FREQUENCY OF PERIPHERAL NEUROPATHY AND INJECTION SITE REACTIONS IN PATIENTS WITH MULTIPLE MYELOMA RECEIVING SUBCUTANEOUS VERSUS INTRAVENOUS BORTEZOMIB

by

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Abstract

Multiple myeloma is an incurable hematological malignancy with patients living on average 3 to 6 years after diagnosis. Bortezomib is widely used to treat multiple myeloma. Peripheral neuropathy has been a major side effect associated with bortezomib treatment, and occurs in 47% to 64% of patients. Therefore, strategies to minimize this dose limiting toxicity have been studied and protocols have been revised accordingly. Bortezomib administered subcutaneously instead of intravenously is one strategy that has shown to decrease the incidence of peripheral neuropathy, is well-tolerated and equally as efficacious as bortezomib administered intravenously. Injection site reactions have been reported as mild. Furthermore, as far as the author is aware there is currently no published literature discussing the safety and tolerability of the back of the arm as an injection site for bortezomib. This was a retrospective, chart review of 53 subjects with multiple myeloma, conducted in two large academic medical centres in British Columbia. Incidence of peripheral neuropathy was collected and compared between those who had received bortezomib via intravenous and subcutaneous routes. Incidence of injection site reactions related to subcutaneous administration of bortezomib were also collected, and a comparison was done between the sites of injection (back of the arm, abdomen and thigh). Overall, peripheral neuropathy rates in this study were 28% (n=15/53). There was no statistically significant difference between frequencies of peripheral neuropathy for patients who received bortezomib via intravenous or subcutaneous routes ($p = .490$). There were a total of 861 injections, with 294 injections to the back of the arm, 487 injections to the abdomen, 130 injections to an unknown site and only one injection in the thigh. Of the 861 injections, there were eight (2%) Grade 1 injection reactions in the abdomen, and one Grade 3 injection reaction, in the thigh. None were reported in the back of the arm. In conclusion, a prospective study with a

larger sample size is needed to examine if subcutaneously injected bortezomib results in less peripheral neuropathy than intravenously injected bortezomib. Furthermore, subcutaneously injected bortezomib is safe and well tolerated when injected in the back of the arm.

Preface

This study was identified and designed by myself in collaboration with Dr. Kevin Song, Associate Professor, Faculty of Medicine at the University of British Columbia, Dr. Leanne Currie and Dr. Tarnia Taverner, Faculty of Nursing at the University of British Columbia. All data were collected by the author and Pharmacist, Linda Hamata at the British Columbia Cancer Agency and Vancouver General Hospital. All data analysis was performed by the author and supervised by Dr. Leanne Currie and Dr. Tarnia Taverner. Ethics approval was obtained from the University of British Columbia Clinical Research Ethics Board on June 13th, 2013, certificate of approval # H13-00772. This study has not yet been published.

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Dedication

For Lillian and Karen. And to all patients with myeloma past, present and future. You have inspired me, and shown me what true courage and hope is.

Chapter 1: Background

1.1 Introduction

Multiple Myeloma is an incurable hematological malignancy with patients living an average of 3 to 6 years after initial diagnosis (de la Rubia & Roig, 2011; San-Miguel, Garcia-Sanz, & Gutierrez, 2013). Bortezomib is a novel agent belonging to the class of drugs called proteosome inhibitors, used to treat myeloma and has been available in British Columbia (BC) since 2004. The term novel agent pertains to drugs that were developed with different mechanisms of action, compared to corticosteroids and alkylators, which were classically used in treating multiple myeloma. The use of novel agents such as bortezomib have significantly improved the survival of patients with myeloma (Delforge, 2011) with many living for more than 10 years from point of diagnosis (San-Miguel et al., 2013). This is an improvement from the era prior to novel agents, with a median survival of about five years for patients who received a stem cell transplant, or three years for patients who did not receive a stem cell transplant (Bladé, Rosiñol, & Cibeira, 2008; Bringhen et al., 2010; Mateos, 2011). While outcomes associated with bortezomib are favourable with regard to extended life, the drug has several side effects, including peripheral neuropathy, fatigue and neutropenia (Delforge et al., 2010). Patient outcomes for both side effects and rates of remission and duration of remission are important factors that impact quality of life, and life expectancy for patients with multiple myeloma (Tariman, Love, McCullagh, & Sandifer, 2008). Bortezomib has become one of the major drugs used in treating multiple myeloma (Kouroukis et al., 2014). It is offered and administered at diagnosis, relapse, and at subsequent relapses, thus patients with multiple myeloma may have repeated exposures to bortezomib throughout the course of their illness (Corso et al., 2010). Due to the amount of this drug they will receive over time, management of side effects is extremely

important to balance quality of life, while maximizing efficacy of the drug, so that patients can live longer and as "well" as possible (Tofthagen, 2010).

1.2 Background

Multiple Myeloma is a hematological malignancy of the plasma cells that affects roughly five in 100,000 people, and accounts for approximately 10% of all hematological malignancies internationally (Delforge, 2011). In 2012, there were 322 British Columbians (seven per 100,000) diagnosed with multiple myeloma, and 163 deaths (four per 100,000) from myeloma in the same year (BC Cancer Agency Care and Research, 2014). The number of diagnoses was estimated to increase to 358 by 2014, with an estimated 163 deaths in the same year (BC Cancer Agency Care and Research, 2014). The overall five year survival rate was estimated at 43% (95% CI: 40.2 - 45.8%) (BC Cancer Agency Care and Research, 2014). Moreover, the five year overall survival between 2003 and 2011 rose from 50% to 70% in patients who received a stem-cell transplant (Venner et al., 2011). Therefore, it can be determined that more than one half of patients who are diagnosed today, and have received a stem-cell transplant, are going to live at least five years and likely longer. Maximum overall survival is still variable and largely unknown at this time due to differing access to novel agents and number of treatment regimens received (Venner et al., 2011). The rise in the overall survival rate has been directly attributed to the novel agents bortezomib and lenalidomide (Delforge, 2011; Delforge et al., 2010; Kumar et al., 2008; Venner et al., 2011). However, as stated previously, there are side effects associated with both bortezomib and lenalidomide. Therefore, if patients are living longer with multiple myeloma, it is important to address and manage all side effects related to their treatments, so that their quality of life is not compromised significantly (Tofthagen, 2010).

1.2.1 Peripheral Neuropathy

Peripheral neuropathy (PN) is one of the most challenging side effects of bortezomib. Baseline PN, which is PN prior to any treatment of the myeloma, has been reported from 11% to as high as 81% in the newly diagnosed myeloma population (Delforge et al., 2010). Furthermore, PN has been reported as high as 80% in advanced stages of the disease (Richardson et al., 2012). PN is often the dose limiting toxicity to bortezomib treatment such that it affects both myeloma patients' quality of life, and efficacy of the treatment (Tofthagen, 2010). PN can be painful and debilitating and is characterized by parasthesias (numbness and tingling) that usually starts in the lower extremities and fingertips. It gradually moves from distally to proximally, following the nerve from the extremities up to the spinal cord. It can also present as motor neuropathy (decreased reflexes, weakness in the arms and legs), or autonomic neuropathy (characterized by labile blood pressures, paralytic ileus). Researchers have reported the incidence of bortezomib induced PN as being from 37% to 64% of patients who have received bortezomib intravenously (Bringhen et al., 2010; Delforge et al., 2010).

Neuropathic pain is defined as “pain caused by a lesion or disease of the somatosensory nervous system” (International Association for the Study of Pain, 2012). Neuropathic pain can be present with peripheral neuropathy, and symptoms are similar. Neuropathic pain symptoms include “burning, painful cold, electric shocks, tingling pins and needles, numbness, and itching” (Taverner & Prince, 2014). Neuropathic pain is not a diagnosis, but rather a “description of clinical symptoms” (International Association for the Study of Pain, 2012). The clinical symptoms listed above are subjective, thus rely on the patient to describe and self-report them to the caregiver.

Nociceptive pain is defined as “pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors” (International Association for the Study of Pain, 2012). This definition is meant to contrast with the definition of neuropathic pain, in that nociceptive pain involves damage to a normal functioning nervous system, and neuropathic pain arises from damage to an abnormally functioning nervous system (International Association for the Study of Pain, 2012).

Chronic pain is defined as “a persistent pain that is not amenable to treatments based upon specific remedies or to the routine methods of pain control” (International Association for the Study of Pain, 2012). Chronic pain is a common, persistent, life altering feature of neuropathic pain that greatly impacts quality of life (Erdemoglu & Koc, 2013). Multiple Myeloma is a disease of the older population, with the average age of diagnosis being 66 years old (Rajkumar & Kyle, 2005). There is no consensus on whether older people experience chronic pain any differently than younger people (Taverner, 2005). What is critical in managing patients care is patients' ability to self-report their painful symptoms coupled with regular monitoring by healthcare professionals, and action must be taken quickly to prevent neuropathic pain from progressing (Richardson et al., 2012).

Peripheral neuropathy is complex in that it encompasses all three of the definitions above. In terms of neuropathic pain, PN arises from pre-existing damage to the nervous system caused by other diseases such as diabetes, and by myeloma itself. Further complicating neuropathic pain is the addition of nociceptive pain, in that further damage can occur from the medications used to treat the myeloma. Consequently, PN can become chronic, with up to one third of myeloma patients experiencing chronic PN (Richardson, Sonneveld, et al., 2009).

1.2.2. Bortezomib-Induced Peripheral Neuropathy

Bortezomib-induced peripheral neuropathy (BiPN) is reversible in three-quarters of cases with either dose reductions, or stoppages, but this can affect efficacy and response rates to bortezomib (Delforge et al., 2010). Recovery from BiPN is possible for roughly 70% of patients, but is slow, taking up to 48 weeks (Delforge et al., 2010; Richardson, Sonneveld, et al., 2009; Tariman et al., 2008). Given that only 70% recover from BiPN, more than one-quarter of patients have this debilitating side-effect for the rest of their lives (Delforge et al., 2010; Richardson, Sonneveld, et al., 2009; Tariman et al., 2008). Treatment of PN consists of narcotics, anti-depressants and anti-epileptics, and rarely topical numbing agents like lidocaine (Richardson et al., 2012). However, these medications treat the symptoms of PN, while possibly adding more side effects associated with the narcotics and anti-depressants (Tariman et al., 2008). Furthermore, research shows little to no efficacy of using these medications for chemotherapy-induced peripheral neuropathy (Gewandter et al., 2014; Gilron et al.; Hammack et al., 2002; Kautio, Haanpää, Saarto, & Kalso, 2008; O'Connor & Dworkin, 2009; Rao et al., 2007). There is anecdotal evidence of patients using prophylactic hydration and vitamins such as folic acid and vitamin B to help the myelin sheath re-grow which may prevent PN (Richardson et al., 2012; Tariman et al., 2008; Visovsky, Collins, Abbott, Aschenbrenner, & Hart, 2007). Management of BiPN should consist of prevention strategies such as assessment prior to each dose given, dose reductions, or early stoppages of bortezomib treatment (Berkowitz & Walker, 2012; Delforge et al., 2010; Richardson et al., 2012; Tariman et al., 2008; Tofthagen, Visovsky, & Hopgood, 2013). Crucially, it is important to manage this side-effect while maintaining response to the drug and good quality of life.

1.2.3. Intravenous versus Subcutaneous Bortezomib

In a multi-center study based in Italy, Bringhen et al. (2010) studied the impact of a once weekly treatment instead of a twice-weekly treatment regimen. They found that when bortezomib was given intravenously in a once weekly dosing schedule instead of twice weekly dosing, patients' remission rate and duration of remission were still the same but PN was decreased in the once weekly group from 28% to 8% (Bringhen et al., 2010). A subsequent study by Reeder et al. (2010) also found that once weekly versus twice weekly bortezomib produced similar remission rates (Overall Response Rates = 88% vs 93% in twice weekly vs once weekly respectively), and all severe side effects (Grade 3 and 4) were reduced in the once weekly regimen. In particular, Grade 3 PN was reduced from 6% to 0%. Of note, the once weekly bortezomib dose was increased to 1.5mg/m^2 instead of the standard 1.3mg/m^2 dosing. This dosing and frequency regimen protocol was later adopted in many Canadian institutions, including British Columbia in December, 2009 (BC Cancer Agency, 2013). According to a study published in 2011 (Moreau et al., 2011), the experimental administration of bortezomib subcutaneously (SC) versus standard administration route, intravenously (IV) demonstrated that overall remission rates were 42% after 4 cycles and 52% after 8 cycles for both SC and IV cohorts. The SC cohort showed a significant reduction in peripheral neuropathy (35% SC vs 49% IV), (Moreau et al., 2011). These were important findings which led British Columbia Cancer Agency (BCCA) to switch administration routes of bortezomib from IV to SC in July 2011 (BC Cancer Agency, 2013).

1.2.4. Bortezomib-Related Skin Reactions

Localised injection site reactions (ISR's) have also been studied in subcutaneously administered bortezomib. An ISR is defined as "a disorder characterized by an intense adverse

reaction (usually immunologic) developing at the site of an injection" (United States-National Institutes of Health, 2009). ISR's are assessed by both nurses and doctors and graded for severity. A grade 1 ISR is defined as "Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)"; a grade two ISR is defined as "Pain; lipodystrophy; edema; phlebitis"; a grade 3 ISR is defined as "Ulceration or necrosis; severe tissue damage; operative intervention indicated"; a grade 4 ISR is defined as "Life-threatening consequences; urgent intervention indicated" and a grade 5 ISR is defined as 'death' (United States-National Institutes of Health, 2009). See also Appendix A.

Bortezomib-related ISR's have been shown to be rare and mild. The most common reaction was erythema surrounding the injection site (84 of 147 or 57% of patients) which on average, disappeared within 6 days. Of the 84 patients who reported ISR's, two patients reported severe ISR's, and nine patients reported one or more ISR's, and finally only two patients needed dose modification or doses held due to the ISR. However, in this trial, only the thighs and abdomen were used as sites for SC administration of the bortezomib. Similarly, in three studies carried out in Japan, only the thighs and abdomen were used as injection sites (Hoy, 2013; Kamimura et al., 2012; Kamimura et al., 2013). It was not reported in any of the published studies why the researchers only used the thighs and abdomen. Therefore, as far as the author is aware there are currently no data available reporting on the safety of using the back of the arm as an injection site for bortezomib subcutaneous injection. A search through the databases only retrieved studies related to subcutaneously administered drugs such as insulin and heparin, and azacitidine (Annersten & Willman, 2005; Fahs & Kinney, 1991; Frid et al., 2010). In these studies, between 30-35% had ISRs when the back of the arm was used, and this was not

statistically different from ISR's in the thighs and abdomen. Therefore, evidence is needed to examine the safety of using the back of the arm for bortezomib SC injections.

1.3 Problem Statement

Peripheral neuropathy is a significant side effect that needs to be managed while patients who have multiple myeloma are on bortezomib treatment. It is important to balance the necessity of delivering the maximum recommended dose of bortezomib without increasing the incidence or severity of PN. If this balance is achieved, patients will be able to stay on bortezomib treatment longer and/or at higher doses. Staying on the treatment longer and at higher doses may optimize their remission rate and duration of remission (Lonial, 2011; Moreau et al., 2011). Furthermore, several studies comparing once weekly and twice weekly bortezomib dosing regimens, as well as IV administered bortezomib to SC administered bortezomib found that remission rates and duration of remission were similar, and BiPN was significantly reduced (Bringhen et al., 2010; Moreau et al., 2008; Moreau et al., 2011; Reeder et al., 2010).

Injection site reactions (ISR's) related to SC administered bortezomib have been shown to be common (57%) but mild (Grade 1 and 2) in two European trials (Moreau et al., 2008; Moreau et al., 2011). Two severe site reactions were reported and only nine subjects out of 147 (6%) needed a dose delay or stoppage of their bortezomib due to an ISR (Moreau et al., 2011). In July 2011, the protocol for administering bortezomib in BC was switched from IV to SC. Furthermore, nurses started injecting bortezomib subcutaneously, using the abdomen and back of the arm as primary sites, and rarely using the thigh as an injection site. They used the back of the arm based on experience with other cytotoxic agents routinely injected there, for example azacitidine in myelodysplastic patients (Demakos & Linebaugh, 2005).

This study examined the incidence of peripheral neuropathy between IV and SC administered bortezomib, as well as incidence and severity of localised injection site reactions from subcutaneously administered bortezomib in a Canadian context.

1.4 Purpose

The purpose of this study was twofold: 1) To compare the incidence rates of peripheral neuropathy between bortezomib injected intravenously versus subcutaneously; and 2) To report incidence rates of localised injection site skin reactions in the thigh, abdomen and back of the arm.

1.5 Research Questions and Hypotheses

There are two research questions and associated hypotheses for this study:

Research question 1: What is the incidence of peripheral neuropathy in the patients who received Bortezomib IV (prior to July 2011) compared with patients who received bortezomib SC (post: between July 2011 and June 1, 2013)?

H_A Peripheral neuropathy will occur less frequently in the SC cohort in comparison to the IV cohort.

Research question 2a: What is the incidence of localised injection site skin reactions in the SC group?

H_A Localised injection site skin reactions overall will be low and mild.

Research question 2b: What is the incidence of localised injection site skin reactions in the back of the arm compared to the abdomen and thigh?

H_A Localised injection site skin reactions in the back of the arm will be less frequent than the abdomen and thigh.

1.6 Summary

Bortezomib is a novel agent used for treating multiple myeloma. Peripheral neuropathy is a dose-limiting side effect of bortezomib, but PN appears to occur less frequently when the medication is administered subcutaneously instead of via the traditional route of intravenously. In 2011 British Columbian hospitals switched from administering bortezomib from IV to SC. Nurses who administer bortezomib via SC route use the back of the arm, but no research reporting on the frequency of injection site reactions in the back of the arm was identified. This study will provide evidence about PN and injection site reactions in the Canadian context and contribute to the growing body of literature on this topic.

Chapter 2: Literature Review

2.1 Introduction

In this chapter a summary of the literature pertaining to the use of bortezomib for the treatment of multiple myeloma (MM) is presented. The pathophysiology, incidence, prevalence and etiology of MM, peripheral neuropathy (PN) and injection site reactions (ISR's) for bortezomib are also presented in this chapter.

This study focuses on data relevant to once weekly and twice weekly dose regimens of bortezomib, intravenous bortezomib in comparison to subcutaneous bortezomib, as well as the side effect PN, and ISR's related to subcutaneous administration of bortezomib. Historically, it is important to note how bortezomib treatment has changed over the years in order to improve remission rates and tolerability in relation to peripheral neuropathy, therefore, these have been explored and summarized in this chapter.

2.2 Methods: Databases Searched

The literature review was conducted first using Medline via EBSCO for a search of articles using the Boolean/phrase search words: bortezomib and multiple myeloma. This combination of search words retrieved 2,575 articles, therefore subject terms were restricted to: bortezomib monotherapy, Multiple Myeloma and Newly Diagnosed with the Limiter, English Language which came up with three articles, of which two did not meet inclusion criteria as they were studies on the effect bortezomib had on osteoclast activity which is beyond the scope of this study. The study by Ludwig et al. (2005) summarized the pivotal trials for bortezomib which were SUMMIT, CREST, and APEX. A search through the reference list of this article provided and additional four relevant articles. The next search conducted used the search words: bortezomib, Multiple Myeloma, and relapsed refractory, with the limiters English Language and

academic journals only. This retrieved six articles, of which one was excluded because the researchers studied acute leukemia (Cortes et al., 2004).

Using Medline via EBSCO for a search of articles using the boolean/phrase mode with the limiters English language and academic journals only and the words multiple myeloma and bortezomib and subcutaneous and peripheral neuropathy, retrieved fourteen articles, of which nine were retained. The other five were excluded due to a number of reasons: one was only available in Chinese (Yuan et al., 2011), two were related to amyloidosis (Gertz, 2013; Shah et al., 2013), one was focused on a different drug called carlfilzomib (Nooka, Gleason, Casbourne, & Lonial, 2013), and another was investigating the effects of an additional adjuvent therapy to decrease bortezomib induced peripheral neuropathy (Tsukaguchi, Shibano, Matsuura, & Mukai, 2013).

The last Medline via EBSCO search used the boolean phrase: Multiple Myeloma, bortezomib induced peripheral neuropathy, and the limiters English Language and journals only. This retrieved twenty-nine articles, all of which were included in the review.

Next CINAHL was searched using the boolean/phrase mode with no limiters: multiple myeloma and peripheral neuropathy and bortezomib, thirty-nine articles were retrieved. When subcutaneous was added to the search, no results were identified. Of the thirty-nine articles, thirty-seven were relevant, and were the same articles previously retrieved from Medline.

2.3 Multiple Myeloma: Pathophysiology

Multiple myeloma (MM) is a hematological malignancy of the plasma cells that affects roughly five in 100,000 people, and accounts for approximately 10% of all hematological malignancies (Delforge, 2011). The average age of diagnosis is 66 years old, making this a disease most often seen in older adults (van Rhee et al., 2010). MM is often referred to as a

cancer of the bone marrow, since this is where the abnormal plasma cells originate. The stem cells in the bone marrow produce the abnormal B-Lymphocytes, which then give rise to malignant plasma cells (van Rhee et al., 2010). These plasma cells are responsible for making immunoglobulins. Malignant plasma cells start a catastrophic chain reaction in the body by invading the bone marrow space and crowding out other normal cells, thus disrupting other normal cell lines which leads to anemia, thrombocytopenia, and neutropenia, with the latter further disrupting immune function (van Rhee et al., 2010). Malignant plasma cells also invade and destroy healthy bone, leading to skeletal fractures (van Rhee et al., 2010). They also produce a monoclonal protein (immunoglobulin of a single type) in excess that is released into the blood and secreted in the urine, leading to hyperviscosity, stroke, heart attack and kidney failure (van Rhee et al., 2010). Although MM is incurable, early diagnosis and treatment with novel agents such as proteosome inhibitors and immunomodulators can extend patients' lives to up to ten years after diagnosis (Kumar et al., 2008; San-Miguel et al., 2013).

2.3.1 **Multiple Myeloma: Incidence & Prevalence**

Internationally, the rates of diagnoses of multiple myeloma have risen over the last thirty years in African American males, Canadians in British Columbia and Quebec, Finland, Denmark, United Kingdom, Spain, and Japan (Osaka and Miyagi) (Baris, 2005). The highest rates are among African Americans, at seven to eight per 100,000 new diagnoses per year, and the lowest rates are in China's Shanghai province and are less than one per 100,000 per year (Baris, 2005).

In Canada, there are approximately 2,500 new diagnoses of MM each year (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2013). Of those 2,500 cases, approximately 1,400 are male and 1,100 are female. It is unknown why more males are

diagnosed with this disease than females (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2013).

2.3.2 **Multiple Myeloma: Etiology**

The etiology of multiple myeloma is unknown. There are many small studies that have examined the correlation between certain factors and the risk of developing MM. Radiation is one factor that has been studied as a possible etiology of MM, including higher and lower doses of exposure (Baris, 2005). There are data on Japanese atomic bomb survivors from the 1950's that show a higher risk of developing MM associated with ionizing radiation, however the number of cases were small, therefore further data are needed to determine the true association (Baris, 2005). Other studies that examined X-ray exposure, environmental radiation (solar and geological), residential (living close to a nuclear power plant), and occupational (radiologists and workers in nuclear power plants) also reported inconsistent results of association, thus the true risk is still unknown (Baris, 2005).

Occupational groups that have higher risk for developing MM include farmers (possibly due to exposure to pesticides and fuels), metal workers, forestry workers, rubber workers, and petroleum workers (Baris, 2005). Other occupational groups that have been studied include "nurses, pharmacists and dieticians, science technicians, childcare workers, female workers exposed to silica, cosmetologists and haircutters, railway construction and repair workers, roofers, meat cutters, tailors, and firefighters" (Baris, 2005). The findings of the latter occupational groups were inconsistent, thus it is still unknown if these occupations pose a higher risk of developing MM (Baris, 2005).

Many chemicals have been studied for their risk associated with multiple myeloma, but the findings have been inconsistent. Chemicals that have been studied include benzenes,

solvents, dioxin, agent orange, asbestos, and chlorine. Most of the published studies have had small cohorts and small clusters of populations with small, but not statistically significant effect sizes (Baris, 2005). Interestingly, cigarette smoking and alcohol consumption have not been clearly linked to multiple myeloma (Baris, 2005).

Other factors that may have some effect on increased risk for MM include: hair dyes (in particular, darker hair dyes and use for 20 years or more), obesity, diet - in particular consumption of liver and dairy products (vitamin C, D, calcium, fish, whole grains and cruciferous vegetables decrease the risk), and lower socioeconomic status. Moreover, one study reported that certain medications such as laxatives, erythromycin, and mineral oil had an increased effect in females developing MM, but not males (Baris, 2005).

Some medical conditions can increase the risk of developing MM, like chronic immune stimulation (i. e., rheumatoid arthritis) and notably monoclonal gammopathy of undetermined significance (MGUS) (Baris, 2005; Kyle, 1987; Kyle & Rajkumar, 2008; Kyle et al., 2002; Landgren et al., 2008). In a study undertaken in the United States, it was found that MGUS consistently preceded a diagnosis of multiple myeloma in all subjects studied (n=71) (Landgren et al., 2008). In a long-term follow-up study, Kyle et al. (2002) found that "the risk of MGUS developing into multiple myeloma was approximately 1% per year". Therefore, although the risk of MGUS progressing into multiple myeloma is small (1% per year), all patients with a confirmed diagnosis of multiple myeloma likely had MGUS preceding their diagnosis. This means that if a patient is diagnosed with MGUS, they should be monitored for signs of MM (Kyle et al., 2002; Landgren et al., 2008). Although there is no evidence to suggest that early diagnosis of MM achieved via monitoring MGUS patients improves MM survival, Kyle et al. (2002) suggest that it is important to monitor for MM in patients with MGUS in order to prevent

complications from the disease, such as renal failure or fractures. “Averting these events would improve the patient’s quality of life and reduce the cost of long-term dialysis or surgical intervention for skeletal complications” (Kyle et al., 2002).

2.4 Diagnosing Multiple Myeloma

2.4.1 Types of Myeloma: Immunoglobulins and Free Light Chains

Multiple myeloma is most commonly diagnosed in patients older than 66 years old, with presenting symptoms of fatigue, recurrent infections and bone pain (Kyle, 2001; Rajkumar & Kyle, 2005). Patients frequently also have skeletal abnormalities called lytic lesions and/or bone fractures (seen in 80% of patients), anemia (seen in 70% of patients), elevated serum creatinine (seen in 50% of patients), and hypercalcemia (seen in 25% of patients) (Rajkumar & Kyle, 2005).

Table 2.1 Diagnostic Criteria for Symptomatic Myeloma

Characteristic	
1) Monoclonal plasma cells in bone marrow ≥ 10%	
2) Monoclonal protein in serum and/or urine	
3) One or more of the following CRAB Criteria:	C - calcium elevation (<10.5 mg/L) R - renal dysfunction (creatinine < 2mg/dL) A - anemia (Hgb < 100g/L or 20g < normal) B - bone disease (lytic lesions or osteoporosis)

Multiple myeloma is further classified by the immunoglobulin subtype, cytogenetics and stage (Kyle & Vincent Rajkumar, 2006). The subtypes of multiple myeloma are differentiated by the monoclonal immunoglobulin that is being produced in excess (called monoclonal protein, m-protein, para-protein or m-spike), and characterized by whether the protein is a heavy or light chain (Kyle & Vincent Rajkumar, 2006). Roughly 80% of patients with myeloma will have plasma cells that produce both the heavy chain and light chain leaving 20% expressing a light

chain only (Rajkumar & Kyle, 2005). The light chains are further characterized as kappa or lambda (van Rhee et al., 2010). Kappa or lambda light chains are "polypeptides that are synthesized by plasma cells, which unite with heavy chains to create classes of immunoglobulins" (Tariman, 2010). Of the heavy chains, the most common subtypes are Immunoglobulin G or IGG, and Immunoglobulin A or IGA. Immunoglobulin D or IGD and Immunoglobulin M or IGM are the most rare (van Rhee et al., 2010). Rarely the myeloma cell may not express either the heavy chain or light chain. This type of MM is called non-secretory myeloma. Some patients will secrete only a small amount of light chains. These patients can be followed with a test called the serum free light chain test (Kyle & Vincent Rajkumar, 2006).

2.4.2 **Cytogenetics of Myeloma**

More recently, it has become apparent that cytogenetics play an important role in prognosis, more so than the sub-type of myeloma (Bladé et al., 2008). This is a very brief overview of the cytogenetics of multiple myeloma, as this area of study is extremely complex as it delves into the micro-environment of the disease. However, due to its important role in treatment options and prognosis, it is summarised briefly here.

Cytogenetic analysis has shown that chromosomal abnormalities more accurately determine prognosis and in some cases can dictate what type of treatment a patient should receive (Bladé et al., 2008; Fonseca et al., 2004). Cytogenetic analysis is done by taking a sample of bone marrow from the patient, and analysing cells for abnormalities such as deletions or translocations of chromosomes. A deletion is when a piece of the gene is missing, a translocation is when a piece of one gene breaks off and fuses to another gene. The highest risk cytogenetic prognostic indicators in MM known today are translocation 4;14, translocation

14;16, deletion 13q, and deletion 17p (Fonseca et al., 2004; Jevremovic & Morice, 2014). These abnormal cytogenetics are seen in roughly 50% - 70% of MM patients (Fonseca et al., 2004).

Cytogenetics are an important prognostic indicator, but will also play a role in treatment options. As research has evolved over the years, new drugs used to target specific cytogenetic abnormalities have emerged, and bortezomib is just one of many being studied. In a study done by researchers in France, bortezomib showed some effect on the cytogenetic abnormality translocation 4;14 but not deletion 17p (Avet-Loiseau et al., 2010).

2.4.3 **Multiple Myeloma Staging Systems**

The stage of multiple myeloma is established using one of two different staging systems: 1) Durie-Salmon Staging System and 2) International Staging System. These staging systems are important to prognosticate a patient diagnosed with myeloma. A patient's survival rate is based on these staging systems, and is estimated in years from their diagnosis (Tariman, 2010). However, with the introduction of novel agents and further research being done in cytogenetics of multiple myeloma, both of these staging systems have been shown to have limitations in light of these new developments, but are still used clinically as a guideline (Bladé et al., 2008).

The Durie-Salmon staging system was developed in 1975 by Drs. Durie and Salmon and uses the patient's m-protein level, hemoglobin, blood calcium level, and number of lytic lesions or bone disease (Bladé et al., 2008) to determine the patient's stage of disease. It is further classified into a sub-group A or B which is determined by the level of renal impairment defined by the serum creatinine levels (See Appendix B) (Bladé et al., 2008). This staging system has been used by physicians for over 30 years, but this mathematical model has been shown to be inefficient as a prognostic tool in light of recent technological advancements such as cytogenetics and genomic sequencing (Bladé et al., 2008; San-Miguel et al., 2013).

The second and newer International Staging System was developed in 2004 and uses only serum albumin, and the serum tumor marker beta 2 microglobulin in staging (See Appendix C). This staging system was determined to be a more efficient prognostic indicator at diagnosis (Bladé et al., 2008) and is currently used routinely. The beta 2 microglobulin level alone was more accurate in showing myeloma tumor burden than the mathematical model proposed by Drs. Durie and Salmon (San-Miguel et al., 2013). However, newer classification systems are being developed that take into consideration other aspects of this disease such as cytogenetics (gene markers showing tumor burden and proliferation), and molecular classifications, but these have yet to go through rigorous validation studies (San-Miguel et al., 2013). The main area of discussion in the literature is to find a classification system that accurately defines a "high-risk" MM group, that should be treated differently than the "standard-risk" group (San-Miguel et al., 2013).

Neither staging systems are as useful after diagnosis, and most patients are diagnosed when they are already stage 2 or worse, using either staging system (San-Miguel et al., 2013). This is because patients usually become symptomatic at stage 2, which manifests as development of recurrent infections or skeletal fractures, which causes the patient to seek medical attention (Tariman, 2010). After initial diagnosis, it is difficult to "re-stage" a patient with multiple myeloma since there is no validated method for re-staging. Re-staging is important to determine if the patient has any cytogenetic changes which would change them from a "standard-risk" to a "high-risk" disease. Patients with high-risk multiple myeloma may need different treatment than standard-risk disease (San-Miguel et al., 2013).

2.5 Treatment of Multiple Myeloma

2.5.1 Historical Summary

The first documented case of multiple myeloma was in 1844 (Kyle & Rajkumar, 2008). There were no conventional treatment options at that time, so physicians used steel, quinine, rhubarb and orange peel to treat it (Kyle & Rajkumar, 2008). Patients during this era lived less than one year from the time they were diagnosed until death (Kumar et al., 2008). More than one hundred years passed (1958) before patients were treated with an alkylator called Melphalan, a type of chemotherapy. This was followed by the invention of corticosteroids (prednisone and dexamethasone) in the 1960's. Patients with MM who were diagnosed during the era of melphalan and corticosteroids lived on average three years or less (Gregory, Richards, & Malpas, 1992). It was another twenty to thirty years until autologous stem cell transplants were discovered and used as a treatment (Kyle & Rajkumar, 2008). An autologous stem cell transplant is a transplant of bone marrow or peripheral blood stem cells, harvested from the patient and then re-infused after they have received a conditioning regimen of chemotherapy which effectively kills their immune system. The stem cells are used to "rescue" the patient and resume normal blood counts. The addition of stem-cell transplant to alkylators and corticosteroids further prolonged myeloma patients' lives up to five years (Attal et al., 1996).

And finally, the discovery of the novel agents: immunomodulators (thalidomide and lenalidomide), and the proteosome inhibitor, bortezomib, occurred between 1999-2002 (Kyle & Rajkumar, 2008). Since early 2000, many more molecules have been discovered and researched in treating multiple myeloma, some with success, and some without. Thus, corticosteroids, chemotherapy, stem cell transplant and novel agents such as lenalidomide and bortezomib, are widely used today. Overall survival since the introduction of novel agents has steadily risen and

is now over ten years for patients with standard risk disease who receive a stem cell transplant (San-Miguel et al., 2013).

This next section will focus on the literature pertaining to bortezomib, how it is used in treating multiple myeloma, peripheral neuropathy, and localised injection site skin reactions from subcutaneous administration.

2.6 Bortezomib: Biology and Treatment Regimens

Bortezomib is the first in its class of proteosome inhibitors, and was approved by the US Food and Drug Administration (US-FDA) in 2003 for the treatment of relapsed and refractory multiple myeloma (Delforge, 2011). Health Canada approved bortezomib in January 2005 (Health Canada, 2005). The proteosome is a key intracellular structure found in the cytoplasm and nucleus of eukaryotic cells that degrades targeted intracellular proteins (Delforge, 2011). Malignant plasma cells depend on this particular pathway for tumor growth, therefore proteosome inhibition is one way to induce apoptosis or cell death (Delforge, 2011). Bortezomib is a reversible proteosome inhibitor, which induces cell death in malignant plasma cells, but as a result of other downstream effects can also target malignant plasma cells in the bone marrow micro-environment (Delforge, 2011). Recent studies have also shown that bortezomib can stimulate osteoblast activity (osteoblasts build bone) through another pathway, thus bortezomib can reduce fractures and even promote healing of lytic lesions for patients with MM (Delforge, 2011).

Studies have shown that bortezomib exhibits a greater “malignant cell kill” when combined with other anti-neoplastic agents like chemotherapy (melphalan and cyclophosphamide) and corticosteroids (dexamethasone and prednisone) (de la Rubia & Roig, 2011; Delforge, 2011; Jagannath et al., 2004; Richardson et al., 2012). For this reason,

bortezomib is often administered in combination regimens. Recent studies have shown that bortezomib in combination can be given as the initial treatment (for patients with a new diagnosis), including pre-stem cell transplant, and as subsequent treatments (for patients who have relapsed or who have refractory MM) (de la Rubia & Roig, 2011; Delforge, 2011; Richardson et al., 2012). Thus, bortezomib is widely used for the treatment of patients with multiple myeloma throughout various stages of the disease.

The most common side effects of bortezomib are asthenia, gastrointestinal disturbances (nausea, vomiting, diarrhea), peripheral neuropathy, thrombocytopenia and neutropenia (Curran & McKeage, 2009). Peripheral neuropathy is considered the most debilitating side effect and can impact both quality of life and treatment of the disease (Tariman et al., 2008; Tofthagen, 2010). In a recent unpublished study presented at the annual Myeloma Canada conference in Winnipeg on September 29th, 2012, the importance of quality of life from the patient perspective was reported (S. Meisles, personal communication, 2012). Their findings suggest that because advancement of treatments has extended patients' lives, making MM a type of 'chronic cancer', patients felt it was extremely important to consider the "long term impact of disease symptoms and increased need to manage treatment tolerability" (S. Meisles, personal communication, 2012).

Peripheral neuropathy (PN) is present in approximately 20% of MM patients at initial diagnosis, and approximately 80% of MM patients after subsequent treatments (Richardson et al., 2012). PN is higher among MM patients after subsequent treatments because over time they are treated with many medications that cause PN, such as bortezomib, thalidomide and melphalan. Pre-existing neuropathy in untreated/newly diagnosed MM patients is often a result of the disease itself (increased abnormal proteins), disease-related weight loss, metabolic or toxic

factors (vitamin B deficiency), and other co-morbidities like amyloidosis, diabetes, and nerve impingement due to fractures that were caused by the disease (Tariman et al., 2008). Therefore it is imperative to assess for and manage any peripheral neuropathy symptoms immediately at baseline (new diagnosis) and throughout all treatment regimens in order to detect symptoms early and modify treatment with dose reductions and stoppages (Lanzani et al., 2008; Tariman et al., 2008).

2.6.1 **Bortezomib-Induced Peripheral Neuropathy**

As stated earlier, bortezomib-induced peripheral neuropathy (BiPN) is usually sensory in nature, characterized by numbness and tingling, burning or frozen feeling, and/or parasthesias (prickling feeling) in the extremities, and increased sensitivity (Tariman et al., 2008). More serious symptoms of neuropathic pain include shooting pain in the legs, severe cramping in the calves or thighs, and joint and muscle pain (Tariman et al., 2008). Although rare, autonomic neuropathy has also been seen in patients with MM receiving bortezomib, with symptoms such as labile blood pressure, hypotension, bladder and bowel paralysis, and breathing problems (Richardson et al., 2012; Tariman et al., 2008). However, given that MM primarily affects elderly patients, a distinct correlation between autonomic events and bortezomib has been difficult to ascertain, as these symptoms are often seen in the elderly as a result of aging (Delforge et al., 2010).

Bortezomib induced peripheral neuropathy (BiPN) usually manifests symmetrically as numbness and tingling or burning sensation to bottoms of the feet and sometimes fingertips, and can be accompanied by weakness (Richardson et al., 2006). Over the course of weeks to months BiPN slowly moves up the calves and to the thighs if bortezomib treatment is not dose reduced or stopped (Richardson et al., 2012). Painful neuropathy is difficult to treat, and can require other

medications to alleviate painful symptoms, which do not work well in this population and come with their own side effects. It can also lead to insomnia and increased fatigue, which then impacts patients' quality of life (Richardson et al., 2012).Treatment of BiPN will be discussed in further detail in the following section.

2.6.2 **Pathophysiology of Bortezomib-Induced PN**

The pathophysiology of bortezomib induced PN (BiPN) is still unknown, but is thought to occur in two ways. One possible mechanism is through damage to the sensory nerve bodies of the dorsal root ganglia. The dorsal root ganglia are vulnerable due to their presence outside of the spinal cord and thus can be affected by chemotherapies, as well as by compression fractures - another common side effect of MM (Delforge et al., 2010). The other possible mechanism is by damage to afferent and efferent axons which are nerve cells going to and from the spinal cord or the central nervous system (Delforge et al., 2010). The theory among myeloma researchers is that since these nerve cells are myelinated, chemotherapy can attack this myelin sheath, resulting in damage and thus PN symptoms. It is also thought that motor neuropathies are more rare in BiPN, perhaps because those nerve cells within the spinal cord are more heavily myelinated, and their cell bodies are protected within the spinal cord (Delforge et al., 2010). Nerve cells (axons) can repair themselves, approximately 2 to 5mm per day, therefore nerve healing is very slow and can take up to one year (Delforge et al., 2010; Schmidt & Baier Leach, 2003). During nerve regeneration, another devastating feature of PN is allodynia and hyperesthesia. Allodynia is defined as “pain due to a stimulus that does not normally provoke pain” and hyperesthesia is defined as “increased sensitivity to stimulus, excluding the special senses” (International Association for the Study of Pain, 2012). Symptoms of allodynia and hyperesthesia are a result of excessive nerve regeneration, which is a common problem with nerve damage (Schmidt &

Baier Leach, 2003; Yiu & He, 2006). Thus, while MM patients with BiPN can recover, roughly 30% never recover completely, and this complicates further treatments with neuro-toxic medications, as well as affects their quality of life (Delforge et al., 2010; Tariman et al., 2008; Tofthagen, 2010).

In older studies, BiPN was thought to be cumulative in nature, i.e., higher cumulative doses of bortezomib leads to higher incidence of PN. However, now that BiPN has been studied in re-treatment (patients received bortezomib as their initial treatment, and then at relapse were again given a bortezomib treatment regimen) bortezomib was not found to increase severity or incidence of PN, which suggests that BiPN may not be cumulative in nature (Delforge et al., 2010). Richardson et al.,(2005, 2009) found that incidence of PN seemed to plateau around cycle 5, or once the patient had received about 30mg/m^2 of bortezomib. That is, if a patient developed PN prior to cycle 5, their PN did not get any worse after cycle 5. And likewise, if the patient did not develop PN prior to cycle 5, they did not suddenly develop PN after cycle 5. This was based on twice weekly, intravenously administered bortezomib and for patients who did not have PN at the start of their treatment.

Reversibility of BiPN is possible with dose stoppages and dose reductions in approximately 70% of patients, which is different than neuropathies caused by other neuro-toxic drugs like thalidomide, and other disease related neuropathies like diabetes where PN is not reversible (Delforge et al., 2010; Richardson et al., 2005; Richardson, Sonneveld, et al., 2009).

2.6.3 **Risk Factors of Bortezomib-Induced PN**

Risk factors of bortezomib-induced PN (BiPN) include pre-existing neuropathy, history of diabetes, vitamin deficiencies, alcohol abuse and viral infections - herpes zoster or shingles in particular (Berkowitz & Walker, 2012; Delforge et al., 2010; Lanzani et al., 2008). Age has not

been found to be associated with BiPN, according to a subset analysis which compared bortezomib in the newly diagnosed patients, with or without melphalan and prednisone (Delforge et al., 2010; Dimopoulos et al., 2011). In that study, of those who developed PN, comparing age less than 75 years old to greater than or equal to 75 years old, Dimopoulos et al. (2011) reported there was no statistically significant difference between the two age groups (46% versus 47% respectively). Pre-existing neuropathy has been associated with para-proteinemias, and recent studies using newer and more sensitive screening tests, have found that between 11-54% of MM patients have peripheral neuropathy at diagnosis (Chaudhry, Cornblath, Polydefkis, Ferguson, & Borrello, 2008; Delforge, 2011; Richardson et al., 2012; Richardson, Xie, et al., 2009). Baseline screening and neurological monitoring in this population is imperative to document any baseline peripheral neuropathy because these patients will be receiving treatments that can increase their PN symptoms over the years to come (Velasco et al., 2010).

2.6.4 **Prevention of Bortezomib-Induced PN**

The primary way to manage BiPN for patients with multiple myeloma is prevention. Assessment should be done at diagnosis, and prior to every dose of bortezomib (Lanzani et al., 2008; Tariman et al., 2008). Assessment tools using a number scale from zero to five have been developed which ask the patient to quantify their symptoms of PN. Questions include any numbness in extremities, discomfort and/or pain, joint or muscle cramps, hearing problems, and trouble walking (Tariman et al., 2008) (see Appendix D - Neurotoxicity Assessment Tool). Grading of peripheral neuropathy is done by using the National Cancer Institute Common Terminology Criteria for Adverse Events (see Appendix E). Nurses assess the patient for symptoms of PN prior to administering each dose of bortezomib by using either the above tool, or tools developed by their own institutions. They then relay this information to the physician.

The physician will grade the neuropathy (if present), and use another tool found in the product monograph to decide whether to proceed with dosing, reduce the dose or withhold treatment (Janssen Inc., 2013) (see Appendix F).

Two strategies have emerged that may prevent bortezomib induced PN or minimize the grade of this toxicity. The first is to change the schedule of dosing from twice weekly to a once weekly regimen (Bringhen et al., 2010; Delforge et al., 2010; Reeder et al., 2010). This was the first strategy, published in 2010, that showed remission rates and duration of remission were maintained and toxicity of PN was reduced when bortezomib was given intravenously once weekly instead of twice weekly (Grade 3/4 PN: 8% vs 28% respectively) (Bringhen et al., 2010).

The second strategy is to change administration of bortezomib from intravenous to subcutaneous. In 2008, Moreau et al. published a pilot study showing that efficacy and safety profiles of bortezomib administered subcutaneously was comparable to bortezomib administered intravenously (Moreau et al., 2008). This encouraged the authors to do a multi-center randomized trial, published in 2011, which also showed that there was no difference in rates of remission and duration of remission between the two groups. Furthermore, PN (of any grade) was significantly reduced in the study subjects who received the medication via a subcutaneous route (38%) compared to the patients who received bortezomib intravenously (53%) (Moreau et al., 2011).

There is anecdotal evidence that some agents may prevent BiPN including: acetyl-L-carnitine, alpha lipoic acid, calcium, magnesium, glutamine, glutathione, N-acetylcysteine, oxcarbazepine, vitamins (B6, B12, and E), and Xaliproden (Berkowitz & Walker, 2012). But because rigorous studies have not been carried out, these agents are not formally recommended to patients.

2.6.5 **Treatment of Peripheral Neuropathy**

Treatment of bortezomib induced PN (BiPN) is limited, but based on literature for treatment of neuropathic pain not related to chemotherapy, physicians have adopted some of the same medications used and approved by the US-FDA. According to the guidelines developed by the International Association for the Study of Pain (IASP), Neuropathic Pain Special Interest Group (NeuroPSIG), first line treatment usually consists of seritonin-norepinephrine reuptake inhibitors (SNRis) and tricyclic antidepressants (TCAs) such as amitriptyline, anti-epileptics (gabapentin, pregabalin) and topical anesthetics (lidocaine) (Jongen, Hans, Benzon, Huygen, & Hartrick, 2014). Second line therapy according to the IASP consists of opiods (morphine, hydromorphone) and tramadol and third line therapy consists of other drugs such as different antidepressants (buproprion, citalopram) and different anti-epileptics (carbamazepine, valproic acid), as well as topical capsaicin, dextromethorpan, memantine and mexiletine just to name a few (Jongen et al., 2014). Due to funding differences in Canada, the Canadian Pain Society recommends as first-line treatment: TCAs and anti-epileptics, second line treatment: SNRis and topical lidocaine, and third line treatment: tramadol and opioids (Jongen et al., 2014).

There is limited and inconsistent data on treatments for chemotherapy-induced neuropathic pain, but there may be some rationale to extrapolate treatment options (listed above) for neuropathic pain not related to chemotherapy. Some studies have reported positive results in treatment of chemotherapy-induced PN with combination of several medications, and showed a synergistic effect with gabapentin combined with either an opioid (morphine and oxycodone), and nortriptyline (Jongen et al., 2014). Research in other chemotherapy-induced peripheral neuropathy has shown minimal to no efficacy in using these drugs (Gewandter et al., 2014; Gilron et al.; Hammack et al., 2002; Kautio et al., 2008; O'Connor & Dworkin, 2009; Rao et al.,

2007). Of note, topical lidocaine and other topical agents are rarely used for any chemotherapy-induced PN, and there are several reasons for this, 1) they are not easily available in Canada, 2) they have to be made by a pharmacist, 3) there is anecdotal evidence only in the use for chemotherapy-induced PN, although future studies are being considered (Pachman et al., 2014). Management of neuropathic pain is complicated and often patients require a trial of drugs to determine their response to the medication and side effects encountered. If the patient experiences too many side effects or the treatment simply is not working they may require switching from one drug to another (Gewandter et al., 2014; Gilron et al.; Hammack et al., 2002; Kautio et al., 2008; O'Connor & Dworkin, 2009; Rao et al., 2007). Several treatment algorithms have been proposed for the treatment of neuropathic pain, however consensus has not been reached given differing pathophysiology and symptomatology of neuropathic pain (chemotherapy-induced versus neuropathy not related to chemotherapy), as well as funding and accessibility differences among countries internationally (O'Connor & Dworkin, 2009; Pachman et al., 2014; Tofthagen et al., 2013).

Some supportive care that may help treat BiPN are acupuncture, biofeedback, massage and physical therapy (Bao, Zhang, Badros, & Lao, 2011; Berkowitz & Walker, 2012). Unfortunately, most of the evidence for these therapies, pharmacological and non-pharmacological, is anecdotal (Berkowitz & Walker, 2012; Visovsky et al., 2007). Therefore, further research is required to determine if these treatments are effective in treating bortezomib induced PN.

2.7 Injection Site Skin Reactions Related to Subcutaneous Bortezomib

Localised injection site skin reactions (ISR's) have been reported in subcutaneously administered bortezomib (Hoy, 2013; Kamimura et al., 2012; Kamimura et al., 2013; Lamm,

Drach-Schauer, Eder, & Drach, 2013; Moreau et al., 2008; Moreau et al., 2012; Ng et al., 2014). A skin reaction is characterized by redness, swelling, bruising at the site of the injection, and can range from mild to severe, with a severe reaction including necrotizing open sores (Ng et al., 2014). These skin reactions are graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4: Grade 1, tenderness with or without associated symptoms (e.g., warmth, erythema, itching); Grade 2, pain, lipodystrophy, edema, or phlebitis; Grade 3, ulceration, necrosis, severe tissue damage or any indication for operative intervention; Grade 4, life threatening consequences, requiring urgent intervention; and Grade 5, death (United States-National Institutes of Health, 2009). See also Appendix A.

According to the study done by Moreau et al. (2011), injection site reactions were reported as generally mild (erythema - 57%) and severe reactions were less common (6%) and resolved on their own within an average of 6 days (Moreau et al., 2011). In their study, only thighs and abdomen were used as sites for injection, and sites were rotated such that each site was used only once per cycle of bortezomib treatment. In their study, the treatment regimen of bortezomib consisted of twice weekly dosing.

In 2012, a retrospective study was published that looked at the rates of skin reaction in 19 subjects (Kamimura et al., 2012). The findings were similar to the study by Moreau et al. (2011); of the 19 subjects in the study by Kamimura et al., 12 developed skin reactions (68%), which manifested as erythema and resolved within 5 days on average. Moreover, only the thigh and abdomen were used as injection sites, and bortezomib treatment regimen was twice weekly dosing of bortezomib. Furthermore, Kamimura et al., (2013) reported a higher incidence of skin reactions related to bortezomib injection in the abdomen and thighs in the first cycle compared to subsequent cycles (16.3% versus 0.91%, $p < 0.001$).

A recent study published by Ng et al., (2014) reported ISR's to be 42% and mostly Grade 1 and 2, with four patients requiring a switch back to IV administration. The bortezomib was administered at a higher maximum volume (3mL's) and at a concentration of 1.0mg/mL (Ng et al., 2014). The authors reported this volume was chosen in order to prevent patients from having to receive their dose of bortezomib in two syringes, which would result in having two injections per visit. The previous studies used a maximum injection volume of 2.5mLs at a concentration of 2.5mg/mL, which reduced the need for dividing doses into two syringes. In the study by Ng et al., (2014), patients were administered bortezomib once weekly instead of twice weekly, and again only thighs and abdomen were used as sites for injection. Site injection reactions were reported as generally mild (40% Grade 1 reactions), and 4% Grade 2 (Ng et al., 2014). Thus, bortezomib administered subcutaneously in the thighs and abdomen has been shown to be very well tolerated. However, to the author's knowledge, there is currently no published data that shows whether bortezomib can be safely injected in the back of the arm. Furthermore, there is no consensus in the literature as to what is the maximum fluid volume that can be injected subcutaneously (Annersten & Willman, 2005; Demakos & Linebaugh, 2005; Fahs & Kinney, 1991; Frid et al., 2010)

2.8 Summary

Bortezomib is widely used to treat patients with MM from diagnosis to relapse. Patients with MM may be at higher risk for peripheral neuropathy due to the pathophysiology of the disease. In addition, peripheral neuropathy is a major side effect of bortezomib treatment, therefore, ways to minimize peripheral neuropathy have been studied and protocols have changed over the years accordingly. Bortezomib administered once weekly instead of twice weekly is one strategy used to prevent and/or decrease frequency of peripheral neuropathy.

Another strategy used to prevent PN is to give bortezomib subcutaneously instead of intravenously. Subcutaneously administered bortezomib has been shown to be well-tolerated and equally as efficacious for life expectancy as intravenously administered bortezomib. Injection site reactions have been reported as mild and infrequent; however, to the author's knowledge, there is currently no literature on the safety and tolerability of the back of the arm as an injection site for bortezomib. This study aimed to provide more evidence on peripheral neuropathy rates in SC vs IV bortezomib as well as the frequency of skin reactions for patients receiving the medication via SC injection.

Chapter 3: Methods

This chapter presents the research design, methods, theoretical framework, hypotheses, inclusion and exclusion criteria, sampling and data collection used in this study.

3.1 Research Design

This descriptive study employed a retrospective chart review method. The study was conducted at two large academic medical centres in British Columbia. Data from all patients with multiple myeloma who received bortezomib from January 1st, 2010 to June 1st, 2013 were extracted. The retrospective design was used in order to collect the data for the intravenous cohort, while capturing data from the changeover from IV to SC in British Columbia. Since bortezomib is no longer given IV, it was only possible to collect these data retrospectively.

3.2 Research Questions

There were two research questions and associated hypotheses for this study:

Research question 1: What is the incidence of peripheral neuropathy in patients with multiple myeloma who received Bortezomib IV (prior to July 2011) compared with patients who received bortezomib SC (between July 2011 and June 1, 2013)?

H_A Peripheral neuropathy will occur less frequently in the SC cohort in comparison to the IV cohort.

Research question 2a: What is the incidence of localised injection site skin reactions for patients with multiple myeloma who received bortezomib via a subcutaneous injection?

H_A Localised injection site skin reactions overall will be low and mild.

Research question 2b: What is the incidence of localised injection site skin reactions in the back of the arm compared to the abdomen and thigh?

H_A Localised injection site skin reactions in the back of the arm will be less frequent than the abdomen and thigh.

3.3 Theoretical Framework: Symptom Management Theory

This study used the Symptom Management Theory (SMT) model as a theoretical framework. SMT was first described in 1994 (San Francisco School of Nursing Symptom Management Faculty Group, 1994), and was later revised in 2001 by Dodd et al.. Dodd et al. (2001) proposed a model that defined the inter-relatedness of three components of symptom management: the symptom experience, symptom management strategies, and symptom outcomes. SMT builds on patient self-care models proposed by Orem (1971), and Sorofman, Tripp-Reimer, Lauer, and Martin (1990). The older models addressed only the patients' role in self-care, and thus did not address a patients' lived experience of their symptoms nor the outcomes related to their symptoms.

The first component of the SMT model is the symptom experience. The authors defined symptom as " a subjective experience reflecting changes in the biopsychosocial functioning, sensations, or cognition of an individual" (Dodd et al., 2001). Cancer patients experience a range of symptoms throughout the course of their treatment. These symptoms are self-reported to healthcare professionals, and are subjective. For example a patient may report numbness, tingling and/or burning sensation in the hands or feet while on bortezomib. This is a symptom that is not observed by the healthcare professional, but is experienced by the patient and reported to the healthcare professional. This is different from a sign which is defined as "any abnormality or disease that is detectable by the individual or others"(Dodd et al., 2001). For example anemia, which is defined as a hemoglobin level less than the lower limit of normal, can be detectable or observed with a blood test. Sometimes signs and symptoms can be in clusters, such as shortness

of breath and fatigue with anemia. They can be caused by the disease, or the treatment of the disease (e.g., radiation or chemotherapy). Quality of life and ability to participate in activities of daily living while on chemotherapy (or other treatments) can be negatively affected by signs and symptoms, and is a significant aspect of a patients' experience to address and manage.

The second component of the SMT model is symptom management strategies, which are described as to "avert, delay or minimize the symptom experience" (Humphreys et al., 2008). This can be accomplished by reducing the frequency of the symptoms, minimizing the severity of the symptoms, or relieving the distress associated with the symptom (Humphreys et al., 2008). Often it is impossible to completely eradicate symptoms without risking disease advancement, so reduction or minimizing may be the best way to promote a positive outcome for the patient.

The third component of the SMT model is outcomes. Outcomes are directly related to both of the first two components: the symptom experience and symptom management strategies (Humphreys et al., 2008). A negative experience or lack of symptom management strategy will negatively impact the outcome for the patient. Outcomes can be measured by quality of life (subjectively) and by health economics. If a symptom is being poorly managed, likely the patient will present to a clinic or hospital and be admitted which increases the costs to the healthcare system, as well as impacting the patient financially due to missed work, sick leave and loss of wages (Linder, 2010).

In this study, only the first component of SMT model was operationalized, that is, to measure the patients' symptoms experience. The symptoms measured specifically were peripheral neuropathy and injection site reactions caused by bortezomib. According to SMT, peripheral neuropathy is considered a symptom (a subjective experience) and injection site reactions are a sign (can be evaluated by a healthcare professional). These signs and symptoms

were measured using the CTCAE tool (United States-National Institutes of Health, 2009), based on physicians and nurses notes in the chart.

It has been reported that 54% of patients stated they "did not feel knowledgeable enough to manage their MM side effects", while another 38% reported "dissatisfaction with how their medical team has helped manage their side effects" (S. Meisles, personal communication, 2012). Thus, application of this model to cancer patients is important in helping nurses to understand the symptom experience and help patients manage those symptoms in order to positively affect outcomes.

3.4 Setting

The study was set in two large academic medical centres in British Columbia. As stated previously, in 2012, there were 322 British Columbians diagnosed with multiple myeloma, and 163 deaths from myeloma in the same year (BC Cancer Agency Care and Research, 2014). The British Columbia Cancer Agency (BCCA) estimated the number of diagnoses to increase to 358 by 2014, with an estimated 163 deaths in the same year. The overall 5 year survival rate was estimated at 43% (95% CI: 40.2 - 45.8%) (BC Cancer Agency Care and Research, 2014). Moreover, the five-year overall survival between 2003 and 2011 rose from 50% to 70% in patients who received a stem-cell transplant (Venner et al., 2011). Therefore, it can be determined that more than half of the patients diagnosed today are going to live at least 5 years and likely longer. This rise in survival is directly attributed to the novel agents like bortezomib and lenalidomide (Rajkumar & Kyle, 2005; Richardson et al., 2005). For newly diagnosed patients with myeloma who are eligible to receive a stem-cell transplant, funding in BC of bortezomib for up to 4 cycles pre-transplant has been granted (BC Cancer Agency, 2013). This treatment is given with an oral corticosteroid (dexamethasone) and with or without an oral

alkylating agent (cyclophosphamide) (BC Cancer Agency, 2013). For those who are not able to receive a stem-cell transplant, up to 9 cycles of bortezomib with an oral corticosteroid (prednisone) plus an oral alkylating agent (melphalan or cyclophosphamide) is standard of care (BC Cancer Agency, 2013).

For patients with relapsed MM, bortezomib re-treatment for up to 8 cycles is funded, to be administered with an oral corticosteroid (dexamethasone) with or without an oral alkylating agent (cyclophosphamide) (BC Cancer Agency, 2013).

Patients can receive up to three therapy episodes of bortezomib during their lifespan. One therapy episode is defined as one entire course of treatment of bortezomib, (i.e., the sum of the total number of cycles received), which average from three to ten cycles, equals one therapy episode. Each cycle consists of four doses of bortezomib, and length of cycle depends on whether their dosing is once weekly or twice weekly. A once weekly dosing schedule consists of 5 weeks, and patients receive bortezomib on days one, eight, fifteen, and twenty-two, followed by one week of rest (i.e., no drugs during the rest week). A twice weekly dosing schedule consists of 4 weeks, and patients receive bortezomib on days one, four, eight, and eleven, followed by one week of rest.

In December of 2009, BC Cancer Agency (BCCA) changed its protocols to give the option of once weekly dosing instead of twice weekly, and in July of 2011 the BCCA again revised the bortezomib protocols to switch to subcutaneous administration. Thus, since July 2011, most patients with MM in BC receive once weekly, subcutaneously administered bortezomib.

The prescribed starting dose of bortezomib consists of 1.5mg/m^2 for the once weekly dosing schedule, and 1.3mg/m^2 for the twice weekly dosing schedule (BC Cancer Agency,

2013). These doses can be reduced to 1.0mg/m^2 and 0.7mg/m^2 sequentially if toxicities develop. Physicians have the option to start treatment at a lower dose if the patient has unresolved toxicities from a previous treatment regimen, and can also increase the dose if such toxicities resolve during bortezomib treatment. Concentration of bortezomib used in BC centers is 1.0mg/mL and the local policy for the maximum volume for injection in one site is 2.5mLs.

3.5 Sampling Plan

3.5.1 Inclusion and Exclusion Criteria

A convenience sample of all patients with multiple myeloma who were treated with bortezomib between the dates of January 1st, 2010 to June 1st, 2013, and who were treated at two large academic medical centres in British Columbia, Canada, were reviewed. The list of patients was generated by the local Pharmacy by identifying all patients who were dispensed bortezomib during the timeframe stated above. This list included a total number of 184 potential patients.

Any patients with a diagnosis of amyloidosis were excluded. Amyloidosis can be diagnosed simultaneously in a small number of patients with multiple myeloma, however this disease could affect their symptoms (patients with amyloidosis have an increased risk of peripheral neuropathy), thus these patients were excluded.

Any charts missing a significant amount of data were excluded, for example there were three charts in which the bortezomib orders and nursing notes were unavailable. They were therefore excluded because they were missing the data on injection site where the bortezomib was administered, and all dosage information was missing. Furthermore, it was found that although the physician who requested approval for bortezomib resided at the local hospital, the patient was actually sent back to their own community for all bortezomib treatment at their local hospital, thus the charts were not accessible.

3.6 Procedures and Data Collection

A list of patients was generated based on date of dispensation of bortezomib. This list was then organized by physician and site/hospital, and all other sites and hospitals were removed except for the two centers involved in this study. The remainder of patients were then stratified into cohorts of intravenous (IV), subcutaneous (SC), or Both (received both IV and SC within any treatment regimen). The administration route of bortezomib was identified in the chart. Data were collected from two different sites by two different abstractors, the author and a pharmacist. The pharmacist was trained in the study protocol, and on the data collection spreadsheet by the author. A code list was kept in order to define terms used in the spreadsheet, as well as to define categories or groups within each column on the spreadsheet (i.e., Sex : 1 = male 2 = female).

Data collected included: patient demographics (sex, age at diagnosis, ethnic group, myeloma subtype, and stage of disease at diagnosis), prescribed dose of bortezomib, dose schedule (once or twice weekly), number of cycles received, total cumulative dose of bortezomib received, whether they developed peripheral neuropathy (PN), when they developed PN, cumulative dose when PN started, whether they required a dose reduction for their PN, baseline PN, grade of PN, and whether they had to stop bortezomib early due to PN. In regards to injection site reactions (ISR's) the data collected included: number of injections, injection site, number of ISR's, where the ISR occurred, grade of ISR, time it took for the ISR to resolve, any treatments used for the ISR, and whether the patient required a switch back to IV due to their ISR. Data were collected per dose of bortezomib.

During the data collection, it became apparent that some patients received bortezomib therapy more than once, also known as bortezomib re-treatment (i.e., they received a course of bortezomib for a number of cycles, experienced a relapse in disease, received a different

treatment followed by another relapse, and then received a second course of bortezomib). This subsequent treatment was captured as well, and within the data spreadsheet was specified as therapy episode 1, 2, and 3.

3.6.1 **Access to the Chart Review**

Data were retrieved from the electronic physicians' notes, and other databases. Data sources included electronic charts, paper charts (for nurses notes, assessment forms, and bortezomib orders), and lab databases. Access to records was granted by the institution for the purposes of research after ethics approval.

3.6.2 **Statistical Analysis**

Data were analyzed using SPSS version 22. Demographic data were analyzed comparing the IV group to the SC group to the Both group using chi-square for independence for categorical data (i.e., sex, ethnic group, myeloma subtype, ISS stage at diagnosis) and t-test for continuous data (i.e., age at diagnosis), and p-values of less than 0.05 were considered statistically significant.

Chi-square was used to compare frequency of peripheral neuropathy between patients who received IV bortezomib, SC bortezomib and both IV and SC bortezomib. Total cumulative dose and cumulative dose at time of PN were calculated. Minimum and maximum dose range, median and standard deviation calculations were performed.

To measure injection site reactions (ISR's), data were collected as a count (actual number) of times the patient received injection per site: abdomen, thigh, and back of the arm, and chi-square was used to examine differences between frequencies of ISR's between different injection sites.

3.7 Ethical Considerations

This study was approved by the University of British Columbia (UBC) Research Ethics Board. In accordance with the ethics board guidelines, this study was deemed minimal risk as only anonymized data were analyzed. Thus, patient consent was not needed since there was no treatment intervention proposed.

3.8 Study Limitations

3.8.1 Study Design

The retrospective design is a weak quantitative design because there is no randomization. Since no randomization occurred, there was lack of a control group, therefore homogeneity of the sample was employed to control for confounding. Homogeneity was controlled by collecting demographics to ensure each group was similar in sex, age at diagnosis, ethnic group, stage of disease at diagnosis, and baseline peripheral neuropathy rates.

Another limitation of the retrospective design was missing data. This was due to issues of omission of data and lack of capture (i.e., nurse or physician did not chart something or a piece of the chart was missing). To deal with this issue, any charts with data missing specific to the research question were excluded.

3.8.2 Issues of Rigor

Rigor was addressed in this study by using a validated tool for grading both peripheral neuropathy and injection site reactions. The tool used in this study was the Common Terminology Criteria for Adverse Events (United States-National Institutes of Health, 2009). This is the most common grading tool used in all cancer studies, and was used in the studies which have been described in the literature review in chapter two.

3.8.3 **Threats to Design Validity**

Internal validity refers to the degree to which an observed effect can be attributed to the intervention (Polit & Beck, 2012). External validity refers to the degree to which the observation can be generalized to an entire population (Polit & Beck, 2012). One major threat to the validity of this study design was lack of power. The number of patients evaluated in this study was small (n=53), thus, all findings were reported conservatively. A power analysis was done prior to commencing data collection which showed that at least 176 subjects would be needed to meet power. This was unattainable due to lack of eligible patients according to the study inclusion criteria within the timeframe specified.

As stated previously, missing data was another threat to internal validity, in that, the observed count of frequency of peripheral neuropathy and injection site reactions could be under-reported, and therefore an under-representation of the true frequency of these side effects with bortezomib treatment.

3.8.4 **Selection Bias**

This study used convenience sampling, therefore all patients who met inclusion criteria were included in the study. Since randomization could not occur in this retrospective study, stratification was employed to separate patients into groups dependent on how the bortezomib was administered (IV, SC, Both), and how many therapy episodes they received (one, two, or three).

Chapter 4: Results

4.1 Introduction

This was a retrospective, chart review, conducted at two large academic medical centres in British Columbia. The chart review consisted of data from all multiple myeloma patients who received bortezomib from January 1st 2010 to June 1st 2013. There were two research questions for this study. The first was: What is the incidence of peripheral neuropathy in patients with multiple myeloma who received Bortezomib IV (prior to July 2011) compared with patients who received bortezomib SC (between July 2011 and June 1, 2013)? The second question was: What is the incidence of localised injection site skin reactions for patients with multiple myeloma who received bortezomib via a subcutaneous injection? And further to this question, a sub-question was: What is the incidence of localised injection site skin reactions in the back of the arm compared to the abdomen and thigh?

This chapter presents the findings of the study, with demographics reported first, and then the peripheral neuropathy data followed by the injection site reaction data.

4.2 Demographics

A total of 53 patients were included in the sample. Thirteen patients (25%) received intravenous (IV) bortezomib, 22 (41%) patients received subcutaneous (SC) bortezomib, and 18 (34%) patients received both IV and SC bortezomib within the first therapy episode. Patient ages ranged from 43 years old to 88 years old (mean=64 years, SD=12). Almost two-thirds of the patients were male (n=33, 62%), with the remaining one-third being female (n=20, 38%). Most of the patients were Caucasian (n=28, 53%), followed by East Asians (n=8, 15%), and then South Asian (n=3, 6%). An additional 5 patients (9%) identified as “other” including Lebanese and other Middle Eastern, and the remaining subjects (n=9, 17%) were of unknown ethnic origin.

Most of the patients were ISS Stage 1 at diagnosis (n=16, 30%), and 15 patients (28%) were Stage 2 at diagnosis, and 13 patients (25%) were Stage 3 at diagnosis. Nine patients (17%) had unknown ISS stage, due to missing beta-2 micro-globulin level. The most common subtype of myeloma in the sample was IGG (n=30, 57%), followed by IGA (n=14, 26%), then SFLC (n=8, 15%), and lastly IGM (n=1, 2%). No one in this sample had IGD myeloma. Table 4.1 shows patient demographics per treatment group (SC, IV or Both). There were no statistically significant differences between the IV, SC, or Both groups based on patients' demographic characteristics.

Table 4.1 Demographics By Treatment Group

Characteristic	**SC N=22 (41%)**	**IV N=13 (25%)**	**Both N=18 (34%)**	**Chi-square**	**p**
Age, n (%)					
Mean (SD)	66 (12.3)	62 (12.9)	63 (12.1)	NA	.616
<= 64yrs	12 (55%)	7 (54%)	9 (50%)	.41	.816
>=65yrs	10 (45%)	6 (46%)	9 (50%)		
Sex, n (%)					
Male	13 (59%)	10 (77%)	10 (56%)	1.63	.443
Female	9 (41%)	3 (23%)	8 (44%)		
Ethnic Group, n (%)					
Caucasian	9 (41%)	10 (77%)	9 (50%)	10.42	.237
South Asian	3 (14%)	0 (0%)	0 (0%)		
East Asian	3 (14%)	1 (8%)	4 (22%)		
Other	2 (9%)	0 (0%)	3 (17%)		
Unknown	5 (22%)	2 (15%)	2 (11%)		
Subtypes n (%)					
IGG	13 (59%)	7 (54%)	10 (56%)	4.67	.587
IGA	7 (32%)	3 (23%)	4 (22%)		
IGM	0 (0%)	1 (8%)	0 (0%)		
IGD	0 (0%)	0 (0%)	0 (0%)		
Serum Free Light Chain	2 (9%)	2 (15%)	4 (22%)		
ISS stage n (%)					
I	9 (41%)	2 (15%)	5 (28%)	5.38	.496
II	7 (32%)	4 (31%)	4 (22%)		
III	4 (18%)	3 (23%)	6 (33%)		
Unknown	2 (9%)	4 (31%)	3 (17%)		

Bortezomib dosing was variable in the sample (see Table 4.2). The most common bortezomib dose was 1.3mg/m2 (SC: n=11, 50%, IV: n=11, 85%, Both: n=14, 78%). The difference between prescribed doses among the groups were not statistically significant (chi-square = 8.08, p = .089). There were two options for treatment dosing, either once weekly or twice weekly doses. There was a statistically significant difference in the number of people who received once weekly versus twice weekly dosing between groups (chi-square = 18.12, p <0.001) with most patients in the SC group being treated with once weekly dosing (n=18, 82%), and most patients in the IV being treated with twice weekly dosing (n=12, 92%). In the Both group, there was no difference between once weekly or twice weekly dosing options (n=9, 50% per each dosing option). Most of the patients in the SC group received 4 cycles or less of bortezomib (n=12, 55%). However most of the patients in the IV group and the Both group received 5 cycles or more (n=8 or 61%, n=12 or 67%, respectively). However this difference was not statistically significant (chi-square = 1.98, p=.371).

Total cumulative dose was not formally analyzed because of the wide variance in dosing, and due to the small sample size per group. The patients in the Both group received the highest total cumulative dose of bortezomib (6.0 - 54.0mg/m^2, Median = 32mg/m2, and SD =14.1). The median total cumulative dose was lowest for the SC group (9.2 - 57.2mg/m^2, Median = 21.3, SD = 13.6). The range for the IV group was 8.0 - 41.6mg/m^2, Median = 26 mg/m^2, and SD = 8.8. Overall, total cumulative dose was 6.0-57.2mg/m2, Median = 26.9mg/m^2, SD = 12.9.

Table 4.2 Bortezomib Treatment Variables

Characteristic	SC N=22 (41%)	IV N=13 (25%)	Both N=18 (34%)	Chi-square	P
Prescribed Dose of Bortezomib, n (%)					
1.0mg/m^2	3 (14%)	2 (15%)	1 (6%)	8.08	.089
1.3mg/m^2	11 (50%)	11 (85%)	14 (78%)		
1.5mg/m^2	8 (36%)	0 (0%)	3 (16%)		
Once or Twice weekly Dosing, n (%)					
Once weekly	18 (82%)	1 (8%)	9 (50%)	18.12	<0.001
Twice Weekly	4 (18%)	12 (92%)	9 (50%)		
Number of Treatment Cycles, n (%)					
<= 4 Cycles	12 (55%)	5 (39%)	6 (33%)	1.98	.371
>= 5 Cycles	10 (45%)	8 (61%)	12 (67%)		

4.3 Frequency of Peripheral Neuropathy

Peripheral neuropathy occurred in 28% of the total sample (n= 15/53). All incidences of peripheral neuropathy (PN) are reported per patient. A larger proportion of patients who received SC or Both IV and SC bortezomib developed PN (SC, n=7, 32%; Both, n=6, 33%) compared to patients who received IV (n=2, 15%). However, a chi-square test for independence indicated no association between route of administration and developing PN, $\chi 2$ (2, n=15) = 1.43, p = .490, phi = .164.

Data related to other factors possibly associated with PN were collected, however, the numbers were too small for sub-analysis. These data included: number of therapy episodes of bortezomib each patient received, prior bortezomib exposure, baseline PN, Grade of PN, and time that PN developed within a cycle. Of the 53 patients, 13 went on to receive a second therapy episode of bortezomib, and of those 13 patients, 2 went on to receive a third therapy episode. One patient within the first therapy episode group received bortezomib prior to January 1st, 2010. All patients in the second and third therapy episode groups received prior bortezomib. Seven of the 53 patients (or 13%), reported baseline neuropathy, prior to receiving bortezomib. Of the

seven patients with baseline PN, 2 developed worsening PN, or painful Grade 2 PN and required a dose reduction. They were the only 2 patients out of the 15 who developed PN in the entire sample who required a dose reduction for their PN. The other 13 patients had developed Grade 1 PN (numbness and tingling) and did not receive a dose reduction related to PN. All fifteen of the patients developed neuropathy prior to cycle 5 day 1, and most developed PN between cycle 1 and cycle 3 (n=11, 73%).

Table 4.3 Frequency of Peripheral Neuropathy

Characteristic	SC N=22 (41%)	IV N=13 (25%)	Both N=18 (34%)	Chi-square	p
Developed PN on Treatment, n (%)					
Yes	7 (32%)	2 (15%)	6 (33%)	1.16	.560
No	15 (48%)	11 (85%)	12 (67%)		

4.3.1 Frequency of Peripheral Neuropathy by Demographics

This analysis was done exclusively on SC and IV groups only per demographics (age, sex, subtype of MM, and ISS stage at diagnosis). The Both group was excluded from this analysis since it does not pertain to the research question, and the ethnic groups were also excluded from this part of the analysis due to too many groups with zero patients. In the SC group, 3 patients less than 65 years of age and 4 patients greater than or equal to 65years of age developed PN (n=3 or 30%, versus n=4, 33% respectively) while the IV group reported the same amount of PN in both age groups (n=1, 15%). Although there were more patients in the SC group who developed PN (n=7 or 32% versus n= 2 or 15%), this was not statistically significant. Therefore age was not significantly associated with developing PN for the given routes (Fisher's Exact p = 1.00, phi = -.049). Four out of 13 males (31%) and 3 out of 9 (33%) females in the SC group developed PN, while 1 male out of 10 (10%) and 1 female out of 3 (33%) developed PN in

the IV group. Thus, sex was not significantly associated with developing PN in either group (Fisher's Exact p = .685, phi = -.126). Comparatively, there were 3 (23%) patients with IGG subtype of MM in the SC group who developed PN and 1 (14%) in the IV group, 3 (43%) with IGA MM in the SC group and 1 (33%) in the IV group, and 1 (50%) patient with serum free light chain MM in the SC group and 1 (100%) patient with IGM MM who also developed PN. These numbers were not statistically significant, thus subtype of MM was not associated with developing PN, Pearson's $\chi 2$ (3, n=35) = 1.757, p = .624, phi = .224. Two (22%) of the patients in the SC group with ISS stage 1 developed PN, while zero in the IV group with the same ISS stage developed PN. There was 1 patient in each group with ISS stage 2 disease that developed PN (or 14% in SC and 25% in IV), and there were 3 patients with ISS stage 3 (75%) in the SC group that developed PN and zero of the same stage in the IV group. There were 6 patients with unknown ISS stage at diagnosis. A Chi-square test for independence indicated that ISS stage at diagnosis was not associated with developing PN, Pearson's $\chi 2$ (2, n=29) = 1.766, p = .414, phi = .247.

Table 4.4 Peripheral Neuropathy by Demographics

Characteristic	SC N=7 (32%)		IV N=2 (15%)		Fisher's Exact p-value
	Yes PN	No PN	Yes PN	No PN	
Age, n (%)					
<= 64yrs	3 (30%)	7 (70%)	1 (14%)	6 (86%)	.603
>=65yrs	4 (33%)	8 (67%)	1 (17%)	5 (83%)	.615
Sex, n (%)					
Male	4 (31%)	9 (69%)	1 (10%)	9 (90%)	.339
Female	3 (33%)	6 (66%)	1 (33%)	2 (67%)	1.00
Subtypes, n (%)					
IGG	3 (23%)	10 (77%)	1 (14%)	6 (86%)	1.00
IGA	3 (43%)	4 (57%)	1 (33%)	2 (67%)	1.00
IGM	0 (0%)	0 (0%)	0 (0%)	1 (100%)	NA
Serum Free Light Chain	1 (50%)	1 (50%)	0 (0%)	2 (100%)	1.00
ISS stage n (%)					
I	2 (22%)	7 (78%)	0 (0%)	2 (100%)	1.00
II	1 (14%)	6 (86%)	1 (25%)	3 (75%)	1.00
III	3 (75%)	1 (25%)	0 (0%)	3 (100%)	.143

4.3.2 Frequency of Peripheral Neuropathy by Treatment Variables

Peripheral neuropathy was highest in both the SC and IV group who received bortezomib at a dose of 1.3mg/m^2 (n=6 or 55% and 2 or 18% respectively). There were no patients in either group who received 1.0mg/m^2 nor 0.7mg/m^2 that developed PN. And there was just 1 patient who received SC bortezomib that developed PN at the 1.5mg/m^2 dose of bortezomib. However, a chi-square test for independence indicated there was no statistical association between SC or IV and dose of bortezomib in developing PN, Pearson's $\chi 2(2, n=35) = 3.768$, $p = .152$, phi = .328. Four patients (24%) in the SC group who received once weekly dosing developed PN, with zero reported in the IV group who received once weekly dosing. For those who received twice weekly dosing, there were 2 (50%) in the SC group who developed PN and 1 (11%) in the IV group who developed PN. There was 1 patient in each group that received both once weekly and twice

weekly dosing of bortezomib (SC = 1 or 100%, and IV = 1 or 50%). A chi-square for independence indicated there was no association between dosing schedule of bortezomib and developing PN between the two groups, Pearson's $\chi 2$ (2, n= 35) = 2.897, p = .235, phi = .288. Highest incidence of PN was reported in the SC group who received 4 cycles or less of bortezomib (n=5, 42%), with zero PN reported in the IV group. For those patients who received 5 cycles or more of bortezomib the SC and IV groups had relatively equivalent incidence of PN (n=2 and 20% versus 25% respectively). A chi-square for independence showed no association between number of treatment cycles, route of bortezomib administered and developing PN (Fisher's Exact p = .711, phi = .082).

Table 4.5 Frequency of Peripheral Neuropathy by Treatment Variable

Characteristic	**SC N=7 (32%)**		**IV N=2 (15%)**		**Fisher's Exact p-value**
	Yes PN	**No PN**	**Yes PN**	**No PN**	
Prescribed Dose of Bortezomib, n (%)					
1.0mg/m^2	0 (0%)	3 (100%)	0 (0%)	2(100%)	NA
1.3mg/m^2	6 (55%)	5 (45%)	2 (18%)	9 (82%)	.183
1.5mg/m^2	1 (13%)	7 (87%)	0 (0%)	0 (0%)	NA
Once or Twice weekly Dosing, n (%)					
Once weekly	4 (24%)	13 (76%)	0 (0%)	2(100%)	1.00
Twice Weekly	2 (50%)	2 (50%)	1 (11%)	8 (89%)	.203
Both Once or Twice weekly	1(100%)	0 (0%)	1 (50%)	1 (50%)	1.00
Number of Treatment Cycles, n (%)					
<= 4 Cycles	5 (42%)	7 (58%)	0 (0%)	5(100%)	.245
>= 5 Cycles	2 (20%)	8 (80%)	2 (25%)	6 (75%)	1.00

4.4 Frequency of Injection Site Reactions for Subcutaneously Injected Bortezomib

This analysis included patients from the SC and Both groups (n=40), thus the IV group was excluded since local ISR does not apply. Of the 40 patients who received SC injections, there were a total of 861 injections, with 294 (34%) injections to the back of the arm, 487 (56%)

injections to the abdomen, 130 (15%) injections to an unknown site and 1(<1%) injection in the thigh. Of the 861 injections, eight patients (2%) reported Grade 1 injection reactions (ISR's) in the abdomen, and one Grade 3 ISR, in the thigh (100%). There were none reported in the back of the arm or unknown sites. Of the 8 ISR's, 4 were reported in the SC group, and 4 were reported in the Both group. The time it took for the skin reaction to resolve was variable from 5 days to 90 days (Median = 14, SD = 28). No patients reported use of any treatments for their ISR, and no patients were switched back to IV administration due to the ISR.

4.5 Summary of Results

Peripheral neuropathy rates overall were 28% (15 of 53 patients). Overall, there was no difference in peripheral neuropathy rates between IV and SC administration of bortezomib, Pearson's $\chi 2$ (2, n= 15) = 1.43, p = .490, phi = .164. Therefore, the null hypothesis is retained, and the alternative hypothesis is rejected.

ISR's were rare and mild (9 out of 861 total injections, 1%). There was a difference between frequencies of ISR's between sites, with back of the arm being the lowest (0, 0%), abdomen was the highest (8 out of 487 injections, 2%), and there was 1 injection in the thigh (1, 100%), and this resulted in a Grade 3 ISR. Therefore the null hypothesis was rejected and the alternative hypothesis is retained.

Chapter 5: Discussion

5.1 Discussion of Findings

This chapter summarizes the findings from this study and compares it to the medical literature that was previously summarized in Chapters 1 and 2. Limitations of the study design are discussed, as well as implications for nursing practice, policy and further research. The thesis concludes with a summary of the findings.

This was a retrospective chart review (n=53) of patient charts, conducted at two large academic medical centres in British Columbia. All 53 patients received bortezomib therapy either intravenously, subcutaneously, or a combination of both administration routes. The route of bortezomib administration they received was determined by when (historically) they were treated, such that patients who received their first treatment prior to July 1st, 2011 received IV bortezomib and patients who received their first or continued treatment on July 1st 2011 or later received either SC or both IV/SC. This study was done to determine if there was a difference in the incidence of peripheral neuropathy depending on which route the bortezomib was administered. This study also examined the number of injections given subcutaneously to each of the sites, including the back of the arm, abdomen and thigh, and compared frequency of local injection site skin reactions from the administration of bortezomib subcutaneously. The findings from Chapter 4 will now be discussed and compared to the relevant literature.

5.1.1 Peripheral Neuropathy

The first research question was: What is the incidence of peripheral neuropathy (PN) in the patients who received Bortezomib IV (prior to July 1st, 2011) compared with patients who received bortezomib SC post July1st, 2011.

Based on the findings of this study, the alternative hypothesis was rejected and the null hypothesis was retained. There was no statistically significant difference in PN between patients who received bortezomib IV compared with patients who received bortezomib SC (n=15/53 or 28%). This was contradictory to the Moreau et al., findings from 2008 and 2011. In the current study, frequency of PN in the IV group was lower (n=2/13 or 15%), than in the SC group (n=7/22 or 32%). In the Both group, where patients received IV and then during treatment switched over to SC, PN was reported in 6/18 patients or 33%. The difference in findings comparatively between this study and the Moreau et al. studies, could be explained by the low number of patients included in this study. The IV group was much smaller than the SC group (n=13 versus n=22) due to many patients stratified into the Both group (n= 18). The difference could also be as a result of the use of different dose intensity and medication protocols comparatively between the studies.

According to other researchers, bortezomib induced PN (BiPN) ranges from 8% and upwards to 80% depending on the dose intensity of bortezomib, and prior exposure to bortezomib and other neuro-toxic drugs, with an average somewhere between 30-40% for all Grades of PN (Bringhen et al., 2010; Hoy, 2013; Moreau et al., 2011; Richardson et al., 2012). In the newly diagnosed setting for patients who received bortezomib twice weekly, intravenously (IV), the reported incidence of BiPN (any grade) is between 47% - 64% (Bringhen et al., 2010). Bringhen et al., (2010) did a study comparing bortezomib once weekly to twice weekly at 1.3mg/m2, and reported BiPN incidence as 8% in the once weekly group and 28% in the twice weekly group which was also statistically significant ($p<0.001$). Richardson et al., (2012) summarized BiPN in six bortezomib trials for newly diagnosed patients with MM, which showed incidence between 14% - 26% for Grade 1/2 PN, and 2% to 28% for Grade 3/4 PN. All six of

these trials used bortezomib in some combination with other drugs such as melphalan, prednisone, thalidomide, and vincristine. Of note thalidomide and vincristine are also neuro-toxic agents. Richardson et al., (2012) also summarized five bortezomib trials for patients with relapsed MM, and the incidence of PN in those trials ranged from 9% to 53% for all grades of PN, with severe PN (Grade 3/4) reported as high as 16%. These trials also utilized combinations of other agents such as doxirubicin, dexamethasone, and lenalidomide. And finally in the SC versus IV study for patients with relapsed MM done by Moreau et al., (2011), bortezomib was administered twice weekly to both groups, and the BiPN was reported as 38% in the SC group and 53% in the IV group, and was statistically significant ($p = .04$). In this study, while there was no statistically significant difference in PN rates reported in comparison of the three groups, the rates of PN were generally at the lower range (28%) compared to what is reported in the literature. It is possible that the differences in the current findings and previous research were related to different treatment protocols in the current study, compared to other studies that have reported incidence of PN.

There are several protocols for treatment with bortezomib in British Columbia. As described in Chapter 3, bortezomib can be given at diagnosis, and for relapsed treatment. It can be prescribed with an alkylator (cyclophosphamide or melphalan) and a corticosteroid (dexamethasone and prednisone). Bortezomib can be given at a prescribed dose of 1.3mg/m2 for twice weekly dosing regimen, or 1.5mg/m2 for a once weekly dosing regimen, and dose reduced as necessary.

It is difficult to compare international protocols with Canadian protocols, since they are so variable, but the trend at facilities in Canada include combination therapy with bortezomib. In this study, patients received a corticosteroid (either dexamethasone or prednisone) with or

without an alkylator (either melphalan or cyclophosphamide). All patients who received bortezomib within the timeframe specified were included in this study, which included newly diagnosed (n=34 or 64%) and relapsed patients (n=19 or 36%). These data were not analyzed as the numbers per subset were too small. In this study, only Grade 1 and 2 PN were reported, with no cases of Grade 3 or 4 PN, and the overall frequency of PN was at the lower range of average at 28%. This finding could be as a result of the low number of patients in this study. A larger cohort would be necessary to further examine these findings.

The incidence of PN reported in this study could also be as a result of under-reporting, either by the patient to the healthcare professional, or from the nurse to the doctor. It has been suggested by Tofthagen (2010), that patients may under-report their symptoms due to fear they will be taken off life-saving treatment. Thus, under-reporting by the patient could result in a seemingly lower incidence of PN. The protocol in British Columbian hospitals specifies that patients be seen and assessed by their physician at minimum every day 1 of each cycle, and then the physician relies on the nurse to report any symptoms throughout the rest of the cycle. It is possible that the relaying of information could get missed or delayed, resulting in a delay of dose reduction or stoppage of treatment, or just not reported at all.

It is possible that bortezomib dose intensity also accounts for the overall lower range of incidence in PN reported in this study, in that most of the patients received once weekly dosing of bortezomib at 1.5mg/m^2 (once weekly : 28/53 or 53% vs twice weekly: 25/53 or 47%). Other studies have shown that when bortezomib is administered at a lower dose intensity (i.e., once weekly vs twice weekly) the PN rates are lower (Bringhen et al., 2010; Reeder et al., 2010; Richardson et al., 2012).

Total cumulative dose of bortezomib was described as a total for the entire treatment, and at the time when PN started. Higher cumulative dose of bortezomib has been shown to be associated with higher incidences of PN (Richardson et al., 2006). Furthermore, studies have shown that there is a plateau or threshold, whereby PN increases in frequency until a plateau or threshold is reached, which is at the point of approximately 30mg/m^2, or around cycle 5 for twice weekly dosing (Richardson et al., 2006). In this study, total cumulative dose when PN started was extremely variable, from 3.9mg/m^2 to 28.5mg/m^2 across the groups (IV/SC/Both), and thus not formally analyzed. It was also found in this study that, for number of treatment cycles patients received, there were no statistically significant differences between those who received 4 cycles or less and 5 cycles or more in developing PN ($p = .245$ and 1.00 respectively). This finding was also likely due to the small sample size between groups, in particular the IV group, 4 cycles or less, had zero patients. The number of cycles of bortezomib patients received is variable due to the different protocols for treatment. Newly diagnosed patients that are eligible for a stem-cell transplant typically receive up to 4 cycles of bortezomib, while those who are not eligible for a transplant can receive up to 9 cycles. For patients with relapsed MM, they can receive up to 8 cycles of bortezomib, and under certain circumstances can receive additional cycles or re-treatment with bortezomib (up to 8 more cycles). This variability among protocols can influence PN rates, as well as small sample sizes per sub-group. In the literature, sample sizes range from 194 to 244 patients, thus, a larger study using stratification for each of these subset groups would be ideal to compare true incidence of BiPN.

As stated previously, the Both group in this study was comprised of patients who started out receiving their bortezomib IV, and then at some point switched over to SC administration. This switch was due to a change in the BCCA chemotherapy protocol in July 2011, based on the

data from Moreau et al, 2008 and 2011. Therefore, any patient who started on their bortezomib treatment prior to July 2011, received the drug IV, and if they continued on bortezomib treatment after July 2011, they were switched to SC administration. This study showed that 9% of the Both group developed PN, it is possible the PN was actually acquired during IV administration, prior to the switchover. Regardless, nobody in the Both group required dose reduction for their PN. Of note, it was unknown at the time this study was being developed how many patients would be considered in the Both group. This group ended up being a large subset within this study (n=18), therefore it was included in the overall PN analysis but excluded from the subset analysis since it does not pertain to the research question.

There were 2 patients who developed painful neuropathy within this sample, and required a dose reduction due to their PN (2/15, 13%). Of the 2 who required dose reduction, 1 patient was getting SC 1.5mg/m^2 once weekly, and was newly diagnosed, so had not received any prior treatment and had no baseline PN. This patient developed PN at C3D15 and was dose reduced at Cycle 4 day 1. This patient received only 4 cycles of bortezomib and then was discontinued for PN. The second patient who required dose reduction received IV bortezomib, 1.3mg/m^2 twice weekly for relapsed refractory, and had a history of PN (Grade 1 at baseline), from previous thalidomide exposure. This patient developed Grade 2 painful neuropathy at cycle 5 day 22 and was dose reduced at cycle 6 day 1. This patient received 6 cycles or 30mg/m^2 and then was discontinued for PN. This is consistent with Richardson et al., (2012) who found that discontinuation of treatment due to PN is between 1-15% in the newly diagnosed setting, and up to 9% in the relapsed setting. This study demonstrated that PN was not the most common dose limiting toxicity for these patients. Further analysis with a larger group is needed to confirm these findings.

Other studies have looked at whether demographics can influence PN. These studies found that age, sex, baseline diabetes, disease stage at diagnosis and kidney function have not influenced rates of PN (Richardson et al., 2012). Richardson et al (2012) did note that there remains a possibility that "different patient populations in other regions" could affect rates of PN. Due to the ethnic diversity found in BC, ethnic groups were included in the demographic analysis for association with PN rates in this study. However, the numbers were too small for a subset analysis. This study did not find any statistically significant associations between any of the demographics and developing PN, which is consistent with the literature.

5.1.2 **Injection Site Reactions**

The second research question in this study was: What is the incidence of localised injection site skin reactions (ISR's) in the SC group? Furthermore, is there a difference in ISR rates comparatively between the back of the arm, abdomen and thigh?

Based on the findings of this analysis, the alternative hypothesis for both research questions is retained and the null hypothesis was rejected. The incidence of localised injection site skin reactions was very low (9/861, 1%) and was statistically significant ($p < 0.001$). The incidence of ISR's in the back of the arm was lower (0/294, 0%) than the abdomen (8/487, 2%) and thigh (1/1, 100%), and this was also statistically significant ($p < 0.001$). The findings in the current study were lower than reports from other researchers in this field. In the Moreau et al. study (2011), skin reactions were 57% for all grades, and only 2 (6%) had severe reactions. In the most recent study by Ng et al (2014), mild skin reactions were reported in 42% of their patients, with no severe reactions (Grade 3 or higher). Two studies based in Japan from 2012 and 2013 compared skin reactions between the abdomen and the thigh, with the thigh showing higher incidence of ISR's, and overall incidence of ISR's at 63% and higher incidence of reactions in

cycle 1 (Kamimura et al., 2012; Kamimura et al., 2013). In the current study, timing of occurrence of ISRs was not collected.

In the current study the frequency of ISRs was found to be 1%. This is much lower than what has been reported in other studies (42% and 63%). There are likely a number of reasons for this difference. One of note is that in the location of the current study, nurses practice problem-oriented charting, which means that documentation about a particular complaint is done only when it is either witnessed by the nurse (objective) or the patient complains of a symptom (subjective). Thus, if the patient did not complain about an ISR, then the nurse likely didn't chart about it. A review of all the nurses and physicians notes in the patients' records revealed that nurses rarely charted about an injection site reaction, and physicians never mentioned it at all. This does not mean that an ISR did not occur, it could mean that the severity did not warrant a complaint by the patient, or the nurse to consider it a 'problem' to record. Therefore, conservative interpretation of these findings should be employed. More on this will be discussed in limitations of the study design.

As stated previously, the back of the arm was a site used in this study, but was not reported as a site used in the literature. It is possible that the use of only thighs and abdomen (i.e., not arms) is due to different nursing policies in the countries where the studies took place, however this is unknown. In this study, injections of bortezomib in the back of the arm was shown to be safe and well tolerated, with zero ISR's reported there (0/294, 0%). This is an important finding for future use of the back of the arm as a site for bortezomib injections.

5.1.3 **Theoretical Framework**

This study used the Symptom Management Theory (SMT) model as a theoretical framework (Dodd et al., 2001). Dodd et al. proposed a model that defined the inter-relatedness of

three components of symptom management: the symptom experience, symptom management strategies, and symptom outcomes. In this study, only the first component of SMT model was operationalized, that is, to measure the patients' symptoms experience. The findings of this retrospective study illustrate that reporting of a patient's symptom experience is complex and can be influenced by under-reporting of symptoms and thus inaccurate to fully explain the patients' experience. Factors that influence under-reporting are lack of capture, that is, lack of the patient reporting their symptom to the healthcare professional, or lack of the healthcare professional reporting the symptom either in the patient record or to the physician. This model theoretically supports the capture of a patients symptom experience, however is very limited in a retrospective design, thus a prospective design with effective tools used to capture patients symptoms at each visit would be a better fit for this model.

5.2 Limitations of the Study Design

A retrospective chart review in and of itself is a weaker study design for any quantitative research study. This is largely due to inability to randomize subjects, data reliability and potential for missing data. In this study, many charts had to be excluded due to missing data, which resulted in under-powering this study for analysis. In regards to relying on nurses' notes and physicians' notes to accurately report a symptom (in this case peripheral neuropathy and injection site reactions), this was variable between each nurse and physician. The accuracy of the data was reliant upon one of the healthcare professionals first assessing for the symptom and then reporting it in their notes, which introduces subjectivity, and can be both unreliable and inconsistent. Routinely, physicians only assess for PN on Day 1 of each cycle, the rest of the cycle they are reliant on nurses to report it to them, which typically only happens if the problem is deemed "severe enough" by the nurse. Furthermore, patients tend to under-report their

symptoms, especially of pain or PN due to a fear that they will be taken off their life-saving cancer treatment if they can't tolerate it (Tofthagen, 2010).

In regards to ISR's, there are issues related to charting including lack of capture of the side effect. It is also possible that, since most patients received once weekly dosing of bortezomib, at the time of the injection no ISR was seen, but one could develop within the week that the patient is at home, and resolve prior to their next injection. Moreau et al. (2011) reported the average resolution time for an ISR was 6 days. It was noted during the chart review that patients occasionally called the clinic to report an ISR, which often occurred during the first or second cycle, and this call was recorded in the chart. However, under-reporting either by the healthcare professional or by the patient could have led to the findings of lower incidence of ISR's within this study compared to the literature.

5.3 Implications of Findings for Nursing Practice and Policy

The findings related to PN in this study were not statistically significant, however there may be implications for nursing practice change or policy change. The findings of this study suggest that patients' symptoms of peripheral neuropathy (PN) and injection site reactions (ISR's) may be under-reported. For this reason, accurate and consistent documentation of PN and ISR's should be performed at each visit. Nurses play a key role in frontline advocacy and intervention on behalf of the patient, thus with consistent assessment and charting, the patients symptoms may be reported earlier so that appropriate intervention can take place. It is possible that intervention had taken place on a verbal level, and omitted in error from the chart. However, charting is an important tool used in relaying information about the patient to each nurse who cares for the patient, thus it is crucially important that these omissions not occur.

The findings related to ISR's were clinically important, but interpretation of these results should be conservative since there could be under-reporting of ISR's. In the literature, a prospective study design was used to capture ISR's in real-time, and therefore superior in collecting this information than in this retrospective study. Yet, these findings are clinically important since all relevant studies that have reported on SC injection of bortezomib only report on safety and tolerability of using the abdomen and thighs as sites for the injection. This study shows that the back of the arm is a suitable site for bortezomib injections, and possibly may be a better site to use than the abdomen or thigh due to the lowest incidence of ISR's. Some centers are still giving twice weekly bortezomib, so having another site in which to rotate injections may be favourable. The fact that there were no ISR's reported in the back of the arm within this study is encouraging.

In this study, there were 130 (15%) injections that were given in an unknown site. These sites were unknown due to lack of capture in the chart. Currently, at the centres involved in this study, there was no tool used in documenting injection sites. Nurses need to consistently chart which site they are using at the time of each injection, so that the sites can be rotated appropriately to reduce the chance of an ISR and to optimize patient comfort. Nurses should also assess the previous site used for injection, to ensure that any ISR is appropriately addressed and ensure charting consistently. This may be easier to implement by using a currently validated tool with a schematic picture of a body map, where the nurse can mark an X on the site used for injection and initial and date it at each visit. This would provide a visual aid to the following nurse as to where the last injection was given to ensure appropriate rotation of sites, as well as serve to document each injection consistently. A separate pictorial could be used for each cycle

to keep an accurate record of where the injections are being administered, and filed with the patient record.

An example of a validated tool that includes a body map is the Leeds Assessment of Neuropathic Signs and Symptoms (S-LANSS) (Bennett, Smith, Torrance, & Potter, 2005). This tool could be used for duel purposes, that is, to document injection sites of bortezomib more precisely as well as PN pain scores. It is a tool that can be either self-administered by the patient, or can be administered by the nurse. This tool has already undergone rigorous validation for assessment of neuropathic pain signs and symptoms, and could easily be implemented in hospitals and outpatient units where bortezomib is frequently administered.

Furthermore, although no difference was shown in frequency of PN associated with IV or SC administration of bortezomib in this study, SC administration generally was found to be well tolerated. SC administered bortezomib saves patients and healthcare workers time at the hospital, since there is no IV set-up needed. This also could result in a cost saving for the institution.

5.4 Implications of Findings for Nursing Research

These data contradict the findings in the study done by Moreau et al., (2011) and suggest that there was no difference in PN between IV administered bortezomib and SC administered bortezomib. However, this was a convenience sample of only 53 patients, thus, the numbers analyzed in this study were small. The sample size was further compromised due to a large number of patients receiving both SC and IV bortezomib, leaving the IV group with a disproportional sample size in relation to the SC group. Therefore, further research with a multi-center, larger sample size is warranted to re-examine these findings.

In regards to SC administration of bortezomib, the back of the arm was safe and well tolerated, thus, is an appropriate site for SC injection of bortezomib. However, documentation of

injection sites and under-reporting of both PN and ISR's was a found to be a problem. There is currently no standard tool used in the two medical centres involved in this study, which document injection sites. A quality improvement project, or a prospective study design, using the S-LANSS tool for the duel purposes of documenting injection sites of bortezomib as well as assessment of neuropathic pain signs and symptoms could be done to test whether this is a practical solution to capture this information.

5.5 Summary of Discussion

Many of the findings in regards to PN in this study were not statistically significant. Issues of rigor and reliability were introduced due to the retrospective chart review design of the study, and to the low number of patient charts included in the sample, thus under-powering the analysis. However, there were some findings that could be considered clinically significant. PN in general was found to be at the lower range (28%), comparatively to the literature. Furthermore, it was encouraging that dose reductions were uncommon (n=2, 13%), which demonstrates that although PN is still a problem, it can be controlled and prevented. Once weekly dosing is ideal for patients in that they only need to come into the hospital once per week for treatment instead of twice per week, thereby promoting quality of life. This also reduces the need for a second appointment in hospitals and day wards, which potentially could reduce healthcare related costs, and drug costs as well.

The relevant literature show that SC bortezomib induces less PN than IV, so administering bortezomib SC instead of IV would be optimal in terms of quality of life for the patient. The low incidence of severe ISR's with SC administered bortezomib in this study and in the literature is encouraging. The SC option has shown to be well tolerated in the back of the

arm, which gives nurses one more optional site for injection when rotating injection sites. This could also result in greater comfort for the patient, which promotes their quality of life.

Consistent documentation by nurses and physicians is necessary to optimize capturing both PN and ISR's, therefore a validated tool should be employed to ensure consistency and accuracy. Use of a tool such as the S-LANSS tool may facilitate consistent reporting of injection sites used for bortezomib injections, ISR's and PN. Consistent documentation may aid in optimizing strategies of prevention and/or intervention of patients' symptoms, thereby improving and promoting quality of life.

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Appendices

Appendix A

Injection Site Reaction Grading System from Common Terminology Criteria for Adverse Events

	Grade				
Adverse Event	1	2	3	4	5
Injection Site Reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.					

United States-National Institutes of Health, N. C. I. (2009).

Appendix B

The Durie-Salmon Staging System

Stage	Findings
1	Hgb > 100 g/L Calcium < 2.88 mmol/L Bones = no more than 1 lytic lesion
	M-protein: IgG < 50 g/L IgA < 30 g/L
	Total urinary light chain < 4 g/24 h
2	Between 1 and 3
3	Any one of these:
	Hgb < 85 g/L Calcium > 2.88 mmol/L Bones = multiple lytic lesions
	M-protein: IgG > 70 g/L IgA > 50 g/L
	Total urinary light chain > 12 g/24 h
Subclassifications:	A = creatinine ≤ 180 mmol/L
	B = creatinine > 180 mmol/L

International Myeloma Foundation. (2002). Staging and Prognostic Classification. Retrieved from: http://myeloma.org/ArticlePage.action?articleId=739

Appendix C

The International Staging System

Stage	Criteria
I	Serum beta-2 microglobulin less than 3.5 (mg/L) and albumin level above 35 (g/L)
II	Neither stage I or III
III	Serum beta-2 microglobulin is greater than 5.5 (mg/L)

International Myeloma Foundation. (2002). International Staging System. Retrieved from:

http://myeloma.org/ArticlePage.action?articleId=889

Appendix D

The Neurotoxicity Assessment Tool

Instructions for Patients
By circling one number per line, please indicate how true each statement has been for you during the past seven days using the following scale.

0 = not at all
1 = a little bit
2 = somewhat
3 = quite a bit
4 = very much

I have numbness or tingling in my hands. 0 1 2 3 4
I have numbness or tingling in my feet. 0 1 2 3 4
I feel discomfort in my hands. 0 1 2 3 4
I feel discomfort in my feet. 0 1 2 3 4
I have joint pain or muscle cramps. 0 1 2 3 4
I feel weak all over. 0 1 2 3 4
I have trouble hearing. 0 1 2 3 4
I get a ringing or buzzing in my ears. 0 1 2 3 4
I have trouble buttoning buttons. 0 1 2 3 4
I have trouble feeling the shape of small
objects when they are in my hand. 0 1 2 3 4
I have trouble walking. 0 1 2 3 4

Instructions for Healthcare Professionals
This assessment tool is provided to help you evaluate peripheral neuropathy in patients receiving chemotherapy. Healthcare professionals may find discussion of patients' responses helpful in determining the grade of neuropathy as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (http://ctep.cancer.gov); however, no direct correlation exists between assessment scores and toxicity grades.

Tariman et al. (2008), based on information from Calhoun et al., (2000); Cella (1997); Cella et al., (1993).

Appendix E

National Cancer Institute Common Terminology Criteria for Adverse Events: Neuropathy and Pain[a]

Adverse Event	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life Threatening or Disabling)	Grade 5 (Death)
Pain in a specific body system (eg, extremity)	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function but not interfering with activities of daily living	Severe pain; pain or analgesics severely interfering with activities of daily living	Disabling	Not applicable
Neuropathy: Motor[b]	Asymptomatic; weakness on examination or testing only	Symptomatic weakness interfering with function but not interfering with activities of daily living	Weakness interfering with activities of daily living; bracing or assistance to walk (eg, cane, walker) indicated	Life threatening or disabling (eg. paralysis)	Death
Neuropathy: Sensory[b]	Asymptomatic; loss of deep tendon reflexes or parasthesias (including tingling) but not interfering with function	Sensory alteration or parasthesias (including tingling) interfering with function but not with activities of daily living	Sensory alteration or parasthesias interfering with activities of daily living	Disabling	Death

a Neuropathic pain is graded as pain.
b Cranial nerve motor or sensory neuropathy is graded as "Neuropathy: cranial" or "Neuropathy: sensory," respectively.

United States-National Institutes of Health, N. C. I. (2009).

Appendix F

Recommended Dose Modification for VELCADE®-Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesia, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce VELCADE® to 1.0 mg/m2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold VELCADE® treatment until symptoms of toxicity have resolved. When toxicity resolves, reinitiate VELCADE® treatment and reduce dose to 0.7 mg/m2 and change treatment schedule to once per week
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life-threatening or leads to paralysis)	Discontinue VELCADE®

Janssen Inc. (2013). Product Monograph Velcade bortezomib for injection.