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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.

MULTIPLE MYELOMA MANAGEMENT: WHAT COMES AFTER LENALIDOMIDE-BASED THERAPY?

Over the past two decades a myriad of new combination strategies and therapeutic agents for the treatment of multiple myeloma (MM) have been developed. Novel drug classes such as proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies have demonstrated very promising efficacy outcomes related to survival endpoints and improvements in quality of life for myeloma patients.¹⁻⁷ Data from the United Kingdom shows that over a fifteen year period from 2003 to 2017, 52.6% of patients with myeloma were alive 5 years after diagnosis and 29% after 10 years. Other researchers have evaluated The Surveillance, Epidemiology, and End Results (SEER) database to assess the probability of survival of myeloma patients, comparing treatment strategies between non-novel and novel therapies (e.g; bortezomib, lenalidomide, pomalidomide) (**Figure 1**).⁸ Overall, 7,139 newly diagnosed patients with MM between 2006–2012 were able to link with the social security administration Master Death File for analysis. Patients younger than 65 years old at diagnosis had better survival than those 65 years and older ($P < 0.01$) and 19.5% of MM patients had an autologous stem cell transplantation (ASCT) during the same time period, with an improved survival experience than those without SCT ($P < 0.01$). Among the newly diagnosed cohort in this analysis who received a MM treatment ($n = 4,902$), patients treated with novel therapies within 1 year of diagnosis showed significantly better survival than those with only non-novel therapies ($P = 0.01$). In this large dataset, a greater proportion of MM patients survived for 2 years post diagnosis in 2012 (87.1%) than in 2006 (69.9%), whereas the 2-year survival was consistent for matched control patients without MM (93.9–97.4%) during the same time period).⁸

Despite the improvements in survival outcomes, the addition of these novel agents to the treatment armamentarium for MM has resulted in a corresponding increase in the lifetime cost of MM treatment. In the above-mentioned study, researchers found that total per patient per month (PPPM) all-cause healthcare costs increased from \$3,263 PPPM in 2000 to \$14,656 PPPM in 2014 among newly diagnosed MM patients, which were primarily driven by costs of outpatient services, such as laboratory, radiology and physician visits, among others.⁸ In Canada, even though over 60%⁹ of the population has private drug insurance, the heavy costs associated with multiple myeloma therapy do predominantly fall under the publicly-funded system. A Canadian analysis from 2014 in patients ineligible for SCT calculated and compared the total annual drug cost of the two maintenance therapy options. Costs were based on 1.3mg/m² of bortezomib on days 1, 4, 8, 11 every three months, plus 50 mg of prednisone every other day, or 10 mg of lenalidomide on days 1 through 21 of each 28-day cycle. Administration costs including oncology nursing time and pharmacist workload, and pharmacy costs including a 10% markup and dispensing fees were added to the acquisition cost of bortezomib and lenalidomide, respectively. Unit and labour costs were obtained from public Canadian sources. The results of this Canadian cost impact analysis demonstrated that the total annual costs of treatment per patient were \$20,106, and \$108,741 for bortezomib and lenalidomide, respectively.¹⁰ As such, access to certain drugs or drug combinations is restricted for myeloma patients and Canadian clinicians despite this being an understandable approach from a public resource utilization perspective.

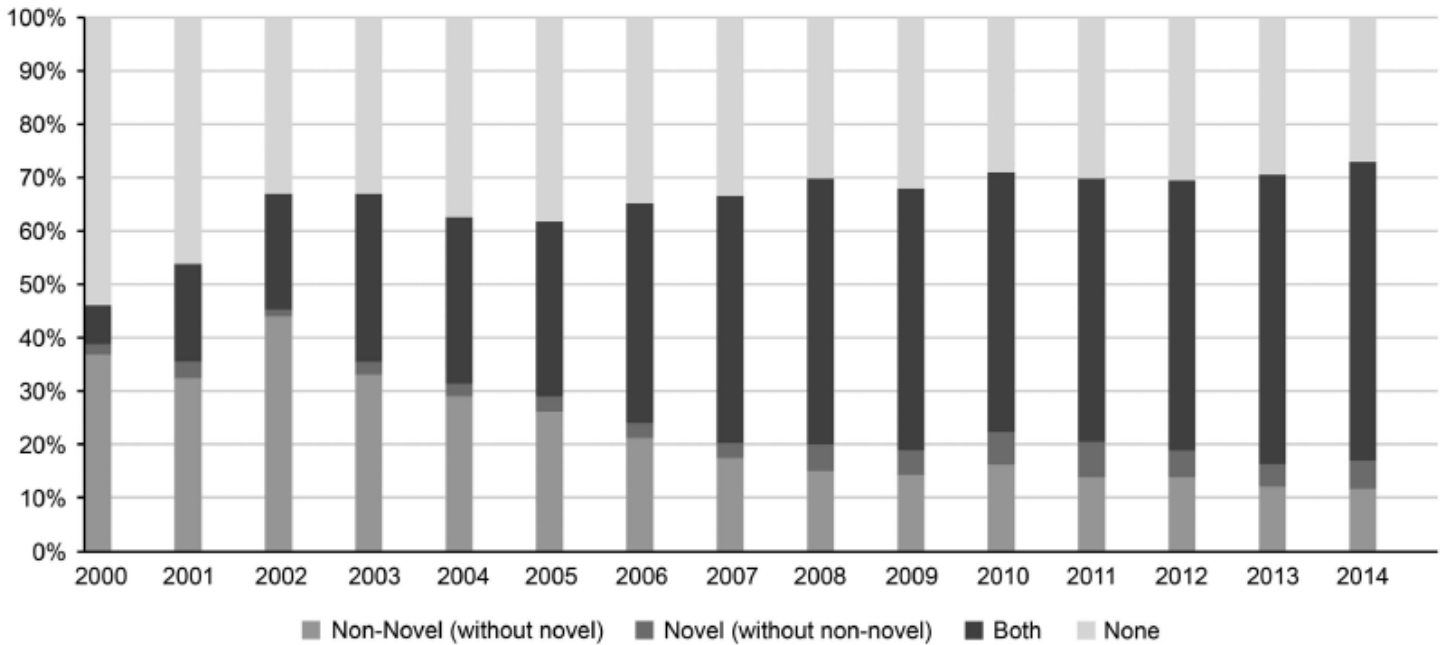


Figure 1. Multiple myeloma treatment used within 1 year after diagnosis, by year of diagnosis. Note: novel treatment include: bortezomib, carfilzomib, lenalidomide, panobinostat, pomalidomide and thalidomide. Non-novel treatment include: arsenic trioxide, bendamustine, busulfan, cisplatin, cyclophosphamide, doxorubicin, etoposide, melphalan, prednisone, dexamethasone, rituximab, vincristine and vorinostat; adapted from Fonseca et al, 2017.

Over the past decade, lenalidomide has become the most widely-used backbone therapy in multiple myeloma (MM), both in the front-line and relapsed settings.¹⁻⁷ In Canada, lenalidomide-based therapy is approved for newly diagnosed, transplant ineligible MM patients in combination with dexamethasone or as triplet therapy in combination with bortezomib and dexamethasone (VRd and RVd Lite) or in combination with daratumumab and dexamethasone (DRd).²⁻⁴ In the transplant eligible (TE) setting, lenalidomide is approved as single-agent maintenance therapy post-ASCT once adequate hematologic recovery [ANC $\geq 1,000/\text{mm}^3$; platelets $\geq 75,000/\text{mm}^3$] is achieved. It may continue until disease progression or unacceptable toxicity occurs. In some jurisdictions, VRd is funded as a pre-transplant option.

The addition of lenalidomide as maintenance post-ASCT has improved progression free survival (PFS) in TE patients as confirmed by the Canadian Myeloma Research group (CMRG) real world evidence study that included 1256 patients of which 57.6% received lenalidomide maintenance. The median PFS was 58.2 months (95% Confidence Interval [CI]: 52.0–64.0) in the lenalidomide group which was significantly superior to the 34.6 months in the non-lenalidomide group (95%CI: 30.7–37.7, $P < 0.0001$).¹¹ In Canada, lenalidomide maintenance is conventionally used to progression given the reimbursement limitations in public funding for drug re-utilization. As a consequence, virtually all patients exposed to lenalidomide will inevitably become refractory to the drug, unless treatment is discontinued early due to adverse events. In addition, the sequencing of therapy post-

lenalidomide poses another challenge, given that several studies have evaluated the outcomes of anti-myeloma therapy after lenalidomide exposure and after lenalidomide refractoriness, suggesting that outcomes may be better for those lenalidomide exposed but not resistant.¹²⁻¹⁴

In the relapsed setting, the first choice in second line therapy for patients who are lenalidomide-naïve includes a combination of daratumumab, a CD-38 monoclonal antibody, lenalidomide and dexamethasone (DRd). In the pivotal POLLUX trial, 569 patients with multiple myeloma who had received one or more previous lines of therapy were randomized to receive lenalidomide and dexamethasone either alone (control group) or in combination with daratumumab (daratumumab group). The primary end point was progression-free survival. At a median follow-up of 13.5 months in a protocol-specified interim analysis, 169 events of disease progression or death were observed (in 53 of 286 patients [18.5%] in the daratumumab group vs. 116 of 283 [41.0%] in the control group; hazard ratio, 0.37; 95% confidence interval [CI], 0.27 to 0.52; $P < 0.001$ by stratified log-rank test). The Kaplan–Meier rate of progression-free survival at 12 months was 83.2% (95% CI, 78.3 to 87.2) in the daratumumab group, as compared with 60.1% (95% CI, 54.0 to 65.7) in the control group. In a long-term follow up, DRd patients achieved a median progression free survival of 47 months.^{6,15}

For patients exposed or refractory to lenalidomide there are several potential options. The OPTIMISM trial evaluated the impact of pomalidomide, bortezomib and

dexamethasone (PVd) versus bortezomib and dexamethasone (Vd) in patients who had received 1 to 3 prior lines of therapy.¹⁶ In this study, all patients had received a prior lenalidomide-containing regimen for at least 2 consecutive cycles. The median PFS in the pomalidomide, bortezomib, and dexamethasone group was 11.2 months compared with bortezomib and dexamethasone group which was 7.1 months (median 11.2 months [95% CI 9.66–13.73] vs 7.1 months [5.88–8.48]; hazard ratio 0.61, 95% CI 0.49–0.77; $p < 0.0001$).¹⁶ A recent subgroup analysis of the OPTIMISMM trial evaluated outcomes in patients at first relapse (N=226) by lenalidomide-refractory status, prior bortezomib exposure, and prior SCT. Results of this analysis shows that second-line PVd significantly improved PFS vs Vd in lenalidomide-refractory patients (17.8 vs 9.5 months; $P = 0.0276$) and it was slightly better in lenalidomide-nonrefractory patients (22.0 vs 12.0 months; $P = 0.0491$). Significant improvement in overall response rate was also observed with PVd vs Vd in lenalidomide-refractory (85.9% vs 50.8%; $P < 0.001$) and lenalidomide-nonrefractory (95.7% vs 60.0%; $P < 0.001$) patients, with similar results regardless of prior bortezomib use or ASCT. No new safety signals were observed. These data demonstrate the benefit of PVd at first relapse, including immediately after upfront lenalidomide treatment failure.¹²

Another pivotal study is the CASTOR trial which evaluated daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone alone in relapsed MM.¹³ In a post-hoc analysis to the original CASTOR trial based on treatment history and longer follow-up, researchers demonstrated that the DVd regimen prolonged progression-free survival (median: 16.7 versus 7.1 months; hazard ratio, 0.31; 95% confidence interval, 0.24-0.39; $P < 0.0001$) and improved the overall response rate (83.8% versus 63.2%; $P < 0.0001$) compared with bortezomib and dexamethasone alone. The progression-free survival benefit of DVd was more pronounced in patients with 1 prior line of therapy (median: not reached versus 7.9 months; hazard ratio, 0.19; 95% confidence interval, 0.12-0.29; $P < 0.0001$).¹⁴ Nevertheless, those refractory to lenalidomide had an unsatisfactory response with median PFS of only 9.8 months.

Other pomalidomide and dexamethasone-based combination regimens are currently under evaluation in phase II and III studies; and include the addition of isatuximab, or carfilzomib, or daratumumab, or cyclophosphamide.¹⁶⁻¹⁸ The vast majority of subjects in these trials included patients who were refractory to lenalidomide after 2 or more prior lines of therapy. The pooled overall response rate across these trials is approximately 70%. However, the pooled median PFS was shown to be around 10 months regardless of the regimen used. Recently, the CMRG presented the results

of 73 real-world patients treated post-lenalidomide maintenance. The median PFS for the entire cohort treated with daratumumab-based regimens was 16.96 months (95% CI 11.47-23.44). The median PFS of the individual regimens was reported as follows: DPd 17.65 months, DRd not reached and DVd 11.47 months ($p = 0.46$).¹⁸

Other MM regimen combinations utilizing Selinexor, an XPO-1 inhibitor have been investigated and show promising results but are currently not publicly funded in Canada but may be available through clinical trials. Emerging agents such as belantamab mafodotin, a BCMA targeted conjugated monoclonal antibody, cereblon modulators, CAR-T cell therapy and bi specific T-cell engagers targeting various MM cell membrane proteins are currently under investigation.

In summary, the sequencing of therapy in MM is complex. Lenalidomide-based regimens represent the cornerstone of treatment for newly-diagnosed transplant-ineligible MM patients and for transplant eligible patients, and in the maintenance phase. Although there are numerous potential drug combinations to be used in a second line setting and beyond, clinical trial results for patients refractory to lenalidomide are somewhat disappointing conferring a median PFS of only 10 to 12 months. Treatment choices must be carefully considered to take into consideration availability, treatment-related adverse events and potential long-term outcomes.

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