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The survival impact of maintenance lenalidomide: an analysis of real-world data from the Canadian Myeloma Research Group national database

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Letter to the Editor

Multiple myeloma (MM) is an incurable malignancy of mature plasma cells. Treatment of MM focuses on obtaining a deep and durable remission to improve overall and progression-free survival (PFS). Patients with good functional status ≤70 years of age are generally considered eligible for treatment with bortezomib-based induction chemotherapy followed by autologous stem cell transplant (ASCT) which has demonstrated a PFS and overall survival (OS) benefit in large, randomized controlled trials. [1–6] The use of lenalidomide maintenance (LM) following ASCT is based on 4 large randomized control trials and a meta-analysis demonstrating improvement in both PFS and OS. [2, 5, 7–9]

Currently, data validating the use of LM in the real-world, Canadian landscape, in which LM is publicly funded, is limited. [10–13] An analysis of the survival impact and adverse effects of LM in large, real-world cohorts is of considerable importance. To address this knowledge gap, we conducted a retrospective, observational study of patients meeting IMWG criteria for MM who were treated with upfront bortezomib-based induction chemotherapy followed by ASCT. [14] Data was collected from the Canadian Myeloma Research Group Database (CMRG-DB), a comprehensive collaborative data-sharing platform that pools data from academic cancer centers across Canada and includes legacy data dating back to 2007. The project was approved by Health Research Ethics Board of Alberta. We included patients receiving either lenalidomide monotherapy as maintenance or no maintenance (non-LM). Charts were reviewed with regard to demographics, response and adverse effects. The primary outcomes of this analysis were PFS, OS and progression-free survival 2 (PFS2) defined as time from initiation of second line chemotherapy to death, relapse or last follow-up. Progression was defined as per the International Myeloma Working Group (IMWG) criteria with an additional endpoint of near complete response (nCR) in in whom CR status was not confirmed by bone marrow biopsy. [15] Data was analyzed using version 9.4 of the SAS system for Windows with Kaplan-Meier curves to evaluate PFS and OS. Chi-squared analysis was used for dichotomous variables. A p-value of <0.05 was considered statistically significant.

We included 1256 patients beginning induction treatment between January 2007 and January 2016. Seven hundred and twenty-three patients (57.6%) received LM and 533 (42.4%) did not. All relevant baseline characteristics of each group are illustrated in Table 1.

The median follow-up was 49.1 months in the LM group (range 8.6 – 124.8 months) and 45.3 months in the non-LM group range (4.5 – 141.1months). At the time of analysis, 397 (54.9%) of the LM group had not yet progressed compared to 198 (37.2%) of patients in the non-LM group.

The median PFS was 58.2 months (95% CI; 52.0 – 64.0) in the LM group compared to 34.6 months in the non-LM group (95% CI; 30.7 – 37.7, $p < 0.0001$), Figure 1A. The five-year OS was 81% in the LM group compared to 61.5% in the non-LM cohort. The median OS was 98.3 months in the non-LM cohort (95% CI 83.5) but not reached ($\geq$ 124 months) in the LM group ($p < 0.0001$, Figure 1B). There was no difference in PFS ($p=0.66$) or OS ($p=0.75$) between 21/28 day and 28/28 lenalidomide dosing schedules. Median PFS2 was NYR in the LM cohort compared to 64.2 months (95% CI; 55.3 – 74.8, $p<0.0001$).

Response rates were deeper in the LM cohort including nCR/CR (52.0% versus 45.2%, $p=0.05$) and ≥VGPR (93.9% versus 80.7%, $p<0.01$). The PFS benefit of lenalidomide persisted in those achieving a nCR/CR ($p<0.0001$), VGPR ($p=0.0006$) and PR ($p=0.03$). The presence of high-risk cytogenetics was associated with reduced PFS and OS in all patients (Table 2). While the worse outcome could not be overcome entirely with the use of maintenance both median PFS and OS were improved regardless of cytogenetic risk (Table 2).

Common indications for dose reduction or medication discontinuation were cytopenias (27.7%), rash (10.8%), infection (9.5%) and fatigue (8.1%). 19.6% discontinued therapy prior to relapse. Venous and arterial thrombosis during frontline treatment was not significantly different between the groups at 2.6% in the non-LM group compared to 5.4% in the LM group ($p=0.5$). Rates of SPMs were observed in 6.4% of the non-LM group and 3.4% of the LM patients ($p=0.32$). Primary sites included skin, lung, bladder and prostate in the non-LM group and breast, brain, lung, kidney and one case of CLL in the LM group.

This analysis from the CMRG-DB is the first dataset analyzing the use of LM following ASCT in the real-world Canadian landscape. Our data validates findings of large, phase 3 randomized controlled trials illustrating a positive impact of LM on PFS and OS in a real-world setting. [2, 4, 7–9] The median PFS data demonstrated a clear advantage for LM. The median OS data also strongly favoured the use of LM. The disease control and survival advantage of LM persisted in patients with standard- or high-risk cytogenetics. Interestingly, patients with high-risk cytogenetics treated with LM had superior PFS and OS compared with standard-risk patients in the non-LM cohort, a finding that supports using LM even in patients anticipated to have the poorer survival outcomes associated with these cytogenetic abnormalities. Lastly, the improved PFS2 outcomes in LM patients demonstrates that non-LM patients do not "catch up" to their maintenance counterparts with second-line therapy.

LM further improved survival outcomes in each response category, including those in the nCR/CR group. This suggests that the impact of LM on PFS and OS goes beyond simply improving patients' response criteria and offers additional survival advantages even in those who achieve a nCR/CR, perhaps through an immune as well as a cytotoxic effect.

Although most patients required a dose reduction or medication discontinuation at some point during their treatment, only 19.6% of patients discontinued therapy prior to relapse. This suggests that LM is well-tolerated.

Limitations of our study include its retrospective, observational nature. Patients were enrolled who started chemotherapy prior to 2016 and significant changes have emerged in the field of myeloma in recent years, particularly with regards to novel chemotherapeutic agents in the setting of relapsed disease. These may have influenced the OS data which depends in part on treatment received for disease recurrence. Given that the non-LM cohort largely comprises of those starting chemotherapy prior to 2012, these patients may not have had the same access to clinical trials or novel combination therapy as their LM counterparts. On the other hand, patients progressing on LM might be expected to experience poorer results with second-line therapy, which was not the case based on PFS2 data. However, the similarity of our data when compared to large scale, randomized, controlled trials suggests that the impact of this temporal relationship

between the LM and non-LM groups may not significantly impact our results. Further, the availability of additional agents only affects the PFS2 and OS outcomes. The cohort presented here is still reflective of the impact of LM on disease control in the post-ASCT setting as measured by PFS.

Lastly, the recent adoption of LM limits our ability to see its full impact on survival outcomes as many of LM patients have not yet experienced their first relapse. Longer follow-up will allow further assessment of the impact of maintenance therapy, particularly in the era of improved therapy for relapsed disease.

Despite the limitations of retrospective data, large multicentre datasets have undeniable merits as they allow for evaluation of the generalizability of new treatments in patients who would not meet eligibility criteria for a clinical trial. Such datasets also provide lengthy and detailed follow-up of real-world data beyond the line of treatment in question, which can be challenging to collect in prospective randomized control trials. [2, 5, 9–11] Furthermore, those with early relapse as well as long-term disease-free survivors are easily identified in these large, retrospective datasets. Examination of their data will be useful in the determination of contributing and prognosticating factors in these, and other, patient subsets.

In summary, our retrospective cohort validates the data seen in large phase 3 trials demonstrating the positive impact LM has had on PFS, OS and response in the real-world setting. This data supports the ongoing use of LM as a current standard of care.

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Table 1. Baseline characteristics of lenalidomide maintenance and non-lenalidomide maintenance groups.

Characteristic	No Maintenance N	Maintenance N	p value
Patients	533	723	
Age at diagnosis, Median (range) in (years)	57.9 (32.4 – 71.4)	58.1 (30.4 – 72.2)	0.711
Male (%)	332 (62.3)	443 (61.3)	0.714
Lab Values at Diagnosis, Median (range)			
Hemoglobin (g/L)	104 (39-169)	107.5 (53-173)	0.0012
Platelets (x10^9/L)	221 (20-576)	219 (10-740)	0.7758
Neutrophils (x10^9/L)	3.4 (0.3-15.3)	3.3 (0.3-17.3)	0.3659
Calcium (mmol/L)	2.5 (1.6-4.4)	2.4 (1.7-5.7)	0.9322
Creatinine level (mmol/L)	96 (42-2705)	84 (32-2700)	0.0112
ISS, Median	II	II	
ISS I (%)	122 (26.8)	232 (35.9)	
ISS II (%)	167 (36.6)	252 (39.0)	
ISS III (%)	167 (36.6)	162 (25.1)	<0.0001
Missing (%)	77	77	
High risk cytogenetics	56/315 (17.8)	137/567 (24.2)	0.028
del 17p* (%)	26/307 (8.5)	76/560 (13.6)	0.026
t(4:14) (%)	30/302 (9.9)	58/545 (10/6)	0.746
t(14:16) (%)	8/176 (4.6)	13/451 (2.9)	0.298
Missing (%)	218	156	
Immunoglobulin Subtype			
IgG (%)	283/483 (58.6)	386/696 (55.5)	
IgA (%)	101/483 (20.9)	148/696 (21.2)	
IgD (%)	1/483 (0.21)	0/696 (0)	0.542‡
IgM (%)	1/483 (0.21)	2/696 (0.29)	
Light Chain (%)	97/483 (20.1)	160/696 (23)	
Induction Regimen Used			
CyBor/CyBorD/P (%)	646 (89.4)	370 (69.4)	<0.001
RVD / RVDD* / VTD (%)	9 (1.24)	18 (3.38)	0.017‡
VD/P (%)	68 (9.41)	135 (25.3)	<0.001
VD-PACE (%)	0 (0)	1 (0.19)	----
Bortezomib monotherapy (%)	0 (0)	9 (1.7)	<0.001‡

Cy = Cyclophosphamide, Bor = Bortezomib, V = Bortezomib, P = Prednisone, D = Dexamethasone, D = Doxil*
R = Lenalidomide, T = Thalidomide, PACE = Cisplatin, Adriamycin, Cyclophosphamide & Etoposide
‡ *fishers exact test*

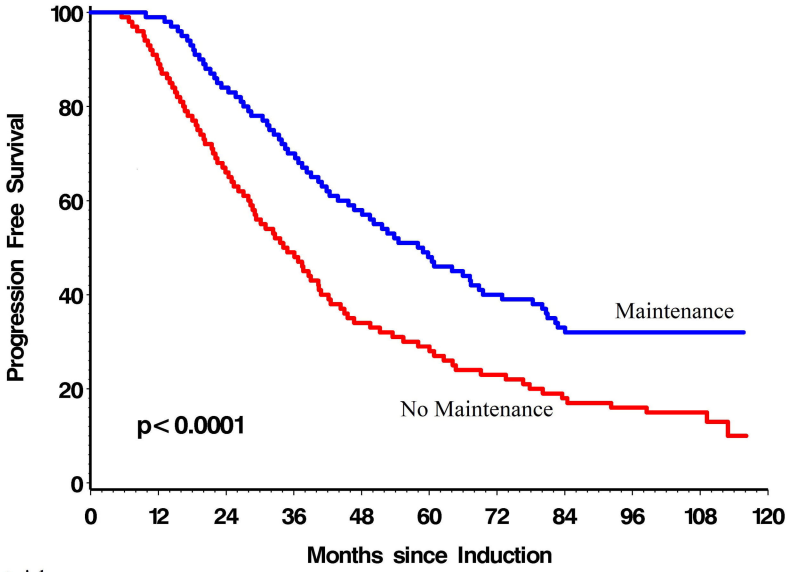
Table 2. Survival and response outcomes in lenalidomide maintenance and non-lenalidomide maintenance groups.

	No Maintenance Group	Maintenance Group	p value	
Median OS				
High risk cytogenetics	45.3 months	NYR	p <0.0001	
Standard risk cytogenetics	NYR	NYR	p <0.0001	
Median PFS				
High risk cytogenetics	22.0 months	53.0 months	p <0.0001	
Standard risk cytogenetics	38.6 months	59.9 months	p <0.0001	
Response				
nCR & CR	145 (45.2%)	297 (52%)	0.05	<0.01
VGPR	114 (35.5%)	239 (41.9%)	0.06	
PR	49 (15.3%)	24 (4.2%)	<0.01	
SD or less	13 (4.1%)	11 (1.9%)	0.08	

NYR = Not yet reached, CR = complete response, nCR = near complete response, VGPR = very good partial response, PR = partial response, SD = stable disease.

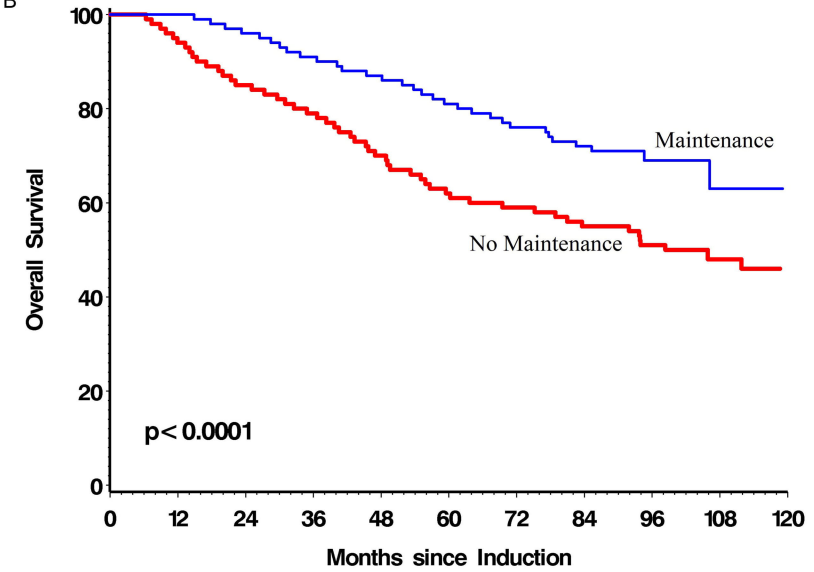
Figure 1. Survival outcomes in patients treated with and without lenalidomide maintenance post autologous stem cell transplant. (A) Progression free survival. (B) Overall survival.

A



Patients at risk											
Maintenance	723	701	562	384	257	138	76	34	12	6	1
No Maintenance	533	421	291	192	121	88	51	30	17	8	2

B



Patients at risk											
Maintenance	723	707	641	496	375	231	136	73	27	10	1
No Maintenance	533	447	375	320	253	187	139	95	59	30	13