Canada's Drug and
Health Technology Agency

CADTH Reimbursement Recommendation

Optimal Pharmacotherapy for Transplant-Ineligible Multiple Myeloma

Therapeutic Review
May 6, 2024

FMEC Recommendations

The Formulary Management Expert Committee (FMEC) concluded that the evidence included in the systematic review and network meta-analysis (NMA) supports the use of first-line daratumumab in patients with multiple myeloma who are ineligible for transplant. FMEC noted that, in patients who are newly diagnosed, daratumumab-containing regimens such as daratumumab plus bortezomib plus melphalan plus prednisone and daratumumab plus lenalidomide plus dexamethasone showed statistically significant differences in progression-free survival when compared to the base comparator with lenalidomide plus dexamethasone. In relapsed or refractory multiple myeloma, daratumumab plus lenalidomide plus dexamethasone also showed statistically significant differences in progression-free survival compared to lenalidomide plus dexamethasone. However, based on the results from the economic analysis using publicly available prices, a reduction in the price of daratumumab is required for this treatment to be considered cost-effective at conventional willingness-to-pay thresholds in the first-line setting relative to being used as a treatment in the second-line setting.

FMEC recommends the choice of carfilzomib plus dexamethasone or pomalidomide plus bortezomib plus dexamethasone in the second-line or third-line setting be left at the physician's discretion for patients with relapsed or refractory multiple myeloma who received a daratumumab-containing regimen in the first-line setting. FMEC also noted that a difference in efficacy between the 2 regimens was not determined; however, pomalidomide plus bortezomib plus dexamethasone is less costly and has an oral formulation, and thus may be preferred. Another important consideration would be the side effect profile of each drug regimen.

Therapeutic Landscape

What Is Multiple Myeloma?

Multiple myeloma is an incurable plasma cell neoplasm, characterized by an uncontrolled growth of plasma cells in the bone marrow. The preferred first-line therapy for newly diagnosed multiple myeloma is high-dose chemotherapy followed by autologous stem cell transplant. For patients who are not eligible for this procedure because of health risks or other reasons, a number of multidrug regimens can be offered. It is estimated that more than 50% of patients may not be eligible for transplant.

Why Did We Conduct This Review?

Publicly funded drug plans requested this therapeutic review to determine what sequences drugs for transplant-ineligible multiple myeloma should be reimbursed to maximize clinical and cost-effectiveness while considering patient safety, characteristics, experience, and preferences.

Person With Lived Experience

A person with lived experience presented her journey living with multiple myeloma after being diagnosed in 2020 at the age of 77. As an avid traveller, she began noticing her energy levels and strength were declining, and her family physician noted a decline in kidney function, leading to further testing and a diagnosis. She began treatment with Revlimid, dexamethasone, and monthly infusions of zoledronic acid. She reported symptoms such as anemia, neuropathy, diarrhea, bone pain, fatigue, cramps, and concerns of infections. She emphasized the need for treatment protocols to consider patient circumstances when looking at treatment options, highlighting that dexamethasone had unbearable side effects for her treatment specifically. Although she hasn't reached remission, her treatment has kept her proteins stable for 44 months now. She emphasized that for patients, treatment method convenience is important, such as an oral form. Finally, she expressed that reducing side effects such as brain fog, stomach issues, shaking and energy levels are critical for patients.

Stakeholder Feedback

What Did We Hear From Patients?

We received input on the project scope from Myeloma Canada. Patients want treatments that balance efficacy, safety, and quality of life; are least invasive; and are financially accessible.

What Did We Hear From Clinicians?

We consulted clinical experts who provided input on the project scope and feedback to the clinical and health economic reports. It was noted that while they welcomed the project, they also expressed caution given the complexity of the disease, the heterogeneity of patients with multiple myeloma, and the constantly evolving treatment landscape. Clinicians have also highlighted that newer therapies are available, such as chimeric antigen receptor (CAR) T-cell therapy and selinexor, since the initiation of this review.

What Did We Hear From the Pharmaceutical Industry?

We have received input and feedback from multiple manufacturers. They provided input on the project scope and feedback to the clinical and health economic reports. The industry feedback described the strengths and limitations of the NMA and the context around the current treatment landscape.

What Did We Hear From Public Drug Programs?

The drug plans requested (and supported) this therapeutic review on multiple myeloma, specifically on the transplant-ineligible patient population.

Refer to the Stakeholder Input section of the report.

Deliberative Summary

FMEC addressed the following questions based on the results of the clinical and economic analyses, patients' input, and clinicians' input, as well as provisional funding algorithms on the management of multiple myeloma.

Of note, the NMA only included drugs that were identified in the project scope published in May 2021; therefore, any new therapy since that date (e.g., CAR T-cell therapies, selinexor) was not included in the analysis of this review.

Table 1: Why Did FMEC Make These Recommendations?

Questions or considerations	Discussion points
Is there sufficient evidence to support the prioritization of daratumumab-containing regimens in the first-line and/or second-line setting based on clinical and cost-effectiveness?	• For patients with newly diagnosed multiple myeloma who are not eligible for a transplant, FMEC recommends prioritizing a regimen that contains daratumumab as first-line treatment. FMEC discussed the publicly available price of daratumumab, and jurisdictions may need to consider negotiating further price reductions to improve the cost-effectiveness of a daratumumab-containing regimen in the first line of treatment. • Based on the economic analysis, FMEC noted that sequences that used daratumumab-based regimens in the first line generated the highest number of QALYs (between 5.3 and 5.7) but also the highest costs (between $800,000 and $1,000,000) based on publicly available prices. Depending on what these sequences were compared to, the incremental cost-effectiveness ratio consistently exceeded $450,000 per QALY gained. A price reduction is therefore required for daratumumab to be considered cost-effective at conventional willingness-to-pay thresholds, if used in the first-line setting. The degree of price reduction will depend on the currently negotiated prices for all treatment regimens used to treat transplant-ineligible multiple myeloma. • FMEC noted that the results of the network meta-analysis demonstrated that daratumumab + lenalidomide + dexamethasone and daratumumab + bortezomib + melphalan + prednisone regimens have shown statistically superior progression-free survival estimates when compared to lenalidomide + dexamethasone in the first-line setting. • FMEC clinical experts suggested that daratumumab + bortezomib + melphalan + prednisone is no longer clinically relevant in Canada due to increased toxicity with melphalan. • The results of the network meta-analysis were similar to the MAIA clinical trial and the FACON NMA and correlate with the clinical experts' opinions, as well as international guidelines. • Given that patient harms were unable to be evaluated in the NMA, FMEC acknowledges that clinicians need to consider the safety profiles of individual treatment when choosing an optimal first-line or second-line regimen for patients. • The results of qualitative reviews have highlighted the impact of treatments for multiple myeloma on quality of life. The chosen regimen should align with patients' preferences and optimize their experiences with the treatment journey. • FMEC's guest specialists identified that treatment options for patients who are transplant-ineligible would be offered to patients who decline to undergo a transplant; as also heard from the patient with lived experience.

Questions or considerations	Discussion points
Is there sufficient evidence to support the prioritization of lenalidomide-containing regimens in the first-line and/or second-line setting in patients who are less fit and cannot take daratumumab based on clinical and cost-effectiveness?	• FMEC was unable to issue any recommendation for this question: • the proportion of patients with newly diagnosed multiple myeloma who are not eligible for transplant nor suitable for a daratumumab-containing regimen because of frailty is small, and it only represents less than 5% of this population according to FMEC clinical experts • there is a lack of certainty in the clinical evidence for lenalidomide in the first-line and second-line setting.
Is there sufficient evidence to support the prioritization of carfilzomib-containing regimens and pomalidomide-containing regimens based on clinical and cost-effectiveness?	• The clinical efficacy between pomalidomide + bortezomib + dexamethasone and carfilzomib + dexamethasone is comparable based on the results from the NMA. FMEC noted that generic versions of pomalidomide were available at the time of the analysis but prices from Ontario were used and do not reflect the prices paid by other jurisdictions. These lower prices paid across Canada reduce the cost of pomalidomide-based regimens in the economic analysis to be less costly than carfilzomib-based regimens. FMEC recommends a note be added to the economic report to this effect. • For patients with relapsed or refractory multiple myeloma who received a daratumumab-containing regimen in the first-line setting, FMEC recommends the choice between pomalidomide + bortezomib + dexamethasone and carfilzomib + dexamethasone in the second-line or third-line setting be left at the physician's discretion. • FMEC discussed that if using a pomalidomide-based regimen in the second line, the preferred regimen is pomalidomide + bortezomib + dexamethasone based on the NMA. • Of note, selinexor was not considered by FMEC in the second-line setting as it was not available at the time of the review nor included at the time of the initiation of the review.
Is there sufficient evidence to support the prioritization of isatuximab-containing regimens based on clinical and cost-effectiveness?	• FMEC was unable to issue any recommendation for this question. • Isatuximab is only relevant at this time for patients who previously received lenalidomide + dexamethasone with or without bortezomib up to 5 years ago and who have relapsed. Isatuximab is not used in patients who have already received a daratumumab-containing regimen as both drugs have a similar mechanism of action.

FMEC = Formulary Management Expert Committee; NMA = network meta-analysis; QALY = quality-adjusted life-years.

Feedback on Draft Recommendations

We received feedback on the draft recommendation from 1 clinician group, 1 patient group, 5 manufacturers, and public drug plans.

All agreed with the committee's recommendation; however, several stakeholders requested clarification on the exclusion of recently reimbursed regimens for transplant-ineligible multiple myeloma from this review. As previously stated, these were out of scope for this project as treatments approved after May 2021 were not included in the analysis.

FMEC Information

Members of the committee: Dr. Alun Edwards, Ms. Valerie McDonald, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, Dr. Emily Reynen (Chair), Dr. Irwindeep Sandhu (guest specialist), and Dr. Darrell White (guest specialist)

Meeting dates: October 17, 2023, and November 30, 2023

Conflicts of interest: None

Special thanks: We extend our special thanks to the individual who presented directly to FMEC on behalf of patients with lived experience as well as Myeloma Canada, a patient organization that represents the community of those living with multiple myeloma, including Jessy Ranger, Martine Elias, and Vivien Lougheed.

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