PERIPHERAL NEUROPATHY AND DIARRHEA SYMPTOMS IN MULTIPLE MYELOMA

by

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Dedication Page

I dedicate this work to my beloved husband Matthew Faiman, my son Max, and my entire family whose unwavering love, support and encouragement have allowed me to achieve my goals. I could not have achieved these goals without your support.
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Peripheral Neuropathy and Diarrhea Symptoms in Multiple Myeloma

Abstract

by

BETH FAIMAN

Background: A symptom is a subjective experience with physical, cognitive, or emotional implications. Approximately 83,000 individuals are living with multiple myeloma (MM) and many suffer with uncontrolled symptoms. Peripheral neuropathy (PNP) and lenalidomide-related diarrhea (LRD) are two common, chronic, and complex symptoms in patients with MM. Symptom management is an appropriate priority for nursing research since a patient’s overall cancer experience is influenced by the nursing care of the patient, which includes effective symptom management. Purpose: Two studies were conducted to examine the two most debilitating symptoms in MM: PNP and LRD. The first was to evaluate the feasibility of using glutamine to treat PNP. The second was to explore whether LRD is related to immunodeficiency or low serum immunoglobulin A levels. Methods: First, a pilot study of 9 patients compared glutamine or placebo to test the effect of glutamine on neuropathy symptoms and the feasibility of a larger trial. Second, a retrospective study was conducted to explore whether diarrhea could be a positive sign and surrogate of an effective anti-myeloma immune response or related to immunodeficiency. Results: In the neuropathy study, high consent (50%) and adherence (99.5%) rates were observed and a medium effect size (.43) of glutamine on neuropathy symptoms. In the diarrhea study, patients with diarrhea were in remission an average of 62.6 months ($SD = 29.01$) and had a longer remission than patients without diarrhea ($t = -2.058$, $df = 42$, $p = .046$). Histopathologic findings of an immune response
were observed in 4/24 (17%) patients with diarrhea and 0/20 (0%) without diarrhea. Serum IgA levels did not correlate with diarrhea. Conclusion: Each study contributed to nursing science as neuropathy and diarrhea symptoms plague patients with this chronic, incurable cancer. These two studies shed initial light on the symptoms and provide direction for future symptom research.
Chapter 1: Introduction to the Study

**Background: Symptom Research**

A symptom is defined as a subjective experience that reflects changes in the physical functioning, cognition, or sensations of an individual (Dodd et al., 2001). It is a well-known and disturbing fact that patients with cancer are living with uncontrolled or inadequately managed symptoms (Farrell, 2010). Consequences of poorly controlled physical symptoms in cancer patients create major public health problems associated with decreased quality of life (QOL), increased healthcare-related costs, and decreased adherence to therapy (Andrew, Derry, Taylor, Straube, & Phillips, 2014; Broyl, Jongen, & Sonneveld, 2012; Peery et al., 2012). Many patients with inadequately controlled symptoms are unable to work, perform household duties, or conduct usual activities of daily living, which can lead to depression or demoralization in the individual (Vehling & Mehnert, 2014). Nurses employ various strategies to intervene in the symptoms experienced in cancer patients. Symptom management is an appropriate priority for nursing research since a patient’s overall cancer experience is influenced by the nursing care of the patient, which includes effective symptom management versus cure of the disease (Lobban & Perkins, 2013; Mateos, Leleu, Palumbo, & Miguel, 2014).

Symptom research in cancer is particularly challenging for several reasons. First, longitudinal data are needed to understand and intervene in the symptoms (Dodd, Miaskowski, & Lee, 2004; Dodd et al., 2001; Thomas et al., 2014). Multiple factors impact the ability to gather longitudinal data in cancer, such as patient withdrawal from clinical studies, inability to adhere to the intervention, lost to long-term follow-
up, and death that occurs from the disease or complications of the disease (Barsevick, Whitmer, Nail, Beck, & Dudley, 2006; Brant, Beck, & Miaskowski, 2010; Thomas et al., 2014). Further, symptoms may be related to the disease, treatment, or other comorbidities (Visovsky, Berger, Kosloski, & Kercher, 2008). The symptoms are difficult to delineate or address, as patients are often too frail to adhere to scheduled appointments required for symptom monitoring and/or study procedures if enrolled in a clinical trial (Jones et al., 2013).

Yet symptom research is especially important in cancer, specifically multiple myeloma (MM), for several reasons. First, the symptom burden of disease and treatments in MM can be substantial and primarily includes bone pain, fatigue, muscle weakness, diarrhea, and peripheral neuropathy (Jones et al., 2013). Cumulative physiologic and psychologic effects of these symptoms on the individual can lead to poor QOL and limit patient access to new and yet undiscovered drugs to treat the MM.

Second, MM is a chronic illness, with many patients living in excess of 10 years (Kumar et al., 2014; Kumar et al., 2012). Clusters of complex symptoms may develop throughout the disease trajectory, and the symptoms may interact and progress in a fluid nature through various stages over time (Brant et al., 2010; Dodd et al., 2004). New symptoms can result from chronic MM treatment and place the individual at risk for worsening polypharmacy, issues with self-management of multiple chronic illnesses, adherence to therapy, and poorer health.

Finally, symptom research would elucidate barriers to prevention and effective treatment of symptoms. Unfortunately, there is a paucity of symptom research in
Known likely barriers to effective symptom management relate to the patient, provider, and healthcare system. Reasons why patients accept the symptoms as part of the disease, underestimate symptom severity, and fail to report symptoms to the clinician need to be identified with further research (Osborne et al., 2014; Osborne et al., 2012; Potrata, Cavet, Blair, Howe, & Molassiotis, 2011).

A major initiative within symptom science research is to advance the science of symptom management across health science disciplines. Progress in symptom management research requires an understanding of the physiologic processes that underpin the symptom, and use of working evidence of biological processes to develop targeted interventions based on the underlying physiology. Existing theoretical models such as the Symptom Management Model provide insight into the complexity of the cancer symptom experience (Dodd et al., 2004; Dodd et al., 2001). However, development of future models that account for the MM patient’s subjective experience (e.g. peripheral neuropathy), the effects of treatment (as with peripheral neuropathy and diarrhea), and the underlying biology of the symptom (diarrhea) are needed. Future development of new instruments and psychometric evaluation of the new instruments are outside the context of this dissertation but would provide an opportunity to better understand the burden of symptoms in MM and be considered in future studies. If symptom science is a priority in nursing research we have to build evidence which is safe for patients, yet this poses many challenges such as lack of funding or qualified researchers to conduct necessary studies.

Thus, the purpose of these studies was to investigate two symptoms that are common, distressing, and have implications for continued treatment. The two most
common and inadequately managed symptoms that patients with MM experience as a result of cancer treatment are bortezomib-induced peripheral neuropathy (PNP) and lenalidomide-related diarrhea (LRD). Both symptoms are often severe enough to warrant dose reduction, delays, or discontinuation in chemotherapy, the most common interventions for these unpleasant symptoms. Unfortunately neither of the symptoms will entirely resolve with these interventions and dose reductions place the individual at risk for disease progression. Such symptoms impede patient adherence and undermine quality of life, and the symptoms are often poorly managed by clinicians.

To address the symptoms, these studies consisted of two focuses. Each is an aspect of the general topic of symptoms in MM. The first was to conduct a pilot study of an intervention based on hypothesized physical effects, PNP. The second was a pilot/preliminary examination of the physical basis of a common but underreported and understudied phenomenon, LRD. The second study also explored whether LRD could be a surrogate of an effective antimyeloma immune response triggered by lenalidomide or whether diarrhea might be related to immunodeficiency.

Both symptoms are critical to understanding the disease trajectory and can be conducted as preliminary investigations testing methodology, with a feasibility focus as well as in obtaining pilot data for future study. Both studies contribute to understanding of phenomena and identify methodologic issues in nursing symptom research. Thus, there is a need for models that account for the patient’s subjective experience (e.g. PNP), the effects of treatment (as with PNP and LRD), and the underlying biology (LRD).
Study of these symptoms is relevant to nursing science, as they address the biology around important supportive care issues from an interventional and pathophysiological perspective in order to maximize quality and quantity of life for patients with multiple myeloma. The neuropathy project aims to reduce a symptom that can limit therapeutic options for a deadly cancer. Results from the diarrhea project can elucidate whether there are risk factors for LRD and if diarrhea is a positive prognostic sign that argues for optimizing symptom control rather than switching drug therapy, which may result in suboptimal disease control.

**Background and Problem: Multiple Myeloma**

Multiple myeloma is a rare cancer of the bone marrow plasma cells that affects approximately 77,000 individuals in the United States (Howlader, Noone, Krapcho, Neyman, & Kroenen, 2014). Plasma cells are responsible for producing intact immunoglobulins, which perform a variety of functions integral to a healthy immune system. Immunoglobulins constitute the humoral immune response to foreign antigens that invade the immune system. Each immunoglobulin molecule consists of two heavy chains and two light chains. The type of heavy chain present determines the class of the immunoglobulin: IgM, IgD, IgG, IgA, or IgE, respectively. The two types of light chains are denoted by the Greek letters \( \kappa \) (kappa) and \( \lambda \) (lambda). Each heavy-chain immunoglobulin molecule has either a \( \kappa \) or a \( \lambda \) subtype of light chain in association with one of the types of heavy chain (i.e., IgG kappa or IgG lambda).
Through a complex series of genetic changes, mutations, and alterations within the bone marrow microenvironment, the plasma cell becomes malignant (Faiman & Bilotti, 2013). One clone of a normal immunoglobulin protein, also known as a monoclonal protein or M protein (i.e., IgG), is overproduced. Following malignant transformation, the cancerous plasma cell secretes a variety of cytokines, which leads to organ damage (Fonseca & Monge, 2013). Hallmarks of MM-related organ damage include hypercalcemia, renal insufficiency, anemia, and bone lesions (Durie et al., 2006; Palumbo et al., 2014).

Although incurable, the survival of patients with MM has increased in part due to newer classes of drugs as compared to standard chemotherapy agents. As of 2014, the list of drugs approved by the US Food and Drug Administration (FDA) to treat MM has expanded. Available drugs include immunomodulatory drugs (IMiDs) such as thalidomide (Thalomid®, Celgene Corporation, Summit, NJ), lenalidomide (Revlimid®, Celgene Corporation, Summit, NJ), pomalidomide (Pomalyst®, Celgene Corporation, Summit, NJ) and the proteosome inhibitors bortezomib (Velcade®, Millennium Pharmaceutical, Inc., Cambridge, MA) and Carfilzomib (Kyprolis®, Onyx Pharmaceuticals, Sunnyvale, CA). In fact, most patients diagnosed with MM will live at least 7 years, while some can expect to live more than 10 years (Kumar et al., 2012). Nearly all patients will receive bortezomib and lenalidomide throughout the disease trajectory (Kumar et al., 2012). With improved survival comes a higher prevalence of drug- and disease-related side effects.

Two of the most commonly used and widely studied drugs to treat MM include bortezomib and lenalidomide (National Comprehensive Cancer Network, 2014). The
proteasome inhibitor bortezomib is currently one of the most potent antimyeloma agents available. By interfering with the ubiquitin-proteasome system it leads to degradation of cell survival factors like nuclear factor kappa B (NFκB). Bortezomib also induces apoptotic and autophagic cell death at low concentration in myeloma cells. Bortezomib also influences the bone marrow microenvironment and angiogenesis in a way that interferes with myeloma cell survival, thus promoting myeloma cell death. Bortezomib enhances the efficacy of chemotherapy, immunomodulatory agents (thalidomide, lenalidomide and pomalidomide), and corticosteroids (prednisone and dexamethasone) (Anderson et al., 2006; Chanan-Khan et al., 2007; Magarotto et al., 2013; Palumbo et al., 2009; Richardson et al., 2003; Richardson et al., 2009; San Miguel et al., 2008).

Lenalidomide is a proprietary IMiD compound of Celgene Corporation. IMiD compounds have both immunomodulatory and antiangiogenic properties that confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess antiangiogenic activity through inhibition of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and tumor necrosis factor alpha (TNF-alpha) induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF (Dredge et al., 2005). Lenalidomide has been shown to be effective alone or in combination with other therapies (Baladandayuthapani et al., 2013; Khan et al., 2012; Kumar et al., 2012; Lazaryan et al., 2013). Continuous doses of lenalidomide have also been shown to improve survival (Attal et al., 2012; Facon et al., 2013; McCarthy, Owzar, Anderson, Hofmeister, & Hurd, 2010).
Cumulative Side Effects Are a Consequence of Longer Survival

Improved survival and a longer lifespan for patients with MM are counterbalanced by deleterious side effects and unpleasant symptoms from ongoing anti-MM therapy and/or from the disease. A major reason why patients are living longer is because more effective treatments are delivered continuously (Ludwig et al., 2012; McCarthy, Einsele, Attal, & Giralt, 2014; McCarthy et al., 2010; Richardson et al., 2013). As a result of the prolonged therapy and longer lifespan, patients with MM may develop one of two common symptoms: peripheral neuropathy or diarrhea.

Peripheral neuropathy and diarrhea symptoms are commonly cited as two side effects of MM therapy that affect one’s quality of life in a negative fashion (Richardson et al., 2012; Smith, Bertolotti, Curran, & Jenkins, 2008; Sonneveld et al., 2013). The PNP symptoms occur in as many as 83% of individuals as a result of disease progression, prolonged exposure to neurotoxic therapies, and the disease itself (Richardson et al., 2012). Moderate to severe PNP secondary to bortezomib generally occurs within 4 to 6 months and limits one’s ability to receive effective antmyeloma therapy with new and yet undiscovered agents (Broyl et al., 2012).

The consequence of diarrhea is significant and can be life-threatening. Late-onset diarrhea occurs in up to 38% of individuals from exposure to oral lenalidomide or quite possibly as an immune effect (Celgene Corporation, 2010; El-Cheikh et al., 2012; Kneppers et al., 2011). There are immediate implications of PNP and diarrhea. The severe PNP and diarrhea symptoms lead the patient to withdraw from treatment due to poor or ineffective management of the symptoms. Despite established guidelines to manage PNP and diarrhea in cancer, these symptoms remain inadequately managed, and
no effective preventative strategies exist (Benson et al., 2004; Richardson et al., 2012). Poorly managed PNP or diarrhea symptoms can lead to physiologic, psychologic, and social distress for patients who remain on the respective treatments for the sake of prolonged disease control (Mohty et al., 2010; Smith et al., 2008; Stephens, McKenzie, & Jordens, 2014).

**Peripheral Neuropathy and Oral Glutamine**

Patients with PNP experience a variety of sensations that range from mild discomfort and loss of sensation, painful burning, and muscle cramping to paralysis in the most severe cases (Richardson et al., 2012; Tariman, Love, McCullagh, & Sandifer, 2008). These deleterious effects are cumulative over time and can cause significant morbidity, limit a patient’s ability to receive the appropriate doses of anticancer medication, and lead to decreased cancer treatment compliance. Preserving nerve function is critical, as even mild PNP can prevent the individual from the benefit of existing and undiscovered agents to treat MM and lead to decreased cancer treatment compliance (Richardson et al., 2012).

Prescription and over-the-counter (OTC) pharmacologic agents can alleviate pain and PNP symptoms but do not prevent or reverse nerve damage and loss of function (Smith et al., 2013). Research is scarce in the area of PNP prevention, treatment, and management. Lack of research is surprising as PNP is cited as a major reason for discontinuation of anticancer therapy (Richardson et al., 2009). Further, no effective prevention for PNP exists. Enhanced treatment compliance, or one’s ability to remain on cancer treatment, may occur with improved management of PNP symptoms (Richardson, Laubach, Schlossman, Mitsiades, & Anderson, 2010).
Oral glutamine is an easily obtained over-the-counter (OTC) amino acid supplement that has been shown to decrease PNP in three studies of breast and colon cancer patients who embark on chemotherapy (Stubblefield et al., 2005; Vahdat et al., 2001; Wang et al., 2007). Anecdotal evidence suggests glutamine is effective in treating PNP in patients with MM receiving drugs such as bortezomib, lenalidomide, and thalidomide. In times of stress, glutamine transitions to an essential amino acid and is required to effectively nourish damaged nerve endings (Argyriou, Iconomou, & Kalofonos, 2008). Patients take glutamine to treat PNP symptoms, yet there have been no randomized controlled trials (RCTs) to date that have evaluated its efficacy and tolerability in the MM patient population. This is a concern as clinicians are recommending this OTC supplement to patients without evidence as to the efficacy of glutamine in the treatment of PNP in MM. Further, glutamine is easily available and relatively inexpensive as an OTC supplement compared to other prescription medications. As pilot studies serve to identify and address issues that could occur with respect to future study conceptualization, study design, sample size, sample selection, data collection, data management, and data analysis, these will be considered for this study (Jairath, Hogerney, & Parsons, 2000).

**Research Questions: Glutamine**

Glutamine can prevent or mitigate symptoms of PNP in patients in other cancers. Therefore it is imperative to study whether or not glutamine works in patients who embark on treatment with bortezomib to protect from nerve damage as even mild PNP can be devastating to the individual. Prior to conducting a large-scale research trial, it is important to determine three key factors that would impact a larger trial: consent,
adherence rates, and effect size. The consent rate would have a direct impact on planning how long it would take to recruit enough MM patients into the trial, with implications for funding and resources. In addition, determining the adherence rate to the intervention is critical. Asking patients with a chronic illness to take a supplemental medication twice daily could prove too taxing for individuals who are battling an incurable cancer and are faced with side effects from the cancer itself or from other medications. The effect size was used to estimate between group differences among severity of PNP and QOL, and to inform future research. Thus, a pilot to test the feasibility of glutamine as an intervention was conducted. The following research questions were be evaluated:

1. What is the proportion of eligible patients who provide informed consent for participation in the trial?

2. What is the adherence rate to the study intervention among patients who participated in the trial at 1 month?

3. What is the effect size of glutamine on the severity of PNP symptoms compared to placebo in patients treated with bortezomib at baseline and 4 months?

4. What is the effect size of glutamine on QOL at baseline and 4 months compared to patients who receive placebo?

These research questions and statistical methods are elaborated upon in Chapter 3.

**Lenalidomide-Related Diarrhea**

Multiple myeloma is an incurable cancer. Lenalidomide is an oral immunomodulatory agent commonly used to treat MM. Several large randomized trials have demonstrated longer rates of remission with continuous lenalidomide therapy (Attal et al., 2012; Facon et al., 2013; Falco et al., 2013; Kumar et al., 2011; McCarthy et al.,
2014; Mikhael et al., 2013; Rajkumar et al., 2010). Thus, patients with newly diagnosed MM will remain on continuous lenalidomide at a range from 24+ months in an effort to extend ones’ remission and decrease the likelihood of disease-related complications (Facon et al., 2013; Rajkumar et al., 2010). Unfortunately, 27% to 38% of patients on long-term lenalidomide have diarrhea as a late side effect of the treatment and at a severity that reduces their quality of life and ability to function (Celgene Corporation, 2010; Simpson, Rajkumar, Lacy, Hayman, & Roy, 2008).

Diarrhea is a major clinical problem for several reasons. First, the diarrhea can be life threatening. Poorly controlled diarrhea can lead to dehydration, nutritional deficiencies, electrolyte imbalances, and hospitalizations (Stephens et al., 2014). Diarrhea is often severe enough to warrant discontinuation of the anticancer drug. Evidence exists in MM patients that stopping the drug or switching to another drug can lead to shortened time to progression compared to individuals who receive continued doses and stay on treatment (Facon et al., 2013; Fouquet et al., 2013; Kourelis et al., 2014). When MM patients are off of anticancer treatment they are not only at risk for organ damage from the disease, but the disease may be more difficult to control at relapse (Lonial, Mitsiades, & Richardson, 2011; San Miguel & Mateos, 2011).

Second, for patients who remain on the drug, the diarrhea symptom is often inadequately or suboptimally controlled. Failure to control symptoms will impact treatment compliance and affect one’s quality of life. Psychological distress from the symptom can occur. The use of long-term antidiarrheal therapy to prevent or mitigate diarrhea is often required but not always effective at controlling the symptom (Reece et al., 2012).
Third, the true etiology of diarrhea is unknown. Diarrhea in patients with MM can stem from immunologic, inflammatory, or infectious causes, and diarrhea as a manifestation of illness can change over time. As the cause of one’s diarrhea in MM is unclear, targeted interventions to appropriately treat the diarrhea are unknown. Knowledge of the root cause of diarrhea would lead to appropriate interventions to control the symptom. Scientific evidence is needed to determine the cause of diarrhea so symptoms can be better managed.

Immunoglobulin A (IgA) deficiency may play a role in the diarrhea observed in MM patients. One or more uninvolved immunoglobulins were reduced in 87% to 91% of patients, and both serum IgA and IgM were reduced in 65% to 73% in two epidemiologic studies (Kastritis et al., 2014; Kyle et al., 2003). IgA deficiency at diagnosis may be due, in part, to elevated clonal Ig levels, but preserved or normal Ig levels may have a longer progression-free survival (PFS) interval (Kastritis et al., 2014).

The main function of IgA is that IgA mediates immune surveillance in the gastrointestinal (GI) tract. Low levels of IgA can cause diarrhea in a multitude of disorders, although the true underlying mechanism of the diarrhea symptom in patients with IgA deficiency is unclear (Baumgart & Sandborn, 2012; Chow, Lebwohl, Reilly, & Green, 2012). Diarrhea is not a common presenting symptom at the initial MM diagnosis but rather a later side effect of lenalidomide therapy, despite the high percentage of patients with IgA deficiency (Kyle et al., 2003).

There has been physical evidence to show that diarrhea is a sign of an immune effect in MM patients. First, diarrhea is commonly seen as an autoimmune symptom in patients with graft-versus-host disease (GVHD). Graft-versus-host disease occurs when
transplanted donor cells react to foreign host cells. The diarrhea is caused by loss of cells that cover the inside of the bowel, leading to loss of fluids and proteins from the body. The small bowel, particularly the terminal ileum, is the main target of the GVHD reaction (Ketelsen et al., 2011). Histopathologic findings of an autoimmune effect secondary to GVHD are characterized by intestinal crypt cell apoptosis or crypt cell loss on biopsy (Shidham et al., 2003). Graft-versus-host disease correlates MM disease control in MM patients who undergo high-dose chemotherapy and stem cell transplantation despite whether the cells were from a donor graft (“allogeneic”) or from the patient (“autologous”) (Cogbill, Drobyski, & Komorowski, 2011; Giralt, 2005).

Second, our group at the Cleveland Clinic has observed a possible immune effect of lenalidomide. We have obtained colonoscopies with biopsies in patients with severe lenalidomide related diarrhea and with excellent long-term MM disease control to rule out amyloidosis or other disorders. In these patients we unexpectedly found changes reminiscent of mild GVHD with crypt apoptosis and lymphocyte infiltration.

Third, the mechanism of action of lenalidomide further supports a possible autoimmune effect. Lenalidomide is an immunomodulatory drug with multiple cellular and molecular effects that modulate the immune system. Lenalidomide acts in part through enhanced natural killer (NK) cell stimulation, inhibits proinflammatory cytokines and has been associated with GVHD after allogeneic stem cell transplantation (Cogbill et al., 2011; Lioznov et al., 2009; Lokhorst et al., 2010; Wu et al., 2008; Zhu, Kortuem, & Stewart, 2013). Diarrhea with long-term lenalidomide therapy has been observed in our study and another study, but it is unclear if the diarrhea is a positive prognostic sign of an
autoimmune effect which allows patients to remain on therapy and in remission (Faiman et al., 2013).

Based on histopathologic findings of diarrhea as a symptom of an immune effect in patients with GVHD, internal histopathologic findings at our institution, and lenalidomide's mechanism of action, we hypothesize that an autoimmune process might underlie diarrhea. The diarrhea can be a long-term side effect of MM. Here we hypothesize that diarrhea may be a surrogate for stimulation of an anticancer immune response triggered by lenalidomide where immune inhibitory signals are broken, resulting in excess activity in the intestinal mucosa.

Diarrhea is a GI manifestation of illness that can be primarily classified as due to an infectious, inflammatory, or immune phenomenon (Conner & Blutt, 2013; Grundmann & Yoon, 2014; Siah, Wong, & Ho, 2014; Surawicz et al., 2013). The mechanistic role of IgA in the physiologic process of diarrhea is unclear despite IgA immune deficiency being closely correlated with the diarrhea symptom.

The diarrhea symptom was examined from an opposite angle based on the hypothesis that perhaps the diarrhea is not due to a GVHD-like immune effect from lenalidomide. In contrast, the diarrhea may be from another cause. Immune disorders exist that are characterized by low serum IgA levels and diarrhea (Conner & Blutt, 2013). An alternate physiologic explanation for diarrhea relates to IgA and was explored.

IgA plays a central role in maintaining GI homeostasis. A low level of serum IgA leads to more diarrhea in some individuals. Immune reconstitution occurs in individuals with primarily clonal IgG-type MM and is observed when patients achieve normal levels of serum IgA with effective disease control during treatment. As the IgA level
normalizes, the diarrhea should resolve. If the alternate hypothesis is true, this means the diarrhea is related to an immune effect and not low levels of serum IgA. As such, a second research question was warranted to explore the relationships between levels of serum IgA and diarrhea at baseline and at 6, 12, and 24 months. The question also asked whether low levels of serum IgA at diagnosis lead to a weakened GI immune system and predispose the individual to develop diarrhea as a late side effect of prolonged treatment with lenalidomide. It was hypothesized that patients with LRD would do the best, stay on drug the longest, and have the best immune reconstitution of IgA levels. It was also determined if IgA levels normalized in patients who did not have diarrhea and if normalization of IgA levels protects the individual against diarrhea.

**Research Questions: Diarrhea**

While a detailed study of the pathologic mechanism of diarrhea in patients who receive lenalidomide is beyond the scope of this dissertation, the study evaluated (1) whether diarrhea is a positive prognostic sign, (2) explored whether LRD could be surrogate of an effective antitymoma immune response triggered by lenalidomide, or in contrast, (3) whether LRD might be related to immunodeficiency. Each of these evaluations would, independent of whether the mechanistic hypothesis is correct, be clinically important. Duration of response would provide a rationale for future studies to outline the exact mechanism. A second question is explorative in nature and focuses on the significance of IgA levels at diagnosis.

The objectives were to investigate the diarrhea phenomenon and entertain the hypothesis that diarrhea is actually a sign of deficient immune system, that low serum IgA levels predispose the individual to develop LRD, and that immune reconstitution, or
normalization of serum IgA levels, protects against LRD. We hope to find that individuals who experience LRD would have high or normal IgA levels ("immune reconstitution") at the onset of diarrhea. Normal IgA levels at the onset of diarrhea or improvement in diarrhea and IgA levels over time would support the argument of immunologic cause of diarrhea. My research questions were as follows:

1. Do patients with LRD have a longer duration of response (DOR) to lenalidomide compared to patients who do not develop LRD?

2. Do low IgA levels in IgG myeloma correlate with lenalidomide-related diarrhea at baseline, 6, 12, and 24 months?

A third research question to address QOL measures was considered. The retrospective data needed for any QOL evaluation are not available.

**Theoretical/Conceptual and Physiologic Frameworks**

Theoretical and physiologic frameworks guided the two studies. The Symptom Management Model conceptualization would be used to inform both PNP and diarrhea symptoms studies. First proposed by Dodd et al. (2001), the model illustrates the complexity and interrelatedness of the cancer symptom experience over time and provides symptom management strategies and outcomes (Figure 2) (Brant et al., 2010; Dodd et al., 2001). The model acknowledges the following: (1) The study of symptoms is based on the perception of the individual who experiences the symptom, (2) a person does not have to experience the symptom but may be at risk to develop the symptom and should be monitored should the symptom emerge, and (3) symptom management is a dynamic process, and symptoms are modified by domains of person, health/illness, and the external environment (Dodd et al., 2001).
Figure 1. Symptom Management Model

The model aims to enhance the understanding, identification, and intervention of patient-reported symptoms throughout the patient’s ever-changing disease trajectory. Each of the studies sought ways to use working evidence of biologic processes to better understand the symptoms and reduce the symptom experience, as PNP and diarrhea are symptoms of underlying disease. Physiological processes that underlie the symptoms affect the patient’s perception of the symptoms. The Symptom Management Model was used as a guide to either modify or examine underlying physiological causes while

measuring the patient’s subjective report, in order to see how both process are related to each other.

Physiological alterations underlie cancer symptoms. Specifically, the Symptom Management Model acknowledges the longitudinal and fluid nature of the complex cancer symptom experience and identifies pathophysiologic antecedents such as immune function and inflammation, which are critical elements of the PNP and LRD studies.

The PNP study sought to improve the individual’s health status by decreasing symptom severity through the use of a glutamine intervention to effectively enhance ones’ quality of life. Thus, Dodd’s Model of Symptoms was applied in the PNP study through the use of (1) validated quantitative measures that capture and account for the patients’ subjective experience (quality of life and severity) whether the individual experiences the PNP symptom or is at risk to develop the symptom, and (2) calculation of adherence rate as nonadherence to the glutamine intervention may impact the outcome of the glutamine intervention and negatively affect the individual’s overall symptom experience.

The Model of Symptoms is closely aligned with the diarrhea study as the basis for calculating diarrhea symptom severity is by patient self-report. Patient self-report is the key mechanism that was used during chart review to determine diarrhea symptom severity and the need for pharmacologic intervention. Dodd’s Model encompasses the importance of identifying the underlying biology of the symptom the use of working evidence of a biological process to study the diarrhea symptom. Knowledge gained from the two studies was used to provide strategies to support the person through both
symptoms, seeks to understand the biology that underpins the symptoms, and generate future research in peripheral neuropathy and diarrhea symptom management.

Symptom research, in general, is impacted by patient report, which affects the overall symptom experience. The nurse’s understanding of the patient’s symptom experience (which includes severity) relies on the patient’s perception of the symptom, response to symptom stimulus, and nurse/patient communication of the symptom. Symptom research is challenging because there is often a discordance between what the patient is feeling and what is communicated to the nurse, which has implications for nursing care. Nurses are charged with the identification and intervening with symptoms to improve the patient outcomes, but whether patients underrecognize, underreport, or do not want to discuss the symptoms has a direct impact on the patient.

Dodd’s Model acknowledges the complexity of the PNP and LRD symptom experience. Effective management of symptoms is an essential component of the nursing care of the MM patient. The model supports selecting clinical interventions to bridge symptoms. By addressing emotional, functional, and social factors that may influence patient outcomes, the symptoms can be addressed and improved. Particularly important for nursing interventions is the role of the nurse in educating patients about the symptom management regimen, including education about how to take oral medications such as glutamine, about likely symptoms that may be distressing, such as diarrhea, and techniques for self-management.

A physiologic framework for both studies was used as an adjunct to the theoretical framework. Dodd’s Model highlights the importance of understanding the physiologic
basis for symptoms, yet the two physiologic frameworks provide specific scientific knowledge and basic scientific rationale for the two studies.

The physiologic framework for the PNP study is based on preclinical research. In animal models the administration of bortezomib can induce sensory and motor peripheral neuropathy by deregulation of neurotrophins in multiple myeloma cell lines and blocks nerve growth factor (NGF) through inhibition of NF-kB (Richardson et al., 2003), thus impairing axon structure and function (Cavaletti et al., 2007; Meregalli et al., 2010). Glutamine can become depleted in times of catabolic stress and cancer and conditionally transition into an essential amino acid. Glutamine has been shown to upregulate NGF in animal models. Hence, administration of glutamine may prevent PNP symptoms in patients with MM through upregulation of NGF.

The physiologic framework for the LRD study is based on prior research and the etiology of diarrhea in patients with MM and immunologic disorders. Diarrhea is a symptom of gastrointestinal GVHD and diarrhea is commonly seen in IgA immunologic disorders. GVHD occurs when immune-competent T cells recognize immunoincompetent recipient tissues as foreign and attempt to destroy them. The loss of crypt cells leads to the diarrhea symptom characteristic of gastrointestinal GVHD. The loss of immunoprotective cells triggers a complex immunologic response. The presence of gastrointestinal GVHD is favorable for MM patients and translates to a longer duration of response in previous research (Lokhorst et al., 2010). In addition, the immune-modulating agent lenalidomide possesses a multitude of immunologic properties that can affect the intestines and has been associated GVHD after allogeneic stem cell transplantation (Dredge et al., 2005; Lioznov et al., 2009; Wu et al., 2008). Therefore, it
is hypothesized that an autoimmune process might underlie diarrhea in patients on lenalidomide.

The Symptom Management Model and physiologic frameworks are integral to this research. The PNP project was a small, pilot intervention that relies on physiologic basis of glutamine, aims to correct altered physiologic processes and alleviate the unpleasant PNP symptoms. The LRD project seeks to understand physiologic and external processes causing diarrhea to determine if diarrhea is a positive symptom of survival from a proposed immune effect. Insight into the cause of diarrhea can lead to better-targeted interventions to alleviate the unpleasant diarrhea symptom. Decreased physiologic PNP or diarrhea symptoms will improve patient tolerability of cancer treatment, compliance with treatment, and overall QOL.

**Theoretical Definitions of Peripheral Neuropathy and Diarrhea**

Peripheral neuropathy is the dependent variable in the PNP study and conceptually defined as the end result of peripheral, motor, sensory, and autonomic neuron damage secondary to neurotoxic chemotherapy agents (Visovsky, Collins, Abbott, Aschenbrenner, & Hart, 2007). For the purpose of the PNP study, peripheral neuropathy was theoretically defined as a symptomatic process that includes changes in nerve sensation or motor symptoms from baseline. Bortezomib-induced peripheral neuropathy (BIPN) describes PNP that occurs as a result of bortezomib administration.

Diarrhea is a disorder characterized by frequent and watery bowel movements (National Institutes of Health, 2009). An increase in frequency of bowel movements to more than three stools is routinely used as a definition for epidemiologic investigations (Guerrant et al., 2001). Diarrhea can be acute or chronic. Diarrhea from infectious
etiology is often accompanied by symptoms such as nausea, vomiting, or abdominal cramping and lasts less than 14 days in duration. Chronic diarrhea lasts in excess of 30 days (Guerrant et al., 2001). For purposes of this study, LRD was theoretically defined as a symptom in which patients experience chronic diarrhea that affects one’s quality of life and warrants pharmacologic or nonpharmacologic management on behalf of the patient and/or provider (National Institutes of Health, 2009).

**Innovation and Significance**

The PNP study is the first of its kind to evaluate the use of glutamine to minimize or delay the onset of PNP symptoms in patients with MM as glutamine has never been studied in MM. Hence, this research brings first-hand evidence and in-depth information into the effect of OTC glutamine in this population. The proposed mechanism behind LRD has never been investigated despite diarrhea being a very common symptom of long-term lenalidomide use. Therefore LRD study provides valuable first evidence as to the biology of the diarrhea symptom.

Both studies are significant as they address potentially devastating symptoms in patients with an incurable but highly treatable chronic cancer. The PNP study seeks to address a potentially debilitating symptom, peripheral neuropathy. LRD study addresses a symptom that could be life threatening. Diarrhea can cause fluid and electrolyte imbalance and place patients at risk for kidney failure, altered skin integrity, and decreased quality of life. Also, there are no trials to date that have studied the diarrhea phenomenon as it relates to lenalidomide, which is a commonly used agent to treat MM. We anticipate that insight into lenalidomide-related diarrhea would provide an
opportunity to identify individuals at an increased risk to develop the diarrhea and create targeted strategies to prevent or treat this distressing symptom.

The PNP and diarrhea projects are relevant to nursing science as nurses are well-poised to generate hypotheses and answer questions to enhance symptom management. The data derived from the two proposed studies provide an opportunity for nurses to stratify each individual’s risk of PNP and diarrhea during therapy and design personalized interventions. With treatment tailored to the individual, the practitioner can test the value of personalized interventions to reduce the impact of cancer treatment-related side effects.
Chapter 2: Literature Review

State of the Science

Introduction

The focus of Chapter 1 was on the background, problem, research questions, and theoretical frameworks that guided the two symptom studies: peripheral neuropathy and diarrhea. Bortezomib and lenalidomide are the two drugs most commonly used to treat MM. Nearly all individuals with MM will receive one or both drugs over their lifespan. In Chapter 2, a thorough review of the literature was performed to identify current knowledge as it pertains to peripheral neuropathy and diarrhea. In the first section, peripheral nerve physiology, measurement of neuropathy, and known prevention and treatment strategies were reviewed. In the second section, a brief review of GI physiology, specific causes of diarrhea, and known treatment strategies was discussed.

Peripheral Neuropathy

Physiology

To understand the pathology of PNP, the normal neurophysiologic function of the nervous system must be reviewed. Each peripheral nerve (neuron) fiber consists of an axon surrounded by Schwann cells that form a myelin sheath, a cell body, and dendrites that synapse with other nerves. The cell bodies of sensory neurons are bundled together within the dorsal root ganglia (DRG). Motor nerve cell bodies are located in the ventral spinal cord. The motor and sensory neurons are responsible for different sensory and motor actions. Large, myelinated neurons are responsible for vibration, proprioception, and light touch, while small, myelinated sensory neurons transmit impulses for
temperature. Pain impulses can be transmitted by either small myelinated or unmyelinated nerve fibers (Poncelet, 1998).

Figure 2. Peripheral Nerve Structure and Organ Innervation

Characteristics of Bortezomib-Induced Neuropathy in MM

Self-reported PNP in patients with MM can be as high as 10-13% in MM prior to treatment (Gorson & Ropper, 2002; Ropper & Gorson, 1998). In addition, several trials have used bortezomib in patients with MM, and a high incidence of PNP was reported (Harousseau et al., 2006; Jagannath et al., 2009; P. G. Richardson et al., 2010; San-Miguel, Harousseau, Joshua, & Anderson, 2008). Most studies have reported an incidence of mild to moderate PNP up to 80% by the end of treatment, and about 10% to 20% of patients need to discontinue treatment because of PNP (Dimopoulos et al., 2010; Jagannath et al., 2009; Richardson et al., 2006).
Bortezomib can induce sensory and motor PNP in the individual through unclear mechanisms. One hypothesis is bortezomib can lead to disregulation of neurotrophins in MM cell lines (Richardson et al., 2003). Damage to the small fiber axons responsible for the detection of pinprick sensation and temperature changes are often affected by bortezomib, as well as large fiber sensory axons responsible for vibratory sense, proprioception, and muscle contraction (Mileshkin et al., 2006; Visovsky et al., 2007; Wolf, Barton, Kottschade, Grothey, & Loprinzi, 2008). Bortezomib-induced peripheral neuropathy represents a common toxicity of this agent as patients are unable to receive the prescribed doses of this antimaloma therapy and BIPN is the most common reason for dose reduction and discontinuation of the drug (Anderson et al., 2006).

Bortezomib-induced peripheral neuropathy usually develops within the first 4 months of treatment and is more severe in the presence of preexisting PNP. In some cases, severe and life-threatening neurotoxicity (or PNP) has been reported (Argyriou et al., 2008; Badros et al., 2007). Age, gender, diabetes, heart disease, and alcoholism may contribute to the worsening of PNP in other cancers but have not been cited as covariates in MM (Ropper & Gorson, 1998). Neuropathy symptoms can be reversed to some degree with dose reductions or discontinuation of bortezomib, but complete resolution of PNP is rarely seen (Argyriou et al., 2008; Richardson et al., 2006).

**Prevention and Treatment of Peripheral Neuropathy**

To date no interventions have been documented to prevent or treat bortezomib-related neuropathy causally although the pain can be alleviated with symptomatic therapy (Argyriou et al., 2008). Dose reduction, a change to subcutaneous route of administration, and discontinuation of bortezomib with the onset of moderate PNP are recommended to
prevent worsening and help resolution (Faiman et al., 2013; Millennium Pharmaceuticals, 2009; Moreau et al., 2011; Richardson et al., 2012; Richardson et al., 2009; Velasco et al., 2010) but this may come at the expense of inferior disease control.

The most widely studied OTC supplements with varying suggested benefits include glutamine, B vitamin group, magnesium, potassium, glutathione (Cascinu et al., 2002; Vahdat et al., 2001) alpha-lipoic acid (Ziegler, Nowak, Kempler, Vargha, & Low, 2004), l-carnitine (Bianchi et al., 2005), and vitamin E (Argyriou et al., 2008; Pace et al., 2003). These supplements may have activity in the prevention and treatment of PNP, but the most promising data have been with glutamine. A naturally occurring nonessential amino acid, glutamine is easy to use, well absorbed, and cost-effective (Hall & Heel, 1996; Klimberg et al., 1992). A widely studied nutraceutical, there are currently over 100 trials displayed on the www.clinicaltrials.gov website that are studying glutamine in alleviating various side effects in cancers, diabetes, and nutrition.

Two key studies support the safety and efficacy of oral glutamine in the prevention of cancer treatment-induced PNP (Vahdat et al., 2001; Wang et al., 2007). In a randomized controlled pilot trial of 86 patients with metastatic colorectal cancer, the addition of 30 grams of glutamine per day resulted in fewer dose reductions of oxaliplatin and a lower incidence of PNP (all grades) after 2 and 4 cycles of treatment (59% and 43.3%), respectively. Specifically, after 4 cycles there was a 73.6% difference in severe grade 3-4 neuropathy in the glutamine versus placebo group, which decreased the need for oxaliplatin dose reduction. Response rates were not significantly different in this small trial (52.4% and 47.8% for glutamine and no glutamine groups, respectively).
which suggests that glutamine does not interact with the efficacy of the chemotherapy regimen (Wang et al., 2007).

Prior research has reported the efficacy and safety of glutamine to ameliorate PNP in other cancers. Even mild neuropathy can produce alterations in touch and temperature sensations that can negatively affect one’s quality of life. To date, no effective prevention or treatment exists. Therefore the effect of glutamine on neuropathy symptoms in MM is important to study.

PNP is the major dependent variable in the neuropathy study. Measurement issues related to the concept of peripheral neuropathy exist as measurement of PNP is both objective and subjective in nature. Objective instrumentation measurement of PNP includes techniques such as electrophysiologic (EPS) testing and nerve conduction studies (NCSs) (Mileshkin et al., 2006). Patient self-report of the PNP symptom provides valuable insight into the severity of the symptom (Griffith et al., 2014; Smith, Cohen, Pett, & Beck, 2011).

Measurement of Peripheral Neuropathy

There is no gold standard for measurement of peripheral neuropathy (Visovsky et al., 2012; Visovsky, 2009). Electromyography (EMG) is a technique that involves the placement of a needle into various muscles to record different stages of muscle activity, including rest, contraction, and activity. This technique can be useful to detect abnormal motor neuropathy. This study uses needles, which may be painful, although small-gauge needles are increasingly more common and allow patients to endure this procedure (Preston & Shapiro, 2005).
Nerve conduction studies can be performed to diagnose PNP. The NCS test measures the amount of electrical charge delivered to a nerve. The velocity and action potential are measured, which allows the neurologist to look at the myelination of the nerve and amplitude of muscle contraction. This procedure can aid in categorizing the pathophysiology of the peripheral neuropathy as demyelinating, axonal, or mixed (Preston & Shapiro, 2005).

There are limitations to EMG and NCS techniques in diagnosing PNP. First, small fiber type is the most common type of PNP in patients receiving treatment for MM. Unfortunately, each NCS and EMG testing assesses only large nerve fibers, which have little involvement in pain, which is a major manifestation of PNP. Further, the individual may have neuropathic pain and normal diagnostic studies. Thus, clinician examination and patient self-report is the standard of care of most practitioners in the evaluation and management of PNP in MM (Poncelet, 1998).

The Neuropathy Impairment Score – Lower Limbs (NIS-LL) is an objective measurement of PNP symptoms. Summed scores range from 0 to 88 of standard items of the neuromuscular examination with three subgroups in three areas. The following are points possible: muscle strength (64); sensory testing assessed by touch pressure, pinprick, vibration, and joint position (16); quadriceps and ankle reflexes (8). Zero reflects no impairment and higher scores represent significant impairment (Bril, 1999). The NIS-LL is a comprehensive objective measure of sensory, muscular, and motor impairment characteristic of BIPN without EMG testing. This instrument is useful in MM as previous studies demonstrate that the NIS-LL is able to detect neurological deficits in response to intervention in patients with small fiber neuropathy in other trials (Apfel et
A mean change in NIS-LL of 2 points difference between comparison groups (not the individual patient score) was classified as having meaningful clinical change as defined by the Peripheral Nerve Society Consensus Committee (Bril, 1999; Dyck, 1995); see Appendix A.

One of the most common subjective self-report measures for PNP symptoms that has been validated in the cancer literature is the GOG-Ntx neuropathy subscale. This 11-item questionnaire addresses patient-reported concerns presumed to be associated with chemotherapy-induced peripheral neuropathy (Calhoun et al., 2003; Cella et al., 1993; Cella & Webster, 1999; Cella et al., 2006; D. Cella et al., 1993). This instrument with scores ranging from 0-44 on a continuous scale has been validated in patients with neurotoxicity associated with ovarian cancer chemotherapy and has been used in several MM studies (Richardson et al., 2006). The reliability and validity of the GOG-Ntx neuropathy subscale have been established with Cronbach’s alpha of 0.70 or greater.

The degree of PNP in the neuropathy study was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events CTCAE (NCI-CTCAE) v4.0. The CTCAE is a 0 to 5 scale that assesses severity of neuropathy related to cancer therapy with higher scores meaning more symptoms. This continuous scale has been most widely used in all types of neuropathy research and allows correlation among groups compared with previous studies.

**Diarrhea**

Diarrhea is an often neglected and undertreated aspect of symptom distress in patients with MM (Hoff et al., 2014; Muehlbauer et al., 2009). Reasons for diarrhea are...
multifactorial and can be related to chemotherapy, a weakened immune system, medications, nutritional supplements, psychologic stress, infection, GVHD, or the cancer itself (Benson et al., 2004). Ineffective diarrhea management can lead to altered physiologic and psychologic processes.

Physiologic consequences of mild diarrhea include electrolyte abnormalities, malabsorption of oral medications and impaired nutritional status while more severe symptoms can cause death (Benson et al., 2004; Hoff et al., 2014; Maroun et al., 2007; Muehlbauer et al., 2009; Sun, Wang, & Hu, 2012). Psychologic consequences include social isolation, low self-esteem, anxiety, and hopelessness (Smith et al., 2008). Ineffective management of diarrhea not only leads to poor clinical outcomes but also has a negative impact on quality of life, including alteration of roles, responsibilities, and interpersonal relationships, and it can cause social isolation (Muehlbauer et al., 2009).

**Physiology of the Gastrointestinal Tract**

The GI tract is a complex system responsible for the disintegration of solid foods, bioavailability of nutrients, and excretion of unnecessary waste (Kong & Singh, 2008). The human gut microbial environment plays a central role in immune protection and contains cells from over 1,000 different bacterial species. Disruption of the normal intestinal flora has been linked to GI illnesses (Nitzan, Elias, Chazan, Raz, & Saliba, 2013). The upper GI tract consists of the esophagus, stomach, and duodenum. The lower GI tract includes the small and large intestines. The motility of the GI tract allows food and excrement to be pushed through the tract and produce bowel movements (Figure 3).
The small intestines are further divided into the duodenum, jejunum, and ileum. Digestive juices from the gall bladder and pancreas mix in the duodenum to break down proteins, bile, and facilitate digestion. Products of digestion are absorbed through intestinal villi, or fingerlike projections that protrude from the intestinal wall in the jejunum, and released into the bloodstream. Additional villi are present in the ileum,
where nutrients and vitamins such as B\textsubscript{12} are absorbed (DeSesso, Jacobson, Williams, & Lyubimov, 2011).

Intestinal crypts are glands found within the small intestinal mucosa and intestinal villi. The crypts and intestinal villi are covered by epithelium, which contains the mucous-secreting goblet cells and enterocytes, which are responsible for water absorption and nutrient secretion. Pathologic processes such as inflammatory bowel disease, colitis, or GVHD can affect the crypt cells and lead to crypt cell loss (Lin, Fan, Zhao, Cummings, & Chen, 2013; Umar, 2010).

The large intestines are comprised of the cecum and the colon. The main function of the large intestines is to absorb water and facilitate excretion of stool. The four parts of the colon are the ascending, transverse, descending, and sigmoid segments. The colon connects to the rectum and then the anal canal. The GI tract terminates with the anus. Crypt goblet cells have the ability to regenerate the mucus layer throughout the GI tract by secretion, as mucous plays an essential role in GI immune protection (Johansson, Sjovall, & Hansson, 2013).

**Pathobiology of Diarrhea**

Four basic pathophysiologic mechanisms are involved in the production of diarrhea. These include (1) abnormal intestinal motility, (2) increased vascular or fluid permeability, (3) impaired intestinal absorption, and (4) intraluminal absorbable solutes. Diarrhea is further characterized as acute or chronic. Acute diarrhea is usually transient and may be have infectious, toxic, or dietary causes. Chronic diarrhea may be secondary to functional bowel disorders, colonic disease, diseases of the small intestine, or drugs.
Once the individual with MM develops chronic diarrhea, the etiology must be determined.

**Etiology of Diarrhea**

Diarrhea, a gastrointestinal manifestation of illness, can be classified as due to one of four factors: infection, inflammation, malignancy, or an autoimmune phenomenon.

*Diarrhea due to infection.* Over 200 million cases of enteric illness occur in the United States per year (Guerrant et al., 2001). Transmission of viral illness occurs from person to person, water, or food. Infectious diarrhea is often acute and transient but can be life-threatening in even healthy individuals (Surawicz et al., 2013). The most common type of intestinal infection in patients with MM is *Clostridium difficile* (Kinnebrew et al., 2014; Nucci & Anaissie, 2009a, 2009b; Tam, Viviani, Rodrigues, & O'Brien, 2013). Infectious diarrheal illnesses are diagnosed based on symptoms history and stool culture (Hong & Rhee, 2014; Kinnebrew et al., 2014; Surawicz et al., 2013).

*Diarrhea due to inflammation.* Intestinal inflammatory disorders will predispose patients to develop diarrhea (Abraham & Cho, 2009; Nitzan et al., 2013). Two main types of inflammatory disorders include Crohn’s disease (CD) and ulcerative colitis (UC) (Baumgart & Sandborn, 2012; Danese & Fiocchi, 2011; Moris, 2014). Both CD and UC can be confirmed by a structural abnormality. Ulcerative colitis, a disease of the colonic mucosa, can be cured with colectomy (Danese & Fiocchi, 2011; Moris, 2014). Crohn’s disease affects the entire gastrointestinal tract from the mouth to the anus (Baumgart & Sandborn, 2012).

Irritable bowel syndrome (IBS) is a common and potentially disabling functional gastrointestinal inflammatory disorder characterized by abdominal pain, bloating, and
erratic bowel patterns (Lee & Park, 2014). Unlike UC and CD, symptoms of IBS cannot be confirmed by a structural abnormality rather the syndrome is likely related to a multitude of disorders. Current research into IBS includes possible etiologies such as low-grade inflammation, altered intestinal flora, and/or infection (Dai, Zheng, Jiang, Ma, & Jiang, 2013; Hong & Rhee, 2014; Konig & Brummer, 2014). A psychological component of IBS focuses on a brain-gut interaction, as there is a high prevalence of psychiatric disorders observed in patients with IBS (Hong & Rhee, 2014; Lee & Park, 2014). No biochemical, histopathologic, or radiologic diagnostic test to diagnose IBS currently exists, and the diagnosis of IBS is based on patient history and symptom assessment (El-Salhy, 2012). Probiotics (Dai et al., 2013), 5HT-3 receptor antagonists (Itagaki et al., 2014), melatonin (Siah et al., 2014), and alternative therapies such as hypnosis, cognitive therapy, and acupuncture have all been studied (Grundmann & Yoon, 2014).

*Diarrhea due to malignancy.* Diarrhea can occur as a result of malignancy. Types of cancers include colon, endometrial, ovarian, and sarcoid as well as T-cell lymphoma (Cho, Kim, Cho, Bae, & Kim, 2002; Kim et al., 2013).

*Diarrhea due to immunodeficiency and the role of IgA in the intestines.* Various forms of immune regulation occur along the length of the intestine depending on the site of the challenge, such as food in the small bowel or intestinal flora (Agarwal & Mayer, 2013). The intestines play a central role in maintaining homeostasis within the immune system (Lamm & Phillips-Quagliata, 2002). Two main cells within the intestines are essential to immune function: gut-associated lymphoid tissue (GALT) and mucosal-associated lymphoid tissue (MALT) (Weiner, 2000).
The bulk of the body's immunoglobulin producing cells reside within the intestinal tract. It is estimated that 80% of plasma cells with IgA predominance reside within GALT (Vighi, Marcucci, Sensi, Di Cara, & Frati, 2008). Immunoglobulin A triggers immune response and effectively binds to proteins, toxins, and foreign invaders against environmental antigens and local microbial flora to maintain homeostasis and provide protective immunity against viruses (Conner & Blutt, 2013). IgA antibodies represent the first line of immune defense against the external environment (Lamm & Phillips-Quagliata, 2002). In primary immune IgA deficiency, decreased IgA levels (less than < 7 mg/dL with normal or increased levels of other immunoglobulins) may be the result of immune dysfunction in the regulation of terminal maturation of B cells into IgA-secreting plasma cells (Agarwal & Mayer, 2013).

**Graft-versus-Host Disease Related Diarrhea.** Graft-versus-host disease is immune related and the most frequent complication after donor allogeneic hematopoietic cell transplantation (HCT) in MM (Deeg, 2007; Lokhorst et al., 2010). The pathogenesis of allogeneic graft-versus-host disease is complex and attributable to immune cell injury induced by chemotherapy prior to stem cell transplantation (Hou et al., 2013). In GVHD, antigenic presentation from the donor (“graft”) to the host (patient) leads to donor T-cell lymphocyte activation and immune system stimulation (Cogbill et al., 2011).

Intestinal GVHD has been reported after nondonor autologous HCT and GVHD plays a role in MM disease-free survival (Melson, Jakate, Fung, Arai, & Keshavarzian, 2007). Histopathologic findings of crypt mucosal cell loss or abnormalities are evident on colonic biopsy. Crypt loss is a hallmark of GVHD and a marker of GVHD severity (Melson et al., 2007). Colon biopsy specimens are graded on a severity scale. Grade 1
shows isolated crypt apoptosis of epithelial cells, and grade 4 shows extensive crypt loss (Cogbill et al., 2011; Sale, Lerner, Barker, Shulman, & Thomas, 1977).

**Measurement of Diarrhea**

Diarrhea is measured according to national guidelines and patient self-report. In randomized, controlled, prospective trials, the Infectious Disease Society of America (IDSA) and/or NCI-CTCAE grading scale version 4.0 may be used. The IDSA defines diarrhea as three or more loose stools per day, and the NCI-CTCAE v. 4.0 considers the severity of one’s diarrhea (Guerrant et al., 2001). The NCI-CTCAE v. 4.0 is a standardized grading system to report treatment-related adverse events. Diarrhea is graded in severity from 1 through 5. Grade 1 is mild, while grade 5 defines a death-associated event. A second mechanism of diarrhea quantification in retrospective studies is patient self-report. A patient’s self-report of diarrhea severity is useful to monitor the severity of the diarrhea symptom and determine the need for intervention (National Institutes of Health, 2009).

*Characteristics of Lenalidomide-Related Diarrhea.* Little is known about the characteristics of LRD, as the concept of LRD itself has not been extensively studied. One review reported the onset of moderate to severe diarrhea in long-term lenalidomide therapy to occur at 19 months (Simpson et al., 2008). Similarly, our center reported onset of diarrhea on lenalidomide to occur at a median of 17.7 months (Faiman et al., 2013). The diarrhea observed in each retrospective analysis was classified as chronic and an increase in stool output from baseline and not graded by other means.
Prevention and Treatment of Diarrhea

There are few effective prevention or treatment strategies for lenalidomide-related diarrhea in MM. In addition, current management strategies fail to resolve the diarrhea symptom in a majority of cases. Guidelines exist to prevent and treat chemotherapy and radiotherapy-related diarrhea in other cancers (Benson et al., 2004; Maroun et al., 2007; Muehlbauer et al., 2009). Drugs such as loperamide, glutamine, somatostatin, and budesonide are four commonly cited drugs used to control chemotherapy-induced diarrhea.

There are a variety of agents that can be used to treat diarrhea. Loperamide is an OTC antidiarrheal agent that has been studied extensively and is considered the gold standard and most effective first treatment for chemotherapy-induced diarrhea (Maroun et al., 2007). Glutamine, the most abundant amino acid in the body, is responsible for cellular growth of rapidly dividing cells such as in the gastric mucosa. The effect of glutamine on chemotherapy-induced diarrhea has been studied in multiple randomized controlled trials but with varying results (Bozzetti et al., 1997; Heys, Walker, Smith, & Eremin, 1999; Sornsuvit et al., 2008). Somatostatin reduces the secretions of pancreatic and gastrointestinal hormones, thereby reducing transit time (Martenson et al., 2008). Somatostatin is fairly effective in treating patients with chemotherapy-induced diarrhea (Hoff et al., 2014; Martenson et al., 2008). Budesonide is a glucocorticoid with high local activity but much lower systemic availability than other corticosteroids such as prednisone; it acts directly on the intestinal lumen (Edsbäcker & Andersson, 2004; Tromm et al., 2011). Clinical trials have demonstrated budesonide as an effective treatment for irritable bowel disease (IBD) and disorders of the microscopic colitis.
spectrum, which includes collagenous, lymphocytic immune and lymphocytic colitis (Baert et al., 2002; Bonderup et al., 2003; Bonderup, Hansen, Teglbjærg, Christensen, & Fallingborg, 2009; Greenberg et al., 1996; Miehlke et al., 2008) (Miehlke et al., 2009; Van Gossum, Schmit, & Peny, 1998). Lastly, live lactobacillus acidophilus and probiotics have been shown to prevent chemotherapy- and radiotherapy-induced diarrhea in cervical cancer (Chitapanarux et al., 2010; Salminen, Elomaa, Minkkinen, Vapaatalo, & Salminen, 1988; Siitonen, Vapaatalo, & Salminen, 1990; Van Neil, Feudtner, Garrison, & Christakis, 2002).

Conclusion

Research into the symptoms of peripheral neuropathy and diarrhea are evident in other cancers and disease states but are conspicuously absent in MM patients. High-quality studies into PN and LRD symptoms are desperately needed due to the major adverse impact these poorly understood complications have on quality of life and control of disease. Peripheral neuropathy occurs in patients with prolonged exposure to neurotoxic therapies and as a result of disease progression. Diarrhea occurs in patients with MM who receive lenalidomide although alternate causes of diarrhea such as infection, inflammation, and the role of IgA must be considered. Preventative strategies of either side effect in patients with MM are unknown. Thus, the purpose of the next chapter is to describe considerations in the design of the PNP and LRD studies designed to provide insight into the phenomena.
Chapter 3: Research Design and Strategy

Introduction

Chapter 3 highlights considerations in a small pilot study of glutamine conducted at the Cleveland Clinic from 2/2013 to 11/2013 to ameliorate PNP symptoms in MM patients who receive bortezomib. The PNP intervention study was designed to test feasibility, get preliminary data on the safety of glutamine, and determine the effect of the intervention. Then, the methodology for a retrospective lenalidomide-related diarrhea study is described. Both studies are innovative and desperately needed to enhance the personalized treatment of MM. Understanding the PNP and diarrhea symptoms will lead to the proactive identification and management of these disease and treatment related complications.

Glutamine and PNP

Study Design

This study was designed to compare glutamine or placebo to test the effect of glutamine on PNP symptoms and to obtain feasibility information for a clinical trial. A total of 9 patients with a diagnosis of symptomatic MM and who were receiving bortezomib at the Cleveland Clinic were randomized in a 1:1 (glutamine to placebo) fashion.

Setting

The study was conducted at the Cleveland Clinic Taussig Cancer Institute from 2/2013 to 11/2013.
Study Sample

A convenience sample of nine eligible patients were consecutively recruited according to the sequence of presentation at the Cleveland Clinic. Patients receiving bortezomib in combination with lenalidomide, melphalan, cyclophosphamide, and/or a corticosteroid such as prednisone or dexamethasone were included. This is because bortezomib is rarely given by itself, and these agents do not impact PNP (Baz et al., 2013; Kumar et al., 2012; Mikhael et al., 2012; Richardson et al., 2013). Following the approval of the FDA, after filing and securing an Investigational New Drug (IND) application, the IRB and hospital administrators, the nursing and medical staff who care for the MM patients, were educated as to the nature of the research through a structured in-service, termed a site initiation visit. Inclusion and exclusion criteria were made available to the staff (Appendix A).

Screening

Patients were screened for eligibility by reviewing laboratory studies, patient history, and a confirmed diagnosis through a chart review. During the scheduled hospital visit, each patient met with the study nurse or me and explained the study purpose, procedures, and rationale. With the patient’s permission, the patient’s eligibility was determined and informed consent was obtained for participation.

Eligibility

Inclusion Criteria

(1) Patients with a diagnosis of multiple myeloma (Durie et al., 2003, 2004; Durie et al., 2007; Fonseca et al., 2009; Kyle & Rajkumar, 2008, 2009) who receive bortezomib at a
dose of 1.3 mg/m² SQ weekly; (2) no evidence of the presence of peripheral neuropathy, NCI-CTCAE v4.03 score of 0, 1, or 2 (1 is considered negligible); (3) age 18 years or older; (4) performance status ≤ 2 on the Eastern Cooperative Oncology Group (ECOG) performance scale.

Exclusion Criteria

(1) Concurrent use of thalidomide, vincristine, platinum compound, or other agent known to cause significant neuropathy; (2) hospitalization with clinical evidence of active infections as manifested by recurrent fevers, positive blood culture results, or requiring intravenous antibiotic therapy; (3) inadequate liver and renal function with liver transaminases three times the upper limit of normal; (4) glomerular filtration rate (GFR) according to Cockroft-Gault < 30 mL/min; (5) uncontrolled congestive heart failure; (6) uncontrolled mood disorders; (7) fasting blood glucose > 150 mg/dL or blood sugar (nonfasting) > 200 mg/dL if no history of diabetes on screening labs, uncontrolled diabetes with HgA1C greater 7% with last evaluation if known diabetes diagnosis; (8) seizure disorder; (9) monosodium glutamate (MSG) allergy or soy allergy; (10) life expectancy of less than 3 months based on clinical laboratory parameters and the investigator’s opinion; (11) uncorrected vitamin B₁₂ or folate deficiency on screening labs; (12) use of OTC supplements other than one multivitamin tablet a day. Potassium and magnesium supplements are acceptable if prescribed to treat deficiency.

Randomization Procedure

Using a prospective, convenience sample, consenting subjects were randomly assigned to one of the two study arms in a 1:1 fashion. Patients were randomized by the
investigational pharmacist at Cleveland Clinic to glutamine or placebo using a permuted blocks randomization scheme stratified by NCI-CTCAE v4.03 peripheral neuropathy grade 0, 1, and 2. Prior to the start of the study randomization, lists were generated by the study biostatistician. Unblinding procedures, if necessary, were in place.

**Study Intervention**

The intervention of the study was the administration of oral glutamine. Patients in the treatment group received glutamine at a dose of 15 grams twice daily (to equal 30 grams a day) for a period of 4 months in a powder format. The dose of 30 grams per day has been studied in randomized trials to assess PNP in cancer (Stubblefield et al., 2005; Vahdat et al., 2001; Wang et al., 2007). The study was double blinded, so the patient and research staff members were unaware of whether the patient was taking glutamine or placebo. A designated pharmacist at Cleveland Clinic dispensed the study medication at the beginning of each cycle. Glutamine was dispensed from the same lot. Internal quality control was performed on behalf of Diplomat Pharmacy to ensure a clean and consistent drug supply.

The justification to assess glutamine effect over 4 months was based upon (1) immediate neuroprotective effectiveness of glutamine and (2) clinical treatment course. Based on prior studies of glutamine, improvement in symptoms was noted 2 weeks after high-dose paclitaxel (Vahdat et al., 2001) and within 2 months’ time in patients receiving oxaliplatin (Wang et al., 2007). Studies of BIPN in MM demonstrated that PNP symptoms develop by 4 months (Argyriou et al., 2008). Given relatively immediate response and anticipated peak occurrence of BIPN, we anticipate detecting any neuroprotective effects of glutamine within 4 months of bortezomib treatment.
Drug Supply

Diplomat Pharmacy compounded oral glutamine and matching placebo as a powder. Diplomat Pharmacy delivered the study medication to the Investigational Pharmacy at Cleveland Clinic. The bottles were numbered with numbered tear-off labels and maintained in a study binder in the Investigational Pharmacy at Cleveland Clinic.

Dose Continuation, Modification and Interruption

It was not anticipated that glutamine would produce significant side effects, but since glutamine is not known to be safe in the setting of severe kidney or liver disease, and since there is a theoretical concern for seizures as a potential side effect, a plan to hold glutamine if the individual experienced NCI-CTCAE v4.03 grade ≥ 3 liver, kidney, or other toxicity was in place (Table 1).

Table 1

Modification of Glutamine or Placebo Therapy

<table>
<thead>
<tr>
<th>Side effect of glutamine</th>
<th>Grade 1/Action</th>
<th>Grade 2/Action</th>
<th>≥ Grade 3/Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease Creatinine</td>
<td>&gt; ULN–1.5x UNL</td>
<td>&gt; 1.5 – 3.0x UNL Dose reduce glutamine by 25% and maintain</td>
<td>&gt; 3.0–6.0x UNL or higher Hold glutamine until resolves to grade 2 or lower and resume at 50% reduced dose</td>
</tr>
<tr>
<td>Liver toxicity: ALT, AST or Alk Phosphatase</td>
<td>&gt;ULN–2.5x UNL No action</td>
<td>&gt;2.5 – 5.0x UNL Hold glutamine. Dose reduce glutamine by 25% and maintain once ALT, AST, or alk phos return to baseline</td>
<td>&gt; 5.0–20.0x UNL Hold glutamine until resolves to grade 2 or lower and resume at 50% reduced dose</td>
</tr>
<tr>
<td>Seizure</td>
<td>Stop therapy for seizure</td>
<td>Stop therapy for seizure</td>
<td>Stop therapy for seizure</td>
</tr>
</tbody>
</table>
Control for the Use of Competing Medications

There are two groups of medications that MM patients are inclined to use for relief of PNP symptoms: (1) pain medications and (2) OTC supplements (Appendix A). Patients were allowed to take pain medication for other morbidities such as bone pain related to the MM diagnosis. If the dose of pain medication was stable, the pain medication would not interfere with the repeated assessments of PNP. Patients who were not receiving pain medications at the beginning of the study may need to receive these medications for PNP if they reach severe grade 3 according to the existing standard of care. Any changes or dose modifications to pain medications, neuroleptics, and tricyclic antidepressants while a patient is on study were documented in the chart. Monthly chart review was performed to document the name and dose of medications in order to control for the effect of concurrent pain medications on patient-reported pain. Other OTC supplements (Appendix B3) have undergone little investigation, and their effect on PNP is unknown. Participants were instructed clearly not to use prohibited OTC products. The use of OTC products was closely monitored and documented on a monthly basis.

Variables, Measurements, and Instruments

Study questionnaires and measurements are defined and described in the following section. Assessments were conducted to measure (1) consent rate, (2) adherence rate to the study intervention, (3) severity of PNP symptoms (4) quality of life, and (5) demographic and medical variables, including the grading of neurotoxicity.

Measures of Consent Rate
Names of all patients who were eligible to participate in the trial were recorded. The total number of people screened, the number of those who responded to the screening, and why the patients were not eligible were reported.

**Measures of Adherence Rate to the Study Intervention**

A diary card was created in a calendar format and used to obtain self-reported adherence to the study intervention (glutamine or placebo). Patients recorded the date, time, and amount of glutamine or placebo taken for each date on a diary card that was generated by the study nurse and provided to the patient at each visit. If diary cards were not returned for any reason, the study nurse recorded the number of missed doses in her study visit note. As diary cards alone are not often reliable, to enhance adherence the study nurse (1) enforced technologic reminders (such as a telephone reminder to take medication and participate in laboratory assessments), and (2) increased communication by visiting the patient on a monthly basis during regularly scheduled hospital outpatient visits to collect diary cards and weigh remaining powder from the month prior. These techniques aimed to enhance adherence to the study intervention and have been effective in previous studies (Zolnierek & DiMatteo, 2009; McDonald, Garg, & Haynes, 2002).

**Peripheral Neuropathy and Measurement**

PNP is the major dependent variable in this study. Sophisticated techniques such as EMG and QST are not readily available because of high cost, which is prohibitive and not feasible in this pilot study (Mileshkin et al., 2006). Scientifically, the benefit of EMG and QST monitoring in patients with MM is unknown. This is because EMG and QST are less sensitive to detect small fiber changes that are predominant in MM patients (Tavee & Zhou, 2009). Physical exam testing by a trained practitioner and patient-reported
symptoms have been used clinically for the detection of small fiber neuropathy symptoms characteristic of BIPN and are standard of care. Thus, the practitioner’s neurologic examination and the patient’s self-report were used for data collection (Calhoun et al., 2003).

The severity of PNP. Administered through a clinical examination, the *Neuropathy Impairment Score–Lower Limbs (NIS-LL)* is the objective measurement of PNP symptoms used in the study with summed scores that range from 0-88 of standard items of the neuromuscular examination. The instrument was described in Chapter 2 and is located in Appendix A (Bril, 1999; Dyck, 1995).

GOG-Ntx neuropathy subscale. One of the most common subjective self-report measures for PNP symptoms that has been validated in the cancer literature is the GOG-Ntx neuropathy subscale. This 11-item questionnaire addresses patient-reported concerns presumed to be associated with chemotherapy-induced peripheral neuropathy (Calhoun et al., 2003; Cella et al., 1993; Cella & Webster, 1999; Cella et al., 2006; Cella et al., 1993). This instrument with scores ranging from 0 to 44 on a continuous scale has been validated in patients with neurotoxicity associated with ovarian cancer chemotherapy and has been used in several MM studies (Richardson et al., 2006). The reliability and validity of the GOG-Ntx neuropathy subscale have been established with Cronbach’s alpha of 0.70 or greater.

Quality-of-Life Measure. Quality of life was measured on the 27-item Functional Assessment of Cancer Therapy General (FACT-G) scale (Appendix A2). This QOL measure has been widely used for purposes of evaluating patients receiving cancer treatment and focuses on four domains: physical well-being (PWB), social/family well-
being (SFWB), emotional well-being (EWB), and functional well-being (FWB) (Cella et al., 1993). FACT-G has demonstrated validity and reliability across many different cancer groups and is an appropriate tool for any patient with a cancer diagnosis (Webster, Cella, & Yost, 2003). The FACT-G total score is based on 26 summed items (responses 0 to 4 to equal a possible total score 0-108) from the PWB (7 items), FWB (7 items), SFWB (6 items), and EWB (6 items). Higher scores represent better quality of life.

**Demographic and Medical Variables.** Patient demographic data were obtained from the patient and the medical chart and recorded on a Demographic Data Form (Appendix B). These variables included age, gender, ECOG performance status, serum beta-2 microglobulin, serum albumin (which correspond with cancer stage), and prior and current therapy.

Medical variables were abstracted from the medical chart review and include (1) MM diagnosis and stage; (2) type, dose, and duration of chemotherapy and any other cancer treatment (such as radiation to the spine that may affect nerve function depending on location); (3) a diagnosis of B₁₂ deficiency and the presence of B₁₂ supplementation; (4) type and number of comorbidity; (5) use of the concomitant medications as listed in a table. This includes the name and dose of medications and supplements used for pain control; and (6) the level of graded PNP toxicity.

**Data Collection Procedure**

There were two main methods of data collection for the study to meet the endpoints: (1) chart review and (2) study assessments completed on behalf of a trained study nurse.
Consent Rate. I obtained a complete list of all patients with MM from an existing IRB approved database of patients at the Cleveland Clinic. The list was used to screen for eligible patients. All potential patients were identified and the medical record numbers were placed in a spreadsheet. All eligible patients were contacted. Patients who agreed to participate in the study embarked on the informed consent process. For those who declined clinical trial participation, reasons cited were recorded on the spreadsheet.

Study Assessments. A specially trained study nurse administered the questionnaires and conducted all of the study assessments, which included adherence to the intervention and the neurologic exam (NIS-LL). The study nurse and I remained blind to subject study group. The initial visit included an office visit, vital signs, weight and height measurement, a physical examination, patient history, and review of the concomitant medications. Laboratory assessments were collected from the medical chart for purposes of eligibility.

The study nurse administered the study instruments to measure severity of symptoms (GOG-Ntx and FACT-G) to each subject at baseline and 4 months. Each subject’s adherence to the glutamine/placebo regimen, any side effects, and use of concomitant medications as well as changes in the subject’s physical condition were monitored on a monthly basis. Patients were removed from study if cancer treatment was changed from a bortezomib-containing regimen to another treatment for purposes of disease progression. Treatment and monitoring of MM was at the discretion of the treating clinician. If patients were removed from study, an exit interview was conducted at the time of discontinuation from this study and included documentation of items listed in Appendix B.
**Data Analysis.** Data management: All clinical data pertinent to the PNP study were recorded by the data management team on case report forms (CRFs) following each scheduled study visit. A codebook contained a listing of each variable, the column in which the variable is entered and the codes associated with the attributes of each variable. Checks for internal data consistency were randomly performed on a monthly basis. A documentation of decisions worksheet was kept on behalf of the researcher that contained decision-making points throughout the study. The sheet was kept separate from the CRFs. Missing values and data were evaluated on a case-wise basis during analysis and categorized as missing completely at random or missing at random. Missed data were responded to by queries to fill any gaps by checking original source documents and querying the clinical staff if data such as vital signs, laboratory values, and clinical documentation corresponding with each study are missing.

Research question 1 asks, “What is the proportion of eligible patients who provide informed consent for participation in the trial?” To answer the question, the consent rate was calculated as the number of patients who actually consented to participate in the trial divided by the number of potential individuals who were eligible and contacted for study participation. The results were represented as a percentage. Research question 2 asks, “What is the adherence rate to the study intervention among patients who participated in the trial at 4 months?” Using the collected information, the total number of doses taken in a 1-month period was calculated and reported as a percentage. Based on the schedule of the study drug, and taking into account periods in which the patient was told not to take the drug, I expected the patients would take the study drug intervention twice daily for a 28-day cycle (1 month), to equal 56 doses each
month, for a 100% adherence rate. The rate was collected from the diary card and from the nursing notes (if a diary card is not available) then divided as a percentage of completion:

\[
\% \text{ ADHERENCE RATE} = \frac{\# \text{ doses of study drug taken}}{\# \text{ expected doses}}.
\]

Reasons cited for missed medication doses were also reported.

Two research questions remain: “What is the effect size of glutamine on the severity of PNP symptoms compared to placebo in patients treated with bortezomib at baseline and 4 months?” and “What is the effect size of glutamine on quality of life (QOL) at baseline and 4 months compared to patients who receive placebo?” Here, the categorical independent variable (IV) of each question is glutamine. The continuous dependent variables (DVs) are the severity of neuropathy (as measured by the NIS-LL at baseline and 4 months), and quality of life (measured by the FACT-GOG scale at baseline and 4 months). The mean difference of each group on the dependent variables was calculated, respectively. The absolute value of the difference between the two groups’ means was obtained and divided by the pooled standard deviation. The following equation for Cohen’s effect size illustrates this calculation:

\[
d = \frac{M_1 - M_2}{\hat{\sigma} D},
\]

wherein \(M_1\) is the mean difference between baseline and 4-month assessments on a dependent variable for group 1 and \(M_2\) is the same variable for group 2. \(\hat{\sigma} D\) is the pooled standard deviation of the dependent variable from both groups.
Ethical Issues and Rationale for PNP Study

The intervention in this study is glutamine, which is a non-FDA-approved nutraceutical. The use of glutamine, its side effects, and all potential study risks were disclosed to all eligible patients during the consent process. The PI and/or her designee met with each patient face to face at a scheduled outpatient visit. At this meeting the study was introduced. All risks, benefits, and alternatives to the study were explained. Patients were given at least 24 hours to consider the informed consent. All subjects were informed of their right to withdraw consent at any time. A detailed account of study risks and preventative measures to reduce or minimize the risks during the study are listed in Appendix B6.

Diarrhea

Approach

Study Design

The proposed was a retrospective, observational study to evaluate whether LRD correlates with improved disease control and/or immune function in patients exposed to lenalidomide over time. The study is based on a prior study that suggested LRD may correlate with longer survival and a possible immunologic component to diarrhea in patients exposed to lenalidomide. In order to have a good sample and a comparable control group since LRD may correlate with DOR, we looked only at responding patients. Response to lenalidomide can take 4 to 6 months to develop with the median time to respond approximately 1.5 months according to prior research (Rajkumar et al., 2010). After four treatment cycles it was considered likely that the patients would have
achieved at least a partial response. In the prior study the onset of LRD occurred after a median of 17.7 months (range 0.3–75.4 months) on lenalidomide therapy (Faiman et al., 2013). As an alternate hypothesis we looked at whether immune reconstitution by lenalidomide treatment and improved serum IgA levels protected the individual against diarrhea, and that the diarrhea is not, in fact, an immunologic component but related to IgA deficiency.

**Setting**

The study was conducted with patient data from the Cleveland Clinic.

**Study Sample**

To determine the appropriate sample size to address the primary endpoint, a G*Power 3.1.9.2 analysis was conducted. Using a two-sample t-test for two independent samples, to achieve a power of 80% at a type I error level of .05 with an estimated effect size of .50, 102 patients (51 in each group) would be needed to address the primary research question. A convenience sample of all patients with multiple myeloma who have received lenalidomide at the Cleveland Clinic for treatment of multiple myeloma between 1/2005 and 12/2013 was obtained from an existing, IRB-approved ONCORE® clinical database at Cleveland Clinic to obtain the study sample.

**Eligibility**

**Inclusion Criteria**

Subjects must meet the three following inclusion/exclusion criteria to be eligible for the study. The analysis was limited to: (1) Patients with newly diagnosed multiple myeloma
and, (2) who have received only lenalidomide (no other agents) to treat newly diagnosed MM, and (3) responded to lenalidomide therapy according to the standard IMWG criteria during the initial induction period as evidenced by a confirmed partial remission for at least 1 month.

Exclusion Criteria

For RQ1, all patients who do not meet the inclusion criteria as stated were excluded, including all individuals with preexisting diarrhea due to chronic conditions. No patients were allowed if the patient has underwent (1) a bone marrow transplant procedure, or (2) a preexisting inflammatory gastrointestinal condition such as *C. difficile* infection or Crohn's disease. To answer the RQ2, patients who have IgA-type MM were excluded.

*Rationale for inclusion/exclusion criteria:* In patients with cancer, an immune response or immune reconstitution can only occur after the cancer has been adequately controlled. In addition, patients experience shorter remissions from therapy as the disease progresses. Thus, including patients who only received lenalidomide during the initial treatment phase and who have responded would ensure the control and treated groups are comparable providing a more balanced sample, limit covariates such as multiple prior regimens which shortens one’s duration of response, and increase the validity of the findings. Patients with preexisting inflammatory gastrointestinal conditions may be more likely to experience diarrheal episodes falsely attributed to lenalidomide, which can also confound results. Graft-versus-host disease can occur in patients who undergo transplantation. Although GVHD is more common in patients who receive a donor marrow graft, these patients were also excluded from the analysis.
Rationale for excluding IgA-type MM patients for RQ2: Various types of MM exist. Two main types of MM are patients with IgG and IgA type. Patients with IgG MM will have low serum IgA levels at diagnosis. These patients would likely have normalization of the IgA level with treatment. Patients with IgA MM will have high levels of clonal IgA at diagnosis, and the IgA levels will not necessarily normalize due to the pathological process of MM disease. No threshold for “normal” IgA has been established in this group with defective IgA-type MM. Thus, including patients with clonal IgA MM would confound the results, and therefore these patients were excluded.

Screening

Following the approval of the IRB, patients were screened for eligibility. The Cleveland Clinic Multiple Myeloma program has an existing IRB-approved database of all patients diagnosed with MM since 1/2005. The research coordinator requested a data pull from the quantitative health sciences department. The data pull included all patients with MM who received lenalidomide. Then, eligibility for the study was determined by performing a chart review by this process to:

(1) Confirm the diagnosis of MM.

(2) Determine that the patient actually received initial therapy with lenalidomide.

(3) If the patient received lenalidomide, the next step would be to determine that the patient achieved at least a partial response to the initial therapy by review of laboratory studies.

(4) If patients received a bone marrow transplant, the patient was excluded.

As the study is based on chart review of an IRB-approved database, patients would not need to be contacted about participation in the study.
Variables and Measurement

**Measurement of diarrhea.** Significant LRD was considered present if the treating practitioner attributed chronic diarrhea to lenalidomide and recommended supportive therapy (drug or dietary modification) in at least two clinic notes. Given the nature of the research as a retrospective chart review, the grade of diarrhea according to CTCAE v4.0 would not be possible for all patients. Severity of diarrhea symptoms by patient report is a reliable method for data collection.

**Measurement of duration of response.** Duration of response was measured according to International Myeloma Working Group Criteria and was calculated from the date of the first confirmed remission until the date of disease progression (Appendix A6).

The timing of when the individual developed LRD is important and was recorded. Those who developed LRD were then compared to those who did not develop LRD to see if LRD correlated with duration of response (reported in months). Immune processes may have kicked in before the diarrhea developed. A confirmed response was essential to determine the DOR. The DOR was calculated from the time of the first remission to the date of disease progression according to the International Myeloma Working Group response criteria.

**Measurement of IgA levels.** Serum immunoglobulin A levels are determined in the clinical laboratory by standard nephelometry assay. Individuals were classified as having low (< 70 mg/dL), normal (70–390 mg/dL), or high serum IgA levels (> 390 mg/dL). The Cleveland Clinic is a clinical laboratory improvement amendment (CLIA) certified lab (number 36D0948064). The majority of serum IgA levels have been processed in the Cleveland Clinic laboratory.
**Demographic and Medical Variables**

Patient demographic data were obtained from the patient and the medical chart and recorded on a Demographic Data Form (Appendix B). These variables included age, gender, and serum beta-2 microglobulin at diagnosis (which corresponds with cancer stage).

Other medical variables were abstracted from the medical chart review and included (1) MM diagnosis (type; IgA, IgG, etc.) and stage, (2) type, dose, and duration of lenalidomide chemotherapy and any other cancer treatment (such as radiation to the pelvis which may impact diarrhea), (3) type and number of comorbid medical conditions, (4) use of the concomitant medications, which included pain medications and corticosteroids, and (5) “high-risk” features (such as elevated serum LDH, B2M, and age at diagnosis as outlined).

**Data Collection Procedure**

A list of patients was pulled from the IRB-approved database at the Cleveland Clinic. The list included medical record numbers. The record of each patient was reviewed to determine (1) the presence or absence of diarrhea including the date of onset of diarrhea and (2) serum IgA levels of patients with IgG myeloma at baseline and at 6, 12, and 24 months, and factors that can negatively affect outcomes.

Data collection was organized in a logical order with information obtained from the electronic medical record. Data was manually abstracted from the chart by accessing each individual medical record. The data were entered into a Microsoft Excel® file and stored on an encrypted laptop. Variables were collected from the chart for both research questions with the following process:
(1) The charts of all patients who received lenalidomide for a diagnosis of MM were reviewed from 1/2005 to 12/2013. Patients who received lenalidomide for at least 12 months were included. (2) Scientifically, it is also important to determine when the diarrhea started. Therefore the onset of diarrhea was recorded. (3) Serum IgA levels were obtained at baseline, 6, 12, and 24 months to address RQ2. Patients were categorized as to having low, normal, or high serum IgA levels: low (≤ 70 mg/dL), normal (71–390 mg/dL), or high (≥ 391 mg/dL).

Potential Problems

Potential problems included (1) misclassification bias and (2) variance in the quality of information recorded by medical professionals.

Misclassification bias. Patients were classified as having diarrhea or not having diarrhea based on whether the provider deemed diarrhea as related to lenalidomide and recommended antidiarrheal agents to treat the diarrhea. The diarrhea may not have been from lenalidomide, however. The misclassification of diarrhea or no diarrhea may have a significant impact on results.

There is also a risk during chart review that a valid date of diarrhea onset may not be accurate (such as the patient may not report or underreport the diarrhea, or the practitioner may fail to document the diarrhea occurrence). This risk was considered.

Variance in quality of information. Multiple providers treat patients with MM at the Cleveland Clinic. Lenalidomide is an oral therapy. Patients may not be seen on the first day the oral lenalidomide was started (an issue when recording stop/start dates for duration of therapy), and the onset of diarrhea may not be reliably recorded by the patient and/or reliably recorded by the provider in the electronic medical record. Start/stop dates
of lenalidomide therapy are fairly accurate with the current documentation however. As long as the patient routinely follows at the Cleveland Clinic, I expect the rate of missing or incomplete data to be low among patients who qualify for the study.

**Possible confounding variables.** Confounding variables can affect interpretation of the results. Factors that can negatively affect one’s duration of response, the presence or absence of diarrhea, and serum IgA levels were considered.

Factors that can negatively affect outcomes. The primary endpoint of the study is duration of response. Several factors have been identified which can lead to shorter duration of response and must be considered as covariates. These factors were collected and include (1) age above 75, (2) fluorescent in situ hybridization (FISH) or chromosomal karyotype analysis positive for t(14;16), t(14;20), and del(17p); (3) primary plasma cell leukemia (PPCL) (≥ 2,000 plasma cells/μL of peripheral blood or ≥ 20% plasma cells in the white blood cell differential), or (4) elevated serum LDH ≥ 2 times the upper limit of normal. The FISH procedures were not routinely performed prior to 2009. Therefore, only high LDH, B2M, and age greater than 75 years at diagnosis were used to estimate one’s individual risk category as high or standard.

Factors that affect diarrhea. The presence or absence of diarrhea may be influenced by medications. Opioid analgesics and corticosteroids are the two most common medications that can influence diarrhea. Therefore, these two drugs were collected and managed as covariates.

Factors that affect IgA levels. Serum IgA levels might be influenced by the individual’s type of MM. For patients who have hypogammaglobulinemia (low immunoglobulin
levels in the blood) from the disease, or cancerous, clonal IgA type of MM, their levels may remain low or very high and never normalize. Thus, IgG type MM was the only type of MM in the analysis of RQ2.

**Data Analysis**

**Measurement of Duration of Response and Rationale.** The immune process may have begun before the diarrhea occurred. Immune processes can occur as early as one responds to lenalidomide treatment, which can be as early as 1 month according to prior studies. Therefore two cohorts of patients were used to answer RQ1: (1) analyze a cohort of patients who have all responded to treatment, and (2) analyze a cohort of patients matched for the median onset of diarrhea, as diarrhea may be a late signal of the immune phenomenon.

**Rationale for Timing and Methods.** Only two prior studies report the median onset of LRD at around 17 and 19 months, respectively, but the population was different (relapsed multiple myeloma versus newly diagnosed patients here). Thus, the median onset of diarrhea cannot be predicted a priori for analysis. Once the median time to diarrhea onset is assessed, individuals in the control group who did not meet the median time to onset of diarrhea for the analysis were excluded.

**Data management.** The PI recorded all clinical data pertinent to the study in an electronic, centralized format. A codebook contains a listing of each variable, the column in which the variable is entered, and the codes associated with the attributes of each variable. Checks for internal data consistency were randomly performed by an independent reviewer. One individual abstracted the data to address intra-rater and inter-rater reliability.
The IBM® SPSS® Statistics V22.0 program was used for all analyses. Standard methods of categorical and continuous data analyses were applied to generate descriptive statistics of demographic characteristics of the study participants.

**Univariate and Multivariate Analyses.** The major endpoint in the study in research question 1 asked, “Do patients with LRD have a longer duration of response (DOR) to lenalidomide compared to patients who do not develop LRD? The IV is categorical (LRD, no LRD). The DV is the duration of response and is a continuous variable measured in months, calculated from the date of the first confirmed remission until date of disease progression. An appropriate statistical test for a continuous DV such as duration and categorical IV (LRD vs. no LRD) is a t-test. Linear regression analysis was performed to test the impact of multiple variables on the continuous DV. Covariates include: medications (opioids or not), high-risk features (age > 75, LDH, and B2M), age, gender, and use of immunosuppressive therapy (dexamethasone or prednisone).

After analysis of the primary RQ is completed, a subset of patients who all responded to lenalidomide treatment and were exposed to the lenalidomide drug for the same amount of time was assessed. The same analysis as in RQ1 was performed with patients who have only received treatment the same length of time, as the presence or absence of LRD may be influenced by many other factors.

Research question 2 sought to explore the relationship between low IgA levels and diarrhea and specifically asked, “Do low IgA levels in IgG myeloma correlate with lenalidomide related diarrhea at baseline, 6, 12, and 24 months?” For RQ2 a correlation analysis was performed at each time point to examine associations between the IgA
levels and the presence and absence of LRD at baseline and at 6, 12, and 24 months in patients with IgG MM.

**Ethical Considerations for Both Studies**

Patient confidentiality was maintained. All data forms were identified only with a study identification number. The interviews for the PNP study took place in a private room with a closed door to protect privacy. A separate list linking study numbers with patient identifiers (name, hospital number) was maintained in a locked file cabinet apart from the data files or on an encrypted computer or laptop device.

All study data and information for the PNP study was managed and maintained electronically on CRFs by using an integrated web-based application for research data management, Oracle Clinical database. The data forms for the PNP study included a protocol entry sheet verifying that each patient meets inclusion/exclusion criteria. Patients signed and received a copy of the IRB-approved consent forms for the PNP study. Clinical notes approved by the researcher on the day of entry into the study included the study number, subject number assigned, and a statement that consent was obtained. Dated and approved notes for each subsequent study visit were included in the CRFs. Any medical concerns regarding abnormal vital signs, lab results, and adverse events were recorded and reported to include their resolution. Office notes regarding concomitant medications taken during the PNP study (including start to stop dates) and the study participant’s condition upon completion of or termination from the study were maintained. All of the CRFs, study file, consent forms, supporting documents, and confidential subject identification list were kept in the data management office for at least
3 years after completion or discontinuation of the study. Participants’ medical records are kept for as long as the patient is receiving care at the participating institution.

**Data Safety Monitoring Plan**

For the PNP study, a Data and Safety Monitoring Board (DSMB) was headed by a quality assurance (QA) team. Two independent reviewers audited all patient charts to ensure that (1) the appropriate forms were filled out and filed in a timely manner, guarding against missing data, and (2) no significant toxicity from glutamine develops. This committee was charged with responsibility of monthly review of internal and external adverse events, confirmation of objective responses, and determination of study termination as appropriate for the degree of risk.

**Adverse Event Reporting**

Adverse event (AE) reporting for the PNP study was done in accordance with the standard operating procedure of the Case Comprehensive Cancer Center IRB to ensure patient safety. This included reporting (1) adverse events that are serious, unexpected, and related or possibly related to participation in the research, (2) serious adverse events that were expected in some subjects, but determined to be occurring at a significantly higher frequency or severity than expected, and (3) other unexpected adverse events, regardless of severity, that may alter the Board’s analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document. Adverse events were recorded and graded according to severity according to NCI-CTCAE v 4.0. Toxicity was scored according to CTCAE version 4.0 for toxicity and adverse event reporting as part
of standard of care. A copy of the CTCAE version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). With the PNP study, patients were advised to call the study nurse as listed in the informed consent document or physician should adverse events occur in between visits. No severe cases of glutamine toxicity were reported.

Serious AEs among patients in the PNP study were observed. If a serious AE did occur, the AE would be reported to the IRB for expedited review to allow more timely monitoring and patient care. Serious grade 3 AEs that were unanticipated would be reported within 5 business days. Life-threatening or disabling (grade 4) AEs, whether expected or unexpected, would be reported within 10 business days. Fatal (grade 5) AEs would be reported immediately.

Conclusion

In this chapter, screening, inclusion/exclusion criteria, methods, and ethical considerations were presented for the two studies. The theoretical and physiologic frameworks provide structure to study the phenomenon. The next steps were to analyze the data and report the findings of both projects in two main sections of Chapter 4. Then, Chapter 5 discussed the implications of the each separate project and provide a summary discussion of what these projects together mean for symptom science, methodology, and future directions.
Chapter 4: Results

Findings of Each Study

This chapter provides results of both projects within two main sections. The sections include findings for the peripheral neuropathy study and findings for the diarrhea study.

Findings: Neuropathy Study

Results and Basic Demographic Data. From 2/2013 through 11/2013, nine patients participated in the pilot study. The average age of participants was 57 years (range 42–66 years). Six patients were male (67%) and three were female (33%). Eight were white/not Hispanic and one was African American. Baseline peripheral neuropathy was graded by the CTCAE scale v. 4.0. The majority of patients (n = 7) had mild (grade 1) neuropathy; one patient had no (grade 0) neuropathy and one patient had moderate (grade 2) neuropathy. Four patients were randomized to receive glutamine, and five patients were randomized to receive placebo. There were no unanticipated adverse events as a result of the glutamine study drug (Table 2).

Table 2

Descriptive Statistics: Glutamine Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>N = 9</td>
</tr>
<tr>
<td>Male</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (33%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>57 years (range 42–66 years)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White/Not Hispanic</td>
<td>8</td>
</tr>
<tr>
<td>African American</td>
<td>1</td>
</tr>
<tr>
<td><strong>Baseline neuropathy</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 0 (none)</td>
<td>1</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>7</td>
</tr>
</tbody>
</table>
Research questions for the pilot study included consent rate, adherence rate, and effect size of the intervention on the severity of neuropathy and quality of life.

**Consent Rate.** Research question 1: “What is the proportion of eligible patients who provide informed consent for participation in the trial?” To answer the question, a list of patients from all Cleveland Clinic sites (Taussig, Independence, Beachwood, Hillcrest, Sandusky, and Florida Family Health centers) and who were receiving bortezomib at the time of the query was obtained from an IRB-approved database. Each patient on the list was screened to determine if eligibility criteria were met. Two patient lists were generated in April and August 2013 for screening purposes. All patients from the lists were merged into one master screening file.

A total of 113 patients were identified from the pooled data retrieval. Out of 113 patients, 23 (20%) initially were deemed to be eligible for the study at the time the medical chart was first reviewed. Five were later determined to be ineligible because the patients went to transplant or switched to another bortezomib schedule (due to how the drug is delivered). Nine of the remaining 18 patients were eligible but refused to participate. Nine of the approached provided written consent for a consent rate of 50% (see Table 3).

<table>
<thead>
<tr>
<th>Grade 2 (moderate)</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td></td>
</tr>
<tr>
<td>Glutamine/Placebo</td>
<td>4/5</td>
</tr>
</tbody>
</table>
### Proportion of Consent Rate

<table>
<thead>
<tr>
<th>Patients who were presented IC</th>
<th>N = 23 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agreed but found ineligible due to:</strong></td>
<td></td>
</tr>
<tr>
<td>Dose reduction of bortezomib to 1.0 mg/m²</td>
<td>2</td>
</tr>
<tr>
<td>Schedule reduction to every other week</td>
<td>1</td>
</tr>
<tr>
<td>Bortezomib stopped due to neuropathy before enrolled</td>
<td>1</td>
</tr>
<tr>
<td>Planned autologous transplant</td>
<td>1</td>
</tr>
<tr>
<td><strong>Declined participation</strong></td>
<td>9</td>
</tr>
<tr>
<td>Frequency of visits/distance</td>
<td>5</td>
</tr>
<tr>
<td>Already on glutamine and effective</td>
<td>2</td>
</tr>
<tr>
<td>Study closed before able to respond to IC</td>
<td>2</td>
</tr>
<tr>
<td>Agreed, signed IC, and randomized</td>
<td>9/18(50%)</td>
</tr>
</tbody>
</table>

Reasons why the 9 eligible patients declined participation were recorded. Five cited frequency of monthly visits and study procedures (specifically, the monthly 24-hr urine collection). One patient did not want to come monthly due to distance (drives 79 miles from the study site each way). One patient was taking OTC glutamine and did not want to risk being randomized to the placebo group as the glutamine alleviated her arthritis and neuropathy symptoms. Finally, two patients did not respond to follow-up calls when they were given time to consider study participation.

Ninety patients from the original list were ineligible to participate. Reasons patients were ineligible for the study included the dose of prescribed bortezomib (patients
were listed as receiving bortezomib at a 1 or 0.7 mg/m² dose instead of the 1.3 mg/m² dose required by the study), the route (IV instead of SC), the schedule of administration (twice versus once weekly schedule), or abnormal laboratory parameters (elevated glucose, elevated serum creatinine, or low vitamin B₁₂ levels). A list of reasons patients were ineligible to participate is provided in Table 4.

Table 4

*Reasons Why Not Enrolled in Glutamine or Placebo Study*

<table>
<thead>
<tr>
<th>Reasons why not enrolled</th>
<th>N = 90</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ineligible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lab values outside of range</td>
<td>28 (31%)</td>
<td></td>
</tr>
<tr>
<td>Off bortezomib for symptoms or disease progression but on the list</td>
<td>21 (23%)</td>
<td></td>
</tr>
<tr>
<td>Wrong bortezomib schedule, dose, or route</td>
<td>16 (18%)</td>
<td></td>
</tr>
<tr>
<td>Location not open to enrollment (Florida, Sandusky, Independence)</td>
<td>25 (28%)</td>
<td></td>
</tr>
</tbody>
</table>

**Adherence Rate.** Question 2: “What is the adherence rate to the intervention among patients who participated in the trial at 4 months?”

Adherence to the glutamine or placebo intervention was documented by patient self-report (as written on the diary cards) or in the nursing notes from the study visit (if a diary card was not available). Two IRB-mandated study hold periods occurred at two different time points during this trial. During the study hold periods, unblinded monitors reviewed drug-dispensing and safety issues to protect the patients and the validity of the study data. Different people experienced different study holds and were not allowed to take the drug during study hold periods. Therefore, adherence was
reported as a percentage based on remaining data after a discount for holding periods.

Doses of study drug expected to be taken for the study duration after the discount (1,106) were calculated. This number was then divided by the total number of actual (1,101) doses of the study drug taken for the study duration. A total of 1,101/1,106 doses were taken, for an adherence rate of 99.5%.

Two patients did not complete the study as they each withdrew consent, coincidentally, during study hold periods. The attrition rate is therefore 22%. One patient assigned to placebo withdrew consent during the first study hold period due to nausea. One assigned to glutamine withdrew consent during the second hold period when the patient planned to move to another state. Table 5 outlines the number of study drug doses taken and expected for each patient taking into account study holds.

Table 5

<table>
<thead>
<tr>
<th>ID</th>
<th>Group</th>
<th># of doses taken for study duration per patient</th>
<th># of doses expected</th>
<th>Individual percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>glutamine</td>
<td>224</td>
<td>224</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>placebo</td>
<td>224</td>
<td>224</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>placebo</td>
<td>129</td>
<td>129</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>glutamine</td>
<td>112</td>
<td>112</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td>placebo</td>
<td>110</td>
<td>110</td>
<td>100%</td>
</tr>
<tr>
<td>6</td>
<td>placebo</td>
<td>51</td>
<td>56</td>
<td>91%</td>
</tr>
<tr>
<td>7</td>
<td>placebo</td>
<td>136</td>
<td>136</td>
<td>100%</td>
</tr>
<tr>
<td>8</td>
<td>glutamine</td>
<td>67</td>
<td>67</td>
<td>100%</td>
</tr>
<tr>
<td>9</td>
<td>glutamine</td>
<td>48</td>
<td>48</td>
<td>100%</td>
</tr>
</tbody>
</table>

# of actual doses taken for study duration for all 9 patients = 1,101
# of actual doses expected for all 9 patients for study duration = 1,106
Adherence for all 9 patients for study duration = 99.5%
Effect Size of Glutamine on Severity of PNP Symptoms. Question 3: “What is the effect size of glutamine on the severity of PNP symptoms compared to placebo in patients treated with bortezomib at baseline and end of study?”

A three-step process was used to calculate the effect size of glutamine on the severity of PNP symptoms using the dependent variable, the severity of neuropathy, as measured by the NIS-LL scale. (1) Using the IBM® SPSS® Statistics V22.0 (to determine effect size and for all statistical calculations in this dissertation), frequencies were run on the glutamine data set. Checks were performed to assess for internal consistency, missing values and the accuracy of the data. The pooled SD of the glutamine and placebo groups from time 1 (baseline severity score) to time 2 (end of study severity score) were obtained from the statistics output. (2) A t-test was used to calculate the mean difference of each group from time 1 to time 2 and obtained from the output. (3) The delta method is one that divides the sample mean difference by the pooled standard deviation of the sample to estimate the effect size. Using the mean and SD values from the output from steps 1 and 2, the combined mean difference and pooled SD values were calculated using the “deltantx” command. The effect size of glutamine on the severity of neuropathy was calculated by dividing the pooled mean difference from baseline to end of study (numerator, 3.40) from the standard deviation baseline to end of study (denominator, 7.83) (M = 3.40, SD 7.83). The result of the calculation was an observed small to medium effect size of .43 (table 6).
Table 6

*Mean (M) and Standard Deviation (SD) Scores for Neurotoxicity (NTX) Effect Size Calculation*

<table>
<thead>
<tr>
<th></th>
<th>Baseline M, SD for NTX severity score (T1)</th>
<th>End of study M, SD for NTX severity score (T2)</th>
<th>Pooled M, SD for NTX severity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean difference</td>
<td>1.15</td>
<td>-2.25</td>
<td>3.40</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>6.09</td>
<td>9.22</td>
<td>7.83</td>
</tr>
</tbody>
</table>

*Note.* All were obtained from frequency output (t-test).

**Effect Size of Glutamine on Quality of Life.** Question 4: “*What is the effect size of glutamine on quality of life (QOL) at baseline and end of study compared to patients who receive placebo?*” The dependent variable, quality of life, was measured by the FACT-GOG instrument. The mean difference in QOL scores between groups from baseline to end of study was calculated in a similar fashion as above using pooled SD calculated in SPSS® (see **Table 7**). The delta approach was also used here with pooled standardized difference scores between time 1 and time 2. The group mean difference (numerator, 10.900) was divided from the pooled standard deviation (denominator, 10.039). A large effect size of 1.09 was observed ($M = 10.900, SD = 10.039$).

Table 7

**FACT-GOG Quality of Life (QOL) and Sub-scores and Effect Size Calculation**

<table>
<thead>
<tr>
<th>FACT General: Total and Subscale scores Baseline, SD values (in points)</th>
<th>Baseline mean group difference (T1)</th>
<th>End of study mean group difference (T2)</th>
<th>Pooled SD</th>
<th>Effect size mean difference/pooled standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-G total score</td>
<td>5.100</td>
<td>-5.88</td>
<td>10.038</td>
<td>1.09</td>
</tr>
<tr>
<td>Physical well-being</td>
<td>2.150</td>
<td>.85</td>
<td>4.76</td>
<td>.273</td>
</tr>
<tr>
<td>Functional well-being</td>
<td>1.80</td>
<td>1.250</td>
<td>2.24</td>
<td>.25</td>
</tr>
<tr>
<td>Social well-being</td>
<td>-.225</td>
<td>-5.500</td>
<td>4.927</td>
<td>1.07</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>.700</td>
<td>-.200</td>
<td>3.12</td>
<td>.87</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>1.150</td>
<td>6.092</td>
<td>19.67</td>
<td>.51</td>
</tr>
</tbody>
</table>

*Note:* All were obtained from frequency output (t-test). The FACT-G total score is based on 26 summed items (responses 0 to 4 to equal a possible total score 0–108) from physical well-being (7 items), functional...
Based on the large observed effect size of glutamine on total QOL scores, the effect size of glutamine on each domain on QOL (PWB, FWB, EWB, and SWB) and for the Gynecologic/Oncologic Group Neurotoxicity (GOG-ntx) subscale were calculated according to the methods above. Once the means and SD of each group were obtained from the SPSS output, pooled mean and SD values were calculated. Large effect sizes were observed with SWB (ES = 1.07; $M = 5.275$, $SD = 4.927$) and EWB (ES = .866; $M = .270$, $SD = 3.12$). A medium effect size was observed on the neurotoxicity subscale (ES = .51; $M = -10.10$, $SD = 19.67$). Small effect sizes were observed with PWB (ES = .273; $M = 1.30$, $SD = 4.76$) and FWB (ES = .25, $M = .550$, $SD = 2.24$).

Findings: Diarrhea Study

Results and Basic Demographic Data. The charts of 602 patients with MM who had taken lenalidomide to treat MM at some point in the disease trajectory were reviewed. Of these patients, 62 met inclusion criteria for the study. Reasons for exclusion from the study were consistent with inclusion and exclusion outlined criteria in chapter 3. The most common reason 378/602 (63%) of patients were not allowed to participate is they did not receive lenalidomide without other chemotherapy agents (such as thalidomide, bortezomib, or cyclophosphamide) as the first treatment for MM. Other reasons the remaining 224 patients were excluded from the analysis can be found in Figure 4.
A total of 62 patients (1) with a confirmed diagnosis of MM, (2) who were treated with lenalidomide for the very first time, (3) achieved at least a partial response (PR) or better to the lenalidomide, and (4) never underwent an autologous stem cell transplant procedure, were identified. Thirty-nine (63%) patients were male, and 23 (37%) patients were female. Thirty-five (56.5%) patients had diarrhea, and 27 (43.5%) did not. The average age was 69 years (range 40–85 years). Six patients had “high-risk” disease...
(based on serum LDH and B2M values), and all others had standard-risk MM. Five (8.1%) patients had kappa and five (8.1%) patients had lambda light chain MM. Forty-four (71%) patients had IgG-type MM. The remaining 8 (13%) had IgA-type MM. A total of 44 (71%) took >10 mg opioids per day, and 18 (29%) did not. Additional descriptive sample data are outlined in Table 8. Other sociodemographic data such as education and income were not available.

Table 8

Descriptive Statistics: Duration of Response, Diarrhea Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>N = 62</td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
</tr>
<tr>
<td>Age</td>
<td>69 years (range 40–85 years)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35</td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Average daily dose lenalidomide</td>
<td>M = 19.27, SD = 6.32</td>
</tr>
<tr>
<td>5–25 mg</td>
<td></td>
</tr>
<tr>
<td>Best response to lenalidomide by IMWG criteria</td>
<td>30</td>
</tr>
<tr>
<td>Unconfirmed CR</td>
<td>13</td>
</tr>
<tr>
<td>VGPR</td>
<td>19</td>
</tr>
<tr>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>Opioid use &gt; 10 mg/day</td>
<td>18</td>
</tr>
<tr>
<td>Yes</td>
<td>44</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>High-risk disease?</td>
<td>6</td>
</tr>
<tr>
<td>Yes</td>
<td>56</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Length of time from first dose of drug to progressive disease</td>
<td>8–110 months M = 44, SD = 30.7 months</td>
</tr>
<tr>
<td>Steroids</td>
<td>41/21</td>
</tr>
<tr>
<td>Yes/No</td>
<td></td>
</tr>
</tbody>
</table>
Duration of Response. Research question 1: “Do patients with LRD have a longer duration of response (DOR) to lenalidomide compared to patients who do not develop LRD?”

The duration of response was measured in months and calculated from the date of the first confirmed remission until the date of disease progression of lenalidomide. The average time since the first dose of drug to disease progression ranged from 8 to 110 months ($M = 44, SD = 30.8$). The median duration of response (remission) in months was 42 months ($M = 36, SD = 30.7$). Simple statistics were run on the dependent outcome variable DOR in months. Thirty-five patients did not have diarrhea ($M = 38.23, SD = 30.84$), and 27 patients had diarrhea ($M = 48.44, SD = 30.22$). A t-test shows that a median duration of response was not statistically significantly different between individuals with or without LRD ($t = -1.31, df = 60, p = .197$) (Table 9).

Table 9

Results for Primary Outcome Values for Duration of Response (DOR) Among 62 Patients: Mean, SD, and Statistical Significance (t-test)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>$t$ value</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide-related diarrhea</td>
<td>38.23</td>
<td>30.84</td>
<td>-1.305</td>
<td>.197</td>
</tr>
<tr>
<td>No lenalidomide-related diarrhea</td>
<td>48.44</td>
<td>30.22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Median DOR = 50.5 months. The median DOR was not statistically significant among patients with/without diarrhea.

Regression analysis was then used to test the effects of multiple variables on the dependent variable, duration of response. The model included the independent variable (LRD) and covariates such as (1) high-risk features (yes or no), (2) the use of opioid analgesic medications (yes or no), (3) immunosuppressive steroid medications (yes or no), age, and gender. A small effect was observed and the results were not significant ($r^2$
Based on the results we can conclude that in this sample, having diarrhea (LRD) was not significantly associated with the duration of response ($\beta = 76.429$, $t = 1.918$, $p = .060$) after controlling for age, gender, one’s risk status, opioid use, and concurrent corticosteroid immunosuppressive therapy. Further, none of the covariates was significantly associated with the duration of response (Table 10). A backward elimination method was also utilized and yielded similar findings.

Table 10

Results of Linear Regression Analysis of the Impact of Variables on DOR in ($n = 62$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>$B$</th>
<th>$SE$</th>
<th>$t$ value</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>15.56</td>
<td>8.613</td>
<td>1.81</td>
<td>.076</td>
</tr>
<tr>
<td>Age</td>
<td>-6.53</td>
<td>.527</td>
<td>1.66</td>
<td>.183</td>
</tr>
<tr>
<td>Gender</td>
<td>1.66</td>
<td>9.078</td>
<td>.183</td>
<td>.855</td>
</tr>
<tr>
<td>Opioids</td>
<td>6.224</td>
<td>9.581</td>
<td>.650</td>
<td>.519</td>
</tr>
<tr>
<td>High risk</td>
<td>14.883</td>
<td>9.087</td>
<td>1.08</td>
<td>.285</td>
</tr>
<tr>
<td>Steroids</td>
<td>-1.84</td>
<td>13.778</td>
<td>-.202</td>
<td>.840</td>
</tr>
</tbody>
</table>

Note. For model: $R^2 = .079$, $p > .595$.

The median onset of LRD occurred at 19 months. Since LRD may take 19 months to occur, some patients did not have the benefit to take the lenalidomide drug as long as the people who took the drug 19 months and beyond. An autoimmune process can develop months before the onset of diarrhea, and the diarrhea may be a late symptom of the autoimmune process. The underlying hypothesis is that patients with LRD have a longer DOR to lenalidomide compared to patients who do not develop LRD, which may be due, in part, to an autoimmune process. We cannot reliably test the hypothesis of LRD on DOR or remission in patients with a shorter length of time on lenalidomide of less than 19 months. This is because patients would be categorized as not having diarrhea (evidence of an immune effect) before 19 months possibly because the individuals were
not given the opportunity for the diarrhea symptom to develop. Thus, to test the hypothesis, a subgroup analysis of 44 patients, who (1) all responded to lenalidomide treatment, and (2) were all exposed to the lenalidomide drug for at least 19 months, was assessed (Table 11).

Table 11

*Results for Primary Outcome Values for Duration of Response (DOR) Among 44 Patients: Mean, SD and Statistical Significance (t-test)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide-related diarrhea (n = 24)</td>
<td>62.58</td>
<td>29.00</td>
<td>-2.058</td>
<td>.046</td>
</tr>
<tr>
<td>No lenalidomide-related diarrhea (n = 20)</td>
<td>45.35</td>
<td>25.93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note. Median DOR = 50.5 months. The median DOR was statistically significant among patients with/without diarrhea (t = -2.058, df = 42, p = .046).*

The demographic data in the 44-patient sample were not significantly different than the larger sample of 62 patients. Of 44 patients in this analysis, 26 (59%) were male and 18 (41%) female. The average age was 69.5 years. The median duration of response to lenalidomide for the 44 patients in the subgroup analysis was higher than in the prior diarrhea sample at 50.5 months (M = 54.7, SD = 28.68). A Levene’s test for homogeneity of variances was performed and not violated (.47). Therefore an independent sample t-test was performed with 20 patients (45.5%) without diarrhea and 24 (54.5%) patients with diarrhea at 19 months.

Results showed there was a shorter and statistically significant difference in DOR between patients with and without diarrhea. Patients without diarrhea were in remission an average of 43.4 months (M = 43.35, SD = 25.93). Patients with diarrhea were in
remission an average of 62.6 months ($M = 62.58, SD = 29.01$). Thus, patients without diarrhea had a shorter DOR than the patients who developed diarrhea ($t = -2.058, df = 42, p = .046$) (Table 12). This suggests that LRD is associated with a longer DOR (i.e., a longer remission) in patients who remain on lenalidomide therapy in this study.

Regression analysis was performed with the alternate data set (n = 44) to test the LRD effects after controlling for high-risk status, opioid use, immunosuppressive steroid medications, age, and gender on the IV DOR. Frequencies were run to examine the sample characteristics and look for missing data. The results of the analysis remained nonsignificant, but a small effect size was observed in the model ($r^2 = .10, p = .669$) (Table 12). Based on the results, we can conclude that in this sample, having diarrhea (LRD) was not significantly associated with duration of response ($\beta = 16.27, t = 1.54, p = .133$) after controlling for covariates. Further, none of the covariates was significantly associated with the duration of response. A backward elimination method was also utilized and produced similar findings.

Table 12

Results of Linear Regression Analysis of the Impact of Variables on DOR in (n = 44)

<table>
<thead>
<tr>
<th>Model</th>
<th>$B$</th>
<th>$SE$</th>
<th>$t$ value</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>16.265</td>
<td>10.569</td>
<td>1.539</td>
<td>.133</td>
</tr>
<tr>
<td>Age</td>
<td>-.213</td>
<td>.505</td>
<td>-.422</td>
<td>.676</td>
</tr>
<tr>
<td>Gender</td>
<td>-4.911</td>
<td>10.056</td>
<td>-.488</td>
<td>.628</td>
</tr>
<tr>
<td>Steroids</td>
<td>-2.335</td>
<td>10.434</td>
<td>-.224</td>
<td>.824</td>
</tr>
<tr>
<td>High risk</td>
<td>-.226</td>
<td>16.058</td>
<td>-.014</td>
<td>.989</td>
</tr>
<tr>
<td>Opioids</td>
<td>-1.497</td>
<td>12.060</td>
<td>-.124</td>
<td>.902</td>
</tr>
</tbody>
</table>

Note. For model: $R^2 = .10, p = .669$.

**Serum IgA Levels.** Research question 2: “Do low IgA levels in IgG myeloma correlate with lenalidomide related diarrhea at baseline, 6, 12, and 24 months?”
To answer RQ2, a sample of 27 patients with IgG-type of MM was identified (Table 13). Correlation analysis was performed at each time point to examine associations between serum IgA levels and the presence or absence of LRD at baseline, 6, 12, and 24 months. Normal serum IgA levels were observed in 13/27 (48%) of patients at 12 months and in 14/27 (52%) of patients by 24 months. There was a moderately small correlation between diarrhea and IgA levels at each time point. The results were not significant, likely because of the sample size (n = 27). The findings between diarrhea and IgA levels at baseline were $r = -0.232$, $n = 27$, $p = .245$; at 6 months $r = -0.196$, $n = 27$, $p = .328$; at 12 months $r = -0.039$, $n = 27$, $p = .846$, and at 24 months $r = -0.205$, $n = 27$, $p = .306$.

Table 13

*Descriptive Statistics: IgA Levels in IgG MM*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>27</td>
</tr>
<tr>
<td>Male / Female</td>
<td>18 / 9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13 / 14</td>
</tr>
<tr>
<td>Best response by IMWG criteria</td>
<td></td>
</tr>
<tr>
<td>Unconfirmed CR</td>
<td>12</td>
</tr>
<tr>
<td>VGPR</td>
<td>6</td>
</tr>
<tr>
<td>PR</td>
<td>9</td>
</tr>
<tr>
<td>Serum IgA levels (categorized as low &lt; 70, normal 71-390, or high &gt; 391)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20</td>
</tr>
<tr>
<td>6 months</td>
<td>16</td>
</tr>
<tr>
<td>12 months</td>
<td>14</td>
</tr>
<tr>
<td>24 months</td>
<td>12</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7</td>
</tr>
</tbody>
</table>
Looking at the correlations output for patients with IgA-type of MM in the above table, the Pearson $r$ (correlation) between IgA and each time point can be squared to determine effect sizes for the correlation coefficient. Following Cohen's rule of thumb for effect sizes, an $r < .10$ ($r^2 = 0.01$) effect is considered small, $r = .3$ is considered medium-sized effects, and large effects are generally considered equal or larger to $r = .5$ ($r^2 = .25$). If we square 0.092, the $r^2 = 0.008$ - a small effect. Effect size findings at each baseline ($r^2 = .05$), 6 months ($r^2 = .04$), 12 months ($r^2 = .001$), and 24 months ($r^2 = .004$) were small.

For the analysis, serum IgA levels were grouped categorically according to low, normal or high levels. A second correlation was run to determine if the results would differ should the actual value be used for the analysis. Simple statistics were first run to determine the average IgA levels at each baseline, 6-month, 12-month, and 24-month time point. Low IgA levels were observed at baseline (43 mg/dL; $M = 60.96$, $SD = 52.89$) and 6 months (60 mg/dL; $M = 113$, $SD = 108.12$). On average, normal IgA levels were observed at 12 months (74 mg/dL; $M = 98$, $SD = 89.77$) and 24 months (129 mg/dL; $M = 152$, $SD = 143.76$). Effect size findings in the actual value at each baseline ($r^2 = .02$), 6 months ($r^2 = .00$), 12 months ($r^2 = .00$), and 24 months ($r^2 = .02$) were small and consistent with the prior categorical analysis.
### Table 14

**Correlations Analysis: Patients With IgG-Type MM (n = 27)**

<table>
<thead>
<tr>
<th>Serum IgA correlation with diarrhea at:</th>
<th>Pearson correlation $r$</th>
<th>$r^2$</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorized as low, normal or high:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-.232</td>
<td>.05</td>
<td>.245</td>
</tr>
<tr>
<td>6 months</td>
<td>-.196</td>
<td>.04</td>
<td>.328</td>
</tr>
<tr>
<td>12 months</td>
<td>-.039</td>
<td>.00</td>
<td>.846</td>
</tr>
<tr>
<td>24 months</td>
<td>.205</td>
<td>.04</td>
<td>.306</td>
</tr>
<tr>
<td>By actual value:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-.131</td>
<td>.02</td>
<td>.516</td>
</tr>
<tr>
<td>6 months</td>
<td>-.014</td>
<td>.00</td>
<td>.944</td>
</tr>
<tr>
<td>12 months</td>
<td>-.003</td>
<td>.00</td>
<td>.990</td>
</tr>
<tr>
<td>24 months</td>
<td>.147</td>
<td>.02</td>
<td>.463</td>
</tr>
</tbody>
</table>

**Other findings.** The underlying hypothesis in the LRD study is that patients with LRD do better because diarrhea is actually a sign of an autoimmune process that underlies diarrhea in patients on lenalidomide. Colonoscopy findings were reviewed among the 44 patients in the subset analysis, with and without diarrhea, to see if there is evidence of an autoimmune effect of the drug. Of the 44 patients in the subset analysis, 11/24 (25%) had diarrhea and a colonoscopy with biopsy during the diarrhea episode. Of these, 4/24 (17%) patients in the LRD group had abnormal findings to suggest an autoimmune effect present: 2 with crypt apoptosis, 1 with collagenous colitis, and 1 with focal active cryptitis. Only patients with LRD had abnormal colonoscopy findings. No patients without LRD had abnormal colonoscopy findings. These results support the underlying hypothesis that LRD is a symptom that underlies an autoimmune effect.
This chapter highlighted findings of the two studies. High consent and adherence rates were observed in the PNP study. A small to medium effect size of glutamine on the severity of neuropathy symptoms (.43) was observed. Quality of life increased in the glutamine group (by 5.1 points) and decreased in the placebo group (5 points) from baseline to the end of study. The change in QOL scores from time 1 to time 2 resulted in a large observed effect size 1.09. In the diarrhea study, a subset analysis of patients who received lenalidomide for at least 19 months and with LRD had a longer median duration of response than those without LRD (62.5 versus 43 months, respectively). Normalization of IgA levels was observed in 48% of people with IgG MM, but normalization of IgA levels did not necessarily protect the individual from LRD, as moderately small correlations between diarrhea and IgA levels occurred at the 6-, 12-, and 24-month time points.

Table 15

*Colonoscopy + Biopsy Results Reviewed (n = 44)*

<table>
<thead>
<tr>
<th>Lenalidomide-related diarrhea (LRD)?</th>
<th># of patients with colonoscopy + biopsy on lenalidomide (n/%)</th>
<th>Abnormal findings to suggest immune effect per group (n/%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes LRD (n = 24)</td>
<td>11/24 (25%)</td>
<td>4/24 (17%)* (4/11 biopsies)</td>
</tr>
<tr>
<td>No LRD (n = 20)</td>
<td>2/20 (10%)</td>
<td>0/20 (0%) (0/2 biopsies)</td>
</tr>
</tbody>
</table>

*Biopsy findings: 2 crypt apoptosis, 1 collagenous colitis, 1 focal active cryptitis.

Conclusion

This chapter highlighted findings of the two studies. High consent and adherence rates were observed in the PNP study. A small to medium effect size of glutamine on the severity of neuropathy symptoms (.43) was observed. Quality of life increased in the glutamine group (by 5.1 points) and decreased in the placebo group (5 points) from baseline to the end of study. The change in QOL scores from time 1 to time 2 resulted in a large observed effect size 1.09. In the diarrhea study, a subset analysis of patients who received lenalidomide for at least 19 months and with LRD had a longer median duration of response than those without LRD (62.5 versus 43 months, respectively). Normalization of IgA levels was observed in 48% of people with IgG MM, but normalization of IgA levels did not necessarily protect the individual from LRD, as moderately small correlations between diarrhea and IgA levels occurred at the 6-, 12-, and 24-month time points.
Chapter 5: Discussion, Conclusions, and Recommendations

Discussion of Findings

In Chapter 5, the implications of each separate project are discussed briefly in terms of result and methodology concerns. A summary discussion of what these projects together indicate for symptom science and next steps also is provided.

Discussion of Findings: Peripheral Neuropathy Symptoms Study

Consent Rate. The consent rate of 50% is a good consent rate especially when compared to other palliative and symptom management trials, which often cite much lower rates around 20% (LeBlanc, Lodato, Currow, & Abernethy, 2013). The rate is most consistent with questionnaire and nondrug interventional trials in cancer, which can range from approximately 45% to 60% (Aranda et al., 2006; LeBlanc et al., 2013; Post-White et al., 2003). Three barriers to study participation in palliative and cancer symptom management trials may have affected the consent rate and should be kept in mind. Barriers are patient related (frailty, lack of motivation to participate), gatekeeping (provider or caregiver does not think the patient would benefit and should not participate), and ethical (whether the patient, in his or her situation, should be participating in a clinical trial in his or her state of health) (Barrett, 2002; LeBlanc et al., 2013). Although these barriers did not seem to dramatically impact the current study, these would be considered in future symptom management research.

Patients who declined consent to participate in the PNP study cited reasons such as the frequency of study visits and procedures. Frequency of visits and time burden have been cited in other intervention studies a barriers to participate (Fletcher, Gheorghe,
As with many interventional trials, monthly office visits were required in the PNP study for patient safety by the Protocol Review and Monitoring Committee (PRMC) in accordance with the IND nature of the pilot study. Although patient convenience is important, patient safety is imperative in any trial. Given the small percentage of patients who declined participation and cited frequency of visits, monthly visits are reasonable for patient safety. Future clinical studies may be designed with more flexibility, but this was not possible in this study.

**Adherence Rate.** The adherence rate to the intervention was high (99.5%) for the duration of the study when taking into account study hold periods. This is surprising when one considers the multiple survivorship issues that individuals with MM experience. Patients with MM are required to balance frequency of outpatient cancer-related clinic visits with work, family, and miscellaneous other responsibilities. Patients with MM often suffer from chronic pain (as evidenced by the patients in the diarrhea study who take opioid analgesics) and take multiple drugs to control other common comorbid illnesses such as diabetes and hypertension (Kurtin, Lilleby, & Spong, 2013; Stephens et al., 2014). The self-selection factor may have contributed to this high adherence rate, as it was observed that these MM patients were highly motivated and made themselves available for the study procedures. The high adherence rate in this MM patient sample can be cited for future supportive care trials, although the rate may vary according to many factors including the characteristics of patient populations, institutional differences, and the geographic location of the study site.

Strategies to enhance adherence to the study drug intervention (telephone calls, study calendars, and monthly office visits, as outlined in Chapter 3) are likely to have
positively affected the adherence findings as similarly demonstrated in previous studies (Zolnierek & DiMatteo, 2009; McDonald et al., 2002). It is difficult, however, with the small sample to determine which interventions may have specifically enhanced patient adherence to the study intervention. Thus, future studies should be aimed at understanding individual factors that impact adherence in MM to develop strategies in this specific population.

Two patients withdrew consent for an attrition rate of 22%. Both patients withdrew consent during study hold periods. These individuals may or may not have withdrawn consent if there were no study holds, although one individual moved. The attrition rate is lower than that cited in supportive care and cancer trials, which can range from 26% to 44% by end of study (Hui, Glitza, Chisholm, Yennu, & Bruera, 2013; Siddiqi, Sikorskii, Given, & Given, 2008).

**Effect Size: Neuropathy Severity and QOL.** An observed small to medium effect of .43 on neuropathy severity is encouraging for two reasons. First, there has been anecdotal evidence of the effectiveness of glutamine to treat neuropathy symptoms, but to date no one has tested the effect of the glutamine intervention on neuropathy severity in this population prior to this study. Second, some patients may actually benefit from the glutamine intervention as this effect size study is the first evidence to show the glutamine actually has an effect on neuropathy severity.

No effect size findings of glutamine on PNP symptoms are available, as the agent has not been studied in MM. However, recent promising studies have focused on ameliorating PNP by other methods such as prescription duloxetine and acupuncture. Effect size findings in the PNP study were slightly lower than the effect size of .51 that
was observed in a randomized study designed to assess the effect of oral duloxetine on pain, function, and quality of life among patients with painful chemotherapy-induced PNP (Smith et al., 2014). Higher effect size findings were observed (range from .86 to .90 at three different time points) in a nonrandomized acupuncture study in patients with bortezomib induced PNP (Garcia et al., 2014). A small to medium effect size in this controlled short study is promising since a larger effect size may be observed when the duration of glutamine use is extended. These results suggest that there is a possible way to find alternative treatment for PNP using this particular agent.

The effect size findings of glutamine on quality of life can be interpreted by examining (1) the total FACT scores and (2) the subscale scores by domain. A large effect size (1.09) observed in the glutamine trial on QOL provides a guide for future QOL research in this population despite the small sample size as the trial was tightly controlled with stringent inclusion and exclusion criteria. An increase in QOL was seen in the glutamine group and was accompanied by a decrease in QOL in the control group which may be explained by 2 hospitalizations in the control group for issues unrelated to the cancer or drug. Improved QOL scores were also observed in prior trials when glutamine was used to ameliorate neuropathy symptoms in colorectal and breast cancer patients (Vahdat et al., 2001; Wang et al., 2007). Caution should be exercised when citing the large ES in future studies due to the small sample and short study duration of 4 months.

Examination of the specific domains on quality of life showed that people in the glutamine group had better improvement in social and emotional well-being compared with the control group. A medium effect size (.51) was observed in the neurotoxicity subscale and was equivalent to the neuropathy severity score (NIS-LL) (.43). The large
effect of glutamine on domains of social and emotional well-being was observed and highest among the five subscales. The improved QOL scores may be explained by these reasons: (1) improved social and emotional well-being in the glutamine group, (2) improved health condition due to the glutamine intervention, and (3) worsening symptoms and QOL without an intervention in the placebo group. Physiological processes which underlie the symptoms may affect the patient’s perception of the symptoms (Dodd et al., 2004). Therefore, the patient may psychologically and emotionally improve as a result of the symptom reduction. Thus, the large observed effect size of QOL, social and emotional well-being subscales, and the medium effect size on the NTX scale suggests that MM patients may actually benefit from the glutamine intervention.

**Study Limitations.** Two main limitations to the peripheral neuropathy study exist: (1) stringent subject eligibility and (2) small sample size. In the randomized setting, control for covariates is important. Stringent inclusion and exclusion criteria are also required in any clinical trial to minimize risks to study participants and protect study validity. However, the stringent inclusion/exclusion criteria limit the study to a very specific subgroup of patients with MM and reduce the possibility of generalizing the study findings on neuropathy severity and QOL to MM patients with more complicated health or treatment conditions. Therefore, future studies should test the effect of the glutamine intervention in other patients who receive bortezomib at a different dose, schedule, or duration. Further, the study sample is small and the obtained effect size estimate can be unstable or biased. With a more representative (larger) sample size, the estimated effect size can be different. A multivariate analysis of covariates was not
possible in this small pilot study but would be controlled for and should be considered in a future study.

**Discussion of Findings: Diarrhea Study**

**Duration of Response.** Patients with LRD had a longer median duration of response than those who do not develop LRD (62.6 versus 43.4 months, respectively), which was identified in the subgroup analysis of 44 patients. Although this preliminary finding has yet to be confirmed in a multivariate study with a larger sample, it provides an initial supportive evidence for a long-held speculation that there is an association between LRD and MM remission. The ultimate testing and confirmation of this association in science will have an important implication for MM patients’ symptom management and nursing science. The onset of diarrhea occurred at a median of 19 months, which was consistent with one prior review (19 months also) (Simpson et al., 2008). It should also be noted that the duration of response for each group is much higher than reported in most trials which use lenalidomide to treat newly diagnosed myeloma (Facon et al., 2013; Palumbo, Falco, Benevolo, Rossi, & Caravella, 2010; Rajkumar et al., 2010).

**Serum IgA Levels.** Two competing hypotheses were proposed in this study. First, diarrhea may be a sign of an underlying immune effect, which can lead to a better duration of response due to the autoimmune effect. As an alternate, IgA deficiency may actually cause LRD, and the LRD is not a sign of an underlying immune effect. If IgA explains diarrhea, we would expect that when the IgA levels become normalized, individuals with normal IgA levels should no longer have LRD.

The data in the correlation analysis did not indicate that when patients experienced a consistent and more normal IgA, the individual would have less diarrhea.
In the study, when the IgA level was normalized in 48% patients at 12 months, the correlation between IgA level and LRD at 12 months ($r = -0.039$) was actually decreased while one would expect the $r$ values to increase if there was a stronger correlation with diarrhea and IgA levels were present. A second analysis was run with the absolute serum IgA value, with similar results. This suggests that if people have LRD, the IgA levels may not be relevant to the diarrhea. Thus, the IgA is less likely the cause of diarrhea, and this strengthens the argument that LRD is autoimmune rather than IgA effect. This hypothesis has never been tested. Therefore, the findings are not able to be compared to prior research.

Although not an endpoint, an interesting finding was histopathologic evidence of autoimmune findings on biopsy in 4 patients who received lenalidomide and experienced diarrhea. None of these findings were evident in patients who did not have diarrhea but took lenalidomide. This suggests that, in fact, an autoimmune process may underlie the diarrhea symptom to an extent. Further investigations are warranted with a larger sample and perhaps a histopathologic study to examine microscopic evidence of an autoimmune process. No prior studies have identified autoimmune findings in patients who have not undergone the transplant procedure (Lin et al., 2013).

**Study Limitations.** The small sample size in the diarrhea study limits the generalizability of the findings. It was surprising to identify such a large number of patients who received lenalidomide ($n = 602$) and then have to exclude a majority of those with diarrhea and on long-term lenalidomide based on the stringent inclusion and exclusion criteria. Less than 10% of patients initially screened for the study were included in the analysis. Widening of inclusion and exclusion criteria would
accommodate people with more complex disease conditions, and a larger effect could result.

The current sample is different from the patient population in the literature and is not necessarily representative of the general MM patients who receive lenalidomide. This can be due to institutional variations (ours may do a better job at managing MM than others), or the sample is biased because only responding patients were included in the analysis. These reasons may limit the generalizability of findings.

Issues with reliability and underreporting or under-recognizing diarrhea might have occurred, especially if diarrhea was mild or a short-term problem for patients. The potential to consistently under-document or under-report diarrhea is unlikely in this study due to standard of care documentation processes at the Cleveland Clinic. The routine clinic notes that are written on a monthly basis specifically address and document the presence or absence of symptoms such as diarrhea in the medical chart at each visit. It is important to note, however, that chart review data have limitations without verification from a subject’s self-report. This potential error could affect the accuracy of the estimate.

Serum IgA levels can fluctuate and be impacted by autoimmune and inflammatory conditions as well as the MM itself (Chow et al., 2012; Conner & Blutt, 2013; Kastritis et al., 2014; Moris, 2014). As no reliable surrogate biomarkers for diarrhea exist, the hypothesis that improved IgA levels would protect the individual from diarrhea and the role of IgA and diarrhea in MM was worthy of further exploring. A larger sample size, however, may have affected study findings.
Implications for Nursing Science and Nursing Practice

The purpose of the two studies was to investigate ways to prevent or mitigate painful PNP and gain initial evidence into what may cause clinically significant diarrhea symptoms. The results of both projects contribute to symptom science, as there is a paucity of trials to address these symptoms in MM.

Implications of the PNP Study Findings. The high consent rate and adherence rate to the PNP intervention provides insight into the patient population and illustrates the MM patient’s willingness to participate in supportive care research. In addition, the glutamine intervention provided first-hand, promising knowledge of effect size on neuropathy severity in MM despite the small sample size and relatively short study duration. Thus, glutamine remains a promising potential agent for modifying PNP symptoms; its effect warrants further investigation using a large study sample.

A large effect size of glutamine on quality of life was observed. Further examination of QOL subdomains showed that social and emotional well-being had most impact on QOL improvement. The observed psychosocial effect may be explained by changes in other aspect of the patient’s life, but the impact of reduced PNP on the patient’s psychosocial well-being warrants further research. Nurses should be aware of the potential benefit of glutamine intervention and document adverse events more carefully and consistently so the symptoms can be better managed. This stresses the importance that nurses record symptoms on a regular basis in order to intervene in the symptoms and improve QOL.

Implications of the Diarrhea Study Findings. Diarrhea symptom science is enhanced based on the findings of the study, as the results suggest that diarrhea may in fact be a
sign of an underlying immunologic phenomenon. If diarrhea is in fact a manifestation of an ongoing immunologic process, and not due to low IgA levels, then nurses should educate patients and providers that the drug should not be stopped. The focus should be shifted to manage the diarrhea symptom and provide strategies to improve adherence if an association between LRD and an immune effect exists. Adherence to lenalidomide would be a challenge for patients who suffer with the symptom and the nurses who care for these patients. More research needs to be carried out in the area of interventions for the diarrhea in this MM patient population.

Dodd’s Symptom Management Model provided a framework to study the diarrhea and symptom and to provide knowledge for future symptom research studies. While the study must be replicated in a larger trial, patients with LRD might remain in remission longer likely due to an immune effect as correlative analysis of IgA and LRD does not support IgA deficiency as the cause of diarrhea.

There are psychologic implications of the study findings, which to this point have not been addressed. Patients may perceive diarrhea as a good thing if they have LRD (e.g., “I have diarrhea. This is good, so I should take my cancer pills so I can live longer”). However, patients who do not have diarrhea may be less optimistic and less likely to adhere to recommendations and may become demoralized (e.g., “Why should I bother taking my cancer pills? I won’t stay in remission as long as the patients with diarrhea.”). Nurses presenting the remission data to patients and families should consider the hypothetical psychological implications of these study findings, which require further study.
**Future Directions.** Key lessons were learned in the context of these two studies:

1. Widening the inclusion/exclusion criteria would be more accommodating for complex situations and allow for a more generalizable sample (both studies), and 2. the importance of drug dispensing and delivery procedures (PNP study). Widening eligibility criteria in the neuropathy study and controlling for covariates in multivariate analyses may have allowed more patients with PNP the opportunity to benefit from the glutamine intervention. Real-world scenarios should be included in future studies, such as allowing all patients with neuropathy the opportunity to participate regardless of the chemotherapy regimen one receives. Eligibility criteria in the diarrhea study led to a small sample (only 10% were eligible), and results are only applicable to a select population of newly diagnosed MM patients with a rare cancer. Expanding criteria for study entry should be cautiously considered in future studies.

Drug delivery procedures should be considered for future PNP studies. Patients were required to scoop and measure the powder twice daily. This method led to study hold periods to assess the accuracy of the dose. There are a couple of months where 5 of 9 participants did not complete all 4 cycles of the study due to study holds for quality monitoring investigation into drug delivery procedures. Inability for patients to complete all recommended cycles affected the results. To limit issues with drug administration procedures in future studies, researchers should use fixed dose of drug (either prepackaged powder packets or pills) to decrease the risk of medication errors.

The findings of the current PNP study (small to medium effect size of glutamine on neuropathy symptoms and large effect size of glutamine on quality of life and specifically social and emotional well-being) warrant future study. Any agents that hope
to ameliorate the PNP symptom severity should be investigated, as insight into peripheral neuropathy prevention and treatment in MM continues to be lacking.

No prior studies of the LRD phenomenon exist in the MM patient population. Future symptom management studies will focus on gaining knowledge of the ways that patients treat the diarrhea symptom using a two-step approach. First, a chart review can be conducted to determine strategies MM patients use to self-manage the diarrhea. Then, various interventions aimed at reducing symptom severity can be tested to learn which strategies are used to manage diarrhea. Knowledge of ways to effectively minimize diarrhea symptoms can enhance adherence to the lenalidomide regimen, which, in turn, may impact the individual’s duration of response to treatment.

Further research into the prevention and treatment of diarrhea is warranted, and understanding the impact of the diarrhea symptom for patients who suffer with the diarrhea as findings in this study also illustrated the chronic nature of the diarrhea. The diarrhea will remain as long as the patient takes lenalidomide, which can be devastating to the individual. Insight into reasons why patients report, do not report, or underreport the diarrhea symptom needs to be clarified. Consequences of uncontrolled diarrhea symptoms in other cancers were outlined in Chapter 1 (physical, psychological, and financial) but have not been studied in MM. Therefore, investigation into the diarrhea symptoms are warranted.

The adherence rate of patients to lenalidomide and who experience LRD should be investigated in future studies. Some patients or providers may consider LRD an unacceptable toxicity and stop the lenalidomide therapy. Stopping therapy may lead to relapse of the cancer, but this is unclear. It was observed during the chart review that few...
patients seemed to stop lenalidomide because of the diarrhea symptom. This may be due to the fact that many providers recommended the patient continue on the drug. Many cited fear of disease relapse as a reason to continue lenalidomide. It would be interesting to investigate adherence rates across a variety of settings throughout the country, whether patients stayed on therapy despite the unpleasant symptom for fear of relapse, or if these findings be limited to my institution.

**Conclusion**

These two small studies contributed to nursing symptom science in the following ways: The glutamine study provides knowledge of the effect of glutamine in this MM population as well as promising effect size data for future studies. No previous randomized studies of glutamine exist to date, and effect sizes of neuropathy severity and QOL have been noted in the literature. In the diarrhea study, evidence showed that diarrhea leads to a longer duration of response when compared to those who do not develop diarrhea and that the diarrhea is more likely based on immune effect rather than IgA deficiency. Peripheral neuropathy and diarrhea symptoms both plague patients with this chronic but incurable cancer, and these research studies shed initial light on the symptoms. Caution is needed, however, in that due to small sample sizes, the findings cannot be generalized; however, the results provide direction for future symptom science studies.
APPENDICES

APPENDIX A STUDY INSTRUMENTS FOR PNP STUDY
A1 GOG-Neurotoxicity Questionnaire, V. 4.0 (FACT/GOG-Ntx)
A2 FACT-G Questionnaire
A3 Glutamine or Placebo Diary Card
A4 Neuropathy Impairment Score of the Lower Limbs (NIS-LL)
A5 International Myeloma Working Group Response Criteria

APPENDIX B STUDY PROCEDURES FOR PNP STUDY
B1 Study Schema
B2 NCI Common Terminology Criteria for Adverse Events V.4.0
B3 Restriction of Concomitant Medications
B4 Dose Modification for Bortezomib
B5 Patient Information Sheet: Glutamine
B6 Ethical Considerations and Preventative Measures
Appendix A1. GOG-Neurotoxicity Questionnaire, Version 4.0 (FACT/GOG-Ntx)
Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
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<tr>
<th></th>
<th>ADDITIONAL CONCERNS</th>
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<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTX 1</td>
<td>I have numbness or tingling in my hands .......</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NTX 2</td>
<td>I have numbness or tingling in my feet ........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NTX 3</td>
<td>I feel discomfort in my hands ..................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NTX 4</td>
<td>I feel discomfort in my feet ..................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NTX 5</td>
<td>I have joint pain or muscle cramps ..................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>H112</td>
<td>I feel weak all over ......................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NTX 6</td>
<td>I have trouble hearing .....................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NTX 7</td>
<td>I get a ringing or buzzing in my ears ........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NTX 8</td>
<td>I have trouble buttoning buttons ..........................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NTX 9</td>
<td>I have trouble feeling the shape of small objects when they are in my hand ....</td>
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<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An6</td>
<td>I have trouble walking ...................................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</table>
### Appendix A2. FACT-G VERSION 4.0 and NTX

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<th>PHYSICAL WELL-BEING</th>
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<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
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<tbody>
<tr>
<td>GP1</td>
<td>I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP2</td>
<td>I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP3</td>
<td>Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP4</td>
<td>I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP5</td>
<td>I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP6</td>
<td>I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GP7</td>
<td>I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</tbody>
</table>

<table>
<thead>
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<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
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</thead>
<tbody>
<tr>
<td>GS1</td>
<td>I feel close to my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS2</td>
<td>I get emotional support from my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS3</td>
<td>I get support from my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS4</td>
<td>My family has accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS5</td>
<td>I am satisfied with family communication about my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GS6</td>
<td>I feel close to my partner (or the person who is my main support)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<table>
<thead>
<tr>
<th></th>
<th>FUNCTIONAL WELL-BEING</th>
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<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>GF1</td>
<td>I am able to work (include work at home) .......................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF2</td>
<td>My work (include work at home) is fulfilling ..................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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</tbody>
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<table>
<thead>
<tr>
<th></th>
<th>EMOTIONAL WELL-BEING</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
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</thead>
<tbody>
<tr>
<td>GE1</td>
<td>I feel sad...............</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE2</td>
<td>I am satisfied with how I am coping with my illness.............</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE3</td>
<td>I am losing hope in the fight against my illness...............</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>GE4</td>
<td>I feel nervous ..........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE5</td>
<td>I worry about dying ........</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GE6</td>
<td>I worry that my condition will get worse .....................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>GF3</td>
<td>I am able to enjoy life..........................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>GF4</td>
<td>I have accepted my illness ......................</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF5</td>
<td>I am sleeping well .....</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>GF6</td>
<td>I am enjoying the things I usually do for fun</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>GF7</td>
<td>I am content with the quality of my life right now</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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</table>
Appendix A3. Glutamine or Placebo Diary Card

Study ID#________ Dates: ___________

Your study medication ________ is to be taken ____ scoop ____ time(s) per day. We will collect the completed diary card at the following study visit.

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
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<th>Day 18</th>
<th>Day 19</th>
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<th>Day 21</th>
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<tbody>
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</table>
Appendix A4. Neuropathy Impairment Score

### NEUROPATHY IMPAIRMENT SCORE (NIS)

**Objective:** To provide a single score of neuropathic deficits and deficits in cranial nerve, muscle weakness, reflexes, and sensation. Abnormalities are abstracted from a neurologic examination in which all of the assessments are made.

**Scoring:** The examiner scores deficits by what he (she) considers to be normal considering test, anatomical site, age, gender, height, weight, and physical fitness.

#### Scoring, Muscle Weakness

<table>
<thead>
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<th>Description</th>
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<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>25% Weak</td>
</tr>
<tr>
<td>2</td>
<td>50% Weak</td>
</tr>
<tr>
<td>3</td>
<td>75% Weak</td>
</tr>
<tr>
<td>4</td>
<td>Paralysis</td>
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</table>

#### Scoring, Reflexes

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<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Decreased</td>
</tr>
<tr>
<td>2</td>
<td>Absent</td>
</tr>
</tbody>
</table>

#### Sensation

- Touch-pressure
- Pin-prick
- Vibration
- Joint position

#### Cranial Nerves

1. 5.

#### Muscle Weakness

- 6. 20.
- 21. Adductor hallucis
- 22. Ankle plantar flexors
- 23. Toe extensors
- 24. Toe flexors

For patients 50-69 years old, ankle reflexes which are decreased are graded 0 and when absent are graded 1. For patients >70 years, absent ankle reflexes are graded 0.

For patients 50-69 years old, ankle reflexes which are decreased are graded 0 and when absent are graded 1.
Appendix A5. Response Criteria for Multiple Myeloma

### EBMT, IBMTR, and ABMTR Response Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
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</thead>
</table>
| Complete response (CR)          | ➢ Negative immunofixation (IFX), maintained for 6 wk  
➢ < 5% bone marrow plasma cells  
➢ No increase in size or number of lytic bone lesions  
➢ Disappearance of soft-tissue plasmacytomas                                                                                                                                                                                                                           |
| Partial response (PR)           | ➢ 50% decrease serum M-protein, maintained for 6 wk  
➢ ≥ 90% decrease 24-hr urine protein, maintained for 6 wk  
➢ For nonsecretory myeloma: ≥ 50% decrease in BM plasma cells  
➢ ≥ 50% decrease soft-tissue plasmacytomas  
➢ No increase in size or number of lytic bone lesions                                                                                                                                                                                                                 |
| Minimal response (MR)           | ➢ 25%–49% decrease serum M-protein, maintained for 6 wk  
➢ 50%–89% decrease 24 h urine light chain excretion, maintained for 6 wk  
➢ For nonsecretory myeloma: 25%–49% decrease BM plasma cells, maintained for 6 wk  
➢ 25%–49% decrease in size of soft-tissue plasmacytomas  
➢ No increase in size or number of lytic bone lesions                                                                                                                                                                                                                 |
| No change (NC)                  | Not meeting the criteria of either minimal response or progressive disease                                                                                                                                                                                                                                                                 |
| Plateau                         | Stable values (within 25% above or below value at time response is assessed) maintained 3 mo                                                                                                                                                                                                                                           |
| Relapse from CR                 | ➢ Reappearance positive IFX or SPEP  
➢ ≥ 5% BM plasma cells  
➢ New lytic bone lesions or soft-tissue plasmacytomas or increase in size of residual bone lesions  
➢ Hypercalcemia not attributable to other cause                                                                                                                                                                                                                     |
| Progressive disease             | ➢ > 25% increase in serum M-protein  
➢ > 25% increase in 24-hr urinary light chain excretion  
➢ > 25% increase in BM plasma cells  
➢ Increase in size of existing bone lesions or soft-tissue plasmacytomas  
➢ New bone lesions or soft-tissue plasmacytomas  
➢ Hypercalcemia not attributable to other causes                                                                                                                                                                                                                     |

---

**International Myeloma Working Group Uniform Response Criteria**

<table>
<thead>
<tr>
<th>Category</th>
<th>Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR, stringent complete response</td>
<td>Normal free light chain (FLC); no clonal BM plasma cells</td>
</tr>
<tr>
<td>CR, complete response</td>
<td>Negative IFX and &lt; 5% BM plasma cells</td>
</tr>
<tr>
<td>VGPR, very good partial response</td>
<td>Positive IFX and negative SPEP; ≥ 90% urine protein decrease; urine M-protein level &lt; 100 mg per 24 hr</td>
</tr>
<tr>
<td>PR, partial response</td>
<td>≥ 50% decrease serum M-protein and ≥ 90% decrease in 24-hr urinary M protein</td>
</tr>
<tr>
<td>SD, stable disease</td>
<td>Not meeting criteria for CR, VGPR, PR, or progressive disease</td>
</tr>
</tbody>
</table>
APPENDIX B  STUDY PROCEDURES FOR PNP STUDY

Appendix B1. Study Parameters

<table>
<thead>
<tr>
<th>Evaluation/Procedure</th>
<th>Screening/ Baseline</th>
<th>Day 1 Cycle 1–4 (within 7 days)</th>
<th>Day 14</th>
<th>Day 28 cycle 4/EOS (within 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vital signs (BP, HR, RR, temp)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Complete blood count w/differential</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Complete metabolic panel</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vitamin B&lt;sub&gt;12&lt;/sub&gt;, folic acid&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HgBA&lt;sub&gt;1c&lt;/sub&gt;&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPEP, 24 hr UPEP, sFLC, serum and urine immunofixation</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Bone marrow aspiration and biopsy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeletal survey&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event monitoring including neuropathy severity (NCl-CTCAE v4.03)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>FACT/GOG-ntx Quality of Life Instrument and Survey</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Diary card review for glutamine and placebo adherence</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Neuropathy Impairment Score – Lower Limbs (NIS-LL)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Telephone encounter&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Electromyography (EMG)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>a</sup>Obtained any time prior to entry on study.
<sup>b</sup>Between days 14–21 of cycle 1.
<sup>c</sup>If physician determines an EMG is necessary this data would be collected.
<sup>d</sup>Screening/baseline labs can be used for cycle 1 labs if obtained within 28 days of enrollment on study.
<sup>e</sup>HgBA<sub>1c</sub> only for patients with a known diagnosis of diabetes for baseline evaluation.
Appendix B2. NCI Common Terminology Criteria for Adverse Events v4.0  
(NCI-CTCAE): Publication Date: May 28, 2009

Nervous System Disorders

<table>
<thead>
<tr>
<th>Name</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral motor neuropathy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL; assistive device indicated</td>
<td>Life-threatening consequences; urgent intervention indicated (e.g., paralysis)</td>
<td>Death</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Asymptomatic; loss of deep tendon reflexes or paresthesia</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

*Note. ADL = activities of daily living.

<sup>a</sup>Definition: A disorder characterized by inflammation or degeneration of the peripheral motor nerves.

<sup>b</sup>Definition: A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.
## Appendix B3. Restriction of Concomitant Medications

<table>
<thead>
<tr>
<th>Name of Medication</th>
<th>Indication</th>
<th>Restrictions</th>
</tr>
</thead>
</table>
| Pregabalin, gabapentin, duloxetine, amitriptyline                                  | Treatment of symptoms related to neuropathy       | - Patients can receive these medications prior to enrollment in the study if documented at baseline.  
- Increasing the dose or initiating these medications while on-study is prohibited. |
| All opioid analgesics                                                             |                                                   |                                                                                                                                                                                                              |
| Vitamin E, alpha-lipoic acid, L-carnitine, Vitamin B complex, glutamine, glutathione | Vitamins that may decrease PN symptoms in other cancer patients | - These vitamin supplements are prohibited at baseline and while on study. Efficacy in MM patients is unknown.  
- Vitamin $B_{12}$ would be allowed if vitamin $B_{12}$ deficiency is diagnosed at the beginning of study.  
- Magnesium and potassium will only be allowed if patients are receiving for electrolyte replacement and not for treatment of PN symptoms such as muscle cramping. |
| Quinine, magnesium, or potassium supplements                                       |                                                   |                                                                                                                                                                                                              |
### Bortezomib Dose-Modification Guidelines for Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Severity of Peripheral Neuropathy Signs/Symptoms</th>
<th>Modification of Dose and Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (paresthesia, weakness and/or loss of reflexes) without pain or loss of function</td>
<td>No action</td>
</tr>
<tr>
<td>Grade 1 with pain or grade 2 (interfering with function but not with ADL)</td>
<td>Reduce bortezomib to 1.0 mg/m²</td>
</tr>
<tr>
<td>Grade 2 with pain or grade 3 (interfering with ADL)</td>
<td>Withhold bortezomib until toxicity resolves. When toxicity resolves, reinitiate therapy with a reduced dose (0.7 mg/m²) and change treatment schedule to once per week</td>
</tr>
<tr>
<td>Grade 4 (sensory neuropathy that is disabling or motor neuropathy that is life threatening or leads to paralysis)</td>
<td>Discontinue bortezomib</td>
</tr>
</tbody>
</table>

Appendix B5. Glutamine information sheet

**Background**
Glutamine is the most abundant amino acid in the blood and tissues. It is primarily formed and stored in skeletal muscles and lungs. Studies indicate that tumors may consume glutamine, resulting in depletion of glutamine. Glutamine may lessen neuropathy associated with some chemotherapies.

**Neuropathy**
Neuropathy is a common side effect of some chemotherapy treatments. It includes one or more of the following: pins and needles, cold and burning, prickling or pinching in hands and/or feet. Some patients can have trouble walking or buttoning shirts.

**Dosing**
Glutamine 15 grams 2x a day

Tips to help you remember to take your glutamine:
1) pill containers will allow you to not miss skipped doses
2) A calendar is provided so you can record that you took your dose and the date and time.
3) Taking lots of pills may be challenging. Taking your pills with food may help to digest and you will remember to take with your meals.
4) Electronic reminders, such as alarm clocks may help you to remember your dose of glutamine is due.

**Side effects to look for:**
Glutamine does not cause many side effects. However, a small number of patients reported stomach upset while taking glutamine. If you take glutamine with food this may help.

Some patients with a history of seizures may be at increased risk for seizures on glutamine. Therefore, if you have had seizures in the past you should not take glutamine.

Patients with allergy to monosodium glutamate (MSG) may develop headaches and possibly a rash if they take glutamine. If you have sensitivity to MSG you should avoid glutamine.

Women who are pregnant should not take glutamine.

If you notice any of these side effects, report them immediately to your doctor or the study PI and stop taking glutamine.

If you have worsening neuropathy symptoms you should report to your doctor or the study PI.
Appendix B6. Additional Study Risks

There are several risks involved in this study.

1. The use of glutamine may cause adverse events. Although, no serious adverse events were reported in published clinical trials using a dose of 30 grams daily, theoretical side effects with its excessive use may include hepatic encephalopathy and seizures. (Garlick, 2001; Gleeson, 2008; Savarese, Savy, Vahdat, Wischmeyer, & Corey, 2003; Stubblefield et al., 2005; Vahdat et al., 2001; Wang et al., 2007)

2. In this study, glutamine is used to prevent bortezomib related PNP, which usually manifest after about 4 months of treatment. We therefore chose to use glutamine for four months. This is one month longer than what has been done in previous studies with cancer patients (usually 3 months of glutamine administration). Thus, there is a possibility of increased and unforeseen risks.

3. Patients may not respond to glutamine and their PNP may get worse. Previous studies indicate as many as 80% of patients who receive bortezomib will develop PNP symptoms. Based on existing literature, 13% of newly diagnosed MM patients receiving bortezomib may develop severe grade 3 PNP (Jagannath et al., 2009), but the chance of severe grade 4 PNP is small < 2% and even less with SC administration of bortezomib (Anderson et al., 2006; Moreau et al., 2011; P. Richardson et al., 2010).

4. Another potential risk stems from withholding OTC supplements. Although we are protecting all individuals from excessive use, some of the individuals in the placebo group could have sought relief of PNP symptoms with the use of OTC supplements (such as alpha-lipoic acid, vitamin B-complex, or glutamine itself) but when enrolled in this study they are not allowed to access such OTC supplements.

5. There is a potential risk of breaching confidentiality. Periodic internal monitoring and published research reports may inadvertently contain identifiable data, which is a risk to participants.

The subject’s burden as a potential risk has been addressed:

6. Glutamine or placebo will be given twice daily instead of three times daily to decrease study burden.

7. Each assessment (baseline and 4 months) takes only 30 minutes to complete, including 15 minutes for questionnaire and 5-10 minutes for the neuropathy exam.

Preventive Measures Taken Against Risks

Measures will be taken to protect our patients from the afore mentioned risks. A checklist will be given to patients who receive glutamine to look for symptoms of glutamate sensitivity or seizures as potential glutamine side effects (Appendix A). Further, high risk patients will be identified and excluded from the study as outlined:

1. Glutamine can exacerbate hepatic encephalopathy as glutamine can be metabolized into ammonia. Patients with abnormal liver function tests are excluded.

2. There is theoretical evidence that glutamine may increase the likelihood of seizures as glutamine can be metabolized into glutamate. Patients with a history of seizure disorder will be excluded from participating. Patients with sensitivity to monosodium glutamate (MSG) should not take glutamine as it is converted to glutamate. Patients will be advised of this in the consent process.

3. Other high risk patients will include patients who have previously been treated with bortezomib or have PNP with significant functional impairment. These individuals are at a higher risk for neurotoxicity or adverse events and therefore will not be included in this study.
4. Women who are pregnant will be excluded from participating in this study as the effect on fetus is not known. Patients receiving bortezomib or any other antimyeloma therapy are advised not to become pregnant due to teratogenic concerns. In this regard, glutamine use in this study will not impose additional limitations.

Additional measures will be taken to further safeguard patients through routine monitoring for toxicity of glutamine. They include (1) conduct a telephone interview at 2 weeks after the beginning of the study drug, (2) give patients an information sheet of the side effects to watch for, and (3) continually monitor glutamine risk by chart review. Routine chart review will assess pregnancy tests for women of childbearing potential, which are standard of care. If a female should become pregnant, she will be removed from study although more danger would be from bortezomib than glutamine. Chart review will also monitor liver function tests, which are performed on a monthly basis and are standard of care for patients with MM. The PI will discuss with physician, unblind and remove patients from study if the liver function tests are 3x ULN and it is related to glutamine.

A plan to monitor for toxicity of bortezomib is in place. Based on the current medical practice, if a patient develops worsening PNP secondary to bortezomib (according to CTCAE v 4.0), the treating physician will adjust the bortezomib treatment schedule according to published guidelines that may include (1) reduction of dose, (2) reduction of number of treatments per 28 days, and (3) interruption of treatment. These dose modification guidelines are considered the gold standard of care management of worsening bortezomib-induced PNP and have been published in numerous studies with MM patients (Appendix B5) (Richardson et al., 2009):

- Mild grade 1 (paresthesias, numbness, tingling, decreased deep tendon reflexes without pain), no intervention will be taken.
- Grade 1 with pain or grade 2 PNP, the dose of bortezomib will be reduced by 20% by the physician as standard of care.
- Grade 2 with pain or grade 3, the dose of bortezomib would be held until the PNP symptoms resolved. The dose would be resumed at 0.7 mg/m².

We will observe this process, which is standard of care, and data will be collected on intent to treat (ITT) basis. Monitoring and grading of PNP toxicity is conducted by treating physicians during patient’s every office visit, using the NCI-CTCAE v 4.0 scale. The PI will review medical charts monthly to determine the PNP status of the patient. If the patient experiences grade 3 toxicity on the NCI-CTCAE v 4.0 scale requiring additional intervention with medications such as opioid analgesic agents, the subject will be allowed to continue on glutamine or placebo as they post no harm to subject’s condition. Patients who have toxicity grade 4 or higher PNP will be terminated and treated for life-threatening conditions according to the standard care; thus they will be removed from the study. If patients experience improvement in PNP symptoms to grade 2 and resume bortezomib, we will observe this process and allow patients to take whatever medications are deemed standard of care and recommended by the provider. We anticipate the incidence of grade 3 PNP to be low in the selected population consistent with prior research approximately 13%. As these are bortezomib naive individuals, it will likely take at least 4 months to develop PNP so they are not likely to experience severe PNP.

The justification for withholding resources and the use of placebo is first and foremost patient safety (as too much glutamine in the treatment group could be potentially harmful if patients were randomized to glutamine and continue to take additional supplements). The existing standard of care does not provide any supplements, hence withholding supplements is not interfering with the standard care. Further, to obtain knowledge on the efficacy of glutamine we cannot allow for additional supplements, which may alleviate symptoms and confound study results. Also, scientifically, without a placebo group we would never been able to gain knowledge as to the efficacy of the glutamine.
Bibliography


doi:10.1016/j.jpainsymman.2005.05.015


Kumar, S. K., Dispenzieri, A., Gertz, M. A., Lacy, M. Q., Lust, J. A., Hayman, S.


Lioznov, M., El-Cheikh, J., Hoffmann, F., Hildebrandt, Y., Ayuk, F., Wolschke, C.,…Kroger, N. (2009). Lenalidomide as salvage therapy after allo-SCT for multiple myeloma is effective and leads to an increase of activated NK (NKp44+) and T (HLA-DR+) cells. *Bone Marrow Transplant*, 45(2), 349–353.


receiving bortezomib-melphalan-prednisone (VMP) in the phase 3 VISTA study.


doi:10.1634/theoncologist.12-3-312


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