HIGH-DOSE WEEKLY CARFILZOMIB, CYCLOPHOSPHAMIDE, AND DEXAMETHASONE IN THE TREATMENT OF PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA – EXPLORING THE FINANCIAL COST AND RARE SIDE-EFFECTS

by

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Abstract

Multiple myeloma

Multiple myeloma (MM) is a malignant disorder of clonal plasma cells based in the bone marrow that leads to devastating symptoms including renal failure, hypercalcemia, anemia, and fractures. Treatment efficacy has improved due to the advent of new therapies; however, there is also an increase in toxicity and cost (1,2).

MYX.1 Trial

The MYX.1 clinical trial is a single arm phase II multi-centre trial that explored the efficacy of high-dose weekly carfilzomib with cyclophosphamide and dexamethasone (wKCD) for relapsed MM. The trial met its primary endpoint with a high overall response rate (84%) (3)

Life-threatening Drug Side-effects

Cases of thrombotic microangiopathy (TMA), a rare but life-threatening syndrome of microangiopathic haemolytic anaemia, thrombocytopenia, and multi-organ dysfunction, have been reported in patients receiving carfilzomib (4–8). Herein, I will determine the incidence, clinical phenotype, and predictive factors associated with TMA and carfilzomib based on the MYX.1 trial data.

Cost of Myeloma Therapy

In Canada, MM represents 1.5% of cancer diagnoses but up to 20% of some provincial oncology drug budgets (G. Mitera, personal communication, March 30, 2020). MM is not curable, and treatment is continuous until the time of disease progression. This study determines the cost of high-dose wKCD, from the perspective of the payer, based on MYX.1 trial data.
Results

A high rate of TMA (4%) was seen in patients treated in the MYX.1 clinical trial. The management of carfilzomib related DITMA should focus on supportive care and cessation of carfilzomib.

Based on the MYX.1 trial data, the mean total cost of high-dose weekly KCD was $203,336.08 CAD per patient (pt). The predominant cost driver was chemotherapy at $179,332.78/pt where the cost of carfilzomib was $162,471.65/pt. The cost of carfilzomib is minimized through this high-dose once weekly KCD dosing schedule. We calculated the cost of biweekly carfilzomib at $300,576.70/pt (compared to $179,332.78 per patient on wKCD), a potential cost savings of $104,663.43/pt from direct drug costs and $16,580.49/pt from drug administration costs.

Conclusions

High-dose wKCD is an active triplet regimen for RRMM associated with reduced total cost compared with twice weekly regimens and its toxicity is provisionally acceptable.
Bibliography


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Statement of Originality

I hereby certify that all of the work described within this master’s thesis is the original work of the author. Any published or unpublished ideas from the work of others are fully acknowledged in accordance with the standard referencing practices.

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Chapter 1

General Introduction

1.1 Background

1.1.1 Multiple Myeloma

Multiple myeloma (MM) is a lymphoproliferative disorder of malignant clonal plasma cells based in the bone marrow. It represents the second most common hematologic malignancy in Canada. It is expected that 3400 Canadians will be diagnosed with MM in 2020 (1). MM can result in significant morbidity and mortality on the basis of renal failure, hypercalcemia, bone disease, immunosuppression, and marrow failure including anemia. It remains a chronic and incurable condition that requires sequential rounds of treatment throughout a patient’s lifetime. In the past two decades there have been major advances in the therapeutic options for MM, now including the regular use of immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, and more recently therapies targeting B cell maturation antigen (BCMA). Treatment strategies in MM frequently involve indefinite duration therapy and/or maintenance therapy where drugs are administered continuously until the time of intolerance or disease progression. This therapeutic approach results in high healthcare expenditures due to the cost of drug acquisition, drug administration, and the management of drug-related toxicities.

1.1.2 Thrombotic Microangiopathy

New drug development and novel drug combinations have had a significant positive impact on the clinical outcomes for patients with MM, however, occasionally new toxicities are reported. One concerning drug-related toxicity seen in patients with MM is thrombotic microangiopathy (TMA). TMA is a life-threatening clinical syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombosis resulting in end organ ischaemia. There are numerous
types of TMA; drug-induced TMA is hypothesized to be the cause of TMA after proteasome-inhibitor exposure. Drug-mediated TMA (immune type) occurs due to the development of drug dependent antibodies whereas drug-mediated TMA (toxic dose-related type) results from various mechanisms perhaps involving the vascular endothelial growth factor (VEGF) pathway.

1.1.3 Canada’s Increasing Healthcare Spending & Rising Costs of Cancer Care

Healthcare spending continues to rise in Canada accounting for a larger proportion of gross domestic product. Based on the Public Health Agency of Canada The Economic Burden of Illness in Canada (EBIC) study, the total current health expenditures in Canada in 2010 was $183.1 billion CAD (1). The top three direct health expenditures were hospitals, prescribed drugs, and physicians accounting for $56.7 billion CAD, $27.6 billion CAD and $27.4 billion CAD, respectively. In particular, the burden of cancer care in Canada is substantial and increasing due to a growing and aging population as well as rising drug costs. Based on the EBIC study, the direct costs by ICD chapter II Neoplasms was $5.4 billion CAD accounting for 4.8% of total direct health care expenditures in 2010, of which, $804.4 million CAD were drug related expenditures. Further, it is important to note that this study did not include the cost of radiation therapy or chemotherapy which make up a substantial proportion of cancer-related expenses. de Oliveira et al. estimate the direct economic burden of cancer across Canada using a case control prevalence-based approach (2). With patient level cost data and prevalence rates of cancer from Statistics Canada, they found the total cost of cancer across Canada was $2.9 billion dollars in 2005 and had increased to $7.5 billion dollars in 2012. Both of these studies are likely to underestimate the cost of cancer care in 2020 with sizeable increases in chemotherapy drug costs.

1.1.4 The Cost of Multiple Myeloma Care

Specific data on the cost of MM in Canada is scarce. In a study based on data from 1997-2007, de Oliveira et al. found that hematologic malignancies including MM and leukemia have the highest net
lifetime costs of all cancer disease sites in Ontario. The mean five-year net cost (undiscounted) of MM was $68,000 (in 2009 CAD) compared to an average of $38,000 for all tumour sites. Similarly, the mean lifetime net costs (undiscounted) of MM was $119,958 (in 2009 CAD) compared to $78,000 for all tumour sites. Another Canadian study found that the cost of initial management of MM was among the highest compared to other cancer sites, with the cost of the 3 month pre-diagnostic phase being $3142 and $2609 for men and women, respectively, due to the cost of hospitalization and diagnostic testing (3).

Today MM represents about 1.5% of cancer cases in Canada yet its’ treatments consume up to 20% of some provincial oncology drug budgets (G. Mitera, personal communication, March 2020). The earlier costs described by de Oliveira et al. are likely an underestimation of costs in 2020 because the period of data collection largely pre-dates the use of many novel drug therapies as well as certain treatment strategies such as indefinite duration maintenance lenalidomide. For instance, more recent Canadian data indicates that maintenance phase lenalidomide (Revlimid®) alone costs $131,700 CAD per person per year and maintenance bortezomib (Velcade®) costs $34,000 CAD per person per year (4). Maintenance lenalidomide is currently recommended and reimbursed for all patients with MM who have received a stem cell transplant, the standard therapy for those age less than 75 years. Consider daratumumab, a monoclonal antibody for use as early as first-line, is one of the most expensive drugs publicly funded in Canada. Further, daratumumab is commonly used in triplet and even quadruplet drug combinations where in the United States a four drug regimen containing daratumumab costs 590,000 United States dollars (USD) per person per year (5). With this, among these other factors, we expect that the cost of myeloma care will continue to climb disproportionately to its low incidence.

1.2 Research Aims

This thesis explores two important therapy-associated outcomes in MM. First, a rare toxicity called thrombotic microangiopathy (TMA). Second, a health economic analysis of all costs associated
with treatment with high dose weekly carfilzomib with cyclophosphamide and dexamethasone (wKCD). Both of these objectives are based on the clinical trial data from MYX1/MCRN003, a single-arm phase 2 study performed collaboratively by the Canadian Myeloma Research Group (CMRG, formerly known as the Myeloma Canada Research Network) and the Canadian Cancer Trials Group (CCTG).

1.2.1 Thrombotic Microangiopathy – Cases from MYX1/MCRN003 Phase 2 Clinical Trial

Evaluating the efficacy of new drugs and new drug combinations in clinical trials requires rigorous parallel monitoring for patient side-effects. Further attention is required when considering rare and potentially lethal toxicities such as thrombotic microangiopathy (TMA). Over the last decade there have been numerous case reports of TMA occurring after exposure to proteasome inhibitors such as carfilzomib (used here in the MYX1/MCRN003 study), bortezomib, or ixazomib. In the present thesis, we evaluated all cases of TMA occurring after treatment with high dose wKCD based on MYX1/MCRN003 clinical trial data. The author reviewed the clinical trial database and secure email records for all information pertaining to the TMA events including those features which could be considered predictive. Further, an extensive review of the literature was performed resulting in a current and comprehensive literature review and case series which was published in 2020 and is included as chapter 2 of the thesis. Maximizing our understanding of the rate of TMA and the clinical scenarios in which it is most likely to arise is important prior to incorporating wKCD into standard practice in Canada.

1.2.2 Descriptive Cost Analysis of MYX1/MCRN003 Phase 2 Clinical Trial

Understanding health care expenditures is an increasing priority for many governments and healthcare payers. Novel drug combinations and indefinite duration therapy in the treatment of MM represent a significant source of cancer-related drug expenditures in countries such as Canada. Clinical trialists are prioritizing such economic evaluations as important secondary outcomes and are increasingly
incorporating cost analyses into protocols of many phase three clinical trials and select earlier studies where results may inform policy and practice. The MYX1/MCRN003 phase 2 clinical trial was designed as a single arm study evaluating the overall response rate after 4 cycles of high dose wKCD. This thesis defines the total cost of treatment per patient, total cost of treatment per patient per cycle, calculates the aggregate and disaggregate cost of each variable, and identifies the predominant cost drivers. The toxicity-related costs including those specifically attributable to TMA are also described. The author hypothesizes that high dose weekly carfilzomib, cyclophosphamide and dexamethasone will have a modest overall cost and will be less costly per cycle than standard dose biweekly carfilzomib and dexamethasone. The comprehensive cost analysis for MYX1/MCRN003 is prepared in manuscript format for submission to the British Journal of Haematology and is included as chapter 3 of this thesis.

The methodology used in the cost analysis was defined and described in extensive detail as such work is not well represented in the literature and represents a unique Canadian costing perspective. The present methods are included in the appendix with planned submission to the journal entitled “Current Oncology”.

1.3 Objectives

The objectives of this study were to:

1. Determine the incidence, clinical phenotype, and predictive factors associated with TMA and carfilzomib exposure in the MYX.1 trial;

2. Determine the prevalence of drug-induced TMA after proteasome inhibitor use through a literature review;

3. Conduct a descriptive health economic analysis, from the perspective of the healthcare payer, of wKCD based on MYX.1 trial data;

4. Compare the costs of wKCD to alternative regimens used for MM treatment.
1.4 Contribution of Research

High-dose wKCD has the potential to be a new standard treatment for MM in Canada based on its relative affordability and provisionally acceptable toxicity profile.

This completion of this work, as described in the subsequent chapters of this thesis, has:

1. Increased awareness of drug-induced thrombotic microangiopathy after proteasome inhibitor exposure;
2. Described rare clinical events through the reporting of three cases of drug-induced thrombotic microangiopathy after carfilzomib exposure;
3. Determined the cost of managing drug-induced thrombotic microangiopathy;
4. Furthered our understanding about the cost of multiple myeloma treatment regimens in Canada;
5. Determined the cost of high dose weekly carfilzomib, cyclophosphamide, and dexamethasone for the treatment of relapsed multiple myeloma;
6. Determined the cost of performing bone marrow biopsy with cytogenetics for the diagnosis of multiple myeloma; and
7. Highlighted the possibility of additional chemotherapy cost savings through the use of smaller vial sizes.

1.5 Organization of Thesis Document

The information presented in this thesis addresses research conducted over a span of 2 years. During this period of time, most of the material presented here was published in or submitted to peer reviewed journals and conference proceedings. One chapter is currently being reviewed for publication
by the British Journal of Haematology. The thesis is prepared in a manuscript format representing a compilation of results presented in these papers. The papers are referenced throughout.

The written thesis document is arranged into the following sections:

Chapter 1 provides background information on multiple myeloma, thrombotic microangiopathy, the cost of cancer and myeloma care, as well as the specific objectives of this thesis.

Chapter 2 outlines three cases of thrombotic microangiopathy occurring in patients who were treated with high-dose weekly carfilzomib, cyclophosphamide, and dexamethasone as part of the MYX.1/MCRN003 phase two clinical trial. It also reviews the current literature of drug-induced TMA occurring after proteasome inhibitor exposure.

Chapter 3 outlines an in-depth descriptive cost analysis of high-dose weekly carfilzomib, cyclophosphamide, and dexamethasone based on MYX.1/MCRN003 clinical trial data.

Chapter 4 summarizes the findings of the thesis and outlines future areas for focused research. It also summarizes our approach to determining the cost of bone marrow biopsies including the cost of cytogenetics.

Appendix A references the REB approval from Queens University for clinical activity at Kingston Health Sciences Centre.

Appendix B outlines the detailed methodology used in this research to estimate the cost of clinical trial variables for the cost-analysis, details considered too lengthy to be included in the main chapters of the thesis.
Bibliography


Chapter 2

Drug-induced Thrombotic Microangiopathy with Concurrent Proteasome Inhibitor use in the Treatment of Multiple Myeloma: A Case Series and Review of the Literature
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2.1 Abstract

Thrombotic microangiopathy (TMA) is a life-threatening clinical syndrome characterized by hemolytic anemia, thrombocytopenia, and microvascular thrombosis resulting in ischemia and organ damage. Multiple myeloma (MM) is a neoplasm arising from clonal plasma cells within the bone marrow. The treatment frequently includes multi-agent immunochemotherapy, often with the use of proteasome inhibitors (PI) such as bortezomib, carfilzomib, or ixazomib. There are increasing reports of TMA in association with proteasome inhibitor exposure.

This review summarizes the epidemiology, pathogenesis, and diagnosis of proteasome inhibitor-related DITMA. We will outline the definition and diagnosis of TMA and explore an important cause of hemolysis in patients with multiple myeloma - drug-induced TMA after PI exposure, an increasingly recognized therapeutic complication. This will be emphasized through the description of three novel cases of TMA. These illustrative cases occurred after treatment with high-dose weekly carfilzomib, cyclophosphamide, and dexamethasone as part of the MCRN003/MYX1 phase 2 clinical trial (NCT02597062) in relapsed MM.
2.2 Introduction

Thrombotic microangiopathy (TMA) is a type of hemolytic anemia characterized by anemia, thrombocytopenia, endothelial cell damage and subsequent formation of microvascular thrombosis in small vessels. The microvascular thrombosis causes ischemic damage to multiple target organs including the brain, kidney, heart, lungs and the gastrointestinal tract, giving rise to a life-threatening clinical syndrome. This review will define primary TMA syndromes, and will explore an important cause of hemolysis in patients with multiple myeloma (MM) - drug-induced TMA, specifically those in association with proteasome inhibitor exposure. This will be further emphasized through three novel illustrative cases from the MCRN003/MYX1 clinical trial (NCT02597062) (1,2).

2.3 Sources and selection criteria

References for this review were identified using Ovid Medline for years 1946 to present. Only peer reviewed articles written in English were included. The following search terms were used in combination including: “thrombotic microangiopathy” or “thrombotic microangiopathies” or “TMA” or “thrombotic thrombocytopenic purpura” and “proteasome inhibitor” or “proteasome inhibitors” or “ixazomib” or “carfilzomib” or “bortezomib”. Articles were selected for review on the basis of title and abstract content and were included on the basis of study design. For the proteasome inhibitor section, all single case reports and case series were included given the rarity of reporting.

2.4 Historical Synopsis and Definitions

TMA is an important life-threatening clinical diagnosis that has been recognized for almost a century. The first case of TMA was described by Eli Moschcowitz in 1924 (3,4). He described a 16-year-old girl who died after presenting with hemolytic anemia, severe thrombocytopenia, neurological symptoms, and microthrombi in the systemic vasculature. In his work, he highlighted a pentad of
presenting TMA (specifically thrombotic thrombocytopenic purpura (TTP)) symptoms including hemolytic anemia, thrombocytopenia, renal failure, neurological symptoms, and fever. However, it is now recognized that this classic pentad is only present in approximately 10% of patients presenting with TTP. In 1962, a case series described the presence of hemolysis within the microvasculature resulting in disease, an entity which was named “microangiopathic hemolytic anemia” (5).

Hemolytic anemia is defined by the destruction of red blood cells through red cell fragmentation via various mechanisms. It can be classified according to causes that are intrinsic or extrinsic to the red blood cell. Intrinsic causes include hemoglobinopathies (ie. sickle cell disease, thalassemia, and hemoglobin variants), cytoskeletal defects (ie. hereditary spherocytosis, hereditary elliptocytosis), and metabolic defects (ie. glucose-6-phosphate dehydrogenase deficiency and pyruvate kinase deficiency). Extrinsic causes include immune mechanisms (ie. autoimmune hemolytic anemia, alloimmune hemolytic anemia, hemolytic transfusion reactions), infections (ie. malaria, babesiosis), burns, hypersplenism, mechanical trauma (ie. valvulopathies, and ventricular assist devices) and microangiopathic processes such as TMA. Microangiopathic hemolytic anemia (MAHA) is a non-immune process that results in red cell fragmentation within the vessels leading to release of free hemoglobin and subsequent hemoglobinemia and hemoglobinuria. MAHA can include many entities such as TTP, hemolytic-uremic syndrome (HUS), disseminated intravascular coagulation (DIC), valve-related hemolysis, solid organ malignancies, vasculitis, copper overload (6), severe hypertension and pregnancy-associated syndromes (e.g. preeclampsia, HELLP syndrome). Most cases of TMA have evidence of MAHA and thrombocytopenia, but the reverse is not true. Some of the MAHA entities listed above can be more precisely classified as primary thrombotic microangiopathy (TMA) syndromes, including TTP (both congenital and acquired), Shiga toxin-mediated HUS, drug-induced TMA (both immune- and toxicity-mediated), and complement-mediated TMA (both congenital and acquired).
2.5 Primary TMA Syndromes

The primary TMA syndromes incorporate 9 subtypes (see Table 2-1) specifically ADAMTS13 deficiency-mediated TMA (ie. congenital TTP and acquired TTP), Shiga toxin-mediated HUS (ST-HUS), drug-induced TMA (DITMA) (both immune- and toxicity-mediated), metabolism-mediated, coagulation-mediated, and complement-mediated TMA (both congenital and acquired)(7). They represent a spectrum of disorders with each subtype being named according to their proposed mechanism of pathogenesis. Of the hereditary causes, ADAMTS13 deficiency-mediated TMA (ie. congenital TTP or Upshaw-Schulman syndrome) results from a mutation in the ADAMTS13 gene (A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13). Congenital complement-mediated TMA arises from uncontrolled activation of the alternative complement pathway from mutations in regulatory genes causing gain or loss of function of complement proteins, such as complement factor H (CFH), complement factor I (CFI), complement factor B (CFB), C3, and CD46. Mutations in the MMACHC (Methylmalonic aciduria and homocystinuria type C protein) gene involved in vitamin B12 metabolism gives rise to metabolism-related TMA. Coagulation-mediated TMA arises from mutations in diacylglycerol kinase epsilon (DGKE gene), plasminogen (PLG gene) and thrombomodulin (THBD gene). Of the acquired causes, ADAMTS13 deficiency-mediated (ie. acquired TTP) TMA results from the formation of inhibitory autoantibodies, both neutralizing and non-neutralizing, against ADAMTS13 metalloprotease enzyme. Shiga-toxin mediated TMA occurs as a result of shiga-toxin secretion and globothiaosylceramide-3 (Gb3) activation in the setting of enteric infection with Escherichia coli or Shigella dysenteriae. Complement-mediated TMA arises from alternative complement pathway activation due to inhibition of CFH, a potent inhibitor of the alternative complement pathway, by autoantibodies to CFH. Drug-mediated TMA (immune type) occurs due to the development of drug dependent antibodies whereas drug-mediated TMA (toxic dose-related type) results from various mechanisms perhaps involving the vascular endothelial growth factor (VEGF) pathway.
Table 2-1 - Primary TMA Syndrome Subtypes

<table>
<thead>
<tr>
<th>Primary TMA Syndromes – 9 subtypes (7)</th>
</tr>
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<tbody>
<tr>
<td>Congenital</td>
</tr>
<tr>
<td>Congenital TTP (ADAMTS13 deficiency-mediated)</td>
</tr>
<tr>
<td>Complement-mediated TMA</td>
</tr>
<tr>
<td>Metabolism-mediated TMA</td>
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<td>Coagulation-mediated TMA</td>
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The first case of drug-induced TMA was described in 1956 in a patient treated with arsenate oxophenarsine for primary syphilis (8). In a recent Blood review article, 78 drugs were identified in association with thrombotic microangiopathy; only 22 of these drugs had definite evidence of a causal relationship (9). There are two proposed mechanisms of drug-induced TMA: immune or antibody mediated and direct-toxic effect with dose-dependence or duration-dependence. Drug-induced TMA (immune type) is an idiosyncratic reaction occurring after a non-dose dependent drug exposure. The best described example is in association with quinine, first described in 1980 (10), where there is reproducible confirmation of drug-dependent antibodies resulting in endothelial cell activation (11,12). Drug-induced TMA (toxic, dose-related type) is a dose and time-dependent reaction. This subtype is not well understood with various proposed mechanisms of pathogenesis including endothelial cell dysfunction, increased secretion of von Willebrand factor, decreased production of prostacyclin and nitric oxide, and dysregulation of the complement pathway. Cyclosporine and tacrolimus are calcineurin inhibitors which are classic for inducing endothelial cell injury and are frequently associated with drug-induced TMA (13). One hypothesized common final pathway results in endothelial cell dysfunction through decreased VEGF expression and inhibition. This has been described in detail by Eremina et al. in their murine model (11).
As well, decreased expression of renal VEGF has been demonstrated in five patients with sirolimus-related drug-induced TMA (14).

### 2.6 Diagnosis of TMA

The diagnosis of TMA requires a high index of suspicion in any patient presenting with anemia and thrombocytopenia (platelet count less than 150 x 10^9/L). Immediate additional testing should confirm the presence of hemolysis with visible schistocytes (>1%) on the peripheral blood (see Figure 2-I), DAT (direct antiglobulin test)-negative, as well as biochemical markers supportive of hemolysis including elevated bilirubin and LDH. Additional hemolytic parameters will almost certainly be present, including an increased reticulocyte count, and a decreased haptoglobin. Coagulation tests including prothrombin time and activated thromboplastin time should be within normal limits; fibrinogen may be normal or elevated. The differential diagnosis often includes a DIC where a coagulopathy predominates, with findings of prolonged prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), and decreased fibrinogen. Other considerations include systemic infection, systemic malignancy, pregnancy-related disorders (preeclampsia, HELLP), organ-transplant, severe hypertension, and autoimmune disease (scleroderma, lupus). Differentiating a primary TMA syndrome from other disorders with overlapping pathologic features of TMA is challenging. Confirmatory testing may take days to be resulted and is only relevant for some types of primary TMA. Further, sometimes the diagnosis only becomes clear after a trial of treatment for the underlying condition or after withdrawal of a suspected drug.
Multiple Myeloma and Hemolysis – An Increasing Rate of TMA?

Multiple myeloma (MM) is a malignant clonal disorder of plasma cells primarily based in the bone marrow, and frequently with increased associated immunoglobulin heavy chain or light chain production. It can lead to devastating clinical effects including renal failure, hypercalcemia, symptomatic anemia and osteolytic lesions and fractures. The treatment of MM typically includes a combination of chemotherapy and, for those individuals eligible, an autologous hematopoietic stem cell transplant. In the last decade, the treatment landscape has changed drastically with the advent, and now regular use, of novel agents (NA) like lenalidomide and bortezomib. A number of additional novel agents have shown disease activity in phase 2 and phase 3 clinical trials and are being adopted as the standard of care including new immunomodulators (ie. pomalidomide), proteasome inhibitors (ie. carfilzomib, ixazomib), and monoclonal antibodies (ie. daratumumab). Despite improvements in effective treatment, there is also an increased incidence of known, and perhaps unknown, toxicities with many of these triplet and quadruplet drug combinations.

Proteasome inhibitors (PIs), such as bortezomib, carfilzomib, and ixazomib, are frequently combined as part of a three- or four-drug myeloma treatment regimen. Bortezomib, the first in class PI, is
administered intravenously or subcutaneously and is routinely used in front line therapy. It is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome and thereby blocks the ubiquitin-proteasome pathway within mammalian cells. This affects numerous downstream signaling pathways including inhibition of NF-kappa B and results in cellular apoptosis of the multiple myeloma cells (15). The second-generation PI, Carfilzomib, has a similar mechanism of action as bortezomib, also blocking the ribosomal proteasome but causing irreversible inhibition of the ubiquitin-proteasome pathway (compared to reversible inhibition with bortezomib). Ixazomib, a third generation oral PI, was recently approved by the FDA in 2015 for the treatment of multiple myeloma. It reversibly binds the 20S ribosomal protease.

The incidence of TMA in cancer is low, with the majority of cases occurring in patients with metastatic disease of solid tumors and rarely in hematologic malignancies (16–18). In our literature review, there are only 4 reported cases of TMA related to myeloma itself; 3 cases were definitively TTP with low levels of ADAMTS-13 levels due to the presence of antibodies (19–21). All other myeloma-related cases have occurred in the context of known risk factors including stem cell transplant (autologous or allogeneic), proteasome-inhibitor use, or other established drug causes. Prior to the use of proteasome inhibitors, the incidence of TMA in patients with MM was much lower, most frequently associated with autologous stem-cell transplant. TMA is reported more frequently in association with lymphoma compared to myeloma. These rare cases of TMA in patients with lymphoma often occur in association with a monoclonal protein and involve the kidney predominately; there are no reported cases of PI-related TMA in patients with lymphoma. However, in patients with myeloma, there have been numerous case reports of DITMA associated with the use of PIs over the last few years. A large number of publications identify bortezomib as the likely cause of DITMA in patients with multiple myeloma. (22–27). Recently, numerous cases of TMA have been reported with the use of carfilzomib (27–32). This adverse event did not appear in the initial phase 2 clinical trials that resulted in FDA approval of Bortezomib in 2003 (33) or in the four original Phase 2 trials leading to carfilzomib approval in 2012. Further, TMA was not a
common feature in the recent phase III studies leading to more widespread use of carfilzomib in the relapsed setting (34–36). The current product monograph reports TMA including TTP and HUS as separate rare complications of carfilzomib with an overall incidence of <0.1% based on 3 cases of TMA and 2 cases of TTP in 3417 patients from 5 pooled phase 3 clinical studies (37). Ixazomib was FDA approved in 2015 and there were no reports of TMA in the original safety studies. But in the last two years, two cases of suspected DITMA were reported after ixazomib exposure (38,39). Newer agents including marizomib and oprozomib are being tested in early clinical trials and it will be important to monitor for TMA as a complication of these therapies.

In a recent review and case series by Yui et al., eleven additional patients with PI-related DITMA were identified, including 3 cases of bortezomib-related DIMTA and 8 cases of carfilzomib-related DITMA (27). The median time to DITMA diagnosis in this report was 21 days. One patient was re-challenged with the drug and did have a second episode of DITMA. Another case of bortezomib-related DITMA was confirmed on renal biopsy by Van Keer et al (22). Subsequent to this paper, Chen et al. reported four further cases of DITMA with carfilzomib use occurring among 24 patients treated with carfilzomib from 2 tertiary hospitals in Singapore (29). Another case of carfilzomib-related TMA was reported by Gosain et al. where the patient was successfully treated with PLEX, hemodialysis, carfilzomib cessation and eculizumab (30). They hypothesized that this could represent a case of drug-induced atypical HUS because of the response to eculizumab, however, complement factor mutational testing was not done. The symptom resolution is temporally associated with carfilzomib withdrawal. The first case of ixazomib-related DITMA was reported in January 2017 where a patient presented with symptoms of TMA 17 days after receiving the first dose of ixazomib (Yui et al., 2017). The ixazomib was stopped, she was treated with PLEX, corticosteroids, and rituximab, and her symptoms gradually resolved. A second case of suspected DITMA after ixazomib exposure was reported in July 2018 with a very similar presentation to the first case (39). The TMA resolved gradually with cessation of ixazomib.
Table 2-2 - Current published cases of proteasome inhibitor-related DITMA

<table>
<thead>
<tr>
<th>Case no.</th>
<th>PI (regimen)</th>
<th>Age and sex</th>
<th>ADA MTS1 3 level</th>
<th>Timing of diagnosis</th>
<th>Renal biopsy</th>
<th>Treatment</th>
<th>Prior PI?</th>
<th>Resolution of TMA (Yes/No, timing)</th>
<th>Rechallenge</th>
<th>Hx HTN</th>
<th>Author reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bor (BD)</td>
<td>54 M</td>
<td>36.5%</td>
<td>Cycle 1, day 8</td>
<td>-</td>
<td>Bor stopped, FFP given</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>(23)</td>
</tr>
<tr>
<td>2</td>
<td>Bor (BTP)</td>
<td>57F</td>
<td>12%</td>
<td>Cycle 1, day 2</td>
<td>-</td>
<td>Bor stopped.</td>
<td>-</td>
<td>Yes</td>
<td>Yes, no recurrence</td>
<td>-</td>
<td>(40)</td>
</tr>
<tr>
<td>3</td>
<td>Bor (CyBorD)</td>
<td>70F</td>
<td>31%</td>
<td>Cycle 3, day 2</td>
<td>-</td>
<td>Bor stopped, RRT, PLEX</td>
<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>(25)</td>
</tr>
<tr>
<td>4</td>
<td>Bor (BD)</td>
<td>52F</td>
<td>-</td>
<td>Cycle 5, day 11</td>
<td>No, gingival biopsy TMA</td>
<td>PLEX</td>
<td>-</td>
<td>Partial</td>
<td>-</td>
<td>-</td>
<td>(24)</td>
</tr>
<tr>
<td>5</td>
<td>Carf (C)</td>
<td>62F</td>
<td>52%</td>
<td>Cycle 1, day 2</td>
<td>No, Autopsy renal TMA</td>
<td>PLEX, steroids</td>
<td>-</td>
<td>No, death at D44</td>
<td>-</td>
<td>-</td>
<td>(41)</td>
</tr>
<tr>
<td>6</td>
<td>Bor (CyBorD)</td>
<td>61F</td>
<td>25%</td>
<td>Cycle 5, day 20</td>
<td>-</td>
<td>Bor stopped, RRT</td>
<td>-</td>
<td>4 weeks</td>
<td>-</td>
<td>-</td>
<td>(26)</td>
</tr>
<tr>
<td>7</td>
<td>Carf (CTD)</td>
<td>62 M</td>
<td>-</td>
<td>6 weeks</td>
<td>Yes, TMA</td>
<td>Carf stopped</td>
<td>Yes, Bor</td>
<td>Yes, 8 weeks</td>
<td>-</td>
<td>Yes</td>
<td>(32)</td>
</tr>
<tr>
<td>Patient</td>
<td>Carf (C)</td>
<td>Age</td>
<td>Gender</td>
<td>Stage</td>
<td>Treatment Response</td>
<td>Treatment</td>
<td>Time</td>
<td>Other Information</td>
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<tr>
<td>8</td>
<td>Carf (C)</td>
<td>63 M</td>
<td>&gt;50%</td>
<td>Cycle 1, day 14</td>
<td>Yes, TMA</td>
<td>Carf stopped, Plasmapharesis</td>
<td>-</td>
<td>Yes, 1 week</td>
<td>-</td>
<td>Yes (31)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Carf (C)</td>
<td>74 M</td>
<td>59%</td>
<td>Cycle 1, day 15</td>
<td>-</td>
<td>Plex</td>
<td>-</td>
<td>Yes, 8 days</td>
<td>-</td>
<td>No, hx CKD (42)</td>
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<td>Carf (C)</td>
<td>73 M</td>
<td>50%</td>
<td>Cycle 2</td>
<td>-</td>
<td>Stop Carf, PLEX, RRT</td>
<td>Yes, bor</td>
<td>Yes, 1 week</td>
<td>-</td>
<td>Yes (43)</td>
<td></td>
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<tr>
<td>11</td>
<td>Carf (C)</td>
<td>72F</td>
<td>91%</td>
<td>Cycle 6</td>
<td>Yes, TMA</td>
<td>Stop Carf, PLEX</td>
<td>Yes, bor</td>
<td>Yes, 3 weeks</td>
<td>-</td>
<td>Yes (43)</td>
<td></td>
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<tr>
<td>12</td>
<td>Bor (CyBorD)</td>
<td>70 M</td>
<td>-</td>
<td>21 days</td>
<td>-</td>
<td>-</td>
<td>Yes, bor</td>
<td>-</td>
<td>- (27)</td>
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<td>13</td>
<td>Bor (BD)</td>
<td>64 M</td>
<td>-</td>
<td>9 days</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>- (27)</td>
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<td>14</td>
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<td>51 M</td>
<td>34%</td>
<td>21 days</td>
<td>Yes</td>
<td>Stop Bor, PLEX</td>
<td>-</td>
<td>Yes, unclear</td>
<td>Yes, recurrence</td>
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<td>15</td>
<td>Carf (C)</td>
<td>80 M</td>
<td>100%</td>
<td>5 days</td>
<td>-</td>
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<td>Yes, Bor</td>
<td>-</td>
<td>- (27)</td>
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<td>16</td>
<td>Carf (CMP)</td>
<td>79 M</td>
<td>-</td>
<td>8 months</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>- (27)</td>
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<tr>
<td>17</td>
<td>Carf (CD)</td>
<td>67 M</td>
<td>-</td>
<td>17 months</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>- (27)</td>
<td></td>
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<tr>
<td>No.</td>
<td>Patient</td>
<td>Age</td>
<td>Gender</td>
<td>Diagnosis</td>
<td>Days</td>
<td>Cycle</td>
<td>Type of Treatment</td>
<td>Days</td>
<td>Recurrence</td>
<td>Notes</td>
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<tr>
<td>18</td>
<td>Carf (CDoxo)</td>
<td>64F</td>
<td>88%</td>
<td>8 months</td>
<td>-</td>
<td>-</td>
<td>Yes, bor</td>
<td>-</td>
<td>-</td>
<td>(27)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Carf (C)</td>
<td>67F</td>
<td>79%</td>
<td>7 days</td>
<td>-</td>
<td>-</td>
<td>Yes, bor</td>
<td>-</td>
<td>-</td>
<td>(27)</td>
<td></td>
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<tr>
<td>20</td>
<td>Carf (CPD)</td>
<td>45 M</td>
<td>-</td>
<td>6 months</td>
<td>-</td>
<td>-</td>
<td>Yes, bort</td>
<td>-</td>
<td>-</td>
<td>(27)</td>
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<tr>
<td>21</td>
<td>Carf (CPD)</td>
<td>44 M</td>
<td>-</td>
<td>8 months</td>
<td>Yes</td>
<td>-</td>
<td>Yes, Bor</td>
<td>-</td>
<td>-</td>
<td>(27)</td>
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<tr>
<td>22</td>
<td>Carf (C)</td>
<td>49 M</td>
<td>82%</td>
<td>6 days</td>
<td>-</td>
<td>-</td>
<td>Yes, Bor</td>
<td>-</td>
<td>Yes, no recurrence</td>
<td>(27)</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Carf (CCD)</td>
<td>70 M</td>
<td>normal</td>
<td>Cycle 2, day 6</td>
<td>-</td>
<td>-</td>
<td>Carf stopped No PLEX, No RRT</td>
<td>-</td>
<td>Yes, 4 days</td>
<td>Yes, no recurrence</td>
<td>(29)</td>
</tr>
<tr>
<td>24</td>
<td>Carf (CCD)</td>
<td>66F</td>
<td>88%</td>
<td>Cycle 2, day 8</td>
<td>-</td>
<td>-</td>
<td>Carf stopped No PLEX, + RRT</td>
<td>-</td>
<td>Yes, 1 week</td>
<td>Yes, no recurrence</td>
<td>(29)</td>
</tr>
<tr>
<td>25</td>
<td>Carf (CD)</td>
<td>63 M</td>
<td>-</td>
<td>Cycle 2 day 18</td>
<td>-</td>
<td>-</td>
<td>Carf stopped No PLEX</td>
<td>Yes,</td>
<td>Yes, 25 days</td>
<td>Yes, no recurrence</td>
<td>(29)</td>
</tr>
<tr>
<td>26</td>
<td>Carf (CD)</td>
<td>58 M</td>
<td>-</td>
<td>Cycle 3, day 7</td>
<td>-</td>
<td>-</td>
<td>Carf stopped No PLEX, + RRT</td>
<td>Yes,</td>
<td>Yes, 10 days</td>
<td>Yes, no recurrence</td>
<td>(29)</td>
</tr>
<tr>
<td>27</td>
<td>Bor (BTD)</td>
<td>51 M</td>
<td>34%</td>
<td>Cycle 3</td>
<td>Yes, TMA</td>
<td>-</td>
<td>Bort stopped, +RRT</td>
<td>Yes</td>
<td>Yes, recurrence</td>
<td>Yes</td>
<td>(22)</td>
</tr>
<tr>
<td></td>
<td>Carf (CD)</td>
<td>61F</td>
<td>100%</td>
<td>Cycle 9, day 5</td>
<td>Carf stopped, PLEX, + RRT</td>
<td>Yes, Bor</td>
<td>Yes, 2 weeks</td>
<td>-</td>
<td>-</td>
<td>(30)</td>
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<tr>
<td>29</td>
<td>Ixa (I)</td>
<td>75F</td>
<td>59%</td>
<td>Cycle 1, day 17</td>
<td>Ixa stopped, PLEX</td>
<td>-</td>
<td>Yes, 1 month</td>
<td>-</td>
<td>-</td>
<td>(38)</td>
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</tr>
<tr>
<td>30</td>
<td>Ixa (ILD)</td>
<td>71F</td>
<td>Normal</td>
<td>Cycle 5</td>
<td>Ixa stopped, PLEX</td>
<td>-</td>
<td>Yes, 3 weeks</td>
<td>-</td>
<td>Yes</td>
<td>(39)</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Carf (CP)</td>
<td>44F</td>
<td>84%</td>
<td>Cycle 1, day 10</td>
<td>Carf stopped, eculizumab</td>
<td>Yes, bor</td>
<td>Yes, day 18</td>
<td>-</td>
<td>-</td>
<td>(44)</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Carf (CCD)</td>
<td>74M</td>
<td>Normal</td>
<td>Cycle 8, day 8</td>
<td>Carf stopped, steroids</td>
<td>Yes, bor</td>
<td>Yes</td>
<td>-</td>
<td>Yes</td>
<td>Reported herein in full detail with previous brief reports (1,2)</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Carf (CCD)</td>
<td>54F</td>
<td>101%</td>
<td>Cycle 1, day 6</td>
<td>Carf stopped, PLEX, steroids</td>
<td>Yes, bor</td>
<td>Yes, 13 days</td>
<td>Yes, no recurrence</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Carf (CCD)</td>
<td>55M</td>
<td>100%</td>
<td>Cycle 6, day 4</td>
<td>Carf stopped, PLEX, steroids</td>
<td>Yes, bor</td>
<td>Yes, 6 weeks</td>
<td>-</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PI=proteasome inhibitor, Bor=bortezomib, Ixa=ixazomib, carf=carfilzomib, PLEX=therapeutic plasma exchange, F=female, M=male, RRT=renal replacement therapy (including hemodialysis, peritoneal dialysis), TMA=thrombotic microangiopathy, HTN=hypertension, CKD=chronic kidney disease, Hx=history, BD=bortezomib plus dexamethasone, BTP=bortezomib plus thalidomide plus prednisone, CyBorD=cyclophosphamide plus bortezomib plus dexamethasone, C=carfilzomib monotherapy, KCD=CCD=carfilzomib plus cyclophosphamide plus dexamethasone, CP=carfilzomib plus pomalidomide, CTD=carfilzomib plus thalidomide plus dexamethasone, CPD=carfilzomib plus pomalidomide plus dexamethasone, CDoxo=carfilzomib plus doxorubicin, I=ixazomib monotherapy, ILD=ixazomib plus lenalidomide plus dexamethasone
and the patient was never trialed on the drug again. A summary of all patients to date with PI-related DITMA is included in Table 2-2.

There are two proposed mechanisms of pathogenesis in PI-related DITMA. Proteasome inhibitors are suspected to result in DITMA through a toxic, dose-dependent pathway. PIs have antiangiogenic activity through decreased proliferation of endothelial cells, secretion of interleukin-6 (IL-6), and blockade of vascular endothelial growth factor (VEGF) which may result in endothelial cell damage and microangiopathy (45). Other drugs that target the VEGF pathway including bevacizumab, sunitinib, and pazopanib are frequently reported in association with DITMA, perhaps reinforcing the biological plausibility of this mechanism (46). Patients with DITMA resulting from a dose-dependent mechanism, present with symptoms after many months of PI therapy, as was the case in two of the three patients reported below. Alternatively, an immune mechanism has been postulated as the culprit mechanism in PI-related DITMA by one research group (40). Furthermore, Yui et al. have suggested that patients with an immune-mediated mechanism can be identified based on the timing of their presentation (i.e. occurring upfront, within 21 days of drug exposure) (27). Further, it is unlikely that the mechanism of PI-related DITMA is related to ADAMTS13 inhibition through the presence of autoantibodies, given that normal levels of ADAMTS13 have been reported in almost all cases of PI-related DITMA.

Paradoxically bortezomib has recently been used for the treatment of refractory cases of acquired ADAMTS13 deficient TMA (e.g. TTP) (47–50). Numerous case reports suggest that bortezomib, through the elimination of plasma cells and decrease in their associated antibody production, is effective for treating patients with refractory TTP. Prospective studies have not yet been done and would be required to better evaluate the utility of bortezomib therapy.

2.8 Illustrative Cases from the MCRN003/MYX1 phase II clinical trial

Herein, we present three novel cases of TMA which occurred after treatment with carfilzomib, cyclophosphamide, and dexamethasone for the treatment of relapsed/refractory multiple myeloma as part
of the MCRN003/MYX1 phase II clinical trial (NCT02597062). The MCRN003/MYX1 clinical trial (1,51) was a single arm phase II, investigator initiated, multi-centre trial run through the Myeloma Canada Research Network and the Canadian Cancer Trials Group (CCTG) assessing the efficacy of high dose weekly carfilzomib, plus cyclophosphamide and dexamethasone for relapsed and refractory MM. In this study, patients received Carfilzomib 20 mg/m² day 1 of first cycle then escalated to 70 mg/m² for all subsequent doses given on days 1, 8, and 15 of a 28 day cycle plus weekly oral dexamethasone (< 70 years, 40 mg; ≥ 70 years 20mg) and weekly cyclophosphamide 300 mg/m² capped at 500 mg. Carfilzomib has known activity in relapsed MM (34); with high doses (70mg/m²) of carfilzomib having improved potency and adequate tolerability when administered over a longer infusion time (ie. 30 minutes)(52–54). There were no cases of TMA reported in the four initial phase 2 trials that lead to the FDA approval of Carfilzomib in 2012. In the MCRN003/MYX1 clinical trial a total of 76 patients were enrolled and 3 patients (4%) developed TMA during their treatment with carfilzomib (2). All cases were reviewed centrally at CCTG to assess the integrity of the TMA diagnosis and determine the relationship of this SAE to carfilzomib.

2.8.1 Case 1

Patient 1 is a 74-year-old male with a history of IgG lambda MM, negative for del17p, t(4;14), and t(14;16). His past medical history was significant for glaucoma and gastroesophageal reflux disease with baseline medications including lansoprazole and travoprost. He was started on perindopril for new hypertension one month before his presentation with TMA.

He enrolled in the MCRN003/MYX1 clinical trial and received 7 full cycles of weekly high dose carfilzomib, cyclophosphamide, and dexamethasone. During his 8th cycle of therapy, one week after receiving the day 1 dose of carfilzomib (70mg/m² or 127mg), he presented to the emergency department with fatigue and was found to have anemia, thrombocytopenia (platelets 24 x10^9/L, normal range 150-400x10^9/L) and renal failure (creatinine 162 µmol /L, normal range 55-105 µmol/L). His blood pressure
was 170/82 mmHg on presentation. Additional investigations revealed an increased LDH level (394 U/L, normal range 0-224 U/L), decreased haptoglobin (0.08 g/L, normal range 0.34-2.0g/L), and schistocytes on peripheral blood film. His ADAMTS13 level was within normal limits. The predominant organ involved was the kidney and he underwent a renal biopsy. The renal biopsy showed diffuse glomerular involvement by a thrombotic microangiopathy with evidence of global glomerulosclerosis effecting 8 of 46 glomeruli. Additional findings included mild tubular damage and mild interstitial edema. There was no immune complex deposition and immunofluorescence showed trace, non-specific glomerular staining for IgM, kappa and C3. His medications at the time of presentation with TMA are included in Table 2-3 (see below), importantly, he was not recently exposed to medications known to cause TMA. He was diagnosed with grade 4 thrombotic microangiopathy, treated with high-dose prednisone, and made a full recovery. He did not receive any further treatment with carfilzomib. At the time of his TMA presentation, his myeloma disease control was excellent, having achieved a VGPR after 8 cycles of wCCD. He continued in very good partial response (VGPR) at the time of the last data review and has not required any further myeloma therapy.

2.8.2 Case 2

Patient 2 is a 54-year-old female with a history of lambda light chain multiple myeloma, negative for del17p, t(4;14), and t(14;16). The patient’s past medical history was significant for insomnia, anxiety, peripheral sensory neuropathy, deviated septum and hypertension. Her baseline medications included calcium supplements, vitamin D supplements, zoledronic acid, lorazepam, acyclovir, zopiclone, ondansetron and rabeprazole.

During cycle 1 of treatment she received two doses of carfilzomib (including an initial low-dose at 20mg/m2 (33 mg IV) per protocol followed by a single high-dose 70mg/m2 (116mg IV) the following week). After this second dose of carfilzomib during cycle 1, she presented to the emergency department with fever (temperature 39.3 C°) and intermittent cough. Her blood pressure on presentation was 142/88.
mmHg. Initial blood work revealed a pattern in keeping with microangiopathic hemolytic anemia (Hbg 63g/L, normal range 115-155g/L) and acute renal failure (creatinine 304 µmol/L, normal range 55-105 µmol/L), including red cell fragmentation on peripheral blood film, severe thrombocytopenia (platelets 3 x10^9/L, normal range 150-400x10^9/L), increased LDH (1536 U/L, normal range 0-224 U/L), suppressed haptoglobin, normal coagulation parameters (INR1.1, PT 11.2, aPTT22), normal fibrinogen, and increased total and indirect bilirubin (83 µmol/L and 75 µmol/L respectively). Clinically there was no evidence of infection. With thrombotic thrombocytopenic purpura on the differential diagnosis, she was transferred to another hospital to receive daily plasma exchange as well as high-dose prednisone 60mg po daily. Subsequently, her ADAMTS13 levels were reported within the normal limit (101%, normal range 50-150%). She continued on daily plasma exchange for a total duration of one week with excellent improvement in hemolytic markers and was discharged home on day 11. She did not undergo a renal biopsy. The patient’s medications at presentation are included in table 2-3, none of which are known to cause TMA. At the time of her TMA presentation, her disease status was inevaluable as per clinical trial protocols because she had not received the minimum amount of treatment (i.e. she had received less than one cycle). Her presentation represented a grade 3 adverse event resulting in prolonged hospitalization; she recovered quickly but with some persistent anemia (however hemolysis resolved entirely). She did not receive any further doses of carfilzomib. Since that time, she has had multiple disease relapses requiring treatment and, most recently, has been retreated with bortezomib without any recurrence of TMA.

2.8.3 Case 3

Patient 3 is a 55-year-old male with history of IgA kappa multiple myeloma, negative for del17p, t(4;14), and t(14;16). The patient’s past medical history is significant for type 2 diabetes, peripheral neuropathy, chronic bone pain (unrelated to MM), and hypertension. His baseline medications include
metformin, pregabalin, aspirin, vitamin B12 supplement, glucosamine supplement, magnesium supplement, hydromorphone, lansoprazole, and perindopril.

He was enrolled in the clinical trial and received 5 full cycles of weekly high-dose carfilzomib, cyclophosphamide and dexamethasone. On day 4 of cycle 6, after receiving carfilzomib 127mg IV (70mg/m2) on day 1, he presented to the emergency department with a headache, upper respiratory tract symptoms, myalgias, and night sweats. His blood pressure on presentation was 120/77 mmHg. Initial bloodwork revealed severe thrombocytopenia (platelets 10 x10^9/L, normal range 150-400x10^9/L), anemia (Hgb 81g/L, normal range 115-155g/L) with multiple schistocytes on the peripheral blood film, elevated LDH (669 U/L, normal range 0-224 U/L), normal coagulation parameters, and normal renal function. He was started on urgent treatment with plasma exchange daily. Subsequently, his ADAMTS13 levels were reported within normal limits (100%, normal range 50-150%). After four days of plasma
exchange, his anemia and thrombocytopenia had started to improve. His bloodwork further improved by 6 weeks, with a hemoglobin of 103g/L (normal range 115-155g/L), platelets 180 x 10^9/L (normal range 150-400x10^9/), and LDH 200U/L (normal range 0-224 U/L). At the time of presentation that patient was not taking any medications known to cause TMA (see table 2-3). The patient had recently received an influenza vaccine. The patient had good control of their myeloma having achieved a VGPR at the time of TMA. This was a grade 4 adverse event resulting in a prolonged hospitalization, however, he recovered fully. He was never retreated with carfilzomib. Approximately one year after treatment with wkCD, he had a biochemical relapse requiring retreatment. He has had no further PI exposure.

Table 2-3 - Summarized Case Series of Carfilzomib-related DITMA

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age and sex</th>
<th>PI (regimen)</th>
<th>Prior PI</th>
<th>Hx</th>
<th>Timing of diagnosis</th>
<th>ADAMTS13 level</th>
<th>Renal biopsy</th>
<th>Treatment of TMA</th>
<th>Resolution of TMA (Yes/No, timing)</th>
<th>Death</th>
<th>Disease control at time of TMA presentation</th>
<th>Other medications at the time of TMA presentation</th>
<th>Rechallenge with PI</th>
<th>History of ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74M</td>
<td>High-dose once weekly Carf (wCCD)</td>
<td>Yes, bor</td>
<td>Yes</td>
<td>Cycle 8, day 8</td>
<td>Normal</td>
<td>Yes</td>
<td>Carf stopped, steroids</td>
<td>Yes</td>
<td>No</td>
<td>VGPR</td>
<td>lansoprazole, travoprost, valacylovir, ondansetron, acetaminophen,</td>
<td>No</td>
<td>Yes, 8 years prior to TMA</td>
</tr>
</tbody>
</table>

30
<table>
<thead>
<tr>
<th>Patient 2</th>
<th>54 F</th>
<th>High-dose once weekly Carf (wCCD)</th>
<th>Yes, bor</th>
<th>Yes</th>
<th>Cycle 1, day 6</th>
<th>101%</th>
<th>No</th>
<th>Carf stopped, PLEX, steroids</th>
<th>Yes, 13 days</th>
<th>No</th>
<th>Inevaluable (did not receive minimum amount of treatment on protocol)</th>
<th>calcium, vitamin D, zoledronic acid, lorazepam, acyclovir, zopiclone, ondansetron, rabeprazole</th>
<th>Yes, no recurrence</th>
<th>Yes, 2 years prior to TMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 3</td>
<td>55M</td>
<td>High-dose once weekly Carf (wCCD)</td>
<td>Yes, bor</td>
<td>Yes</td>
<td>Cycle 6, day 4</td>
<td>100%</td>
<td>No</td>
<td>Carf stopped, PLEX, steroids</td>
<td>Yes, 6 weeks</td>
<td>No</td>
<td>VGPR</td>
<td>metformin, pregabalin, aspirin, vitamin B12, glucosamine, magnesium, hydromorphone, lansoprazole, acyclovir, perindopril, recent influenza vaccine</td>
<td>No</td>
<td>Yes, 4 years prior to TMA</td>
</tr>
</tbody>
</table>
There was an unexpectedly high rate (4%) of TMA seen after treatment with high-dose weekly carfilzomib, cyclophosphamide and dexamethasone as part of the MCRN003/MYX1 phase II clinical trial. Two of the three patients had a history of hypertension and the third patient developed hypertension during his treatment course. The baseline rate of hypertension in the entire clinical trial population is 39%. Two patients developed TMA after many months of treatment while one patient presented within the first two weeks of initial carfilzomib exposure. The variability in timing of presentation is previously reported in the literature and may relate to the mechanism of pathogenesis as discussed below. The type of MM is varied across the three patients. The ADAMTS13 levels were normal in all three patients suggesting that the mechanism of TMA is something other than TTP (or acquired ADAMTS13 deficiency), namely drug-induced via direct toxic effects or immune mechanism as previously hypothesized. All three episodes of TMA resolved after cessation of carfilzomib and none of the patients were re-challenged with the drug. All patients were previously exposed to bortezomib without TMA. One patient has subsequently been retreated with bortezomib and has not developed TMA. The role of plasma exchange in all cases is not defined. None of these patients were treated with eculizumab.
2.9 Discussion

TMA is a life-threatening clinical syndrome characterized by hemolytic anemia, thrombocytopenia, and microvascular thrombosis resulting in organ ischemia and damage. Primary TMA syndromes represent a spectrum of disorders with unique mechanism of pathogenesis. Early diagnosis and early treatment of TTP with plasma exchange has resulted in drastic improvement in modern-day mortality. The treatment of drug-induced TMA, both immune and toxic subtypes, relies on the removal of the suspected offending agent and supportive care including renal replacement therapies and blood transfusions as needed. PIs are important drugs as part of triplet or quadruplet multiple myeloma treatment regimen. Since their respective FDA approvals, 34 cases of DITMA after bortezomib, carfilzomib, or ixazomib exposure have been reported. Interestingly, the majority of reported cases of PI-related DITMA to date have been in the setting of carfilzomib use despite this medication being used less frequently than bortezomib due to fewer indications and a recent FDA approval in 2012.

We reported three novel cases of DITMA after treatment with carfilzomib, cyclophosphamide, and dexamethasone in patients enrolled in the MCRN003/MYX1 phase 2 clinical trial (NCT02597062) (1,2). These cases add to the growing literature about PI-related DITMA, now totaling 34 cases related to this drug class and 23 cases specifically related to carfilzomib exposure. This highlights the importance of early recognition and treatment of DITMA including the cessation of any offending agents and supportive care, including renal replacement therapies and blood transfusions as needed. The incidence of TMA in this clinical trial (4%) appears much higher than anticipated from previous reports with only rare events reported in the Product Monograph for carfilzomib. We consider that this trial uses a unique dosing regimen with high dose, once weekly carfilzomib as opposed to lower dose twice weekly regimens used by other groups. In the recently published ARROW study, there was one case of TMA and one case of HUS (out of a total 238 patients) in the once weekly Carfilzomib dosing group compared to no reported cases in the twice weekly dosing group (55). Certain drug combinations may have a cumulative effect on the endothelium and increase the rate of TMA. A recent phase III study of upfront standard-
dose carfilzomib with cyclophosphamide and dexamethasone for 4 cycles prior to melphalan autologous stem cell transplant (FORTE study) did not report any TMA events (56). However, the combination of cyclophosphamide with high-dose carfilzomib are infrequently reported and this drug-dose combination may have a potential cumulative adverse effect on the endothelium. Of the 23 cases of carfilzomib-related DITMA reported here, 5 of them occurred in combination with cyclophosphamide. The incidence of TMA is reported as being higher with the combination of two drugs compared to the summative incidence of TMA with each individual drug. For example, tacrolimus and sirolimus used in combination has a rate of TMA of 10-15% compared to less than 5% for each individual drug (57). Further, given the rising number of reports of carfilzomib-related DITMA, there may be unique drug effects that are contributing to this pathogenesis (i.e. irreversible binding of the ubiquitin-proteasome pathway) compared to bortezomib and ixazomib which have reversible binding and possibly lower rates of DITMA.

However, so far, there are no scientific models to support this hypothesis. The role of complement pathway mutations in PI-related DITMA is unknown and none of the three cases presented here have undergone complement testing. This is an important limitation and may represent an area for further inquiry.

The management of carfilzomib related DITMA should focus on supportive care and cessation of carfilzomib. The role of PLEX is not well-defined in this patient population especially given normal levels of ADAMTS13 metalloprotease enzyme in most patients with PI-related DITMA. Upfront treatment with PLEX may be appropriate when disorders of ADAMTS13-deficiency are considered in the differential, but once normal enzyme levels are confirmed then PLEX should be stopped to prevent prolonged exposure to the potential adverse effects of this treatment.

PI-related DITMA is an important newly recognized complication of MM therapy. The morbidity and mortality of TMA is notable and necessitates clinical vigilance for detection and early intervention. Our understanding regarding the mechanisms of pathogenesis needs to be further explored through scientific collaboration.
Bibliography


Chapter 3
A Descriptive Cost-Analysis of MYX.1/MCRN003, a Phase 2 Clinical Trial –
The Use of High-dose Weekly Carfilzomib, Cyclophosphamide, and
Dexamethasone in Relapsed and Refractory Multiple Myeloma
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3.1 Abstract

3.1.1 Background

The prevalence of multiple myeloma is increasing and there is a need to evaluate the associated escalating therapy costs (1). The MYX.1 phase II trial showed that high-dose weekly carfilzomib, cyclophosphamide, and dexamethasone is efficacious in relapsed and refractory disease (2,3). We conducted a descriptive cost analysis, from the perspective of the Canadian public healthcare system, using trial data.

3.1.2 Methods

The primary outcome was the mean total cost per patient. Resource utilization data were collected from all 75 patients enrolled in the MYX.1 trial over a trial time horizon. Costs are presented in Canadian dollars (CAD, where 1 CAD = 0.58 British Pound Sterling (GBP)).

3.1.3 Results

The cost of treatment was calculated from the time of patient enrolment until the time of the second data lock. The mean total cost per patient was $203,336.08 (range $17,891.27 – $505,583.55) Canadian dollars (CAD, where 1 CAD = 0.58 British Pound Sterling (GBP)). The median number of cycles was 15. The mean cost per patient per cycle was $14,081.45. The predominant cost driver was the cost of chemotherapy accounting for an average of $179,332.78 per patient or $12,419.17 per patient per cycle. Carfilzomib acquisition accounted for the majority of chemotherapy costs – $162,471.65 total per patient or $11,251.50 per patient per cycle. Fifty-six percent (56%) of patients had at least one hospitalization during the trial period with an average cost of $12,657.86 per hospitalization. The average cost to treat each patient with thrombotic microangiopathy (TMA) was $18,863.32 including the cost of hospitalizations and therapeutic plasma exchange.
3.1.4 Conclusions

High-dose wKCD is an active triplet regimen for RRMM associated with reduced total cost compared with twice weekly regimens.
3.2 Introduction

Multiple myeloma (MM) is an incurable lymphoproliferative disorder of malignant clonal plasma cells based in the bone marrow. MM represents about 1.5% of new cancer diagnoses in Canada and in 2020 it is expected that 3400 Canadians will be diagnosed with myeloma (1). The clinical phenotype is characterized by anemia, renal failure, hypercalcemia, lytic bone disease, and rarely spinal cord compression. MM is an incurable cancer and patients require intermittent courses of treatment, including chemoimmunotherapy, maintenance immunomodulating therapy, and autologous stem cell transplant. The MYX.1/MCRN 003 study was a phase 2 clinical trial performed collaboratively by the Canadian Myeloma Research Group (CMRG, formerly known as the Myeloma Canada Research Network) and the Canadian Cancer Trials Group (CCTG). It was designed to test the efficacy and safety of high-dose weekly carfilzomib (Krypolis®), cyclophosphamide, and dexamethasone (wKCD) in patients with relapsed and refractory multiple myeloma (RRMM) who had previously received 1-3 prior lines of therapy. The study met its primary objective of overall response rate greater than 80% (ORR 84%) after 4 cycles of wKCD (3). This regimen was intentionally designed to minimize the cost of chemotherapy and prioritize the ease of administration for patients.

Cancer-related expenditures are on the rise in Canada. de Oliveira et al. report the total cost of cancer in 2005 was $2.9 billion dollars and rose to $7.5 billion dollars in 2012 (4). Based on the Public Health Agency of Canada Economic Burden of Illness in Canada (EBIC) study, the direct costs by ICD chapter II / Neoplasms was $5.4 billion Canadian dollars (CAD) in 2010, accounting for 4.8% of total direct health care expenditures (5). The net cost of treating multiple myeloma is the highest of all cancer disease sites in Canada with 5-year net cost for all phases of treatment being $68,000 CAD, compared to $31,000 for lung cancer and $40,500 for breast cancer, based on data collected between 1997-2007(5). Since then the cost of MM care has continued to rise likely reflecting emergence of new chemoimmunotherapeutic agents, an increasing incidence (1), improved life expectancy, as well as changes in treatment paradigms now with the frequent use of triplet and quadruplet regimens and the use
of maintenance/indefinite duration therapies. Based on 2014 data, maintenance-phase lenalidomide (Revlimid®) costs $131,700 CAD per person per year in Canada and maintenance-phase bortezomib costs $34,000 CAD per person per year (6). The CCTG MYX.1/MCRN 003 study was designed to minimize the cost of administering a carfilzomib-based triplet regimen, by using a once weekly dosing, and combining it with cyclophosphamide and dexamethasone, the latter being relatively inexpensive yet effective anti-myeloma drugs. With this once weekly high-dose carfilzomib regimen, we hypothesize that the cost of the drug acquisition and administration would be minimized and that the indirect costs to the patient and/or family would also be minimized. Herein, we report the mean total cost per patient and a descriptive presentation of disaggregated costs in order to identify predominant cost drivers based on the MYX.1 study.

3.3 Methods

The clinical trial was conducted according to Good Clinical Practice (GCP) standards and in accordance with the Declaration of Helsinki. All trial participants provided written informed consent. Research Ethics Board approval was obtained by each of the 10 participating centers. An example of the Queen’s University Research Ethic Board (REB) approval for Kingston Health Sciences Center is included in Appendix A. The present economic secondary analysis is based on existing clinical trial data; it was not pre-specified in the trial protocol.

The intention of this secondary analysis is to determine the total cost of wKCD per patient with a description of per cycle costs and estimated annual costs. This was a single-arm study and cost utilities were not collected; therefore, a cost-utility analysis was not possible. Resource utilization data were collected from all clinical trial patients from the time of enrolment until 4-weeks after completion of protocol therapy or until the time of data lock, whichever occurred first. Direct medical costs were calculated using costs obtained from Canadian or provincial data sources, multiplied by resource utilization unit data obtained for each patient from the clinical trial database. The data sources used to
estimate the cost generated by each patient on clinical trial are described below and summarized in Table 1. The primary outcome was the total cost of wKCD per patient and secondary outcomes included the cost of wKCD per patient per cycle, estimated annual costs, and exploration of disaggregated costs including identification of predominant cost drivers. The cost of carfilzomib wastage was estimated using 60mg vials and the actual dose administered in the clinical trial case report form. This was compared to the estimated cost of carfilzomib if 10mg vials had been used.

**Table 3-1 - Source of Resource Costs in MYX.1/MCRN003**

<table>
<thead>
<tr>
<th>Resource</th>
<th>Valuation Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy costs, including institutional overhead</td>
<td>Ontario Health Cancer Care Ontario Provincial Drug Reimbursement Program (7) Ontario Health Canada Care Ontario Regimen Monograph (8) and The Cost of Chemotherapy Administration (9)</td>
</tr>
<tr>
<td>Supportive Medication costs</td>
<td>Ontario Drug Benefits Formulary (10) and Alberta Health Interactive Drug Benefit List (11)</td>
</tr>
<tr>
<td>Physician fees</td>
<td>2020 Ontario Health Insurance Plan (OHIP) – Schedule of Benefits for Physician Services (12)</td>
</tr>
<tr>
<td>Nursing and Pharmacist wages</td>
<td>2014 Ontario Collective Agreement for nurses with &gt; 8 years (13), The Cost of Chemotherapy Administration (9)</td>
</tr>
<tr>
<td>Hospitalizations Costs</td>
<td>Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD) (14)</td>
</tr>
<tr>
<td>Radiology, laboratory, and procedure costs</td>
<td>2020 Ontario Health Insurance Plan – Schedule of Benefits for Laboratory Services (15), Kingston Health Sciences Center Fee Schedule, Alberta Society of Radiologists Overhead Costs Mirror Study (16)</td>
</tr>
<tr>
<td>Transfusion costs</td>
<td>Canadian Blood Services (17), A Costing Model for Canadian Hospitals (18)</td>
</tr>
</tbody>
</table>


3.3.1 Cost of chemotherapy

The doses and the duration of chemotherapy was obtained directly from the clinical trial database case report forms. The cost of chemotherapy included both drug acquisition and drug administration costs. Drug acquisition costs were obtained from Ontario Health Cancer Care Ontario (OH-CCO) Provincial Drug Reimbursement Programs (PDRP) and the Ontario Drug Benefit Formulary (7,10). Carfilzomib was supplied in 60mg vials. Intravenous drug administration costs were estimated using an hourly rate of $171 CAD/hour (9), which included chair time with institutional overhead, nursing wages, pharmacy wages, and physician fees. Chemotherapy chair time was estimated using OH-CCO published workflow time estimates (8). Pharmacy time was estimated via personal communication with an oncology pharmacist (T. Carasco, personal communication, July 15, 2020). Missed doses were not counted in the total cost. Dose reductions were assumed to take the same amount of time for mixing and administration as the full dose.

3.3.2 Supportive Medication costs

The utilization of supportive drug therapies was modeled based on the protocol recommended dosing. Supportive therapies included antivirals (e.g. acyclovir, valacyclovir), antacids (e.g. pantoprazole, lansoprazole), and antiemetics (e.g. ondansetron). The drug type and the duration of use was derived from the clinical trial database case report forms. The cost of growth factors was not included because the duration of use was difficult to determine from the case report forms; however, the proportional use of growth factors was determined and reported descriptively. Drug dosing and costs were otherwise derived from the Ontario Drug Benefits E-formulary and Alberta Drug Benefit List (10,11).
3.3.3 Cost of Hospitalizations

The frequency and duration of hospital admissions were derived from the clinical trial database case report forms. Hospitalizations that occurred while patients were on treatment and up until 4 weeks after completion of protocol therapy were included. The reason for admission was determined based on manual review of the event description in the database. A diagnostic code was assigned by the study investigators using International Classification of Diseases 10 designations (19). The daily costs were calculated using case mix costing or top-down costing based on case mix groups (CMG) using the Canadian Institute for Health Information’s Discharge Abstract Database (CIHI-DAD) (14). Mean daily costs were calculated for each diagnostic code based on resource intensity weights (RIWs) for average Canadian patients aged 60-79, including alternative level of care (ALC) admission days. Conservatively, the cost of emergency department visits were not included to avoid double counting.

3.3.4 Cost of Clinic Visits

The frequency of clinic outpatient visits was derived from the trial protocol and case report forms. The cost of outpatient clinic visits included nursing wages, overhead costs, and physician fees. Nursing wages were estimated using the 2014 Ontario Collective Agreement for nurse with 8 years’ experience (13). The duration of nursing assessment was based on personal communication with oncology nurses (S. Martinek, personal communication July 16, 2020). Outpatient overhead costs included administration, maintenance, housekeeping, porter supplies, medical records, and equipment costs. These were determined using the hotel-approximation method where the ‘hotel’ price was obtained from the Princess Margaret Hospital (PMH) finance department at $100 CAD per hour plus inflation (20–22). The duration of clinic visit was estimated based on personal communication with two oncologists. Physician fees were calculated based on the Ontario Health Insurance Plan (OHIP) Schedule of Benefits (version March 19, 2020) where all oncology visits were costed as follow-up visits (12).
3.3.5 Cost of Investigations

The frequency of blood tests, imaging, and cardiac testing was based on the clinical trial protocol. The cost of investigations included the cost for laboratory investigations including blood tests, urine test, and bone marrow biopsy, as well as the cost of diagnostic imaging. The cost of the required blood and urine tests were based on the cost of each individual test which was determined from the fee schedule used at Kingston Health Sciences Center. These costs are comparable to those listed in the OHIP Schedule of Benefits for Laboratory Services (15). The cost of bone marrow biopsy included the following aspects: procurement (physician fee and nursing wage), hematopathology interpretation, hematopathology technical components (including overhead, reagents, technician wage), genetics interpretation, and genetics technical components (including overhead, reagents, technician wage). Radiological investigations were required at diagnosis and at relapse and could include skeletal survey, whole body MRI, low-dose whole-body CT or PET/CT scan as per the clinical trial protocol. The cost of radiological investigations included the physician fees as per OHIP Schedule of Benefits as well as estimated overhead costs of 70% based on Alberta Mirror Study (12,16).

3.3.6 Cost of Transfusion

The frequency of packed red blood cell (pRBC) and platelet transfusion was obtained from the clinical trial database case report forms. The costs of transfusions include both blood acquisition costs and administration costs. The cost of blood product acquisition was obtained from the Canadian Blood Services (17). The administration costs including overhead, nursing wages, and laboratory costs was estimated as $243.10 per unit of pRBC or 1 adult dose of platelets (e.g. 4 unit adult buffy coat derived-platelets)(18).
3.3.7 Cost of Thrombotic Microangiopathy (TMA)

The incidence of TMA was determined from clinical trial database case report forms. Manual review of the event description was completed by study investigators to determine the duration of apheresis and presence of other component costs. The total cost of TMA included cost of hospitalizations, apheresis, physician fee, and blood transfusion. The cost of apheresis (not including replacement fluid) was estimated at $750.80 CAD per day (23). Replacement fluid was assumed to be fresh frozen plasma (FFP) due to the public availability of pricing. We note that exchange with cryosupernatant plasma is frequently used; pricing is likely similar given manufacturing methods. The volume of plasma was calculated based on the patient’s weight at the time of enrolment, where the plasma volume = 60ml x weight (kg) as per the “Canadian apheresis study” (23). Therapeutic plasmapheresis volume was estimated as 1.5 plasma volumes per exchange as per usual clinical practice. The volume of each unit of FFP was 283 mL per Canadian Blood Services (17). The pricing per unit of FFP was obtained from the Canadian Blood Services (17). Physician fees were estimated as per OHIP Schedule of Benefits for Physician Services (12).

3.3.8 Data Analysis

Total and disaggregated mean costs per patient were presented descriptively with mean, standard deviation, and ranges. Costs were estimated over an indefinite time horizon. Costs were presented in 2020 Canadian dollars (1 CAD =0.58 GBP = 0.75 United States dollars (USD)) with inflation calculated using the Bank of Canada Consumer Price Index (24). Costs were not discounted given the brief time horizon from enrolment to data lock.

3.4 Results

The MYX.1 clinical trial was activated in June 2016 and completed accrual in January 2018. The present cost-analysis is based on the data available at the time of the database lock on June 19th, 2019. A
total of 76 patients were accrued from 9 Canadian centres and 75 patients were eligible for treatment (one patient was ineligible due to bortezomib refractory disease). The cohort eligible for the economic analysis included all 75 patients.

Full clinical trial results are published separately (25). The study met its primary endpoint with overall response rate after 4 cycles of 84% (95% confidence interval: 76% to 92%) and the best overall response rate (ORR) was 85% (95% confidence interval: 77% to 93%). The two-year overall survival (OS) rate was 62% (95% CI, 49 to 72%). The median duration of follow-up for the 75 treated patients was 24.6 months (range 0.23 months to 33.8 months). The median age was 66.0 years (range 44.0 to 82.0, IQR 60.0 to 71.0). Twenty-eight (28) of the 75 patients were female (37%).

The total cost of treatment for all 75 patients on the clinical trial was $15.3 million CAD. The mean total cost per patient was $203,336.08 or $14,081.45 per patient per cycle. The distribution of cost per patient is presented in Figure 1. On average, patients completed 14.4 cycles of chemotherapy at the time of data lock. The total annual cost (or 13 cycles) was $183,058.79 per patient. The predominant cost driver was the total cost of chemotherapy including drug acquisition and administration cost. This accounted for 88% of the total treatment cost, or $13.5 million CAD for all patients. The mean chemotherapy cost was $179,332.78 per person or $12,419.17 per person per cycle. Ninety-one percent (91%) of the total drug costs were attributed to the cost of carfilzomib at $12.2 million CAD. The mean cost of carfilzomib acquisition was $162,471.65 per person or $11,251.50 per person per cycle. The total annual cost (or 13 cycles) of carfilzomib per person was $146,269.49. The cost of carfilzomib wastage was estimated using commercially available vial sizes (10mg, 30mg, and 60 mg vials) compared to the 60mg vial size used in the trial and the actual dose given as recorded in the case report form. The estimated cost of carfilzomib using available smaller vial sizes was $133,777.93 per person versus $162,471.65 per person using 60mg vials. This represents an average cost savings of $28,693.72 per person over the duration of treatment or an 18% cost reduction. Figure 2 and Table 2 lists the aggregate and disaggregated cost incurred during the period of observation.
Note: These costs occurred throughout the entire duration of the study period.
The average number of cycles per patient was 15.

Figure 3-1 - Distribution of Total Treatment Cost per Patient (in $1000 CAD)

Table 3-2 - Predominant cost drivers of wKCD – Aggregate and disaggregate costs

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>Total cost for all patients ($CAD)</th>
<th>Mean cost per patient ($CAD)</th>
<th>Estimated Annual cost per patient ($CAD)</th>
<th>Mean cost per patient per cycle ($CAD)</th>
<th>Percentage of total cost (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy costs</td>
<td>$13,449,958.76</td>
<td>$179,332.78</td>
<td>$161,449.18</td>
<td>$12,419.17</td>
<td>88.2%</td>
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<tr>
<td>(including drug acquisition and administration costs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supportive medication costs</td>
<td>Hospitalizations costs</td>
<td>Office visit costs</td>
<td>Investigation/Monitoring costs</td>
<td>Transfusion costs</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------------</td>
<td>------------------------</td>
<td>-------------------</td>
<td>--------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Supportive medication</td>
<td>$140,502.58</td>
<td>$1,873.37</td>
<td>$1,686.55</td>
<td>$129.73</td>
<td>$0.9%</td>
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<td>Hospitalizations</td>
<td>$772,129.61</td>
<td>$10,295.06</td>
<td>$9,268.44</td>
<td>$712.95</td>
<td>5.1%</td>
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<td>Office visit costs</td>
<td>$238,541.58</td>
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<td>Investigation/Monitoring</td>
<td>$538,107.23</td>
<td>$7,174.76</td>
<td>$6,459.27</td>
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<td>3.5%</td>
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<tr>
<td>Transfusion costs</td>
<td>$79,845.27</td>
<td>$1,064.60</td>
<td>$958.44</td>
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<td>0.5%</td>
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<td><strong>Total</strong></td>
<td><strong>$15,250,205.69</strong></td>
<td><strong>$203,336.08</strong></td>
<td><strong>$183,058.79</strong></td>
<td><strong>$14,081.45</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

**Figure 3-2 - Disaggregate costs of wKCD (% of total)**

A total of 61 hospitalizations occurred during the treatment period costing a total of $772,129.61 or an average of $10,295.06 per patient. Fifty-six percent (56%) of patients were hospitalized at least once during their treatment course. The mean duration of hospital stay was 10 days. The most common reason for hospitalization was infection accounting for 61% of admissions.
Baseline and monitoring investigations accounted for 3.5% of treatment costs. The cost of investigations for all patients was $538,107.23 or $7,174.76 per patient. These investigations cost included the cost of bone marrow biopsy and cytogenetic testing totalling $276,719.88 or $3,689.60 per patient. Radiology accounted for 7.8% of the investigational cost, $42,422.05 in total.

Blood transfusions costs represented a small proportion of overall costs, a total of $65,861.27 or an average of $878.15 per person. Seventy-three red blood cell (RBC) transfusions and 46 platelet transfusions were administered during the clinical trial.

The total cost of managing TMA for the three affected patients was $56,589.96. All three patients were admitted to hospital where the average length of stay was 9 days (range 8-10 days). Two of the three patients received plasma exchange (PLEX), where they received therapeutic plasma exchange for an average of 6 days. The predominant cost driver for the treatment of TMA was the total cost of plasmapheresis (including institutional overhead, plasma acquisition and physician time) at $31,120.80 for both patients. The cost of plasma acquisition for use in plasmapheresis accounted for $22,040.00. The total cost of hospitalizations for TMA was $25,469.15. These findings are summarized in Table 3.

Table 3-3 - Cost of Managing TMA

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>Description</th>
<th>Total cost ($CAD)</th>
<th>Mean cost per patient ($CAD)</th>
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</thead>
<tbody>
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<td>PLEX</td>
<td>Plasmapheresis costs (including overhead, line placement)</td>
<td>$31,120.80</td>
<td>$10,373.60</td>
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<td></td>
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<td>$8,258.80</td>
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<td></td>
<td>Fresh frozen plasma</td>
<td>$22,040</td>
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<tr>
<td></td>
<td>MD assessments</td>
<td>$822.00</td>
<td>$273.00</td>
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<tr>
<td>Hospital admission</td>
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<td>$25469.15</td>
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<tr>
<td>Blood Transfusions</td>
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<td>$0</td>
<td>$0</td>
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<tr>
<td>(non-plasma)</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
3.5 Discussion

Despite the rising tensions between government resources and the demands of health care budgets in many jurisdictions, the cost of MM care is rarely reported in the literature. In Canada, MM accounts for a minority of cancer cases but up to 20% of some provincial oncology drug budgets (G. Mitera, personal communication, March 30, 2020). Future healthcare spending needs to prioritize therapies that are safe, effective and offer value for money. The present study provides important information about the cost of high-dose wKCD in Canada.

The National Comprehensive Cancer Network Clinical Practice Guidelines and the American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) Joint Clinical Practice Guidelines recommend the use of triplet drug combinations over doublets for MM treatment (26,27). With this in mind, the MYX.1 study investigators proposed a triplet drug combination that may be affordable for use in the Canadian healthcare system or other public payer healthcare systems worldwide. Carfilzomib (Krypolis®) is a safe and effective proteasome-inhibitor but the cost of drug acquisition is considerable (although provided here by the pharmaceutical company for patients on trial). When carfilzomib is used in combination with dexamethasone it is dosed twice weekly at 56mg/m2 (i.e. total weekly dose of 112mg/m2). In the MYX.1 study, carfilzomib was used in combination with oral cyclophosphamide and dexamethasone and carfilzomib was administered once weekly but at a dose of 70mg/m2. The cost of drug acquisition of carfilzomib, the predominant cost driver in MYX.1 is minimized through this weekly dosing schedule. Assuming that the other cost components are stable including the cost of managing toxicities, we calculated that the cost of biweekly carfilzomib would be $300,576.70 per patient (compared to $179,332.78 per patient on wKCD). The once weekly dosing strategy is potentially associated with significant cost savings including $104,663.43 per patient from direct drug costs and $16,580.49 per patient from drug administration costs. This regimen provides an example of how we
may be able to help mitigate the rising costs of cancer therapy, after appropriate testing of novel regimens in clinical trials.

Choosing optimal vial sizes for chemotherapy drugs is a simple strategy to reduce wastage and minimize chemotherapy costs (28–31). Carfilzomib was initially only available in Canada as a 60 mg vial. Now it is available in 10mg, 30mg, and 60mg vials; however, some pharmacies continue to only stock the largest vial size. By using a combination of vial sizes, we can minimize drug wastage and thus the cost of carfilzomib acquisition. For example, in MYX.1 an average of $28,693.72 or 18% of total costs per person could have been saved if a combination of 60mg and 10mg vials were used. Although the unused portion of a carfilzomib vial can be used for another patient, the drug is only stable for 24 hours, limiting the viability of sharing partial vials. Sharing of partial vials in this timeframe is especially challenging for centres who treat a small to moderate volume of patients with RRMM where it is possible to treat a patient with carfilzomib only once a week.

Consider bortezomib, a first-generation proteasome inhibitor, which is frequently used as part of first line therapy for MM. The dose and vial size of bortezomib (standard 3.5mg vial) differs from carfilzomib; however, the same principles of drug wastage and optimization apply. Bortezomib is stable for 7 days after the vial is opened allowing for better use of partial vials between patients especially given the frequency of bortezomib use in the frontline setting. Meanwhile, a study in Brazil suggests that further cost savings could be realized with the availability of even smaller vial sizes of bortezomib (32). They estimate that the availability of 0.5mg and 2.5mg vials could reduce wastage (and therefore cost) by an additional 62%. In the UK, both 1.0mg and 3.5 mg vials are available, this after much advocacy from National Institute for Health and Clinical Excellence (NICE) and other stakeholders (28,33,34). By the same token, the availability of additional vial sizes for carfilzomib, specifically a 5mg vial could further reduce costs. In addition, pharmacy managers should be made aware of the up-to-date available vial sizes so that they can stock a combination of vial sizes and minimize local drug wastage.
The present study is comprehensive in its inclusion of direct healthcare MM care costs that occurred while patients were on the treatment or follow-up phases of the clinical trial. In particular, this study explored the complete costs of bone marrow biopsies for the diagnosis of MM including the cost of cytogenetics. Previous estimates of bone marrow biopsy costs have been restricted to the billing fee for the physician acquiring the biopsy. Presently, we have accounted for many more aspects including the wages of the hematopathologist, laboratory overhead costs, and the cost of completing cytogenetics such as Fluorescence in situ Hybridization (FISH). The costs of FISH cytogenetics at Kingston Health Sciences Center (KHSC) using 3 probes (IGH MAF, FGFR3 IGH, and TP53) is estimated at $1975 per patient. Molecular and cytogenetic techniques are increasingly being used in MM for both diagnosis and monitoring of disease. It is important that we capture the cost of these new techniques to accurately estimate the total cost of MM care.

We have attempted to improve upon the comprehensiveness of cost estimates in MM; however, this study is limited in its ability to account for societal or indirect costs. For instance, it does not estimate the cost of work absenteeism incurred by both the patient and caregivers, lost work productivity due to illness or premature death, the cost to travel to and from appointments, cost of supportive medications not provided on the clinical trial or by provincial or private insurance. A recent publication by a group in Slovakia reported indirect costs of MM to be €133,000 in the first year after initial diagnosis (35). The societal and indirect costs of MM therapies are likely significant for Canadians as well, but these costs have not previously been described in Canada and represents an opportunity for future exploration.

Further, health utilities were not collected in this study and this was a single arm study therefore a cost-effectiveness analysis could not be conducted. Future studies would ideally include health utilities in order to facilitate the calculations of quality adjusted life years (QALYs) or willingness to pay for a MM regimen.
Globally, healthcare systems are under serious budgetary constraints. Policy makers and funding bodies often lack the detailed information on cost alongside clinical benefit, with which they can determine the value of an intervention, and if it can or should be made available to a population. Researchers must prioritize health economic-analyses as part of clinical trial design and research funders should support such studies (36). With this, as new treatments continue to come onto the market, patients, physicians and policy makers will be equipped to assess the most cost-effective means to extend life and improve its quality, within their willingness and ability to pay.

3.6 Acknowledgements

We thank Dr. Susan Crocker and Dr. Graeme Quest for their guidance and collaboration in determining the cost of cytogenetics and laboratory tests. We thank Tricia Carasco and Sarah Martinek for their help in estimating pharmacy and nursing workloads.
Bibliography


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Chapter 4

Discussion and Conclusions
4.1 Introduction

In this chapter the key findings of the MYX.1 clinical trial are discussed in reference to the safety of wKCD with a focus on thrombotic microangiopathy (TMA) and in reference to the descriptive cost-analysis. In addition, further methodology used in the cost-analysis to determine the cost of bone marrow biopsy (with cytogenetics) is explored in detail. Additional methodology use for the other cost components are presented in Appendix B.

4.2 Discussion of Results

4.2.1 Thrombotic Microangiopathy

Thrombotic microangiopathy is a life-threatening clinical syndrome characterized by hemolytic anemia, thrombocytopenia, and microvascular thrombosis resulting in ischaemia and organ damage. It is rarely encountered in clinical practice but given the potential for high mortality, awareness and clinical vigilance is required. We saw an unexpectedly high rate (4%) of TMA occurring in patients treated on the MYX.1 clinical trial. All three patients were suspected to have drug induced-TMA (DITMA) from carfilzomib exposure and received supportive care. Two of the three patients received plasmapheresis. All three patients made a complete recovery. Two of the three patients had a history of hypertension and the third patient developed hypertension during their treatment course (and prior to their TMA presentation). None of the three patients have been re-treated with carfilzomib. One of the three patients has since been re-exposed to a proteasome inhibitor (bortezomib) without recurrence of DITMA.

In review of the literature, we identified 31 other cases of DITMA after proteasome inhibitor exposure, 20 of these cases specifically after carfilzomib exposure. The rate of TMA reported in the product monograph and prior clinical trials is much lower, approximately 0.1%. The rate of TMA seen on the MYX.1 clinical trial was much higher than anticipated and led us to consider the possible reasons for this. The present study uses a unique dosing regimen with high dose once weekly carfilzomib and
perhaps this results in an increase rate of endothelial cell injury. Counter to this point, the ARROW study used once weekly carfilzomib and reported few cases of TMA (<1%) (1). Perhaps the combination of carfilzomib with cyclophosphamide could have a cumulative effect on the endothelium with increased endothelial cell injury. Again, this seems less likely given the low rate of TMA seen in the FORTE trial, a 2017 phase 3 study using carfilzomib and cyclophosphamide in combination (2). All three patients had hypertension, a condition with an increased rate of endothelial cell injury due to sheer force on the vessel wall from vascular flow. Certainly, this cannot be the only contributing factor given the high rates of hypertension in the general population and in the MYX1 study cohort. The exact reason or combinations of reasons is unknown, but this case reporting allows for hypothesis generation and raises awareness about a rare but potentially deadly adverse effect.

4.2.2 Descriptive Cost-analysis

Multiple myeloma continues to be an incurable malignant condition with a high rate of mortality. There have been numerous therapeutic advances in the last 20 years; ongoing testing of new therapies in clinical trials is needed. Carfilzomib (Krypolis®) is approved by Health Canada for use in patients with RRMM on the basis of numerous randomized control trials demonstrating its efficacy (2–6). Carfilzomib is an expensive medication and carfilzomib-based 3- and 4-drugs regimens are especially expensive because they contain additional costly novel agents. The MYX.1/MCRN003 study investigators intentionally combined high-dose once weekly carfilzomib with two inexpensive medications and hypothesized that wKCD would be an effective triplet regimen and offer patient convenience with once weekly dosing (compared to twice weekly) and an acceptable cost to Canadian healthcare payers.

The total cost of wKCD based on the MYX.1 clinical trial data was $203,336.08 per patient or $14,081.45 per patient per cycle. The cost of carfilzomib acquisition was the predominant cost driver accounting for 80% of total treatment costs. We compared the cost of chemotherapy administration and
drug acquisition of wKCD to that of standard dose biweekly carfilzomib with dexamethasone (KD) and demonstrated a cost savings with the use of wKCD.

We determined that further chemotherapy costs could be minimized through the use of optimal vial sizes. When comparing the cost of carfilzomib drug acquisition, an additional 18% can be saved by using 10 mg vials compared to typical 60 mg vials. We hypothesize that drug wastage, and therefore cost, could be minimized further if a 5 mg vial was available on the Canadian market.

We endeavoured to establish a comprehensive estimate of the direct health care costs of multiple myeloma based on MYX.1 clinical trial data. In particular, we gave careful consideration to accurately estimate the cost of a bone marrow biopsy for the diagnosis of multiple myeloma. Prior estimates placed the cost of a bone marrow biopsy at $79.20 CAD. Our detailed estimate, described in the subsequent paragraph and in Appendix B, is that the total cost of a bone marrow aspirate and biopsy (including the cost of cytogenetics) is $2788.01 CAD, a 35-fold increase.

4.2.3 Exploration of Cost for Bone Marrow Biopsy including Cytogenetics

Previous studies have estimated the cost of a bone marrow biopsy by using the OHIP schedule of benefits for the physician performing the bone marrow (e.g. fee code Z408 or $79.20) and have not include any other aspects of bone marrow testing. The cost of bone marrow investigations should be comprehensive and include the costs associated with obtaining the biopsy, preparing the biopsy material, interpretation of the biopsy material by the hematopathologist, as well as the cost of ancillary tests, which in the case of multiple myeloma the cost of cytogenetics testing such as Fluorescence in situ Hybridization (FISH). A comprehensive list of the hematologist, hematopathologist and technical billing codes commonly used for reimbursement of bone marrow biopsy costs are included in Table 4-1; these total costs are estimated at approximately $800 per person per bone marrow. Cytogenetic costs are described separately. The cost of sterile equipment (e.g. bone marrow needles, syringes, local anesthetic) and hotel costs (e.g. building heating and cooling, laundry for patient linens) were not included.
If one was to estimate the cost of cytogenetics using only the OHIP fee schedule it would also be a gross underestimation. Although FISH itself does not appear in the fee schedule another cytogenetic technique, karyotyping, does. The combined fee for g-bandng and karyotype interpretation is $191.29 per patient. In contrast, consider that the costs of FISH cytogenetics at Kingston Health Sciences Center (KHSC) using 3 probes which is standard local practice for MM is estimated at $1975 per patient (see table 4-2). This cost estimate includes the cost of reagents, cost of labour, cost of consumables as well as initial setup of the slides. The cost of reagent is based on the reagent cost charged by the supplier multiplied by the volume of reagent required to create both a control sample and a patient sample for each probe. The labour costs are estimated based on the technologists’ salary including benefits multiplied by the labor time required which includes time to process, score, collate, and file the FISH probe results. The technologist labour costs are minimized through batching of FISH tests given the high clinical volumes. These labor cost do not however include the cost of the cytogeneticist salary which is estimated between $90 - $150 CAD / hour. Service and machine maintenance costs were estimated at 10% of the overall cost per tests with the intention of accounting for the cost of degradation of fluorescent microscopes (e.g. bulbs, filters, cables), camera maintenance for microscopes, software maintenance agreements for microscopes, ThermoBrite slide processing system technical fees, and the maintenance of centrifuges, incubators, and thermatron. FISH validation costs were not included in the estimated overall cost of cytogenetics at KHSC. Each FISH probe requires a validation process consisting of at least 20 normal controls in order to build an interference cut off table and determine 95% confidence intervals. As well, if there are any changes in the company providing reagents or probes, then the validation testing must be repeated for the new company’s product. The building overhead such as heating, cooling, maintenance, and building acquisition were not included in this KHSC estimate.
### Table 4-1 - Component Cost of Bone Marrow for Multiple Myeloma at KHSC

<table>
<thead>
<tr>
<th>Probe</th>
<th>OHIP Billing Code</th>
<th>OHIP code description</th>
<th>Total cost per test (CAD)</th>
<th>Subtotal</th>
<th>Total cost per patient (CAD)</th>
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<td>Procurement</td>
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<td>Z408</td>
<td>Bone Marrow - Trephine and aspirate</td>
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<tr>
<td></td>
<td>Nursing time (30 minutes)</td>
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<td>Hematopathology Interpretation</td>
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<td>L864</td>
<td>Bone Marrow - Trephine</td>
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<td>L800</td>
<td>Blood film</td>
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<td>L849</td>
<td>Decalcification process</td>
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**Abbreviations:** FISH = fluorescence in situ hybridization, KHSC = Kingston health sciences center, CAD = Canadian dollars, IgH = immunoglobulin heavy chain MAF = v-musculoaponeurotic fibrosarcoma oncogene
homolog, FGFR3 = fibroblast growth factor receptor 3, TP53 = tumour protein p53, CD = clusters of differentiation

Table 4-2 - Component Cost of FISH Cytogenetics at KHSC

<table>
<thead>
<tr>
<th>Probe</th>
<th>Component</th>
<th>Cost per component (CAD)</th>
<th>Total cost per probe (CAD)</th>
<th>Maintenance costs and service contracts</th>
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Abbreviations: FISH = fluorescence in situ hybridization, KHSC = Kingston health sciences center, CAD = Canadian dollars, IgH = immunoglobulin heavy chain MAF = v-musculoaponeurotic fibrosarcoma oncogene homolog, FGFR3 = fibroblast growth factor receptor 3, TP53 = tumour protein p53, CD = clusters of differentiation
4.3 Limitations and Future Directions

Case reports and case series are important types of medical publications from the perspective of documenting rare diseases and generating hypotheses. Our case series add to the growing body of literature about DITMA after PI-exposure. However, this type of study is limited on numerous fronts. In the reporting of the above three cases of DITMA, we are unable to establish a cause and effect relationship between the exposure to carfilzomib and the clinical outcome. Further, the generalizability of our findings is unknown but likely limited. Future work exploring the pathogenesis of DITMA through the development of a scientific model including laboratory correlatives could help further out understand of this disease and insights into appropriate prevention and treatment strategies.

While improving upon the comprehensiveness, this study’s descriptive cost-analysis is limited in its ability to account societal or indirect costs. We do not account for indirect costs incurred by patient and caregivers such as work absenteeism, lost work productivity due to illness or premature death, travel-related expenses, or the cost of supportive medications.

This was a single arm-study and neither health utilities or quality of life information was collected from the patients; therefore, a cost-effectiveness or cost-utility analysis could not be conducted. A future randomized trial collecting patient reported outcomes would facilitate calculation of the cost per quality adjusted life year and the incremental cost effectiveness ratio. With such information, as new treatments continue to come onto the market, patients, physicians and policy makers will be equipped to assess the most cost-effective means to extend life and improve its quality within a given society's willingness to pay threshold.
Bibliography


Appendix A
Research Ethics Board Approval
QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD (HSREB)

HSREB Amendment Acknowledgment/Ethics Clearance

August 16, 2016

Dr. Annette Hay
Canadian Cancer Trials Group
Cancer Research Institute

ROMEO/TRAQ: #6018671
Department Code: OCRED 15-092
Study Title: MYX.1 "A Single Arm Phase II Study of High-Dose Weekly Carfilzomib Plus Cyclophosphamide and Dexamethasone in the Treatment of Relapsed Multiple Myeloma After 1-3 Prior Therapies"
Review Type: Delegated
Date Ethics Clearance Issued: August 16, 2016

Dear Dr. Hay,

The Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB) has reviewed the amendment application and granted ethics clearance/acknowledgement for the documents listed below.

- Information/Consent Form – Main Study – Version Date: 14 June 2016
- OCREB amendment approval – 7/4/2016

Yours sincerely,

[Signature]
Chair, Health Sciences Research Ethics Board

The HSREB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations, Canadian General Standards Board, and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP). Federalwide Assurance Number: FWA#00004184, IRB#00001173

HSREB members involved in the research project do not participate in the review, discussion or decision.
Appendix B

Methodological Approach to Defining Cost for Clinical Trial Variables
Authors: Bethany E. Monteith¹², Matthew C. Cheung¹, Susan Crocker², Graeme Quest², Tricia Carasco², Lois Shepherd¹, Harriet Richardson¹, Joe Pater¹, Annette E. Hay¹²

Affiliations: ¹Queen's University, Canadian Cancer Trials Group, Kingston, Ontario, Canada, ²Queen's University, Cancer Center of Southeastern Ontario and Kingston Health Sciences Center, Kingston, Ontario, Canada, ³University of Toronto, Odette Cancer Centre, Toronto, Ontario, Canada

For submission to Current Oncology
Estimating the Cost of Myeloma Care in Ontario – A Compendium of Costs

Introduction

Presently, there is limited published data on the total cost of multiple myeloma (MM) regimens, or the component costs required to deliver MM care to Canadians. Given that MM accounts for an increasing proportion of health care budgets, there is a pressing need for well conducted, impartial health economic analyses. Consideration of such unbiased health economic analyses can help prioritize drug regimens for funding and strengthen healthcare policy decisions. Clinical trials provide an important opportunity to document resource utilization and associated costs of specific regimens. Herein, we describe our experience in determining the aggregate and disaggregate costs of high-dose weekly carfilzomib combined with cyclophosphamide and dexamethasone in the treatment of relapsed and refractory MM based on the MYX.1/MRCN003 Phase 2 clinical trial. We considered the cancer associated costs by distinct aspects of care including blood work investigations, diagnostic imaging, bone marrow investigations including cytogenetics, stem cell transplant, drug acquisition and administration, supportive drugs, transfusions, hospitalizations, physician visits, and the cost of managing adverse events. The details of such approach as they pertained to MM care are subsequently explored.

Cost Component A - Bloodwork

The clinical trial protocol specified require blood tests at study enrolment, during treatment and at relapse. The cost of these bloodwork investigations are frequently estimated based on a fee schedule for laboratory billing (1–3). In Ontario, blood tests are commonly estimated based on the Ontario Health Insurance Plan (OHIP) schedule of benefits for laboratory services (4). This document reflects the “willingness to pay” on the part of the provincial government or the direct billing reimbursement that an individual commercial laboratory receives from the Ontario government for services rendered. However, it does not directly account for the additional cost of laboratory overhead such as technician wages,
building costs, reagent use. Consider that some testing may occur at a net financial loss to the private laboratory but is still offered in order to compete for a larger market share of business. Some groups estimate overhead between 25-40% as has been used in other industries (5) but it remains unclear if this estimate is accurate for most clinical laboratories. We based our laboratory fee estimates on the fee schedule used at Kingston Health Science Center. These estimates take into account the cost of overhead, consumables, and personnel wages but are not intended to be revenue generating. The cost per test based on the KHSC schedule are approximately two-fold higher than the OHIP schedule of benefits for laboratory services.

Cost Component B – Bone Marrow Testing, including Cytogenetics

Previous studies have estimated the cost of a bone marrow biopsy by using the OHIP schedule of benefits for the physician performing the bone marrow (e.g fee code Z408) and did not include any other aspects of bone marrow testing. The cost of bone marrow investigations should be comprehensive and include the costs associated with obtaining the biopsy, preparing the biopsy material, interpretation of the biopsy material by the hematopathologist, as well as the cost of ancillary tests, which in the case of multiple myeloma the cost of cytogenetics such as Fluorescence in situ Hybridization (FISH). Our comprehensive estimate of bone marrow biopsy costs is included in Table 4-1. The OHIP fee schedule does not completely account for the substantial costs associated with cytogenetic testing. Although FISH itself does not appear in the fee schedule another cytogenetic technique, karyotyping, does. The combined fee for g-bandng and karyotype interpretation is $191.29 per patient. In contrast, consider that the costs of FISH cytogenetics at Kingston Health sciences Center (KHSC) using 3 probes which is standard local practice for MM is estimated at $1975 per patient (see table 4-2). This cost estimate includes the cost of reagents, cost of labour, cost of consumables as well as initial setup of the slides. The cost of reagent is based on the reagent cost charged by the supplier multiplied by the volume of reagent
FISH validation costs were not included in the estimated overall cost of cytogenetics at KHSC. Each FISH probe requires a validation process consisting of at least 20 normal controls in order to build an interference cut off table and determine 95% confidence intervals. As well, if there are any change in the company providing reagents or probes, then the validation testing must be repeated for the new company’s product. The building overhead such as heating, cooling, maintenance, and building acquisition were not included in this KHSC estimate.

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<th>Probe</th>
<th>OHIP Billing Code</th>
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<td>L846</td>
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<td>$455.40</td>
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</table>

**Hematopathology technical**

| L378       | Bone marrow preparation | $7.76 |
| L379       | Bone marrow staining | $11.89 |
| L393       | Complete blood count | $3.98 |
| L375       | Blood film | $5.70 |
| L398       | Reticulocyte count | $3.30 |
| L731       | Immunohistochemistry (3 units) | $79.98 |
| L720       | Cell block | $38.78 |
| L525       | Flow cytometry | $103.40 |
|            |                        | $254.79 |

**Cytogenetics**

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$2,788.01

**Abbreviations:** FISH = fluorescence in situ hybridization, KHSC = Kingston health sciences center, CAD = Canadian dollars, IgH = immunoglobulin heavy chain MAF = v-musculoaponeurotic fibrosarcoma oncogene homolog, FGFR3 = fibroblast growth factor receptor 3, TP53 = tumour protein p53, CD = clusters of differentiation

**Table 4-4 - Component Cost of FISH Cytogenetics at KHSC**

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<th>Maintenance costs and service contracts</th>
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Abbreviations:  FISH = fluorescence in situ hybridization, KHSC = Kingston health sciences center, CAD = Canadian dollars, IgH = immunoglobulin heavy chain MAF = v-musculoaponeurotic fibrosarcoma oncogene homolog, FGFR3 = fibroblast growth factor receptor 3, TP53 = tumour protein p53, CD = clusters of differentiation

### Cost Component C – Diagnostic Imaging including PET/CT Scans

Previous cost-analysis studies in Canada have estimated the cost of diagnostic imaging (DI) based on the billing fee for the radiologist alone. In Ontario, the OHIP schedule of benefits outlines the payment to physicians for interpreting a DI study (range $10.65-$368.35). However, there are many other costs associated with performing a DI study and using only the physician billing fees leads to an underestimation of total DI costs. Additional aspects that should be considered include technician wages, capital costs including purchase and financing of the imaging unit, maintenance of the imaging unit, technical support fees, computer support, data storage, building overhead (e.g. heating, lighting, maintenance), and if applicable, the generation and storage of radioisotopes.

A recent study in Alberta reviewed the overhead costs to provide publicly funded diagnostic imaging studies in various outpatient community settings in 2018. This study was performed by MNP’s Economics and Research Consulting Group as commissioned by Alberta Society of Radiologists to
develop independent overhead estimates for Diagnostic Imaging physicians. The study reviewed self-reported line by line expense data as provided by individual radiologists or physician groups. Participation in the study represented 80% of radiologist practicing in Alberta, 89% of whom report working in a community office offering in-person, in-patient services (6). The total overhead costs reported was $282.9 million for 336 radiologists or an average annual total cost per radiologist of $842,000. The total fee-for-service payments to Radiology in 2017/18 was $451.3 million amongst 417 radiologists. The overhead ratio estimate was 69.7% based on the proportion of radiologists that practice in a community clinic setting.

This study represents one of the only contemporary Canadian studies looking at estimates of DI overhead costs. It is a comprehensive estimate with inclusion of capital costs, making up a large proportion of DI overhead. The main limitation with this methodology is that the overhead estimate is based on community outpatient clinic services and may not fully account for overhead costs in hospital DI departments. Nevertheless, this study is the only recent comprehensive study of its kind in Canada. Therefore, we used this study as the basis for our overhead estimates of 70% for all DI test except PET/CT scans.

Positron emission tomography (PET) is a nuclear medicine study that is used widely in oncology and has recent indications for use in MM (7). The estimated cost of a PET scan if based on the OHIP billing fee schedule alone would be $237.50 per test. Certainly, this is an underestimation of the true cost when we consider the additional cost components required to generate a PET scan. Logically, the true cost of a PET scan is much higher than the billing fee alone and must include estimates of capital costs and other overhead expenses. A recent Canadian Agency for Drugs and Technologies in Health (CADTH) report, estimates the cost per PET/CT scan in Canada to be approximately $1050 (2012 CAD) (8). Using a micro-costing approach, Klose et al. estimated the direct cost of FDG-PET/CT for lymphoma in Ulm, Germany to be €961 (1999 EUR) including staff, materials, investment, maintenance and overheads (9). In Germany, the costs per examination range between approximately €600 and €1,000
(2010 EUR) plus the cost of radioisotopes of approximately €180–€260 (2010 EUR) per scan (10). In a British survey, the costs per PET or PET/CT scan varied from £635 to £1,300 (2007 GBP) (11).

Capital funding of scanners makes up a substantial proportional of the total cost of diagnostic imaging. As of 2015, there were 45 publicly funded PET scanners distributed across 34 centres in Canada (12). According to a 2007 national survey of selected medical imaging equipment with supplemental information from the provincial health ministries, 6 new PET/CT scanners were planned to be purchased in Canada in 2006. The total capital spending estimates for each PET/CT scanners by province were as follows: $5.5 million in Nova Scotia, $5.1 million in British Columbia, $3 million (government subsidy only) plus private contributions in Quebec, and more than $7 million for 2 scanners in New Brunswick. Separately, Nova Scotia and British Columbia reported capital costs of over $5 million per PET/CT scanner (13).

In the present cost-analysis, the cost per PET/CT scan was estimated at $1050 (2012 CAD) plus inflation. This method was selected because it is informed by Canadian data. It is also aligned with the costs estimated in European countries recognizing both similarities and differences in the respective health care models (9–11). This estimate of PET/CT scan costs by CADTH is likely more accurate than the previous methods where cost was based on OHIP physician billing alone ($237.50) (12). There are certainly limitations with this estimate mainly due to lack of contemporaneous and comprehensive data highlighting the need for updated estimates of PET/CT scanning cost in Canada.

Cost Component D – Rare Toxicities – Thrombotic Microangiopathy

The cost of managing drug side-effects can be substantial especially if these side-effects result in additional hospitalizations, the second largest driver of health care spending based on MYX.1 trial data. Thrombotic microangiopathy is a rare but life-threatening syndrome of microangiopathic haemolytic anaemia, thrombocytopenia, and multi-organ dysfunction. Over the past 10 years there have been 34 case reports of drug-induced TMA (DITMA) occurring after proteasome inhibitor exposure, including 23
cases after carfilzomib exposure. In the MYX1/MCRN003 study, 3 cases of TMA developed in the 75 patients treated with high-dose weekly carfilzomib (70mg/m2), cyclophosphamide, and dexamethasone. The cost of managing TMA could be substantial and therefore the present study explores this aspect specifically.

The management of TMA almost always requires hospitalization in order to facilitate supportive therapy. The differential for DITMA includes thrombotic thrombocytopenic purpura (TTP), a condition characterized by low levels of ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) due to the presence of autoantibodies, and therefore upfront supportive treatment with plasmapheresis is indicated for most patients. Additional therapies such as renal replacement therapy and/or blood transfusions may be required for some patients.

Plasmapheresis is an apheresis technique whereby a patient’s plasma is removed from their circulation and replaced with donor plasma. In the instance of TTP, the preferred product for reinfusion is cryosupernatent plasma (CSP). In the present study, cost of acquisition of the exchange product was estimated using the cost of fresh frozen plasma (FFP) because the cost of CSP is not publicly available. As per personal communication with the KHSC hospital transfusionist (G. Quest, July 8th, 2020), the cost of CSP and FFP are comparable. Canadian Blood Services estimates one unit of FFP to cost $95 CAD (14). As per the “Canadian apheresis study” the volume of plasma required per plasma exchange for TTP is 1.5 times the patient’s plasma volume, where plasma volume is estimated as 60ml per kilogram bodyweight (15). The volume of each unit of FFP is approximately 283ml (16). The total volume of FFP required for plasmapheresis was calculated based on the above factors and the duration of plasmapheresis treatment as recorded in the clinical trial database.

The average daily cost of plasmapheresis in Canada in 2002 was $550 CAD not including replacement fluid or capital costs (15), similar to other studies. In the Unites States, the cost for therapeutic plasma exchange (TPE) was estimated at $2908 (2011 USD) per exchange by the University of Rochester Billing Office. Similarly the cost of TPE for Guillain-Barré at the Mayo Clinic in
Rochester, Minnesota was $4,638.16 USD (2011) per 5 exchanges with albumin (not FFP) including tubing sets, central venous catheter supplies, nursing wages, service contract amortization, TPE equipment amortization (17). This estimate did not include physician billing fees for TPE oversight or radiology fees for line placement.

The cost of hospitalizations for TMA was calculated using the CIHI-DAD database as per the methods outlined below. The cost of transfusions, aside from plasma used for TPE, was calculated using acquisitions cost per Canadian Blood Services and administration costs per a recent Alberta study (14,18) (see section “Cost Component F – Transfusions” for more details). Physician costs were estimated using the OHIP schedule of benefits, where billing was based on one daily consultant visit for the duration of the in-hospital admission (4).

Cost Component E – Hospitalizations

The CIHI discharge abstract database (DAD) contains approximately 75% of all inpatient hospital separations from most hospitals in Canada, excluding Québec (19). Hospital separations include hospital discharges, deaths, sign outs, and hospital transfers for acute care hospitals, day surgeries as well as some rehabilitation and psychiatric hospitals. In the present study, cost data for each patient’s hospital stay was derived from the CIHI-DAD (version 2017-2018, most recent closed year) using the resource intensity weights (RIWs) method. Using RIWs method allows for improved reliability when calculating expenditures by disease as it takes into account the intensity of resource use based on patient characteristics, primary diagnosis and treatment. The cost to those age 60-79 was selected as it encompasses the average age of the patients enrolled in the MYX1/MCRN003 study. The cost per day for each diagnosis was calculated by dividing the total cost of hospital stay for a specific diagnosis by the number of hospital days (including alternative level of care days). The length of hospital stays as recorded in the clinical trial database was multiplied by the calculated daily cost for each diagnosis.
Cost Component F – Transfusions

The cost of red blood cell (RBC) transfusion was estimated using the cost of RBC acquisition and administration plus inflation when indicated. A 2017 study by Lagerquist et al. estimated the cost of RBC transfusion to be $666.10 (2014 CAD), including the cost of RBC acquisition and administration (18). RBC acquisition cost was $423.00 per unit based on Canadian Blood Services pricing (14). The administration cost was $243.10 using activity-based accounting methods based on the total in-hospital costs including personnel, consumables, and capital costs. Similarly, the cost of platelet transfusion was estimated using the cost of platelet acquisition and administration plus inflation as necessary. The cost of platelet acquisition plus inflation was $327 based on Canadian Blood Services pricing for 4 units of buffy coat derived platelets. We assumed that the administration cost of one adult dose of platelets was the same administration costs as one unit of RBCs, $243.10. There are some limitations with this assumption including differences in time for product infusion, patient monitoring, and frequency of possible side effects. However, we are accepting of these limitations given that there are few alternatives studies which outline disaggregated cost of blood product administration in the Canadian context.

Cost Component G - Chemotherapy

The cost of chemotherapy included the drug acquisition costs as well as the drug administration cost. Drug acquisition costs were based on the Provincial Drug Reimbursement Programs (PDRP) and the Ontario Drug Benefit Formulary pricing for carfilzomib, cyclophosphamide and dexamethasone (20,21). The cost per drug is as follows: carfilzomib $1533.33 per 60mg vial, cyclophosphamide $0.474 per 50mg tab, and dexamethasone $0.3046 per 4mg tab. Drug administration costs were estimated based on a recent study by Sohi et al. where “center costs” for chemotherapy administration were estimated at $181.71 per hour (or $128 per hour, 2019 USD) plus inflation (22). Their estimate includes the cost of pharmacist wages, nursing wages, and most overhead expenses at seven Canadian sites. Chair time and nursing time was estimated based on Cancer Care Ontario workflow estimates. Pharmacy time was
estimated based on personal communication with an experienced cancer centre oncology pharmacist (T. Carasco, July 15th, 2020).

**Cost Component H - Supportive therapies**

The cost of supportive therapies included only those medications required by the clinical protocol. Each supportive medication was assumed to be used according to typical dose and duration for myeloma and/or chemotherapy prophylaxis. The unit price per drug was obtained from the ODB eFormulary or Alberta Health Formulary (21,23).

The use of granulocyte colony-stimulating factor (G-CSF) such as Neupogen was not required by the protocol and its use was left at the discretion of the investigator. Due to incomplete data in the clinical trial database, G-CSF use was excluded from the total cost of supportive therapies. Various modelling techniques were considered in order to account for this missing data. The proportion of patients receiving at least one dose of GCSF was 18/75 with 7 of 18 receiving more than one dose G-CSF. Unfortunately, we cannot determine exact duration of G-CSF treatment due to missing data.

**Conclusion**

This compendium of costs serves to increase awareness of the total and disaggregate costs required to deliver MM care. This summary highlights the need for additional work including even more comprehensive description of costs in the Canadian health care system as such information may allow for better cost comparison across studies. Our Canadian healthcare system is unique, and it is important that our cost analyses include component costs that reflect the accurate use of provincial resources. Having accurate cost information alongside clinical efficacy data will help policymakers prioritize those investigations and interventions that are most cost-effective.
Bibliography


