hodgkin lymphoma; NS = nonsignificant; L = lymphoma.

chemotherapy (cyclophosphamide) as the initial mobilization strategy. Plerixafor plus G-CSF successfully mobilized at least the minimum CD34+ collection target in 84% of the patients (100% of patients with MM and 67% of patients with NHL). The study reported by Calandra *et al.*[20] reported that the success of patients collecting $\geq 2\times10^6$/kg CD34+ cells exceeded 66% overall and was higher for patients with Hodgkin disease (77%) and MM (71%), but not for patients with non-Hodgkin disease (60%).

The remaining seven studies reported results from 13 European countries (Austria, Belgium, Croatia, Czech Republic, France, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain, and the United Kingdom) that enrolled patients in a compassionate use program that provided plerixafor to patients who had failed prior mobilization attempts[17–19,21–23,26]. In a subgroup analysis from the European Consortium of Stem Cell Mobilization, Hubel *et al.*[22] reported results for 580 patients enrolled in European CUPS. In a second report, the same authors[23] presented results for a subgroup of 60 patients from 23 centres in Germany who participated in a CUP. Basak *et al.*[19] reported results for a cohort of 61 patients from 11 Polish centres and for a subgroup of 76 patients from Poland with MM who also participated in a CUP[18]. Duarte *et al.*[21] reported outcomes for a subgroup of 56 patients from 15 participating centres in Spain and the United Kingdom. The study reported by Arcaini *et al.*[17] involved 35 patients from 7 Italian centres participating in a CUP. Malard *et al.*[26] reported outcomes for 83 patients enrolled in a CUP who had previously been treated with fludarabine or lenalidomide. Overall, success in collecting 2×10^6/kg CD34+ cells for patients who participated in European CUPS was significantly higher in those with MM than with NHL (82% vs. 65%, $p < 0.0001$) and also in patients with HL than in patients with NHL (82% vs. 65%, $p = 0.017$)[22]. For the remaining studies, the rates of adequate CD34+ cell collection ranged from a low of 37% in patients with NHL and patients with HL combined[17] to a high of 100% in patients with Hodgkin disease[23].

Peripheral Blood CD34+ Cell Count and Number of Apheresis Procedures: Results from a subgroup analysis of the European Consortium of Stem Cell Mobilization (580 patients) found that, overall, the CD34+ collection yield (given here as millions per kilogram body weight) was significantly higher in patients with MM than in patients with NHL (3.60 vs. 2.56, $p < 0.0001$) and also in patients with HL than in patients with NHL (3.14 vs. 2.56, $p = 0.013$). No differences between the groups in the time of collection were detected[22]. Similarly, Lor *et al.*[25] and Calandra *et al.*[20] reported higher CD34+ cell collection yields in patients with MM than in patients with NHL, but statistical significance was not reported. No significant differences between groups in the time of collection were reported by those authors.

Proportion of Patients Who Proceed to ASCT: DiPersio *et al.* found that 84% (52 of 62) of patients with NHL[6] and 100% (7 of 7) of patients with MM[7] who had failed a prior mobilization regimen underwent ASCT after remobilization with plerixafor. Calandra *et al.*[20] reported that more than 70% of patients who had failed prior mobilization regimens proceeded to ASCT after having been remobilized with plerixafor. Five additional studies reported ASCT rates ranging from a low of 17%[17] to a high of 88%[23].

Survival Rate After ASCT: Only DiPersio *et al.* reported a 12-month survival rate after remobilization with plerixafor. That rate was 86% in patients with NHL and 100% in those with MM[6,7]. None of the other studies reported on this outcome[13,17–23,25,26].

DISCUSSION

Plerixafor is a novel mobilization agent that has been approved for use in Canada with G-CSF in the mobilization of stem cells in patients with NHL or MM who require high-dose chemotherapy and ASCT. The available studies on the use plerixafor for initial mobilization could not answer the question of how mobilization with plerixafor plus G-CSF compares with mobilization using chemotherapy plus G-CSF. Mobilization with plerixafor plus G-CSF appeared to be superior to mobilization with G-CSF alone in patients with lymphoma, but not necessarily superior in patients with myeloma.

Administering chemotherapy for mobilization can introduce additional adverse effects that could contribute to morbidity and might delay patients in reaching transplantation, but the available studies were not designed to answer that type of question (a focus on health care utilization or trade-offs). We therefore felt that the standard mobilization of chemotherapy plus G-CSF was a reasonable practice to continue, but that in patients with lymphoma who could not receive chemotherapy plus G-CSF (because, for example, of renal insufficiency), an initial mobilization with plerixafor plus G-CSF appears to be preferred and is therefore recommended.

The use of plerixafor plus G-CSF "on demand" for patients who appear to be mobilizing poorly was felt to be a useful strategy to maximize the benefits of plerixafor and to minimize the risk of requiring remobilization, therefore allowing patients to proceed to transplantation in a timely fashion. It is accepted that a uniform definition of a poor mobilizer might not have yet been developed, but commonly used measurements of peripheral blood CD34+ cells or stem-cell yields on the 1st day of apheresis were felt to be quite reasonable.

The use of plerixafor plus G-CSF for remobilization is completely endorsed despite the nature of the available literature. Patients who are candidates for ASCT have no other option than to try to reach transplantation and therefore the use of plerixafor plus G-CSF is strongly recommended. With many health care centres opting to use plerixafor plus G-CSF "on demand" in poor mobilizers, the number of patients requiring remobilization is expected to decline over time.

The current Health Canada recommendation is to use plerixafor plus G-CSF in patients with NHL or myeloma. The biologic activity of the drug and the similarities of the stem-cell mobilization process in HL and germ-cell tumours are expected to resemble the activity and mobilization process in NHL and myeloma. Some studies did include some patients with HL and other indications. We therefore

felt that the benefits of plerixafor could be generalized to patients with HL or germ-cell tumours and that plerixafor should be used for those patients in a way similar to that for patients with NHL or myeloma.

REVIEW PROCESS

The health research methodologist (NPV) in collaboration with the lead author (CTK) wrote the initial recommendations and qualifying statement pertaining to the benefit associated with the use of plerixafor for hematopoietic stem-cell mobilization and collection in patients considered for ASCT. That report was circulated to the members of the Stem Cell Transplant Working Group and was discussed during a teleconference, after which the draft recommendations were generated. The ensuing recommendation report was reviewed by the PEBC's Report Approval Panel (scientific director, the PEBC assistant director, and two health research methodologists) to ensure that the guideline development was methodologically rigorous and that the evidence-based recommendations are indeed supported by the evidence in a transparent way. After internal review, the refined report was presented to the entire Stem Cell Transplant Steering Committee to ensure the clinical relevance and utility of the recommendations, and to obtain final approval.

Practice guidelines and recommendation reports developed by the PEBC are reviewed and updated as needed. Please visit the Cancer Care Ontario Web site (http://www.cancercare.on.ca) for the full report and subsequent updates.

PRACTICE GUIDELINE

Evidence from a systematic search of the primary literature, consensus of expert opinion, feedback obtained through the review process, and a final approval given by the Stem Cell Transplant Steering Committee and the PEBC's Report Approval Panel collectively form the basis of this recommendation report, completed in September 2015.

Target Population

The target population for this guideline includes all adult patients considered for ASCT and meeting one of the following criteria:

- Not previously mobilized (that is, upfront mobilization in naïve patients who might or might not be at risk of being poor mobilizers)
- Failing initial mobilization (based on peripheral blood CD34+ cell count before 1st day of apheresis, or total number of CD34+ cells collected on the 1st day of apheresis)
- Failed a prior mobilization attempt (that is, poor mobilizers)

Recommendation 1

- Adding plerixafor to G-CSF is an option for final mobilization in patients with NHL or MM who are eligible for ASCT when chemotherapy cannot be used and only G-CSF mobilization is available.

This recommendation is based on the results of five studies involving patients with NHL, relapsed or refractory HL, and MM who received G-CSF either alone or as part of the initial mobilization therapy. Two randomized controlled trials[6,7] detected that, in patients with NHL or MM, the addition of plerixafor to G-CSF resulted in a greater yield of stem cells and fewer days of apheresis, and allowed more patients to proceed to ASCT. Likewise, three nonrandomized trials with historical controls[8,11,14] reported significantly higher response rates in favour of adding plerixafor.

Qualifying Statements

- The available evidence used patients receiving G-CSF alone as the control group. Therefore, the option of plerixafor as an upfront therapy is specific to patients undergoing initial mobilization with G-CSF and without chemotherapy.
- The evidence is insufficient to support the addition of plerixafor to G-CSF after chemotherapy as initial mobilization in patients eligible for ASCT.
- Adding plerixafor to G-CSF for initial mobilization therapy when chemotherapy cannot be used and only G-CSF mobilization is available is an option regardless of the underlying malignancy [that is, in plasma cell dyscrasias (myeloma, amyloidosis), NHL and HL, and germ-cell tumours].
- Using plerixafor upfront with G-CSF might not be cost-effective (that strategy was not examined in the present review), particularly if compared with the plerixafor "on demand" strategy already recommended. The members of the Working Group therefore determined that, rather than making upfront use a strict recommendation for routine use, such use might be an option when compared with the use of G-CSF alone.

Recommendation 2

- For patients with low peripheral blood CD34+ cell counts (for example, <10/μL) at the anticipated time of stem-cell harvesting or with an inadequate 1st-day apheresis collection, it is recommended that plerixafor be added to the mobilization regimen to maximize stem-cell collection and to prevent the need for remobilization.

This recommendation is supported by seven nonrandomized studies that reported a variety of outcomes, including number of stem cells collected and number of days of apheresis[10,11,13,15,16,24,27]. In general, those studies detected that a better mobilization response is achieved in patients failing their first mobilization attempt when plerixafor is added to their existing mobilization regimens. Additionally, three studies demonstrated that a significant proportion of patients were able to proceed to ASCT with plerixafor[13,15,27].

Qualifying Statements

- Poor mobilization was variably defined in the applicable studies, but fewer than 10/μL CD34+ cells in peripheral blood is a commonly used criterion. Historical data and consensus opinion have identified that the likelihood of successful stem-cell harvest is

low for patients with fewer than 10/μL CD34+ cells in peripheral blood. In such patients, who appear to be at high risk of failing initial mobilization, a strategy of on-demand plerixafor could prevent the need for remobilization and therefore minimize further delays in proceeding to ASCT.
- Plerixafor is recommended regardless of the underlying malignancy [that is, plasma cell dyscrasias (myeloma, amyloidosis), NHL and HL, germ-cell tumours].

Recommendation 3

- For patients in whom a previous mobilization attempt has failed, remobilization with G-CSF and plerixafor with or without chemotherapy is recommended.

Several single-arm studies detected that, with plerixafor and G-CSF with or without chemotherapy, a significant proportion of patients can still collect enough CD34+ cells to proceed to ASCT[6,7,13,17–23,25,26].

Qualifying Statement

- The definition of failed mobilization in this group of studies is variable and includes patients who did not attain at least the minimum number of CD34+ cells or patients who had low numbers of circulating CD34+ cells before apheresis. It is recognized that every attempt should be made to collect enough CD34+ cells in such patients to allow them to proceed to definitive therapy with ASCT.
- Plerixafor is recommended regardless of the underlying malignancy [that is, plasma cell dyscrasias (myeloma, amyloidosis), NHL and HL, germ-cell tumours].

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and the authors of this recommendation report disclosed potential conflicts of interest relating to the topic. One author declared no conflicts of interest, and four (CTK, CB, JK, AX) declared conflicts. CTK reported receiving honoraria for work regarding plerixafor as a clinical reviewer for the Canadian Agency for Drugs and Technologies in Health. CB reported being the president-elect of the Canadian Blood and Marrow Transplant Group, which had received $5000 or more in a single year from Sanofi, the clinical developer of plerixafor. CB, JK, and AX declared that they had received research grant support from Sanofi. JK also declared that he had been a principal investigator for a clinical trial involving plerixafor.

The conflicts of interest declared above did not disqualify any individuals from performing their designated role in the development of this recommendation report.

AUTHOR AFFILIATIONS

*Division of Malignant Hematology, Juravinski Cancer Centre, and Department of Oncology, McMaster University, and †Cancer Care Ontario, Program in Evidence-Based Care, McMaster University, Hamilton; ‡Ottawa Hospital Research Institute and Department of Medicine, University of Ottawa, Ottawa; §Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto; and ‖Division of Hematology, London Health Sciences Centre, Department of Medicine, London, ON.

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