The Survival Impact of Lenalidomide Maintenance Therapy in Patients with Multiple Myeloma; An Analysis of Real-World Data from the Myeloma Canada Research Network Canadian Multiple Myeloma Database.

By

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Abstract

Historically, the treatment of multiple myeloma in transplant eligible patients has included induction chemotherapy followed by autologous stem cell transplant (ASCT) and a watch and wait approach until relapse. The introduction of maintenance chemotherapy has changed the traditional observation period into active treatment time.

We examined the impact of lenalidomide maintenance on survival outcomes in the front line and relapsed setting. Our population included patients treated with bortezomib based induction followed by ASCT who went on to receive lenalidomide maintenance or no maintenance. Patient data was taken from the Myeloma Canada Research Network Canadian Multiple Myeloma Database (MCRN CMM-DB) which includes data from 13 academic cancer centers across Canada.

Our data demonstrates that lenalidomide maintenance is associated with improved progression free (PFS) and overall survival (OS) as well as higher rates of favourable responses. We did not observe any unanticipated adverse effects. Rates of discontinuation for reasons other than relapse were low.

Analysis of relapsed patients demonstrates that lenalidomide maintenance did not results in worse second PFS (time from second line therapy to second relapse, death or last follow-up) in patients who received the drug again in second line therapy. Lenalidomide maintenance was associated with improve overall survival from time of initiation of relapse therapy. Additionally, lenalidomide maintenance did not negatively impact second PFS, OS from time of initiation of relapse therapy, and rates of favourable response when lenalidomide used again in second line treatment.

Our data is the first analysis of transplant eligible patients from the MCRN CMM-DB. Our data supports the continued use of lenalidomide maintenance as standard of care following ASCT. Importantly, our data suggests that the use of lenalidomide maintenance does not negatively impact survival or response outcomes when used again in second line therapy. As such, use of

or relapse on lenalidomide maintenance should not be considered an exclusion criteria for use of lenalidomide in second line therapy.

Preface

This thesis represents original work completed by Dr. Hannah Marie Cherniawsky. Work completed in this thesis has been approved by the Health Research Ethics Board of Alberta. Studies described in chapters 3 and 4 was completed as part of a national research collaboration in co-operation with the Myeloma Canada Research Network under the supervision of Dr. Christopher Venner. My responsibilities included application for ethics approval, local data collection, analysis and presentation as well as manuscript preparation. Co-authors contributed by way of data collection and coordination, manuscript revision and statistical analysis of national level data.

Data represented in this thesis has not yet been published in article format but has or will be presented at the meetings listed below with corresponding online abstracts.

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Lenalidomide Maintenance Positively Impacts Outcomes in Multiple Myeloma Without Negative Impacts In Relapse: An Analysis Of Real World Data From The Myeloma Canada Research Network National Patient Database. **Cherniawsky, H.,** *et al.*

Canadian Conference on Lymphoproliferative Disorders (2019), Lake Louise, AB.

The Impact of Maintenance Lenalidomide on Overall Survival and Response to Subsequent Lines of Lenalidomide Containing Chemotherapy Regimens. **Cherniawsky, H.,** *et al.*

International Society of Hematology (2018), Vancouver, BC.

The Real-World Impact of Lenalidomide Maintenance After Autologous SCT and Bortezomib-Based induction in Multiple Myeloma. **Cherniawsky, H.,** *et al*

American Society Hematology Annual Congress (2018), Atlanta, GA

Internal Medicine Resident Research Day (2018), Edmonton, AB

The Survival Impact of Lenalidomide Maintenance Chemotherapy in Multiple Myeloma Patients Treated with Autologous Stem Cell Transplant and Bortezomib-Based Induction; An Analysis of Real World Data. **Cherniawsky, H.,** *et al.*

Dedication

This thesis is dedicated to my loving husband C. Scott Mullen.

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CHAPTER 1:

Introduction

Epidemiology

Multiple myeloma represents an incurable clonal disease of mature plasma cells. It encompasses 1.7% of new cancer diagnoses in men and 1.3% in women annually ranking the 14 & 15 most frequently diagnosed malignancy in men and women in Canada.[93] It is most frequently diagnosed in the 6th and 7th decade of life with a median age at diagnosis of 69.[1,93] Multiple myeloma is slightly more common in men with a male to female predominance of 1.6:1, as well as Caucasian and Black individuals.[1] Risk factors for the development of myeloma include a personal history of chronic inflammatory disorders or family history of the disease.[2] Other factors that have been implicated in the development of myeloma include exposure to radiation, organic solvents and HHV-8 infection.[2]

Pathophysiology and Diagnosis

Multiple myeloma is a lymphoid malignancy of B-cells, specifically mature plasma cells. The major role of the plasma cells is to secrete immunoglobulins, proteins that recognize specific antigens in the human body. B-cell precursors differentiate into mature plasma cells through three main steps. In the bone marrow, B-cell precursors undergo spontaneous heavy then light chain rearrangements that, once complete, results in the expression of IgM or IgD on the cell surface marking it as a mature B cell.[2] Naïve mature B-cells migrate to the germinal centres of lymph nodes where they are exposed to many antigens.[2] Following antigen exposure, somatic hyper-mutation occurs by which mutations are introduced into the genes encoding the variable region of the immunoglobulin to produce cells with greater affinity for a given antigen.[2] Finally, class switching of the heavy chain occurs allowing cells to express IgG, IgA or IgE immunoglobulins.[2] Upon migration back to the bone marrow, these mature plasma cells are able to secrete a highly specific immunoglobulin in response to antigenic stimulus. Mutations in mature plasma cells impart proliferative advantages leading to abnormal, clonal expansion of a given population. These diseased plasma cells retain their potential to produce immunoglobulin secreting large quantities of a monoclonal protein detected in the blood or urine. This protein is often referred to as an M-protein and is identified through electrophoresis or immunofixation. During electrophoresis, a patient's serum or urine is deposited into several lanes of an agrose gel.

An electrical current is then applied to the gel which causes charged particles such as proteins and immunoglobulins to move down the gel at different speeds based on their size and electrical charge. When the electrical current is removed the proteins will have migrated through the gel creating bands of like proteins along the lane. This information is then translated into a graph where the area under the curve can be used to quantify the amount of protein migrating in each area of the electrophoresis. During immunofixation, different anti-sera that react with specific immunoglobulin subtypes are added to each lane of the gel. If a protein with which the anti-sera reacts is present in the gel, a dark band will become visible in that lane. For example, a patient with an IgG kappa monoclonal protein will have a visible band in the IgG lane and kappa light chain lane of the gel where anti-IgG and anti-kappa are added respectively.

In normal serum, free light chains are detectable due to over production of kappa and lambda light chains by normal B cells in the order of 500mg/day.[94] A slight predominance of circulating kappa over lambda chains is seen due their delayed renal excretion.[94] Due to mutation genes encoding heavy chains, clonal plasma cell populations may lose their ability to secrete intact immunoglobulin and may secrete only light chains. Free light chains can be detected on serum based turbidimetric testing.[76] Latex conjugated antibodies that react with hiden epitopes on the light chain that are masked when they are bound to heavy chains in an intact immunoglobulin.[76] Higher turbidity correlates with higher concentrations of light chains.[76] Light is then shone through the sample and the amount transmitted is transformed into a kappa or lambda light chain measurement.[76] Due to their small size and concentrations, light chains but may not be seen on serum electrophoresis. They are renally excreted thus may be more readily detected on urine electrophoresis.

In the urine, monoclonal immunoglobulins or free light chains are referred to as Bence Jones protein after Dr. Bence Jones who first protein in the urine of patients with brittle bones that precipitated with alcohol and dissolved in nitric acid prior to the discovery of multiple myeloma as a unifying diagnosis.[97] Monoclonal proteins or free light chains may be more readily detectable in the urine due the concentration of urine by the kidneys. The proteins can directly damage the renal tubules or form protein casts, two of several causes of renal dysfunction in patients with multiple myeloma.

Table 1.1. Definition of MGUS, smoldering multiple myeloma and overt myeloma adapted from the IMWG Criteria for the Diagnosis of Multiple Myeloma.[7]

Disease	Definition
MGUS monoclonal gammopathy of undetermined significance	1) Serum monoclonal protein <30g/L 2) Clonal bone marrow plasma cells <10% 3) Absence of myeloma defining event or amyloidosis attributed to plasma cell proliferative disorder
Light Chain MGUS	1) Free light chain ratio (kappa/lambda) <0.26 or >1.65 with increased level of the appropriate light chain 2) Absence of immunoglobulin heave chain expression on immunofixation 3) Absence of myeloma defining event or amyloidosis attributed to plasma cell proliferative disorder 4) Clonal bone marrow plasma cells <10% 5) Urinary monoclonal protein <500mg/24hr
Smouldering Multiple Myeloma	**Both of the following** 1) Serum monoclonal protein (IgA or IgG) >30g/L or urinary monoclonal protein >500 mg/24hr and/or clonal bone marrow plasma cells 10-60% 2) Absence of myeloma defining events
Multiple Myeloma	**Serum M protein >30gr/L and clonal plasma cells >10% of bone marrow on biopsy OR extramedullary plasmacytoma AND at least one of the following:** 1) Serum calcium>0.25 mmol/L above the upper limit of normal OR >2.75mmol/L 2) Creatinine clearance <40mL/min OR serum creatinine >177mol/L 3) Hemoglobin >20g/L below lower limit of normal or <100g/L 4) One or more osteolytic lesions on skeletal radiograph, CT or PET/CT 5) Clonal plasma cells encompassing >60% of bone marrow on biopsy 6) Serum involved / uninvolved free light chain ratio of 100 or more provided the involved light chain is at least 100mg/L 7) Two or more focal lesions on MRI 5mm in size or greater

Multiple myeloma is thought to universally evolve from a preceding condition termed monoclonal gammopathy of undetermined significance, MGUS.[3] MGUS refers to the presence of a monoclonal protein in the absence of myeloma defining events (table 1).[7] In the US, MGUS is present in roughly 1.8-3.7% of persons over 50 years with higher frequency in Black persons followed by Caucasians then Hispanics.[4,5] Age is the greatest risk factor for development of MGUS.[6] The risk of progression from MGUS to overt myeloma is quoted at 1% per year meaning that the majority of persons with MGUS will never go on to develop myeloma.[6] Large epidemiological data from the Mayo Clinic demonstrate an abnormal kappa to lambda free light

chain ration, non-IgG M-protein and high serum M protein (>1.5gr/L) as high risk factors for progression.[6,77]

Large observational data suggest that the progression of MGUS to multiple myeloma first starts with an abnormal response to antigenic stimuli resulting in the abnormal expression of toll-like receptors leading to increased IL-6 and IL-1B.[77] This leads to an initial (primary) cytogenetic abnormality such as an immunoglobulin heavy chain (IgH) translocation of hyperploidy.[77] It is thought that a second cytogenetic "hit" is required for progression to myeloma such as a p53 mutation or m*yc* abnormality.[77]

Individuals may develop a condition called smouldering multiple myeloma defined as >10% (but <60%) of plasma cells in the bone marrow and measurable M-protein in the serum or urine in the absence of myeloma defining events (table 1.1). As with MGUS, there is a risk of progression to overt myeloma. Risk of progression is 10% per year in the first five years falling to 3% per year in the proceeding 5 years then 1% per year in the following 10 years.[17] Certain risk factors such as presence of circulating plasma cells, high risk cytogenetics, extent of bone marrow involvement and presence of urinary light chains are associated with higher rates of progression to over myeloma.[14, 17] Traditionally, smouldering myeloma has been treated with a watch and wait approach. However, this approach has come into questions particularly in the case of high risk patients who are likely to progress to myeloma and is an area of ongoing research.[15, 16] Results from the phase 2, Centaurus trial demonstrate improved progression free survival (PFS) in patients with intermediate and high risk smouldering multiple myeloma when treated with daratumumab.[78] A phase 3 trial is planned for further evaluation.[78]

The diagnosis of overt multiple myeloma is made based on bone marrow biopsy with corresponding serologic and radiologic investigations. Distinguishing characteristics of multiple myeloma include a plasma cell population encompassing >10% of cells on bone marrow biopsy with evidence of a myeloma defining event as per table 1.1. Development of overt multiple myeloma represents the crossing of a threshold at which point chemotherapeutic treatment becomes necessary.

Prognosis

The treatment of multiple myeloma is an area that has seen many changes over the past decade. The advent of novel therapies and treatment paradigms has translated into dramatic changes in patient survival. As per American data from the SEER statistics database, 5-year overall survival in patients diagnosed with multiple myeloma was 50.7% from 2008-2014.[1] However, this may be an underestimation of overall survival given the significant number of therapies developed for relapsed disease from the later portion of this era until present. More recent data cites a 3-4 fold increase in overall survival over the past decade and a 30% 10 year overall survival rate.[10,11] Prognostic factors in multiple myeloma can be divided into disease related and patient related.[2] Scoring systems such as the widely used International Staging System (ISS) and Revised International Staging System (R-ISS) primarily evaluate disease related factors and are useful in staging and prognostication of patients (table 1.2).[12] It is important to note the differences in median overall survival between patients with equivalent numerical staging in the ISS and R-ISS system. This is likely reflective of the more recent development of the R-ISS staging system and these patients access to novel, more effective therapy.

Table 1.2. Prognostic data based on the International Staging System and Revised-International Staging System.[12,13]

ISS Stage	Definition	5yr OS	Median OS (months)		R-ISS Stage	Definition	5yr PFS	Median PFS (months)	5yr OS	Median OS (months)
1	Serum B_2-microglobulin <3.5mg/L **AND** serum albumin >35gr/mL		62 mos		1	ISS stage 1 **AND** standard-risk cytogenetic analysis by FISH **AND** Normal Serum LDH	55%	66	82%	Not yet reached
2	No meeting criteria for ISS stage 1 or 3 disease		45 mos		2	Not meeting criteria for R-ISS stage 1 or 3 disease	36%	42	62%	83
3	Serum B_2-microglobulin >5.5mg/L		29 mos		3	ISS stage 3 **AND** High risk cytogenetic analysis by FISH **OR** Serum LDH above the upper limit of normal	24%	29	40%	43

Additional disease related prognostic factors not included in the ISS and R-ISS paradigms include the presence of circulating plasma cells, proliferative rate of involved plasma cells and presence of a (t14:20) translocation.[9,14] Patient specific prognostic factors include age, functional status and baseline renal function.[2,9]

Treatment – Response

Given that multiple myeloma is an incurable malignancy, the major goals of treatment are to obtain a deep and durable remission under the assumptions that this will translate to improved overall survival and delayed relapse. Traditionally, patient's response to therapy has been graded in accordance with the International Myeloma Working Group criteria (table 1.3*).* However, focus has recently shifted to the concept of minimal residual disease (MRD) negativity which has been incorporated into the 2016 IMWG updated response criteria.[59,60] MRD negativity is defined as less than 10^{-5} clonal plasma cells in the bone marrow by molecular assays (next generation sequencing (NGS)) or flow cytometry (next generation flow (NGF)) after having met complete response criteria. [59,60] During next generation sequencing, PCR is used to sequence the VDJ (variable, diversity, joining) region of lymphocytes DNA to detect clonality at the level of 1 in 10^6.[96] With flow cytometry, cells are incubated with fluorochromes specific to certain cell markers. Cells are then dripped one by one through an aperture to detect fluorochromes attached to each cell. Individual cells or "events" are then plotted graphically based on their expression of the given markers. For example, non-diseased plasma cells express CD38 and CD19 but only dimly express CD56 where as myelomatous cells express CD 38 but tend to have low expression of CD19 and increased expression of CD56.[96] These plots can be analyzed to detect the number of cells expressing marker of myeloma. MRD negativity by molecular and flow cytometry testing has been demonstrated in clinical trials and meta-analysis to correlate positively with increased survival in transplant eligible and ineligible patients.[61-65] This prompted its inclusion into a 2016 update to the IMWG response criteria and use as an endpoint in recent clinical trials.[59]

Table 1.3 Response criteria for treatment of multiple myeloma.[50-52,59]

Response	Criteria	Free Light Chain Disease (or serum M Protein <5mg/dL at diagnosis)
Sustained MRD negative	Imaging and bone marrow MRD negativity by NGS or NGF confirmed at least 1 year apart.	
Flow MRD negative	Bone marrow NGF negativity by EuroFlow standards with minimum sensitivity of 1 in 10^5	
Sequencing MRD negative	Bone marrow NGS negativity on two identical, sequential reads using LymphoSIGHT platform (or validated equivalent) with minimum sensitivity of 1 in 10^5	
Imaging plus MRD negative	Bone marrow negativity by NGS or NGF AND PET/CT demonstrating response of ALL areas of increased tracer uptake as follows: 1) Disappearance of all plasmacytomas 2) Decrease to SUV less than mediastinal blood pool 3) Decrease to SUV less than surrounding tissue	
sCR *Stringent Complete Response*	Serum & Urine: Negative immunofixation AND 1) Normalization of FLC[1] ratio[2] 2) Absence of clonal cells in the bone marrow 3) Disappearance of extramedullary plasma cell tumors if present	
CR *Complete Response*	Serum & Urine: Negative immunofixation AND 1) BMBx <5% plasma cells 2) Disappearance of extramedullary plasma cell tumors if present	Additional endpoint of normalization of FLC[1] ratio 0.26-1.65 required if FLC[1] is the clonal marker being followed
VGPR *Very Good Partial Response*	Serum M protein reduced >90% AND <100mg/24hr urine M protein OR detection of M protein in urine and blood by immunofixation but not electrophoresis	>90% decrease in the absolute difference between involved and uninvolved FLC[1]
PR *Partial Response*	>50% reduction in M protein AND >90% reduction in Urine M protein OR to <200mg/24hr If FLC & Serum/Urine M protein not measurable at diagnosis then >50% reduction in clonal plasma cells in bone marrow biopsy (provided baseline level was >30%) AND >50% decrease in size of extramedullary plasmacytomas if present at diagnosis	50% reduction in the absolute difference between involved and uninvolved FLC[1]
SD *Stable Disease*	Does not meet above criteria	

1 – Free Light Chain
2 – A minimum of 100 plasma cells are required for accurate analysis of an abnormal kappa/lambda free light chain ratio with an abnormal ratio being >4:1 or <1:2.

Treatment – Candidacy for Transplantation

The initial major decision point in the treatment of patients with multiple myeloma is assessment of their ability to tolerate autologous stem cell transplantation (ASCT). The benefit of ASCT has been demonstrated in several randomized control trials.[18-21],[53-57] Allogeneic stem cell transplant is not often used in the treatment of myeloma as it has not consistently demonstrated improved survival outcomes when compared to autologous stem cell transplant and carries serious treatment related morbidity and mortality.[24-27]

A patients' ability to tolerate ASCT is largely based on age and performance status though inclusion criteria vary from center to center. Broadly speaking, patients with good functional status and age 70 or younger can be considered for ASCT.

Treatment – Transplant Ineligible Patients

Treatment of transplant ineligible patients with multiple myeloma includes bortezomib based chemotherapy.[82] The addition of bortezomib to melphalan and prednisone has demonstrated improved progression free and overall survival as has bortezomib and lenalidomide in comparison to MPT (melphalan, prednisone, thalidomide).[79, 95] The addition of bortezomib to lenalidomide and dexamethasone has also demonstrated improved progression free and overall survival.[80] Cyclophosphamide, bortezomib and dexamethasone (CyBorD) has demonstrated improved response rates and is currently first line therapy in transplant ineligible patients.[81] CyBorD is given for 9-12 cycles or disease progression.[8] Monoclonal antibody based treatments have demonstrated improved PFS and OS as front-line therapy in transplant ineligible patients but are not funded in Canada in this setting.[83] Transplant ineligible patients may also wish to be considered for a clinical trial in their first line therapy.

Treatment – Transplant Eligible Patients

Transplant eligible patients are initially treated with 4-6 cycles of induction chemotherapy aimed at quickly obtaining disease control prior to initiation of ASCT.[8] Currently, induction

chemotherapy largely comprises triplet, proteasome inhibitor (PI) based therapy.[2] PIs in clinical use include bortezomib and the next generations PIs such as carfilzomib and ixazomib though neither are funded in Canada. Plasma cells are very sensitive to proteasome inhibitors due to their highly developed endoplasmic reticulum. Cellular stress or toxins can disrupt protein folding in the endoplasmic reticulum. The body response to misfolded proteins by activating the unfolded protein response (UPR). The UPR results in a decreased in protein synthesis and retention of misfolded proteins in the endoplasmic reticulum.[84] If the proteins cannot be properly refolded they are targeted for degradation by the proteasome.[84] Proteasome inhibitors prevent this leading to accumulation of misfolded proteins in the endoplasmic reticulum and continuation of the UPR which leads to cell death.[23,84] Bortezomib specifically inhibits the 26s subunit of the proteasome in a reversible fashion.[22] Bortezomib based induction therapy has been shown to increase progression free survival and 3-year overall survival though it is associated with higher rates of peripheral neuropathy.[22] Following induction chemotherapy, patients undergo peripheral stem cell collection with GCSF mobilization. Patients are then treated with a high dose melphalan conditioning therapy with the goal of eradication the remaining multiple myeloma cells in the bone marrow.[39] In small trials, the addition of bortezomib has been shown to increase rates of minimal residual disease (MRD) negativity, a favourable response associated with longer overall survival, with no clinically significant, additive toxicity.[49]

Additional chemotherapy given after ASCT is referred to as consolidation therapy. Consolidation therapy aims to deepen treatment response in the hopes of improving overall survival. [8] In Alberta, consolidation therapy consists of bortezomib and lenalidomide based on current evidence showing improved rates and depth of response and progression free survival in both prospective and retrospective data.[40-45]However, this is only funded for those achieving a partial response or less after ASCT, table 1.3.[8]

Double ASCT, also known as tandem transplant, has also been investigated as a modality of consolidation therapy. Double ASCT has shown a positive impact on progression free and overall survival particularly in high risk disease based on cytogenetics or ISS stage.[46-47,58] Cavo *et al.* (2018) recently published 10-year follow-up data of their randomized, phase three trial comparing single to double ASCT which demonstrated persistent positive effects on PFS in low

and high risk patients and OS in only high risk patients over the decade long follow-up.[58] However, this strategy is not routinely used in Canada.[8]

Current Evidence for Maintenance Therapy

After induction and consolidation therapy the historical approach has been to watch and wait for evidence of biochemical or symptomatic relapse. However, this approach has raised the question as to whether maintenance therapy could be used to delay disease relapse in the hopes of improving progression free and overall survival. Though several medications have been investigated as potential maintenance strategies, immunomodulators (IMIDs) have been the mainstay of modern day maintenance chemotherapy. Current IMIDs used in the clinical setting include thalidomide, lenalidomide and pomalidomide. Thalidomide, an oral IMID, was initially investigated as maintenance chemotherapy and continues to be used today. There have been several clinical trials investigating the impact of thalidomide maintenance therapy on progression free and overall survival.[28-33] Improved progression free survival has been uniformly demonstrated.[28-33] A meta-analysis by Morgan *et al.* (2012) demonstrated improved OS which was not reliably demonstrated in individual trials. However, there is significant heterogeneity between the compared trials with respect to transplantation status, use of combination maintenance therapy with steroids and study design.[28-33] The risks of thalidomide therapy include teratogenicity, neuropathy, cytopenias, fatigue, venous thromboembolism and constipation as well as increased rates of secondary primary malignancies.[28]

Lenalidomide, another oral IMID, has now been more widely adopted as a maintenance strategy though direct comparison of thalidomide and lenalidomide maintenance has not been undertaken in randomized clinical trials. Lenalidomide is pleomorphic in its mechanisms of actions.[70] Lenalidomide is cytotoxic resulting in cell cycle arrest and subsequent apoptosis.[11] It also inhibits myeloma cells' adhesion in the bone marrow micro-environment.[11] Lenalidomide's primary target is cereblon (CRBN) a protein component of the E3 ubiquitin ligase complex.[11] Lenalidomide changes the target of CRBN resulting in decreased production of IRFA4, a regulatory growth factor that drives lymphocyte growth.[11] Additionally, lenalidomide decreases pro-inflammatory cytokines such as VEGF, IL-6 and TNF-a and activates natural killer T cells against myeloma cells through increased production of IL-2.[70] Lenalidomide in better tolerated

than thalidomide with its main toxicities including teratogenicity, cytopenias, fatigue, GI upset, neuropathy and increased risk of thrombosis and secondary primary malignancy. [34] Lenalidomide must be dose adjusted in renal failure, a distinct characteristic compared to thalidomide and pomalidomide.

Higher rates of secondary primary malignancies have been noted in many trials evaluating the use of lenalidomide in both the treatment and maintenance setting.[85-87] Incidence of secondary primary malignance increases with time from induction chemotherapy.[85] A meta-analysis of 9 trials by Palumbo, *et al* (2014) demonstrated a 5 year secondary primary malignancy risk of 6.9% in patients treated with lenalidomide compared to 4.8% in those who were not ($p = 0.037$).[87] They noted a higher risk of solid organ malignancies compared to hematologic malignancies in patients treated with lenalidomide (3.8% versus 3.1%).[87] However, there was only a statistically significant different in frequency of hematologic secondary primary malignancies between patients who did and did not receive lenalidomide (3.1% vs 1.4%, $p = 0.029$).[87] Jones, J., *et al.* (2016) describe more recent data from the Myeloma XI trial also noting an increased rate of secondary primary malignancies in patients treated with lenalidomide specifically in the maintenance setting at 8.9% versus 4% ($p=0.0110$).[85] They too observed a higher frequency of solid organ malignancies but not increase in the rates of hematologic malignancies.[85] Mortality from secondary primary malignancy was low at 1% suggesting the survival benefits of lenalidomide outweigh the increased risk of secondary primary malignancies.[85]

Patients with malignancy are at higher risk of thrombosis that the general population. Patients with multiple myeloma are thought to be at one of the highest risk of thrombosis at 3%-10% compared to roughly 1%.[89,90,91] Lenalidomide use has been associated with an increased risk in thrombosis.[88-90] A dose dependent increased risk of thrombosis with concurrent steroid use has been described.[88,89] Current IMWG guidelines suggest use of ASA prophylaxis for thrombosis prevention in patient being treated with lenalidomide maintenance and low dose steroids, melphalan or doxorubicin and full dose warfarin or low molecular weight heparin in patients on high dose steroids.[92,93]

Single randomized control trials looking at lenalidomide maintenance have demonstrated improved progression free survival following ASCT; however, the impact on overall survival was not demonstrated in all trials due to differences in trial design and limited follow-up.[35-38] A recent meta-analysis by McCarthy, *et al.* (2017) looking at three landmark trials demonstrated an improvement in overall survival following ASCT though none of the individual studies were powered for this endpoint.[34] The trials included in this meta-analysis had far more homogenous methodology and patient population but variation in lenalidomide dosing schedule was present.[34] More recently, these results were again demonstrated in a phase 3, randomized clinical trial by Jackson, *et al.* (2019) showing improved progression free survival but median overall survival endpoints were not yet reached.[38] A detailed analysis of these 4 landmark trials is as follows.

Palumbo *et al.* (2012) conducted a multicenter, double-blind, randomized, phase 3 trial with a 2 by 2 factorial designs to compare survival outcomes in patients treated 1) with or without ASCT and 2) with or without lenalidomide maintenance.[37] Patients were 65 years of younger with a Karnofsky performance status >60%, neutrophil count >1.5 x^9/L, platelets >70x^9/L and creatinine clearance $\geq$30 ml/minute.[37] They excluded patients with grade 2 or higher peripheral neuropathy, abnormal cardiac or pulmonary function and history of previous malignancy.[37] All patients were treated with lenalidomide and dexamethasone induction.[37] The study followed a 2 by 2 factorial design where half the patients received 6 cycles of MPR consolidation (melphalan, prednisone and lenalidomide (10 mg orally daily 21 of 28 days)) while the other half received 2 four month cycles of melphalan 200mg/m^2 plus autologous stem cell transplant (ASCT).[37] All patients were then randomized again to receive oral lenalidomide maintenance at a dose of 10 mg, 21 of 28 days or no maintenance.[37] Progression free survival (PFS) was defined as time of enrolment to time of progression, death or last follow-up. Median progression free survival was highest in those that received high dose melphalan consolidation, ASCT and lenalidomide maintenance (54.7 months) followed by those treated with high dose melphalan and ASCT but no maintenance (37.4 months), table 1.4.[37] Patients treated with MPR had shorter PFS at 34.2 months in those who received maintenance and 21.8 months in those that did not, table 1.4.[37] When patients were grouped and analyzed solely based on receipt of maintenance, the PFS benefit of maintenance lenalidomide persisted (41.9 months versus 21.6 months, HR 0.47; 95% CI, 0.33-0.65; p <0.001), table 1.4.[37] Median OS was not yet reached at time of analysis.[37] Five-

year overall survival favored those treated with lenalidomide maintenance at 78.4% versus 66.6% in the high dose melphalan group and 70.2% versus 58.7% in the MPR group, table 1.4.[37] Statistical significance of these endpoints was not reported.[37]

Table 1.4. Summary of the survival outcomes from Palumbo, *et al.* (2014).[37]

	Median PFS	Median PFS	5 yr OS	OS	Grade 3 & 4 AE
Mel + ASCT & maintenance	54.7 months	41.9 months	78.4%	NYR	23%
MPR & maintenance	34.2 months		70.2%	NYR	
Mel + ASCT & no maintenance	37.4 months	21.6 months	66.6%	NYR	0%
MPR & no maintenance	21.8 months		58.7%	NYR	

The positive impact of lenalidomide persisted across all subgroups except those with stage 3 disease.[37] Grade 3 or 4 adverse effects were experienced at higher frequencies in the lenalidomide maintenance group as anticipated.[37] The most common adverse effects included neutropenia (23.3% versus 0%, $p < 0.001$), infection (6.0% versus 1.7%, $p = 0.09$) and rash (4.3% versus 0%, $p = 0.03$). Fourteen-point seven percent of patients required dose reductions of lenalidomide and 5.2% of patients discontinued due to toxicity.[37] After consolidation, an equal number of patients had secondary primary malignancies in the lenalidomide maintenance and no maintenance groups (4.3% versus 4.3%)[37] In conclusion, Palumbo *et al.* (2012, NEJM) demonstrated improved progression free survival with lenalidomide maintenance at a 10mg PO 21 of 28 days dosing schedule.[37]

Attal *et al.* (2012) conducted a multicenter, randomized, phase 3 trial comparing lenalidomide maintenance at a dose of 10mg PO daily (increased to 15mg PO daily if tolerated) to placebo in patients under 65 years old who had undergone ASCT.[36] Partway through the trial an amendment introduced 2 cycles of consolidation lenalidomide at a dose of 25mg PO 21 of 28 days for all patients.[36] There were no limitations regarding type of induction regimen.[36] The average age was 55 in both groups.[36] The majority of patients were ISS stage 1 and 2.[36] High risk cytogenetics,

which tested only t(4;14) and del 17, were present in 20% of the maintenance group and 11% of the non-maintenance group though not all patients underwent cytogenetic testing.[36] Progression free survival was defined from time of randomization to progression, last follow-up or death. Improved PFS was observed at 41 months versus 23 months ($p<0.001$).[36] This benefit persisted across all analyzed groups.[36] Median OS was not yet reached though estimated 4 years OS was 73% in the maintenance group and 75% in the placebo group.[36] Both groups had high rates of adverse events though the maintenance group had nearly double the rate of grade 3 and 4 toxicity.[36] Rates of VGPR or greater were not statistically different at 61% in the maintenance group and 59% in the placebo group ($p = 0.55$).[36] Attal *et al.* demonstrated that maintenance lenalidomide improved progression free survival by 18 months. [36]

Table 1.5. Summary of the survival outcomes from Attal, *et al.* (2012).[36]

	Lenalidomide Maintenance	**No Maintenance**	
PFS	41 months	23 months	p <0.001
OS	NYR	NYR	
4 year OS	73%	75%	
VGPR or greater	61%	59%	

McCarthy *et al.* (2012) examined lenalidomide maintenance in transplanted patients under 70 years old with ECOG of 1 or less in their blinded, randomized, phase 3 clinical trial.[35] In this trial, they compared maintenance lenalidomide at a starting dose of 10mg PO daily (dose range 5-15mg) continued until progression and placebo.[35] Age and disease stage was equal between groups but cytogenetic analysis was neither reported nor a requirement of the study.[35] Progression free survival was measured from time of ASCT to time of progression, death or last follow-up. At a planned interim analysis (median follow-up time of 18 months), patients were unblinded due to significant PFS benefit of lenalidomide maintenance at 39 months compared to 21 months ($p <0.001$).[35] Eighty-six of 128 eligible patients crossed over from placebo to lenalidomide.[35] At final analysis (median follow-up 34 months) progression free survival was 46 months in the maintenance group compared to 27 months in the non-maintenance group ($p <$

0.001).[35] Estimated three-year overall survival was 88% in the maintenance group and 80% in the placebo group (p = 0.008, HR 0.62; 95% CI, 0.40-0.95).[35] There were higher rates of grade 3 and 4 adverse effects in the lenalidomide maintenance group as expected (p <0.001).[35] There were also higher rates of secondary primary malignancies in the experimental group (9.5% versus 3.9% p = 0.008).[35] In summary, McCarthy *et al.* (2012, NEJM) demonstrated improved progression free and overall survival with daily low dose lenalidomide maintenance.[35]

Table 1.6. Summary of the survival outcomes from McCarthy, *et al.* (2012).[35]

	Lenalidomide Maintenance	**No Maintenance**	
PFS	46 months	27 months	p <0.001
3 year OS	88%	80%	p= 0.008
Grade 3 AE	32%	12%	p <0.001
Grade 4 AE	16%	5%	p <0.001
SPM	9.5%	3.9%	p= 0.008

Most recently, Jackson *et al.* (2018) analyzed the impact of lenalidomide maintenance in the Myeloma XI study, an open label, randomized, phase 3 trial conducted at 110 UK hospitals.[38] The trial included newly diagnosed, transplant eligible and ineligible patients.[38] Transplant eligible patients were randomized 1:1 to CTD (cyclophosphamide, thalidomide, dexamethasone) or CRD (cyclophosphamide, lenalidomide, dexamethasone) induction until 2013 when an amended protocol randomized transplant eligible patients 1:1:2 to CTD, CRD and KCRD (carfilzomib, cyclophosphamide, lenalidomide, dexamethasone).[38] Transplant ineligible patients were assigned 1:1 to attenuated CTD or attenuated CRD induction.[38] Patients with partial or minimal response to induction, regardless of transplantation status, were randomly assigned 1:1 to CyBorD (cyclophosphamide, bortezomib and dexamethasone) intensification or no consolidation.[38] KCRD treated patients were not included in this randomization.[38] All patients were randomized 1:1:1 to lenalidomide, lenalidomide plus vorinostat (not analyzed in current publication) or observation.[38] An additional protocol amendment in 2013 randomized patients 2:1 to lenalidomide and observation.[38] In transplanted patients, maintenance therapy was started 100 days post-transplant.[38] In non-transplant patients, maintenance was started once maximal response to induction and intensification therapy was achieved.[38] Lenalidomide monotherapy

was originally dosed at 25mg PO 21 of 28 days before being reduced to 10 mg PO 21 of 28 days in 2011 based on emerging results from trials at the time demonstrating possible increased rates of secondary primary malignancies.[38] Analysis of survival endpoints pooled data from transplanted and non-transplanted individuals.[38] Progression free survival was measured from time of maintenance randomization to time of progression, death or last follow-up.[38] A 19 month increase in PFS was observed with lenalidomide maintenance (39 months versus 20 months, HR 0.46; 95% CI 0.41-0.53, $p < 0.0001$).[38] Median overall survival was not reached in either group.[38] Based on 3 year and 5 year overall survival, no difference in overall survival was detected between the groups (HR 0.87; 95% CI 0.73-1.05, $p = 0.15$).[38] The benefit of maintenance persisted across all groups including transplant eligible and ineligible, high risk cytogenetics, induction and intensification therapy and ISS stage.[38] Though all subgroups benefited from maintenance therapy, those who achieved unfavorable responses (partial or minimal response) benefited more than those who achieved favorable responses (very good partial or complete response) ($p < 0.0001$).[38]

Table 1.7. Summary of the survival outcomes from Jackson, *et al.* (2019).[38]

	Lenalidomide Maintenance	**No Maintenance**	
PFS	39 months	20 months	p <0.0001
OS	NYR	NYR	
5yr OS	60%	50%	HR= 0.74 p = 0.15
VGPR +	83%	85%	

Use of lenalidomide maintenance in Alberta was adopted in 2012 with drug access granted through a compassionate release program supplying maintenance up to 10 mg PO daily. As with most chemotherapies, lenalidomide carries a significant cost which likely played a role in delaying its approval for provincial formulary coverage. As per Alberta Blue Cross pricing, a 10mg tablet of lenalidomide costs $361 pricing a 21 of 28 day cycle at $7581 ($98,553 per year) and a 28 day continuous cycle at $10,108 ($131,404 per year).[66] As such it is no surprise that

there is hesitancy to fund lenalidomide maintenance despite resounding evidence of its positive impact on progression free and overall survival.

Unfortunately, data regarding cost effectiveness of lenalidomide maintenance in multiple myeloma is scarce. Kim, M., *et al.* (2014) analyzed data from the clinical trial by Palumbo *et al.* (2012) to analyze cost effectiveness.[37, 67] They used two endpoints in their analysis, Average Cumulative Cost per Patient (ACCP) defined as the average cost to date per treated patient, and Average Cumulative Cost per Progression Free Survivor, defined as average cost per patients who had not yet progressed at time of analysis.[67] Notably, their cost analysis also incorporated estimated prices of adverse effects, clinic visits, laboratory tests and associated medications such as ASA and prophylactic antibiotics.[67] ACCP was highest in those treated with MPR induction and lenalidomide maintenance (USD 309,173) followed by those treated with MP induction and lenalidomide maintenance (USD 167,862) then MP induction without maintenance (USD 18,218). When evaluating cost using ACCPFS over 36 cycles, MP induction with lenalidomide maintenance was most expensive (USD 1,555,443) followed by MPR with lenalidomide maintenance (USD 690,111) then MP induction with no maintenance (USD 313,592). LeBlanc, *et al.* (2016) compared the cost effectiveness of bortezomib versus lenalidomide maintenance in Canada demonstrating lower annual costs with bortezomib ($33,967) compared to lenalidomide ($131,765).[68] However, bortezomib monotherapy maintenance is not the standard of care in Canada making their analysis relatively inapplicable.[68] Though both of these papers present interesting findings their cost analysis is very one sided as no analysis of the quality adjusted life years or patient centered outcomes were presented.

Given this information, there are many ways to view the cost of lenalidomide maintenance. One could argue that the costs of lenalidomide maintenance translates to less time spent in hospital from relapsed disease or suffering complications such as thromboembolisms, renal failure or fractures which are most likely to occur in the setting of active disease. Additionally, it is well known that initial chemotherapies tend to portend the greatest improvements in progression free survival therefore it is logical to use lenalidomide maintenance upfront where it is maximally effective. From a patient-based perspective it seems reasonable that delaying relapse for 18 months or greater, even in the context of similar overall survival, is a desirable outcome.

Additionally, if we assume lenalidomide maintenance has no impact on overall survival this would mean that patients who do not receive maintenance spend relatively more time on second line therapies, many of which are much more expensive than lenalidomide such as KRD (carfilzomib, lenalidomide dexamethasone), estimated in a 2015 cost analysis at USD 24,293 to 27,422 per month.[69] As such, further data regarding the cost effectiveness of maintenance therapy may be of utility in our publically funded system.

Additional concerns with the use of maintenance chemotherapy include the potential for selection of resistant clones that preclude the effective use of these chemotherapeutic agents at relapse. This is of great concern given that the most efficacious chemotherapy regimens used in the relapsed setting include lenalidomide.[71-74] Many of these trials excluded patients who were previously exposed to lenalidomide. Therefore, it is difficult to extrapolate from this data whether the use of lenalidomide maintenance confers a negative impact on outcomes achieved from second line therapies incorporating full, treatment dose lenalidomide. Jones, *et al.* (2019) published data on a subgroup of patients from the Myeloma XI study who relapsed within 30 months of treatment.[75] Examination of genetic mutations and tumor micro-environment suggested that use of maintenance lenalidomide did not promote emergence of resistant clones.[75] This concept has given rise to the idea of optimal therapy sequencing, the idea that the order in which therapies are delivered impact their efficacy. With novel therapies leading to longer and longer progression free survival the follow-up time and massive patient numbers needed to study optimal therapy sequencing in the randomized control setting is unlikely to be undertaken. However, large retrospective datasets provide us with an opportunity to address this question with lesser costs and data from a real-world setting. The Myeloma Canada Research Network Canadian Multiple Myeloma Database (MCRN CMM-DB) was developed to address such questions. It combines the data from 13 academic cancer centers across Canada allowing for analysis of largescale data. Additionally, the dataset allows for validation of results from large scale clinical trials in the Canadian landscape and allows investigators to assess whether or not we are meeting target outcomes achieved in such trials.

Summary & Objectives

In conclusions, the use of maintenance chemotherapy with lenalidomide is supported by four phase 3, randomized control trials and a meta-analysis. The purposes of the work surmised in this thesis is to evaluate the impact of lenalidomide maintenance in transplant eligible patients treated in the real world, Canadian landscape. This examination will provide useful data regarding real world survival outcomes in those treated with lenalidomide and determine whether we are meeting survival outcomes delineated in the landmark trials that led to the adoption of lenalidomide maintenance as the standard of care. Additionally, we will explore the impact of lenalidomide maintenance on survival outcomes in patients who received the drug again in the relapsed setting. This examination will provide useful information for clinicians with regards to optimal therapy sequencing and to policy makers with regards to funding of effective second line treatments in lenalidomide exposed patients.

CHAPTER 2:

Methods

Background

Given the evolving landscape in the field of myeloma, particularly with respect to greatly improved patient survival, a need for long term follow-up has been identified to better elucidate clinical outcomes. Many clinical trials have limited follow-up time due to funding constraints, limited patient recruitment and pressure to publish data quickly. As such, endpoints such as progression free survival or 3-year survival are often used as surrogate markers of overall survival. This data must be cautiously interpreted given that improved progression free survival does not necessarily translate into improved overall survival. Furthermore, overall survival is often included as a secondary endpoint in randomized controlled trials. However, these secondary endpoints should also be interpreted with caution given that studies are generally not powered for detecting differences in secondary end points.

Data Collection

Locally, we sought to address the lack of long-term survival data in patients with myeloma specifically in the real-world setting. A local databank was developed comprising data of patients with bone marrow biopsy proven multiple myeloma treated at the Cross Cancer Institute in Edmonton Alberta. The database was approved by Health Research Ethics Board of Alberta. Information collected at the local level includes epidemiologic and disease related factors as well as information pertaining to treatments received and responses achieved (table 2.1). Our local efforts have been matched by several other centers and contributed to the development of the Myeloma Canada Research Network Canadian Multiple Myeloma Database (MCRN CMM-DB). This dataset contains information of over 5,000 patients with multiple myeloma from 13 centers across Canada and allows for investigation of large-scale data representative of the real world, Canadian landscape. Development of the database was also approved by the Health Research Ethics Board of Alberta in keeping with the MCRN CMM-DB governance structure. Data from chapters 3 and 4 include information gathered from the local and national datasets.

Table 2.1 Patient, disease and treatment characteristics recorded at the local and national level.

EPIDEMIOLOGY
• ACB number • Date of Birth • Age at diagnosis • Gender
BASELINE DISEASE CHARACTERISTICS
• Date of Diagnosis • Immunoglobulin subtype (IgG, IgA, IgD, IgE, IgM, Light Chain, Non-secretory) • Serum M protein level • Serum Free Light Chain concentrations and ratio • Plasma cell percentage • Presence of high risk cytogenetics (p53*, t4:14, t14:16, t14:20) • Serum LDH at diagnosis • Serum Albumin at diagnosis • Serum Beta-2-microglobulin at diagnosis • ISS score • R-ISS Score
FIRST LINE TREATMENT
• Induction regimen o Date of induction initiation • Autologous Stem Cell Transplant (yes/no) o Date of stem cell transplantation • Consolidation regimen • Maintenance therapy (yes/no) o Date of maintenance initiation o Maintenance regimen including dosage & schedule o Adverse effects o Dose reductions & treatment delays Date & duration indication o Date of maintenance discontinuation o Reason for discontinuation (relapse or non-relapse) • Maximal response achieved as per IMWG criteria • Date of relapse
SECOND LINE TREATMENTS AND BEYOND
• Line of therapy • Regimen • Date of initiation • Maximal response achieved as per IMWG criteria • Date of relapse
ADVERSE EFFECTS
• Secondary Primary Malignancies o subtype • Thrombosis o arterial or venous o occurring while on maintenance lenalidomide (yes/no)

Patient Selection

We included patients meeting IMWG criteria for multiple myeloma who were treated with autologous stem cell transplantation following bortezomib based induction chemotherapy to improve homogeneity and minimize the survival impact of variable induction regimens.[2] Specific inclusion criteria are as follows;

- Bone marrow biopsy proven multiple myeloma meeting IMWG criteria for diagnosis[2]
- Treated with bortezomib based induction chemotherapy
- Treated with autologous stem cell transplant
- Received either no maintenance chemotherapy or lenalidomide maintenance
    - *Maintenance lenalidomide is defined as the receipt of lenalidomide monotherapy*
- Began treatment prior to January 2016
    - *To ensure 2 year follow-up*

We excluded patients meeting any of the following exclusion criteria;

- Diagnosis of MGUS or smoldering myeloma at time of analysis or AL Amyloidosis
- Did not survive 100 days following autologous stem cell transplant
- Treated with alternative maintenance regimen such as thalidomide

Patients who did not survive 100 days post ASCT were excluded as they were likely to have died from transplant related complications before the main factor in question would have been started. Furthermore, maintenance chemotherapy is often initiated near the 100-day post-transplant mark. As such, these patients are unlikely to have received maintenance chemotherapy due to the timing of their depth and thus would be allocated to the no maintenance group by default introducing bias into our data.

Notably in our second analysis detailed in chapter 4 we included only patients who had had a documented relapse as per IMWG criteria or where deemed significant by the treating physician and who went on to receive second line therapy.

<u>Outcomes</u>

Outcomes were split into two phases. Firstly, we sought to investigate the survival impact of lenalidomide based maintenance specifically in the real-world setting which is described in chapter 3. Secondly, we sought to investigate the impact of lenalidomide based maintenance on patients' response subsequent lines of lenalidomide containing chemotherapy which is described in chapter 4.

For our initial analysis, we focused on comparison of survival outcomes in patients who had received lenalidomide based maintenance compared to those who had not. Our primary outcomes were:

- **Progression free survival (PFS):** time from initiation of induction chemotherapy to progression, death or last follow-up
- **Overall survival (OS):** time from initiation of induction chemotherapy to death or last follow-up

Our secondary outcomes in this analysis examined the tolerability of lenalidomide by measuring the frequency of adverse effects and dose reductions. Additionally, we examined the depth of response achieved in the presence or absence of lenalidomide based maintenance.

- **Proportion of cycles delivered at the initial dose and schedule**: mean percentage of cycles delivered at the intention to treat dose across all patients on the same initial dosage schedule
- **Number of patients requiring dose reductions, treatment delays or medication discontinuation for reasons other than relapse**
- **Adverse effects including rates of thrombosis and secondary primary malignancies (SPMs)**
- **Depth of response:** greatest response occurring at any time prior to progression as per IMWG response criteria[1]

For our second analysis, we sought to compare the impact of lenalidomide based maintenance on patient's response to subsequent receipt of lenalidomide containing therapy. We included

patients from our first analysis who had experienced at least one relapse and began second line chemotherapy. Our primary outcomes include:

- **Second progression free survival (2nd PFS):** time from initiation of second line chemotherapy to progression, death or last follow-up
- **Second overall survival (2nd OS):** time from initiation of second line chemotherapy to death or last follow-up
- **Progression free survival 2 (PFS2):** time from initiation of induction chemotherapy to progression, death or last follow-up
- **Overall survival (OS):** time from initiation of induction chemotherapy to death or last follow-up

Secondary outcomes in this analysis examined depth of response from second line therapy:

- **Depth of response:** greatest response occurring at any time prior to progression as per IMWG response criteria[1]

Progressive disease was defined as per the IMWG criteria.

- An increase in the serum M protein by 25% or more from the lowest response value
- Development of hypercalcemia, anemia, new lytic bone lesions or plasmacytomas

Data Analysis

Data analysis was undertaken in keeping with the two phases previously eluded to; however, the same methods of analysis where used in both phases. SPSS statistical software was used for variable analysis at the local level. Nationally, data analysis was completed by a professional statistician.

Survival outcomes including progression free survival, second progression free survival, overall survival and second overall survival were interpreted using Kaplan-Meyer curves. A log-rank

hypothesis was used to determine the statistical significance between survival outcomes of the groups. Given that we included patients with a minimum of 2 years of follow-up we anticipated that there would be a sizable number of patients who had not yet relapsed or died resulting in skewing of our data. Thus, the log-rank test, a non-parametric test, more accurately represents the level of significance between the data.

For differences in baseline characteristics a chi-squared analysis was used to determine the presence or absence of statistically significant differences. A p-value of <0.05 was considered significant. For differences in discrete outcomes namely depth of response, rates of thrombosis and secondary primary malignancies, a fisher's exact test was used to determine the presence or absence of statistically significant differences. This was used due to relatively small event rates. Again, a p-value of <0.05 was considered significant.

CHAPTER 3:

The Survival Impact of Maintenance Lenalidomide: An Analysis of Real World Data From The Myeloma Canada Research Network National Database

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INTRODUCTION

Multiple myeloma (MM) is an incurable malignancy of mature plasma cells. Treatment of MM focuses on obtaining a profound and durable remission to improve overall and progression free survival. Patients with good functional status under age 65 - 70 are eligible for treatment with bortezomib based induction chemotherapy followed by autologous stem cell transplant (ASCT) which has demonstrated a progression free and overall survival benefit in large, randomized controlled trials.[1,5-8,16] Following ASCT, patients may be given 2 – 4 cycles of consolidations therapy such as VRD (bortezomib, lenalidomide and dexamethasone) followed by maintenance chemotherapy. In Canada, this step is rarely pursued due to lack of funding and conflicting phase III data. Maintenance chemotherapy generally consists of lenalidomide monotherapy, an oral immunomodulator, continued until relapse. In those with high risk cytogenetics defined as presence of del17p, t(4:14) or t(14:16), bi-weekly bortezomib maintenance may be added.[1,2]

The use of maintenance lenalidomide is based on 4 large randomized control trials showing indisputable improved in PFS.[3,4,7,18] Only data from Jackson, *et al* Lancet Oncol (2019) was powered to detect differences in OS as a primary endpoint.[18] At time of publication median OS had not been met in either group but 3 and 5 year OS showed no statistically significant difference between maintenance and non-maintenance groups.[18] McCarthy, *et al.* NEJM (2012) demonstrated a 3 year OS benefit with maintenance lenalidomide; however, their trial was not powered for this endpoint. A recent meta-analysis pooling data from 3 randomized control trials confirmed statistically significant benefits in both OS and PFS.[16]

Currently, there is no published survival data validating the use of lenalidomide based maintenance in the real-world, Canadian landscape. As such, an analysis on the survival impact and adverse effects of lenalidomide maintenance in the Canadian landscape is of critical importance. To address this, we conducted a retrospective analysis of patients with multiple myeloma using data from the Myeloma Canada Research Network Canadian Multiple Myeloma Database (MCRN CMM-DB), a collaborative data sharing platform that pools data from academic cancer centers across Canada.

METHODS

Patient Evaluation

We conducted retrospective, observational study of patients meeting IMWG criteria for MM who were treated with upfront bortezomib-based induction chemotherapy followed by ASCT.[11] The project was approved by Health Research Ethics Board of Alberta in keeping with the database governance structure. Data was collected from the MCRN CMM-DB with patient information input from 10 Canadian cancer centers. Patient selection was limited to those with at least 2 years of follow-up. Additional inclusion criteria included those receiving no maintenance or lenalidomide monotherapy as a maintenance. We excluded patients with a diagnosis of smouldering myeloma or AL amyloidosis and those who were treated with alternative maintenance strategies such as thalidomide or combination maintenance chemotherapy. Patients who did not survive 100 days post ASCT were also excluded as they likely died of transplant related complications and may not have survived long enough to receive maintenance where available, thus falsely allocating them to the no maintenance group and introducing bias. Patients were grouped based on intention to treat with respect to treatment with lenalidomide based maintenance chemotherapy. Individual charts were reviewed for patient demographics, dates of chemotherapy initiation and relapse, response criteria and regimens used at each line of chemotherapy. With respect to lenalidomide administration, intention to treat dose and schedule (21/28 days, 28/28 days or other) was recorded. Dose reductions, delays and medication discontinuation was recorded as well as indication for each event where available. Frequency of adverse effects including development of secondary primary malignancies and thrombotic events were recorded when deemed significant by the treating physician.

Endpoint Evaluation

The primary outcomes of this analysis were overall survival (OS) and progression free survival (PFS). OS was defined as time from initiation of induction therapy until death or last follow-up. PFS was defined as time of initiation of induction therapy to detection of relapse, death or last follow-up. Relapse was defined as progression meeting IMWG criteria or clinical progression defined by the treating physician such as clinical progression defined by worsening disease related symptoms.[12] The IMWG criteria for clinical response were used to assess best response

to treatment after induction and at any time thereafter.[12] We included the additional endpoint of near complete response (nCR) where serum and urine M-protein disappeared and free light chain ratio normalization but where CR status was not confirmed with bone marrow biopsy or immunofixation as is often the case in the real world settting.[12]

Statistical Analysis

Data was analysed by the MCRN statistician. Local data was analysed using SPSS statistical software. Kaplan-Meier curves were constructed to evaluate OS and PFS. Chi-squared analysis was used to evaluate for significant difference in the maintenance and non-maintenance control groups with respect to baseline variables. A fisher's exact test was used in the comparison on frequency of thrombotic events, secondary primary malignancies and response rates given the relatively small number of events in certain categories. A p-value of <0.05 was considered statistically significant.

RESULTS

1256 patients met the aforementioned inclusion criteria and began treatment between January 2007 and January 2016. 723 patients (57.6%) received lenalidomide maintenance and 533 (42.4%) did not. Baseline characteristics of each group are illustrated in Table 3.1. Median ISS was 2 in both groups. ISS 3 disease represented 29% of the maintenance group and 36.6% of the non-maintenance ($p < 0.01$). Cytogenetic data was collected where available. High risk cytogenetics were defined as the presence of t(4:14), t(14:16) or any functional abnormality in p53 representing a 17p deletion in keeping with IWMG consensus.[17] In the maintenance group, 137 of 567 patients had high risk cytogenetics compared to 56 of 315 non-maintenance patients (24.2% VS 17.8%, $p = 0.03$). The majority of patients had IgG myeloma followed by light chain disease then IgA.

Table 3.1. Baseline characteristics of the lenalidomide based maintenance and no maintenance groups.

Characteristic	No Maintenance Cohort n (%)	Maintenance Cohort n (%)	p value
# Patients	533	723	
Age at diagnosis (median)	57.9yr	58.1yr	0.711
Gender			
Female	201	280	0.714
Male	332	443	
Baseline creatinine level (mmol/L, median)	155.91	128.99	0.023
Median ISS	2	2	
ISS 1	122 (26.8%)	232 (35.9%)	0.001
ISS 2	167 (36.6%)	252 (39.0%)	0.6
ISS 3	167 (36.6%)	162 (25.1%)	<0.0001
missing	77 (14.4%)	77 (10.7%)	
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 (40.9%)	156 (21.6%)	
Immunoglobulin Subtype			
IgG	283/483 (58.6%)	386/696 (55.5%)	0.541
IgA	101/483 (20.9%)	148/696 (21.2%)	
IgD	1/483 (0.21%)	0/696 (0%)	
IgM	1/483 (0.21%)	2/696 (0.29%)	
Light Chain	97/483 (20.1%)	160/696 (23%)	

*del17p is defined as any loss documented above local laboratory cut-off.

In both groups, most patients were induced with cyclophosphamide and dexamethasone or prednisone in combination with bortezomib. Frequency of other induction treatments are illustrated in Table 3.2. At time of analysis 41.1% of the maintenance group and 52.3% of the non-maintenance group had relapsed and gone on to receive second line chemotherapy.

Table 3.2. Frequency of induction regimen used in patients treated with and without lenalidomide maintenance.

Induction Treatment	No Maintenance Cohort n (%)	Maintenance Cohort n (%)	p value
CyBorD / CyBorP / VC	370 (69.4%)	646 (89.4%)	<0.001
RVD / RVDD* / VTD	18 (3.38%)	9 (1.24%)	0.017*
VD / VD-PACE / VP	136 (25.5%)	68 (9.41%)	<0.001
Bortezomib monotherapy	9 (1.69%)	0 (0%)	<0.001*

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

Median follow-up was 49.1 months in the maintenance group (8.6 – 124.8 months) and 45.3 months in the no maintenance group (4.5 – 141.1months). At the time of analysis, 54.9 % (397) of the maintenance groups had not yet progressed compared to 37.2% (198) of patients in the no maintenance group. The median OS was 98.3 months in the non-maintenance cohort (95% CI 83.5 – NYR) but not yet reached in the maintenance group. However, Kaplan-Meier survival curves demonstrate statistical significance in favour of maintenance (p <0.0001, figure 2.3). Five-year OS was higher in the maintenance group at 81% compared to 61.5 % in the no maintenance cohort.

Figure 3.1. Overall Survival

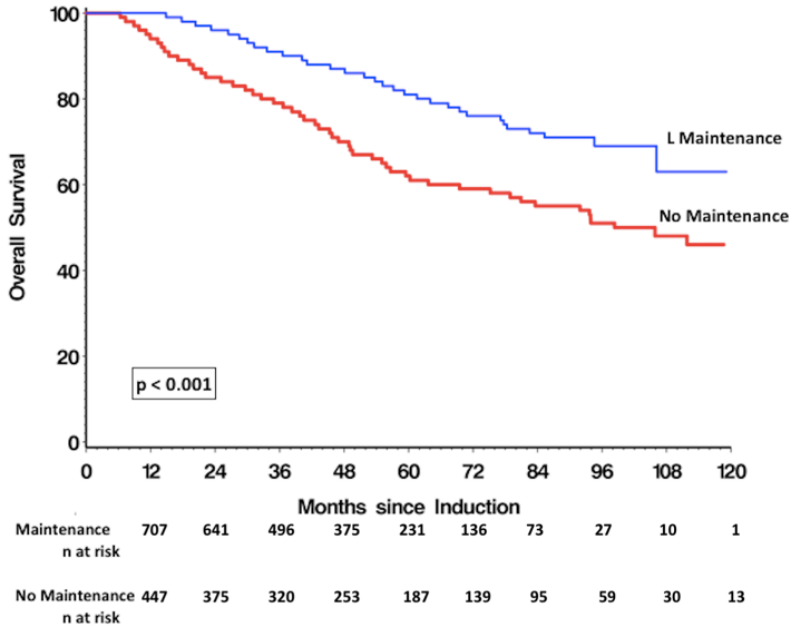

Figure 3.1. Overall survival based on receipt of lenalidomide based maintenance. The maintenance cohort has not yet reached the median overall survival; however, the distinct difference in survival between the two groups have already reached the level of statistical significance.

Median PFS was two years longer in the lenalidomide maintenance group at 58.2 months (95% CI; 52 – 64.0) compared to 34.6 months in the non-maintenance group (95% CI; 30.7 – 37.7), p < 0.0001, shown in figure 3.3.which is in keeping with results from large phase 3 randomized clinical trials.[3,4,8] Estimated 5-year PFS was 48.0% in the maintenance cohort compared to 28.6% in the non-maintenance groups

Figure 3.2. Progression Free Survival

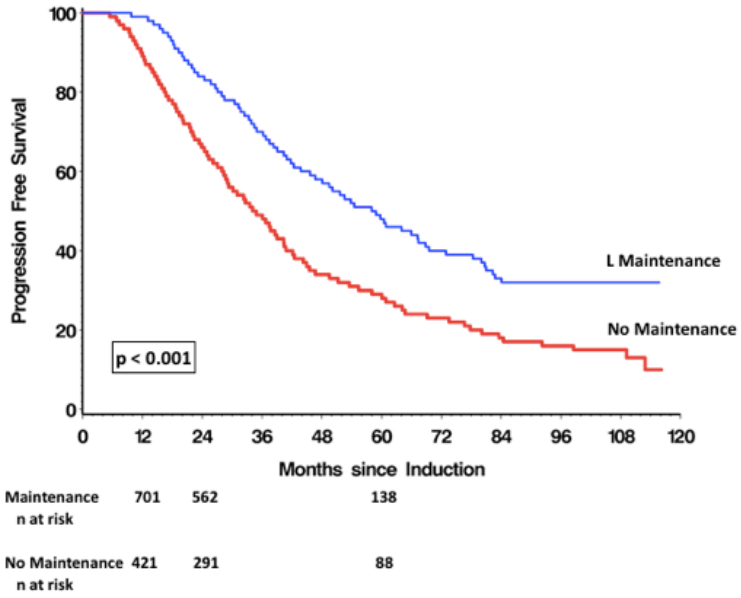

Figure 3.2. Progression free survival based on receipt of lenalidomide based maintenance. The maintenance group demonstrates a significantly longer progression free survival than the no maintenance group (58.2 months versus 34.6 months, p <0.001).

Survival outcomes were also analyzed with regards to the receipt of maintenance at an intention to treat dose of 10 mg 21 of 28 days or 10 mg daily. There was no difference in progression free survival between the 21 of 28 day and continuous dosing schedule (p = 0.66, Figure 3.3). Results for overall survival between the groups also demonstrated no statistically significant difference (p = 0.75, Figure 3.4).

Figure 3.3 Overall Survival

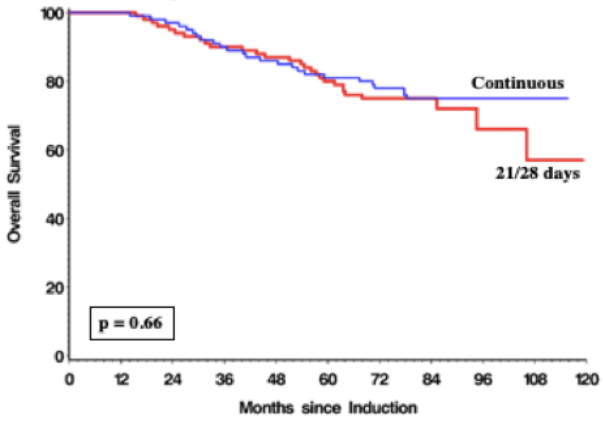

Figure 3.3 Overall survival of a 21 of 28 day or continuous dosing schedule. No statistically significant difference in overall survival was demonstrated.

Figure 3.4 Progression Free Survival

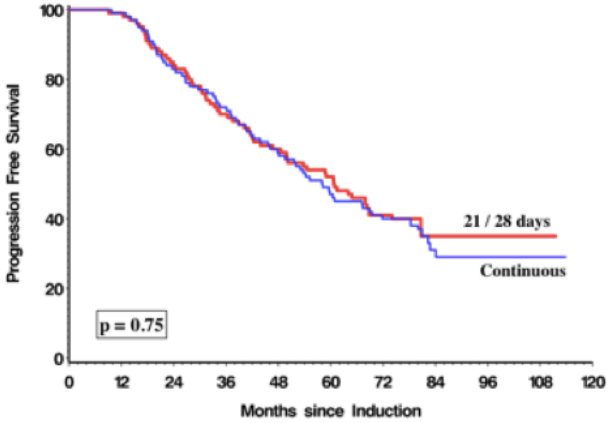

Figure 3.4 Progression free survival of a 21 of 28 day or continuous dosing schedule. No statistically significant difference in progression free survival was demonstrated.

Patient treated with lenalidomide-based maintenance had higher rates of favourable responses (VGPR or greater) than their non-maintenance counterparts. Fifty-two percent achieved a nCR/CR (compared to 45.2%, p =0.05) and 93.9% achieved VGPR of greater (compared to 80.7%, p <0.01). Similarly, patients treated with maintenance had lower rates of less favourable outcomes with 4.2% achieving partial response or less compared to 15.3% in the non-maintenance group (p < 0.01), Table 3.3.

Table 3.3. Maximal response achieved at any time following induction chemotherapy based on receipt of lenalidomide maintenance.

Response	No Maintenance Cohort n (%)	Maintenance Cohort n (%)	p value	
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	

nCR = near complete response, CR = complete response, VGPR = very good partial response, PR = partial response, SD = stable disease.

Overall and progression free survival was analyzed with respect to maximal response achieved in keeping with IMWG response criteria.[12] The survival benefit of lenalidomide persisted in patients achieving a complete response (p = 0.03) or VGPR (p = 0.0002) compared to their no maintenance counterparts. Median overall survival was only reached in the VGPR without maintenance group at 105.9 months (95% CI: 55.7 – NYR). Similar benefit was seen with regards to progression free survival in those achieving a nCr/CR at 80.7 months (95% CI 61.4 – NYR) versus 44.3 months (95% CI: 39.0 - 51.1), p < 0.0001. This PFS benefit of lenalidomide also persisted in those achieving a very good partial response at 41.6 months (95% CI: 37.2 – 48.1) versus 28.1 months (25.0 – 31.8), p < 0.0001. Achieving a response of nCR/CR as opposed to a VGPR was associated with statistically significant improvement in overall survival in patients who had and had not received maintenance (p = 0.02 and p = 0.003 respectively). Improved PFS in patients achieving a nCR/CR compared to those achieving a VGPR was also seen in patients treated with and without maintenance (p < 0.0001 and p < 0.0001 respectively).

Data from 226 patients treated at the Cross Cancer Institute in Edmonton, Alberta was analyzed in greater detail regarding dosage schedule, discontinuation and adverse effects of lenalidomide maintenance therapy. The mean number of maintenance cycles received was 30 cycles (0.5 - 97). 32.4% of patients were started on a 10mg, 21 of 28 days schedule compared to 59.5% who started on a 10mg continuous schedule. Over half of patients (56.8%) required dose reductions or discontinuation due to adverse effects excluding relapse. Of all the cycles of lenalidomide administered, 73% of the 10mg continuous cycles and 81% of the 10mg 21 of 28 day cycles were delivered at the respective intention to treat dosage schedule.

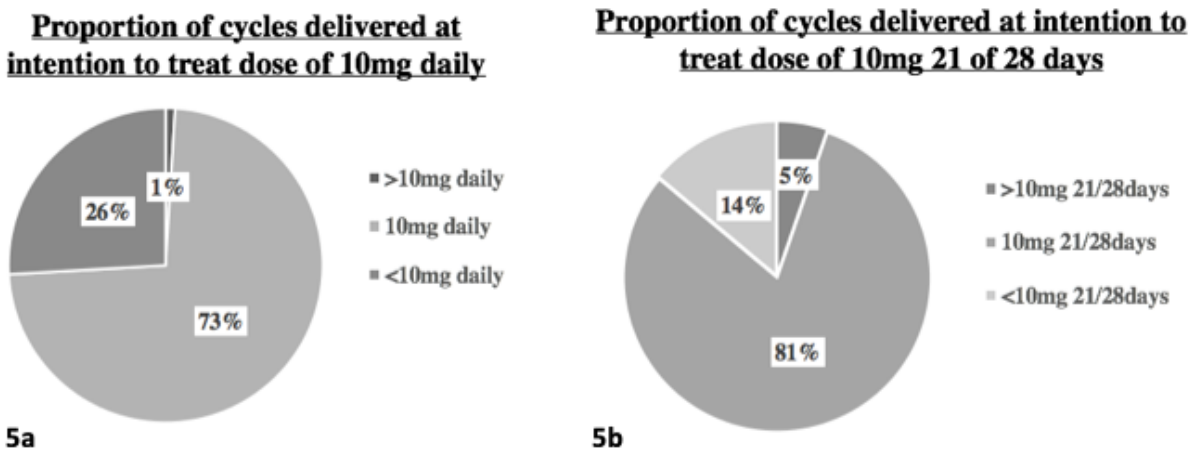

Figure 3.5. Proportion of cycles delivered at the intention to treat dosage. The vast majority of cycles were delivered at the intention to treat dosage schedule of 10mg daily continuously or 10 mg 21 of 28 days.

Common indications for dose reduction or medication discontinuation were cytopenias (27.7%), rash (10.8%), infection (9.5%) and fatigue (8.1%). Notably, one case on Guillian-Barre syndrome was recorded in a patient treated with lenalidomide maintenance which has not previously been reported and may be a concurrent finding rather than a causal one. 19.6% discontinued therapy prior to relapse. Venous and arterial thrombosis during front line treatment was not significantly different between the groups at 2.6% in the no maintenance group compared to 5.4% in the maintenance group prior to relapse ($p = 0.5$, table 4. Rates of secondary primary malignancies (SPMs) were observed in 6.4% of the non-maintenance group and 3.4% of the maintenance patients ($p = 0.32$).

Table 3.4. Frequency of arterial and venous thrombosis in the maintenance and no maintenance cohorts prior to relapse.

	No Maintenance n (%)	Maintenance n (%)	p-value
Thrombotic event prior to first relapse	2 (2.6%)	8 (5.4%) *	0.5

*only 1 event occurred while a patient was off lenalidomide maintenance but had not yet relapsed.

DISCUSSION

This analysis from the MCRN DM is the first of its kind analyzing the use of lenalidomide maintenance following ASCT. Our data validates findings of large, phase 3 randomized control trials illustrating a positive impact of lenalidomide maintenance on PFS and OS in a real-world setting.[3,4,7,16,18] Both groups had similar baseline characteristics with regards to demographics, disease stage and presence of high risk cytogenetics and were treated with similar induction regimens. The median OS data strongly favours the use of lenalidomide maintenance ($p < 0.001$) despite the endpoint of median OS in the maintenance cohort having not yet been reached. Five-year overall survival data confirms this finding (81% versus 61.5%). The median PFS data also strongly favoured maintenance lenalidomide (58.2 months 34.6 months ($p < 0.0001$)).

Patients treated with lenalidomide based maintenance have significantly greater frequencies of favourable response defined as VGPR or greater ($p < 0.01$). Recent data regarding grading response in MM with next generation sequencing has shown that a patients' depth of remission correlated with survival outcomes.[14,15] Our data supports this emerging evidence as patients achieving nCR/CR compared to VGPR has superior OS and PFS in both those who had and had not received maintenance chemotherapy.

Though most patients required a dose reduction or medication discontinuation at some point during their treatment, the majority of cycles were administered at the intention to treat dose schedule (figure 3.4) with only 19.6% of patients discontinuing therapy prior to relapse. This suggests that lenalidomide is a well-tolerated medication most patients can remain on until relapse. Side effects noted by the treating physician were similar to those found in large phase 3 clinical trials with cytopenias being the most frequently reported. Historically, thrombosis and

incidence of secondary primary malignancies have been a concern with the use of lenalidomide maintenance however we did not detect differences in frequency between the groups at the level of statistical significance ($p = 0.5$ and $p = 0.32$ respectively).

Limitations of our study include its retrospective, observational nature. Patients were enrolled who started chemotherapy prior to 2016 during which significant changes have emerged in the field of myeloma particularly with regards to novel chemotherapeutic agents in the setting of relapsed disease. Given that the non-maintenance cohort is largely represented by those starting chemotherapy prior to 2012, these patients may not have had the same access to clinical trials or novel combination therapy as their maintenance counterparts which could bias our results. Conversely, the relatively recent adoption of maintenance lenalidomide in the 2011-2012 years limits our ability to see the full impact of lenalidomide maintenance on survival outcomes. With limited follow-up, the positive impact of lenalidomide is likely under-estimated. Nevertheless, the similarity of our data when compared to large scale, randomized, controlled trials suggests that the impact of this temporal relationship between the maintenance and non-maintenance groups may not be significantly impactful on our results. Greater follow-up time is needed to further examine the impact of maintenance therapy.

Despite the limitations of retrospective data, large multicentre datasets have undeniable merits as they allow for lengthy follow-up of real world data which is not necessarily reflected due to the constraints of randomized control trials.[3,4,8,16,18] Furthermore, early relapsers and long-term disease-free survivors are easily selected out of large, retrospective datasets. Examination of their data will be useful determination contributing and prognosticating factors in these patient subsets.

CONCLUSIONS

Our retrospective review validates the data seen in large phase 3 trials demonstrating the statistically significant, positive impact of lenalidomide maintenance on PFS and OS in the real-world Canadian landscape. Patients treated with lenalidomide based maintenance were more

likely to achieve more favourable treatment response of CR. Side effects were as anticipated based on RCT data with no significant difference in the frequency of thrombosis and secondary primary malignancies between the groups. This data supports the ongoing use of lenalidomide based maintenance as current standard of care.

AKNOWLEDGEMENTS & DISCLOSURES

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CHAPTER 4:

The Impact of Lenalidomide Maintenance on Second Line Chemotherapy in Transplant Eligible Patients with Multiple Myeloma in the Canadian Setting.

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INTRODUCTION

With the advent of novel agents, patients with multiple myeloma are experiencing longer survival than ever. As patients are often treated with multiple lines of chemotherapy, the idea of optimal therapy sequencing has come into question. The use of maintenance lenalidomide (LM), an oral immunomodulator, has been shown to have a positive impact on progression free (PFS) and overall survival (OS).[1-4] However, its use as daily low dose maintenance has raised questions about its impact on the efficacy of subsequent lines of treatment. Specifically, whether daily, low dose maintenance lenalidomide promotes the emergence of resistant clones that limit the efficacy of lenalidomide when used in subsequent lines of therapy. This has been demonstrated in vitro namely through down regulation of CRBN, a target of immunomodulators.[11-13] However, studies of human bone marrow in the context of relapse on lenalidomide maintenance has not demonstrated promotion of clonal resistance.[14]

Early large scale trials examining newer treatments in the setting of relapsed/refractory multiple myeloma have historically contained low number of patients who had previously been exposed to lenalidomide therapy in the range of 10-21%.[7-10] This limits their generalizability particularly in the era of widely adopted lenalidomide based maintenance and leaves unanswered questions regarding optimal therapy sequencing in patients who relapse on lenalidomide maintenance. More recent clinical trials have sought to include high numbers of IMID exposed or refractory patients to fill this knowledge gap.[15-17]

As such, we sought to evaluate the differences in survival outcomes in patient treated with lenalidomide maintenance following autologous stem cell transplant (ASCT) with a bortezomib based induction regimen who were re-exposed to lenalidomide in subsequent lines of chemotherapy. Our investigations sought to analyze trends in the real-world Canadian landscape utilizing data from the Myeloma Canada Research Network Canadian Multiple Myeloma Database (MCRN-CMM DB), a collection of data from 13 academic cancer centers across Canada incorporating data from over 5,000 patients.

METHODS

Patient Evaluation

We retrospectively analyzed data from the MCRN CMM-DB of patient undergoing front line therapy for multiple myeloma. Patients who met all of the following inclusion criteria were selected for analysis:

1) Diagnosed with multiple myeloma as per IMWG criteria[5]
2) Treated with front line bortezomib based induction and ASCT
3) Treated with no maintenance chemotherapy or lenalidomide maintenance after front line induction and ASCT
4) Experiences at least one relapse defined by IMWG criteria or clinical progression as determined by the treating physician
5) Treated with second line chemotherapy

Patients who fulfilled the following exclusion criteria were removed from the study population:

1) Diagnosed with smouldering myeloma or AL amyloidosis
2) Treated with thalidomide maintenance or combination lenalidomide maintenance therapy
3) Did not survive 100 days post autologous stem cell transplantation
4) Had not yet experienced a relapsed
5) Did not receive second line chemotherapy

Data of patients meeting the aforementioned criteria were reviewed by data representatives at each center. Basic demographics were recorded including age and gender. Characteristics of patients' multiple myeloma were also recorded including ISS stage at diagnosis, baseline para-protein levels, immunoglobulin subtype and cytogenetic results where available. Dates of initiation of each line of chemotherapy were recorded as well as dates of relapse, death and last follow-up.

Patients were grouped into 4 categories based on 2 variables using an intention to treat strategy. Variables included receipt of lenalidomide based maintenance and receipt of lenalidomide in second line of chemotherapy, table 4.1.

Endpoint Evaluation

Primary endpoint was second progression free survival (2^{nd} PFS) which was defined as time from initiation of second line therapy to second relapse, death or last follow-up. This end point was chosen given that it focuses specifically on the progression free interval obtained from second line chemotherapy. Overall survival (OS) from initiation of relapse therapy was analyzed as a secondary survival outcome and defined as time of initiation of second line therapy to death or last follow-up. Additional outcomes recorded included depth of response to second line chemotherapy defined as best response achieved at any point in time. Responses were coded as per IMWG response criteria with an additional endpoint of near complete response (nCR) where blood and urine testing met the criteria for a CR but in whom immunofixation and bone marrow biopsy was not repeated as is often the case in the real world setting.[6]

Statistical Evaluation

Survival statistics including 2^{nd} PFS and OS from initiation of relapse therapy were determined using Kaplan-Meier survival curves by an independent statistician. Chi-squared analysis was used to determine differences in baseline and outcome variables between the maintenance and non-maintenance groups. A p value of <0.05 was considered significant.

RESULTS

Five hundred and seventy five (575) patients from 9 Canadian centers were included in our analysis. 297 (52%) patients were treated with lenalidomide maintenance (LM) of which 136 (24%, group 1) received lenalidomide at relapse and 161 (28%, group 2) did not. 278 (48%) patients did not receive lenalidomide maintenance of which 209 (36%, group 3) received lenalidomide at relapse and 69 (12%, group 4) did not (Table 4.1).

Table 4.1. Intention to treat allocation based on receipt of lenalidomide based maintenance and receipt of lenalidomide in second line chemotherapy.

		Receipt of Lenalidomide in Second Line Chemotherapy		
		Yes	**No**	
Receipt of Lenalidomide Based Maintenance	**Yes**	**Group 1** **136** (24%)	**Group 2** **161** (28%)	**297** (52%)
	No	**Group 3** **209** (36%)	**Group 4** **69** (12%)	**278** (48%)
		345 (60%)	**230** (40%)	**575** (100%)

Baseline characteristics of the four groups are illustrated in table 4.2. There was no significant difference in ISS stage (p = 0.17), or presence of high-risk cytogenetics (p = 0.24) which were recorded where available.

Table 4.2. Baseline characteristics.

	Group 1 **LM** **L in 2nd line therapy**	**Group 2** **LM** **No L in 2nd line therapy**	**Group 3** **No LM** **L in 2nd line therapy**	**Group 4** **No LM** **No L in 2nd line therapy**	**p - value**
n (%)	136 (24%)	161 (28%)	209 (36%)	69 (12%)	-
Mean Age at Diagnosis (yrs)	57.54	58.30	57.41	55.48	0.0838
Gender					
Female	58 (42.7%)	66 (41%)	85 (40.7%)	25 (36.2%)	0.8518
Male	78 (57.4%)	95 (59.0%)	124 (59.3%)	44 (63.8%)	
Creatinine Prior to Treatment	113.24	130.86	140.31	134.92	0.2528
ISS					
1	36 (27.5%)	42 (30%)	53 (28.5%)	14 (22.2%)	
2	58 (44.3%)	62 (44.3%)	66 (35.5%)	22 (34.9%)	0.1668
3	37 (28.2%)	36 (25.7%)	67 (36.0%)	27 (42.7%)	
missing	5	21	23	6	
High Risk Cytogenetics*	30/113 (26.6%)	35/122 (28.7%)	22/118 (18.6%)	10/32 (31.3%)	0.2397
del 17p	12/113 (10.6%)	21/120 (17.5%)	11/116 (9.5%)	4/31 (12.9%)	0.2576
t 4:14	16/108 (14.8%)	12/115 (10.4%)	13/114 (11.4%)	5/32 (15.6%)	0.7075
t 14:16	2/93 (2.2%)	4/96 (4.2%)	0/64 (0%)	2/21 (9.5%)	0.1014**
missing	23/136 (16.9%)	39/161 (24.2%)	91/209 (43.5%)	37/69 (53.6%)	
Immunoglobulin Subtype*					
IgG	74 (55.6%)	77 (50.7%)	114 (59.4%)	34 (57.6%)	
IgA	27 (20.3%)	39 (25.7%)	44 (22.9%)	13 (22.0%)	
IgM	2 (1.5%)	0 (0%)	0 (0%)	1 (1.7%)	0.2343**
IgD	0 (0%)	0 (0%)	0 (0%)	1 (1.7%)	
FLC	30 (22.6%)	36 (23.7%)	34 (17.7%)	10 (17%)	

*indicates results described where available

**indicates Fischer's exact test

Lenalidomide monotherapy or with dexamethasone was the most commonly used second line therapy (table 4.3). Use of novel agents such as monoclonal antibodies and next generation proteasome inhibitors were more common in patients treated with lenalidomide maintenance.

Table 4.3. Second line chemotherapeutic regimens used in patients treated with and without lenalidomide maintenance

Second Line Regimen	Received lenalidomide maintenance	
	YES n (%)	NO n (%)
Lenalidomide (R) Monotherapy or with Dexamethasone (D)	80 (27%)	161 (57.9%)
Proteasome inhibitor singlet or doublet (velcade/VD/VC/KD)	22 (7.4%)	12 (4.3%)
Proteasome inhibitor triplet or more (CyBorD/KCD/SelVD/IsoVC/VenetVD)	63 (21.3%)	32 (11.5%)
Lenalidomide (R) or thalidomide (T) containing triplet (RCD/EloRD /SelRD/BiRD/TCD/DT-PACE)	10 (3.4%)	17 (6.1%)
Lenalidomide (R) and proteasome inhibitor combination (RVD/KRD/RVCD)	33 (11.2%)	23 (8.3%)
Pomalidomide (Pom) containing regimen (PomVD/PomD/PomCD/PomKD/PomVP)	27 (9.1%)	3 (1.1%)
Daratumumab (Dara) containing regimen (DaraCD/Dara/DaraPomD/DaraPomCD/DaraKD/DaraVD)	41 (13.9%)	5 (1.8%)
Ixazomib (Ixa) containing regimen (IxaCD/IxaPomD/IxaRD/IxaCP)	19 (6.4%)	7 (2.5%)
Other (Selinexor/ASCT/CD/D-PACE)	1 (0.3%)	18 (6.5%)

Additional abbreviations are as follows: V/Velcade/Bor = Bortezomib, Cy/C = cyclophosphamide, K = Carfilzomib, Sel = selinexor, Iso = Iso906, Venet = Venetoclax, Elo = Elotuzumab, PACE = cisplatin, doxorubicin, cyclophosphamide & etoposide, P = prednisone, Bi = Biaxin, ASCT = autologous stem cell transplant.

Median patient follow-up from second line chemotherapy was 22.9 months, 12 months, 26.1 months and 17.7 months in groups 1 through 4 respectively. At the time of analysis 217 (37.3%) of patients had died and 557 (96.9%) had progressed or died. Focusing on the cohort of relapsed patients who had received lenalidomide maintenance (n = 297), the median second PFS was 10.2 months (95% CI: 7.1 – 13.9 months) in those that received lenalidomide in second line therapy comparted to 14.0 months (95% CI: 11.5 – 15.5 months) in those who did not (p = 0.53), figure 4.1. In patients who did not receive lenalidomide maintenance (n = 278), those who received lenalidomide in second line therapy had a second PFS of 18.1 months (13.4 – 25.1 months) while those who received no lenalidomide in second line therapy had a second PFS of 12.0 months (95% CI: 9.0-20.1 months) which was clinically significant (p = 0.0495), figure 4.1.

Figure 4.1 Second Progression Free Survival

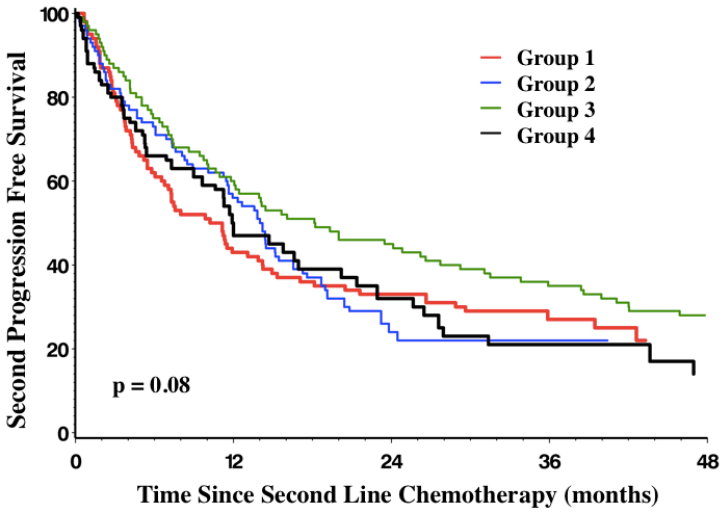

Figure 4.1. Second progression free survival in of patients based on receipt of lenalidomide based maintenance and lenalidomide containing therapy at relapse.

At the time of analysis, group 2 had the highest number of patients who had not yet relapsed at 47.8% follower by group 1 (36.7%), group 3 (33%) then group 4 (29%). In a one-on-one comparison of each group, statistically significant differences in second PFS were present only when comparing patients who had not received maintenance lenalidomide but received lenalidomide at relapse (group 3) to all other groups, table 4.4.

Table 4.4 Level of significant of differences in median second PFS between groups.

Versus	**Group 1** **LM** **L in 2nd line therapy**	**Group 2** **LM** **No L in 2nd line therapy**	**Group 3** **No LM** **L in 2nd line therapy**	**Group 4** **No LM** **No L in 2nd line therapy**
Group 1 **2nd PFS:** 10.2 months (95% CI: 7.1 – 13.9 months)		p = 0.53	**p = 0.04**	p = 0.9
Group 2 **2nd PFS:** 14.0 months (95% CI: 11.5 – 15.5 months)	p = 0.53		**p = 0.0467**	p = 0.8
Group 3 **2nd PFS:** 18.1 months (13.4 – 25.1 months)	**p = 0.04**	**p = 0.0467**		**p = 0.0495**
Group 4 **2nd PFS:** 12.0 months (95% CI: 9.0-20.1 months)	p = 0.9	p = 0.8	**p = 0.0495**	

Overall survival (OS) from initiation of relapse therapy was also examined. With respect to patients treated with lenalidomide based maintenance who received lenalidomide in second line therapy (group 1) median OS from initiation of relapse therapy was 55.3 months (95% CI: 49 months – NYR) compared to 37 months (95% CI: 22.5 – 49.4 months) in those who did not receive lenalidomide in second line therapy (group 2). This difference was statistically significant (p = 0.004). In the cohort of patients who did not receive lenalidomide maintenance, those who received lenalidomide at relapse (group 3) had a median OS from initiation of relapse therapy of 49 months (95% CI: 33.8 – 70.8 months) compared to 26.7 months (95% CI: 20.1 months – NYR) in those who did not receive lenalidomide at relapse (group 4). This comparison was not statistically significant (p = 0.15).

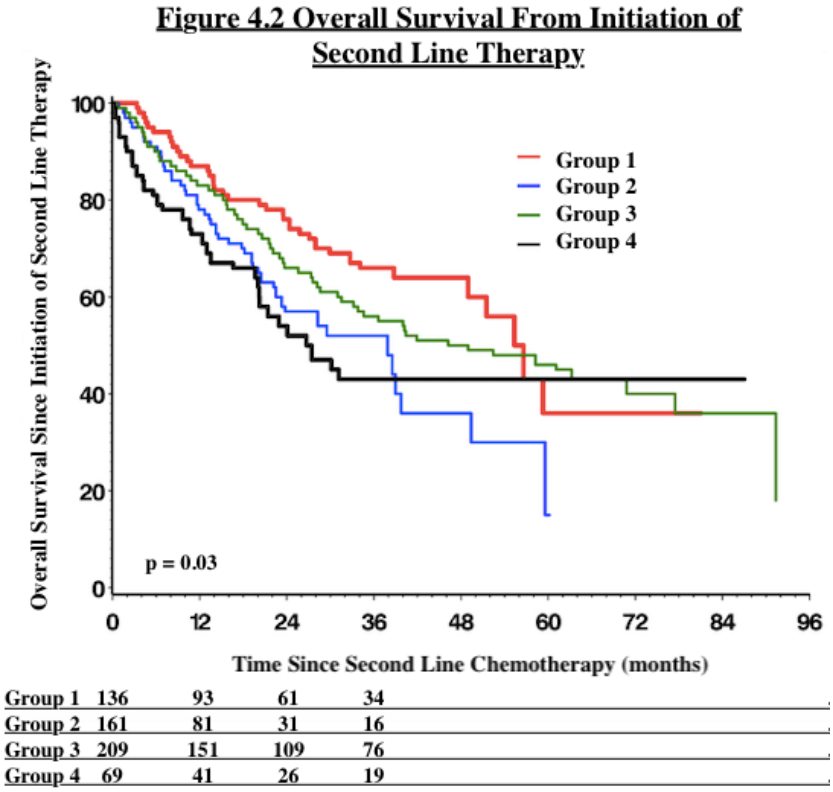

Figure 4.2. Second overall survival in of patients based on receipt of lenalidomide based maintenance and lenalidomide containing therapy at relapse.

In additional one-on-one comparison of each group a statistically significant difference in OS from initiation of relapse therapy was only found in comparing those who received lenalidomide in maintenance and second line therapy to those who receive no lenalidomide (group 1 versus group 4, p = 0.02), table 4.5.

Table 4.5. Level of significant of differences in median OS from initiation of relapse therapy between groups.

Versus	Group 1 LM L in 2nd line therapy	Group 2 LM No L in 2nd line therapy	Group 3 No LM L in 2nd line therapy	Group 4 No LM No L in 2nd line therapy
Group 1 **2nd OS:** 55.3 months (95% CI: 49 months – NYR)		**p = 0.004**	p = 0.22	**p = 0.02**
Group 2 **2nd OS:** 37 months (95% CI: 22.5 – 49.4 months)	**p = 0.004**		p = 0.06	p = 0.8
Group 3 **2nd OS:** 49 months (95% CI: 33.8 – 70.8 months)	p = 0.22	p = 0.06		p = 0.15
Group 4 **2nd OS:** 26.7 months (95% CI: 20.1 months – NYR)	**p = 0.02**	p = 0.8	p = 0.15	

Maximal response to second line therapy, at any point in time, was documented in keeping with IMWG criteria (table 4.6).

Table 4.6 Maximal response to second line therapy based on receipt of lenalidomide based maintenance and receipt of lenalidomide at relapse.

	Group 1 LM L in 2nd line therapy	Group 2 LM No L in 2nd line therapy	Group 3 No LM L in 2nd line therapy	Group 4 No LM No L in 2nd line therapy	p value	
nCR/CR	54 (41.2%)	50 (32.7%)	73 (39.7%)	21 (37.5%)	0.45	0.000334
VGPR	66 (50.4%)	90 (58.8%)	71 (38.6%)	24 (42.9%)	0.002188	
PR	6 (4.6%)	12 (7.8%)	29 (15.8%)	11 (19.6%)	0.001424	
SD	4 (3.1%)	1 (0.7%)	7 (3.8%)	0 (0%)		
PD	1 (0.8%)	0 (0%)	4 (2.2%)	0 (0%)		

Patients treated with lenalidomide maintenance had higher rates of favourable response to second line therapy (VGPR or higher) when compared to those who did not at the level of statistical significance (table 4.7). There was no difference in the frequency of favourable responses in

patients treated with lenalidomide maintenance based on receipt of lenalidomide in second line therapy.

Table 4.7 Comparison of differences rates of favourable responses (VGPR & CR) between groups.

Versus	Group 1 LM L in 2nd line therapy	Group 2 LM No L in 2nd line therapy	Group 3 No LM L in 2nd line therapy	Group 4 No LM No L in 2nd line therapy
Group 1		p = 0.975957	**p = 0.0015333**	**p = 0.0288**
Group 2	p = 0.975957		**p = 0.000885**	**p = 0.025192**
Group 3	**p = 0.0015333**	**p = 0.000885**		p = 0.737
Group 4	**p = 0.0288**	**p = 0.025192**	p = 0.737	

DISCUSSION

Our data represents the first analysis of the impact of lenalidomide maintenance on outcomes in second line chemotherapy from the MCRN CMM-DB. Baseline demographics of the 4 groups in our analysis were similar. There were no statistically significant differences in age, gender, ISS score, or presence of high-risk cytogenetics between the 4 groups. Lenalidomide monotherapy or in combination with dexamethasone was the most common treatment regimen used in second line treatment (table 4.3). There were higher rates of novel combinations of chemotherapy used in second line therapy in the group who had received lenalidomide maintenance. This may be due to the more recent nature of these cases thus increased access to novel therapies through clinical trials and otherwise.

Higher rates of favourable responses (VGPR, nCR, and CR) to second line therapy were seen in patients treated with lenalidomide maintenance when compared to those who were not (table 4.6). Importantly, there was no significant difference in the frequency of favourable responses in patients treated with lenalidomide maintenance regardless of their receipt of lenalidomide in second line therapy (group 1 versus group 2, p = 0.98). This suggests that the use of

lenalidomide maintenance does not results in unfavourable responses when lenalidomide is used again in second line therapy.

Analysis of our primary outcome, second PFS was longest in group 3, patients who did not receive lenalidomide maintenance but received lenalidomide at relapse (group 3). This cohort is of historical interest but minimal clinical relevance given the status of lenalidomide maintenance as standard of care. With time, the number of patients represented by this group are diminishing. Most importantly, there was no difference in second PFS between groups 1 and 2 (10.2 months VS 14.0 months = 0.53. This suggests that in patients who receive lenalidomide maintenance, the repeat use of lenalidomide in second line therapy at treatment doses does not result in worsened second PFS. As such, patients should not be denied second line full-dose lenalidomide containing chemotherapy solely on the basis of having received lenalidomide maintenance. Of note, lenalidomide maintenance was adopted between 2012 to 2014 across Canada. Given that our data is retrospective and observational, the non-maintenance cohort generally began therapy in the years prior. As such, patients included in groups 1 and 2 are those who relapsed sooner than expected on lenalidomide maintenance based on data previously analyzed by our group and put forth in landmark randomized, clinical trials.[1-4,18] Therefore, the shorter PFS in groups 1 and 2 may be reflective of patients with more aggressive disease who are prone to early relapse thus underestimating the true impact of lenalidomide maintenance on outcomes in second line therapy. Longer follow-up time will help clarify this.

It is worth noting the discrepancy between second PFS results and response to second line treatment observed in our results. Patient response to therapy has been shown to correlate with PFS and OS.[12] However, our lenalidomide maintenance patients experienced a higher frequency of favourable responses despite a lower second PFS. A possible explanation for this would be that maximal response to therapy is evaluated as an earlier time than the event of a relapse. At time of analysis, a higher number of patients in groups 1 and 2 had not yet had a second relapse in comparison to groups 3 and 4 (36.8% and 47.8% vs 34% and 29%). Thus, their maximal second PFS is not yet known. As such, it is possible that those who remain on therapy have achieved a greater depth of response that, with further follow-up, may translate into a longer second PFS in patients represented by groups 1 and 2.

Overall survival from initiation of relapse therapy (2^{nd} OS) was longest in patients who received lenalidomide maintenance and lenalidomide in second line therapy (group 1). In patients who received lenalidomide maintenance, those who received lenalidomide again at relapse had longer 2^{nd} OS at the level of statistical significant (55.3 months VS 37 months, $p = 0.004$). The difference in overall survival from initiation of relapse therapy was not significant between groups 1 and 3 ($p = 0.22$) which suggests that the improved 2^{nd} PFS seen in group 3 could not overcome the impact of lenalidomide maintenance on second overall survival. As such, our data reaffirms the importance of lenalidomide in maintenance in second line therapy even in patients who have been exposed to the drug in maintenance. This also argues against the belief that lenalidomide selects for the emergence of IMID resistant clones when used as a maintenance strategy.

Important limitations in our data include its retrospective nature. As such our data does not reflect the stringent methodologies of large, phase 3 clinical trials. Additionally, the more recent adoption of lenalidomide maintenance means that this cohort has had less opportunity for follow-up meaning that those included in our trial are those who have relapsed relatively early in their treatment course and certainly in comparison to their non-maintenance counterparts. As such, the patients included in the maintenance cohorts of our study (groups 1 and 2) are likely biologically higher risk independent of their ISS stage or cytogenetics. As a result, the true impact of lenalidomide maintenance may be underestimated as it is being evaluated in the patients with the most aggressive disease making our survival results even more reassuring.

CONCLUSION

Our data suggests that receiving lenalidomide based maintenance does not negatively impact second progression free survival in patients who go on to receive lenalidomide-based therapy at relapse. Additionally, our data also suggests that omission of lenalidomide at relapse in patients who received lenalidomide maintenance results in inferior overall survival from initiation of relapse therapy. Patients treated with lenalidomide maintenance had significantly higher rates of

favourable treatment responses to second line therapy. The repeat use of lenalidomide in this population did not alter rates of favourable responses. We acknowledge limitation in our data due to its retrospective nature. Additionally, the recent adoption of lenalidomide (and thus shorter follow-up of the cohort) limits our ability to see the full impact of lenalidomide maintenance and its role in optimal therapy sequencing.

In summary, low-dose lenalidomide does not appear to negatively impact survival outcomes with the use of lenalidomide in the relapsed setting. This is likely due to the predominant immunomodulatory mechanism of lenalidomide at low doses. Patients treated with lenalidomide base maintenance have historically been under-represented in landmark, phase 3 clinical trials of multi-agent lenalidomide containing regimens.[7-10] As such, large retrospective datasets allow for reflection on real world data help to fill this gap providing a means to elucidate the impact of lenalidomide maintenance on multi-agent lenalidomide containing regimens used in the relapsed setting. Further investigation regarding optimal therapy sequencing, particularly optimal second line therapy for treated with lenalidomide maintenance, is of the utmost importance given the emergence of numerous novel therapies for relapsed and refractory myeloma.

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CHAPTER 5:

Emerging and Current Topics in Myeloma

Emerging and Current Topics in Myeloma

The field of multiple myeloma is rapidly changing. Over the past decade several novel agents have come to market largely in the relapsed setting.[8-11] However, novel agents are not the only revolution the field has seen. Changes in front-line therapy regimens, the role of autologous stem cell transplantation in the era of novel agents and a response-adapted approach to treatment are issues clinicians may soon be facing.

The introduction of novel agents such as next generation proteasome inhibitors like carfilzomib and monoclonal antibodies like daratumumab have largely been examined in the relapsed setting.[8-11] These agents show promising survival outcomes in these populations.[8-11] As such, their use in upfront setting is an active area of investigation. Daratumumab, a CD38 monoclonal antibody, is an example of a novel agent undergoing active investigation as a frontline treatment option. Facon, *et al.* (NEJM 2019) examined the use of daratumumab in combination with lenalidomide and dexamethasone as frontline treatment in the transplant ineligible population in their randomized, open label, phase 3 trial.[12] At a median follow-up time of 28 months, 240 patients had died or experienced disease progression.[12] In the daratumumab, lenalidomide and dexamethasone (DRd) group, 70.6% (95% CI: 65-75.4) were alive without evidence of progression as compared to 55.6% (95% CI: 49.5-61.3) in the lenalidomide dexamethasone (Rd) arm (HR = 0.56, 95% CI: 0.43-0.73).[12] Median progression free survival was not yet reached in the DRd group and was 31.8 months in the Rd group (95% CI: 28.9 mo – NYR).[12] Importantly, there was a higher rate of MRD negative CR at the level of 1×10^{-5} in the DRd population at 24.2% versus 7.3% ($p < 0.001$).[12] These progression free survival results are similar to those presented in our analysis of transplant eligible patients in chapter 3 despite this trial population being significantly older with 99% of patients over the age of 65.[12] This study raises questions as to whether these agents may be superior to conventional treatment of induction therapy and ASCT with regards to survival outcomes in the transplant eligible population. Therefore, their role in transplant eligible patients is a natural venue of future investigation.

Voorhees, P., *et al.* (2017) published results of a phase 2 trial evaluating the combination of daratumumab (Dara) in addition bortezomib, lenalidomide and dexamethasone (VRd) followed

by ASCT in transplant eligible patients.[13] Patients received an additional 2 cycles of Dara-VRd consolidation followed by 24 months of daratumumab and lenalidomide maintenance.[13] Of the 16 patients enrolled in the phase 2 trial no new safety signals were observed and all patients continued on therapy.[13] Half of the patients achieved MRD negative CR at 1 x 10^{-5} by the end of consolidation therapy, twice as high as the frequency of MRD negative CR seen in the MAIA trial.[12, 13] Moreau, P., *et al.* (2019), recently published results of the CASSIOPEIA trial comparing daratumumab, bortezomib, thalidomide and dexamethasone (Dara-VTd) to VTd, in the transplant eligible population.[17] Patients were randomized to receive 4 cycles of their assigned treatment pre-ASCT and 2 cycles at consolidation doses post-ASCT.[17] At 100 days post-transplant, the Dara-VTd group had higher rates of MRD negativity (1 x 10^{-5}) at 64% compared to 44% ($p<0.0001$).[17] Further follow-up regarding PFS and OS is needed.[17] Sonneveld, *et al.* are currently conducting an ongoing clinical trial evaluating VRd with and without daratumumab in transplant eligible patients.[14]

Though these clinical trials using novel agents in the transplant eligible setting are of great interest, they still do not differenciate what benefits are imparted from the chemotherapy (specifically the monoclonal antibody component) and which are from the ASCT. PFS results of the MAIA trial are not dissimilar to those seen in the transplant eligible population treated with bortezomib based induction such as those presented in chapter 3. As such, one could question whether ASCT provides any additional survival benefits to transplant eligible patients being treated with these agents. In the recent update from the Forte trial, Gay, F., *et al* (Blood 2018) indirectly examined the impact of ASCT in patients treated with a proteasome inhibitor (PI) and IMID based induction.[15] They conducted a randomized trial comparing three treatment strategies;

1) KRd-ASCT-KRd: 4 cycles of carfilzomib, lenalidomide and dexamethasone (KRd) induction plus Mel200-ASCT and 4 cycles of KRd consolidation
2) KRd12: 12 cycles of KRd
3) KCd-ASCT-KCd: 4 cycles of carfilzomib, cyclophosphamide and dexamethasone (KCd) induction plus Mel200-ASCT and 4 cycles of KCd consolidation

After completion of the aforementioned therapy, patients were then randomized to maintenance with lenalidomide alone or in addition to carfilzomib.[15] the KCd-ASCT-KCd group had clearly inferior outcomes to the other two groups with regards to achievement of complete response and MRD negativity.[15] As such, subsequent analysis focused on the KRD12 and KRd-ASCT-KRd groups.[16] Recent updates from the trial were presented at the American Society of Clinical Oncology in June 2019.[16] At a median follow-up of 25 months, patients treated with KRd-ASCT-KRd had higher rates of MRD negativity (1×10^{-5}) at 1 year (90% vs 78%) and lower rates of early relapse (12% vs 23%, $p = 0.015$) compared to the KRd12 group.[16] This suggests that, at least in the case of a carfilzomib-lenalidomide-based approach, there may still be something be gained by undergoing ASCT in patients treated with more potent PI-IMID based induction.[16] The role of ASCT with use of other novel agents in the transplant eligible population is under active examination as an area of significant interest.

The emerging use of minimal residual disease (MRD) negativity in clinical practice may change the traditional myeloma treatment paradigm that is largely focused on completing treatment protocols rather than a response based model. Minimal residual disease refers to the absence of clonal plasma cells in the bone marrow at a level of 1 in 10^{-5} by PCR or flow cytometry.[3] Trials have demonstrated a positive correlation between MRD negativity and overall survival.[4-7] As such, it has been added to updated response criteria from the International Myeloma Working Group.[3] As access to laboratory infrastructure to assess MRD negativity becomes standard of care in the clinical setting, the idea of a universal treatment regimen may change to an algorithmic one based on patient response. Currently, a complete response to therapy is seen as the ultimate goal. However, not all patients who achieve a CR will be MRD negative. As such, without MRD testing we cannot know which patients harbor residual disease and may benefit from further chemotherapy. In their article, Sherrod, *et al.* (2016) discuss a response-based model where patients achieving MRD negativity after induction may proceed directly to maintenance, forgoing autologous stem cell transplant as the risks of melphalan may outweigh any benefits. However, the results from the FORTE trial suggest that there is additional benefit of an ASCT as demonstrated by the lower rates of early relapse and higher rates of MRD negativity in transplanted patients.[16] Further data evaluating this approach as well as the role of

response based models in the treatment of multiple myeloma will be of great utility in the development of more personalized and hopefully more effective chemotherapeutic regimens.

Large, retrospective datasets provide the opportunity to analyze data representative of a real-world setting. They allow for lengthy, low cost follow-up of a large number of patients and allow for analysis of research questions unlikely to be answered in the randomized control setting due to funding and time constraints. Additionally, they allow for identification of long-term disease free survivor and early relapse, patients whose data may provide clues into future biomarkers of disease or prognostic relevance. As with all retrospective data, the lack of stringent treatment protocols of the clinical trial setting leaves the possibility for bias to be introduced into results. Strict inclusion and exclusion criteria are required to maximize sample homogeneity and minimize bias.

In summary, the field of multiple myeloma remains one that is constantly evolving. In particular the use of novel therapies and MRD testing may shift the treatment of myeloma to a response based approach rather than a one size fits all strategy. The additional survival benefits of ASCT in the era of novel agents is another topic of interest for future research. Large, retrospective data sets allow for low cost, long term follow-up of patient populations to answer questions unlikely to be analyzed in the clinical trial setting. As with any research methodology, they too have their own disadvantages. As clinicians and researchers our ongoing participation in innovative areas of study is critical to continue to improve the lives of our patients.

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Chapter 1

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