


**SPECIAL  
SUPPLEMENT**

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# CANADIAN HEMATOLOGY TODAY



## **ROUNDTABLE DISCUSSION: NAVIGATING CHALLENGING TREATMENT DECISIONS IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM)**

**Martha Louzada, MD, MSc**  
**Arleigh McCurdy, MHA, MD, FRCPC**  
**Michel Pavic, MD**  
**Chris Venner, MD, FRCPC**

# ABOUT THE AUTHORS



## **Martha Louzada, MD, MSc**

Dr. Martha Louzada, BSc, MD, MSc is a Brazilian-born Hematologist where she completed her medical training. She is an Associate professor of Medicine and a Hematology Consultant at the University of Western Ontario/London Health Sciences Centre in London, Ontario, Canada, joining the Department of Medicine in July 2010. She also holds a Cross Appointment in Oncology through the London Regional Cancer Program and a Cross Appointment as Associate Professor in the Department of Epidemiology and Biostatistics, UWO 2013 to present. Dr. Louzada is currently the Multiple Myeloma Working Group Director at LRCP. She came to Canada in 2006 where she completed a 3-year postdoctoral fellowship in Thrombosis along with a Masters in Epidemiology and Community Medicine Program at the University of Ottawa/Ottawa Hospital, Canada. Since then she has had multiple publications in the thrombosis and myeloma fields. In October 2009 she was awarded the Phil Wells Trainee Research Award at the University of Ottawa recognizing Excellence in Haematology Research. She received her Master's in Epidemiology degree in January 2011. Dr. Louzada is a member of CanVECTOR, the Canadian Myeloma Research Group and Member of the Steering Committee of the Canadian Myeloma Research Group Database. Dr. Louzada has a special interest in venous thromboembolism and cancer and also translational research in myeloma. She has over 50 peer reviewed publications and 30 oral or poster publications at International Hematology Meetings.

## **Arleigh McCurdy, MHA, MD, FRCPC**

Dr. Arleigh Robertson McCurdy is an Assistant Professor in the Faculty of Medicine at the University of Ottawa and Lead of the Myeloma Program at The Ottawa Hospital. Her clinical research is focused on multiple myeloma and related disorders. She is an active member of the Canadian Myeloma Research Group and the Canadian Cancer Trials Group Myeloma Committee. She is a member of the Myeloma Canada Board of Directors and the International Myeloma Working Group.



## **Michel Pavic, MD**

Dr. Michel Pavic is a medical oncologist and the head of the hemato-oncology department of the CIUSSS de l'Estrie CHUS. He specializes in the treatment of myeloma. Dr. Pavic is also the director of medical research in oncology at the Cancer Research Institute for the University of Sherbrooke (IRCUS). He graduated from University Claude Bernard Lyon 1 (France). Dr. Pavic currently serves as the President of the Quebec Plasma Cell Diseases Group (GMPQ).



## **Chris Venner, MD, FRCPC**

Dr. Chris Venner completed his medical training at the University of Calgary and the University of Alberta. He later attended the University of British Columbia to complete a sub-speciality degree in Hematology. He then went onto pursue a Plasma Cell Dyscrasias Fellowship jointly through the Leukemia/Bone Marrow Transplant Program of British Columbia, St. Bartholomew's Hospital and the London School of Medicine and the National Amyloidosis Centre. He subsequently joined the National Amyloid Centre as a staff physician before returning to Edmonton and the Cross Cancer Institute and led the Malignant Hematology Program and the Myeloma/Plasma Cell Dyscrasias group. In 2021 he joined the BC Cancer-Vancouver Centre to advance the Plasma Cell Dyscrasias Program. In addition to being actively involved in hematology clinical trials, his current academic interest involves clinical outcomes research in plasma cell dyscrasias, examining the evolution of therapy in these diseases and the impact novel combinations have on survival. Much of this work is done through the Canadian Myeloma Research Group through activities in the CMRG Canadian Multiple Myeloma Database initiative which he led as Chair (2014-2021), and the CMRG clinical trials group. He is also the co-chair of the Myeloma Sub-Committee with the Canadian cancer Trials Group.



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## Introduction

**Treating relapsed and refractory multiple myeloma has been challenging, due to a lack head-to-head trial comparisons of the various available regimens and poor cross-Canada access to currently approved regimens. New therapeutic combinations in this setting open up more options to consider, and also the possibility of greater efficacy and more judicious use of available drug classes to avoid resistance. Oncologists shared insights on how they choose between these therapeutic regimens for various patient subgroups.**

**Dr. Christopher Venner:** For relapsed and refractory multiple myeloma, the new Canadian Agency for Drugs and Technologies in Health (CADTH) algorithm supports two new anti-CD38-based regimens: isatuximab plus pomalidomide and dexamethasone (Isa-Pd), and isatuximab plus carfilzomib and dexamethasone (Isa-Kd). What are some of the clinical and treatment history features that would sway you toward one regimen over the other?

**Dr. Michel Pavic:** Isa-Kd is especially valuable from my perspective, as it is an option for patients relapsing after autologous stem cell transplants (ASCT) and lenalidomide maintenance therapy. These patients are not eligible for daratumumab, lenalidomide, dexamethasone (DRd), which would normally be our first choice in the second-line setting. In Quebec, pomalidomide is not available in the second-line setting, but only in the third-line setting. By that time, most patients would already have received an anti-CD38 medication.

**Dr. Arleigh McCurdy:** I agree that Isa-Kd is best for patients who are lenalidomide-refractory and naïve to anti-CD38 in the second-line setting. In Ontario, we also don't yet have access to pomalidomide as second-line therapy. However, I do find Isa-Kd challenging in older patients, due to the treatment frequency burden and higher degrees of cytopenia and fatigue on this treatment, compared to the previous combination of daratumumab, bortezomib, and dexamethasone (DVd), though the efficacy is much better. I expect Isa-Pd will be used in the future for the dwindling population of people in the third line setting who are anti-CD38 naïve.

**CV:** In British Columbia, we will be giving carfilzomib weekly, with Isa-Kd and I believe there is data to support that, which will be presented at an upcoming meeting. I do agree that the most likely populations for these new isatuximab-based regimens will be patients who are refractory to lenalidomide. Most of our frontline patients will have already been initiated on daratumumab.

**Dr. Martha Louzada:** I think these regimens will also be reserved for fitter patients who underwent ASCT and can tolerate carfilzomib. In the non-transplant eligible setting, carfilzomib can cause significant harm.

**MP:** In my practice, we use Isa-Kd immediately before ASCT in patients who relapse after induction treatment for ASCT, and who don't respond well to lenalidomide, bortezomib, dexamethasone (RVd).

**CV:** As a Canadian community, we need to look at dedicated, prospective clinical trials for this population of patients who relapse after induction treatment for ASCT. I would also preferentially choose Isa-Kd, as I would for any patient relapsing on RVd. Assuming the patients are still transplant eligible, the patients should still be able to tolerate Isa-Kd. There is especially scant data, however, on whether patients should continue on the Isa-Kd regimen post-transplant.

**AM:** Historically, in Ontario, when we would use CyBorD and then switch to RVd, we could access lenalidomide maintenance after the transplant. It would be nice to have uniform assurance across the country that clinicians wouldn't be affecting patients' future ability to access Isa-Kd for these patients prior to ASCT. It seems archaic to not use Isa-Kd, and to have to use more toxic medications instead.

**CV:** With the CADTH provisional funding algorithm, virtually all patients will be exposed to three classes after only one to two lines of treatment. For patients refractory to all three classes, the options are somewhat primitive, such as carfilzomib, cyclophosphamide, and dexamethasone (KCd). The new kid on the block, so to speak, is the combination of selinexor, bortezomib, and dexamethasone (XVd). For patients who are naïve or still sensitive to proteasome inhibitors, would you recommend KCd or XVd?

**ML:** This is a difficult question. Those patients who are refractory to immunomodulatory drugs and anti-CD38 medications are just starting to emerge. If they don't have a private drug plan, there are few options. Even though CADTH says cyclophosphamide is a potential addition, we don't have access in Ontario. Getting pomalidomide in the second-line setting can also be difficult, though compassionate supply may be available. Selinexor is an oral medication, which can be appealing from a convenience perspective.

**MP:** In Quebec, selinexor isn't yet reimbursed for patients, but we have compassionate access. When a patient is refractory to lenalidomide and already exposed or refractory to anti-CD38 medications, the question is whether to use the best proteasome inhibitor first. If we think that patients will not require a third or fourth line, I think that it's better to go with KCd. However, for a young patient for whom we want to provide a lot of options, I think it's better to first give XVd, and then KCd.

**AM:** It's very difficult to distinguish efficacy outcomes via indirect treatment comparisons of KCd versus XVd. We have to instead consider which regimen is best suited to the patient.

**CV:** The most challenging type of patient population regarding the decision between the proteasome inhibitor-containing regimens is the frontline post-DRd patients, as these patients won't have access to pomalidomide. If the patient doesn't tolerate XVd, but there is still activity with the bortezomib backbone, one can always switch to a cyclophosphamide-based regimen. I do think it is best to save carfilzomib. However, for a more aggressively relapsing patient, a carfilzomib-based option may be better first.

**AM:** In the situation of treating a post-DRd patient where pomalidomide isn't accessible, I would also lean towards XVd and not KCd. Even for patients who have a more aggressive relapse, carfilzomib can work quickly but the response is usually not durable in this clinical context. I'm not sure that it would be superior to XVd for this patient population.

It will be interesting to see what the impact of Ciltacabtagene autoleucel (cilta-cel) is in this second-line setting. The requirement may be that three lines are required for eligibility, but as a [clinical] group, we should be very vocal about the difference between lines and classes of drugs, so that cilta-cel can be considered earlier for these patients. So far, we are seeing the efficacy benefit of moving the anti-BCMA [B-cell maturation antigen] agents to second or third line, as opposed to the fourth-or-higher line.

**CV:** I would agree that these clinical trials are vital, and the landscape will be changing much more rapidly than we anticipate. Regarding nuanced patient populations who can be challenging in the relapse setting, I do have some minor hesitation with carfilzomib in patients with advanced renal impairment. With XVd, patients do not require dose adjustments. What about patients with more high-risk

cytogenetics in the relapse setting?

**MP:** As long as we do not have access to minimal residual disease (MRD) testing, it is difficult to change our treatment approach. When it is possible to monitor the response better, and to add other molecules to try to achieve a better response, we could have a specific treatment for these patients.

**MP:** For second-line patients who relapse with high risk disease, if I have a choice between XVd and KCd, I may try XVd first, to be sure that the patient has a second option in case it's needed.

**CV:** I have two other extreme cases that I have struggled with recently. For patients with plasma cell leukemia, are there any therapies at our disposal?

**ML:** It's an unmet need. We need to focus on this population. At our practice, we have had some success in inducing these patients with bortezomib, epirubicin, and dexamethasone followed by bortezomib, cyclophosphamide, and dexamethasone (PAD-VCD). However, after the patient goes through their first ASCT, they progress while awaiting a second transplant or a reduced-intensity conditioning allogeneic stem cell transplant.

**CV:** For patients with CNS involvement, given that both selinexor and pomalidomide cross the blood brain barrier reasonably well, would you choose this option?

**AM:** In the context of CNS myeloma in the relapse context, I would choose XVd. However, we only see this once or twice a year in our centre.

**CV:** I want to hone in on the supportive care for the regimens that we've discussed tonight. How do you practically approach GI toxicity with selinexor?

**MP:** It's very important to be very proactive, and not to wait for side effects, but to anticipate it and maximize the patient's anti-nausea treatment before the first dose. It's also important to decrease the dose of selinexor quickly if the patient develops nausea. It's been demonstrated that adjusting the dose does not reduce efficacy in these scenarios.

**CV:** In patients who have relapsed after a few lines of therapy, thrombocytopenia can become a big issue. Do you push on with maximal supportive care with transfusions or start with a lower dose of the drug?

**ML:** This is somewhat patient specific. If the patient is tolerating a full dose or a higher dose from a GI side effect or peripheral neuropathy side effect perspective, I don't reduce the dose.

**MP:** I agree. I also tolerate a lower platelet count. However, I may decrease the dose if the platelet count drops to 20,000 or 30,000 platelets per microliter.

**ML:** If the patient is receiving bortezomib each week, they can get a complete blood count every week as well. If the disease is well-controlled, you can dose reduce, and get disease control with less side effects, not only regarding

cytopenia, but other side effects as well. However, if you have a patient who is tolerating the treatment, but you know from their history that the disease will bounce back if you reduce the dose, then you may be less likely to dose reduce in order to avoid thrombocytopenia. This is where some of the art of medicine comes in.

**AM:** I agree, when the disease is behaving aggressively, you have to respond in kind. I treat aggressively and treat cytopenia with supportive care.

**CV:** Let's move on to carfilzomib. Would there be any patients for whom you would not choose this treatment due to the cardiovascular risks?

**MP:** Some patients tolerate carfilzomib very well, and others not only develop cardiac insufficiency, but also develop extreme fatigue and high blood pressure. This is difficult to predict. If the patient's tolerance is not good, I reduce the dose. I try to do an echocardiogram every four to six months for patients taking this medication.

**AM:** If the patient is over 75 with a cardiac history, that would make me pause with going ahead with carfilzomib. In practice, upwards of 50% of people on carfilzomib end up initiating or up-titrating their hypertension drug.

**CV:** I also find it's difficult to define which patients will have challenges. With older patients, I have used a step-wise approach to see what they can tolerate and I have successfully treated them with carfilzomib. However, it's important to be very cognizant of the many comorbidities that can be exacerbated by this drug.

**MP:** Patients should be educated on when and how they should alert their provider, so that their dose can be modified immediately. I encourage physicians not to wait until the next cycle, but to see the patient after two weeks to ensure they are tolerating the new regimen.

**In the end, Canadian hematologists/oncologists are fortunate to have numerous novel therapies at their disposal for the treatment and management of RRMM patients. Although reimbursement challenges remain and there is still a need for the emergence of longer-term data with novel classes and agents, clinicians have a broader armamentarium available to them today. Specific patient sub-populations present unique challenges in terms of the sequencing of therapies, with the ultimate goal being the need to manage potential adverse events and to choose regimens that are best suited to the individual patient.**

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