CHAPTER 1

Myeloma Care: Challenges and Opportunities

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The Basics: What Is Multiple Myeloma?

Multiple myeloma is a B-cell cancer of the most mature form of B lymphocytes called *plasma cells*. The diagnosis of multiple myeloma is confirmed when the classic triad of osteolytic lesions, monoclonal plasmacytosis, and serum or urine monoclonal immune globulin protein is observed clinically (Kyle, Nobrega, & Kurland, 1969). The most common presenting signs and symptoms at initial diagnosis include anemia (73%), bone pain (68%), renal insufficiency with a serum creatinine level of 2 mg/dl or more (19%), and hypercalcemia with serum calcium level of 11 mg/dl or more (13%); less common signs and symptoms include a palpable liver (21%), a palpable spleen (5%), and a 7% incidence of amyloidosis among newly diagnosed patients with multiple myeloma (Kyle, 1975; Kyle et al., 2003). The presenting signs and symptoms of multiple myeloma at the time of diagnosis are quite heterogeneous, and in some patients, symptoms such as hyperviscosity, extramedullary disease, recurrent infections, and neurologic symptoms such as confusion, paraplegia, or polyneuropathy also may be present (Dimopoulos & Terpos, 2010).

According to the most recent cancer statistics report, multiple myeloma remains a rare form of cancer accounting only for approximately 1% of all new cancer cases and 15% of all new hematologic cancer cases. Multiple myeloma has an estimated annual incidence of 26,850 new cases and 11,240 myeloma-related deaths (Siegel, Miller, & Jemal, 2015). Multiple myeloma is the second most common hematologic malignancy after non-Hodgkin lymphoma, and it occurs slightly more often in men (14,090 new cases) than in women (12,760 new cases) based on the most recent National Cancer Institute Surveillance, Epidemiology, and End Results Program data and the National Pro-

gram of Cancer Registries figures (Siegel et al., 2015). In 2013, the number of new cases of myeloma was 5.9 per 100,000 men and women per year while the number of deaths was 3.4 per 100,000 men and women per year, age-adjusted and based on 2006–2010 censuses of cases and deaths (National Cancer Institute, 2013).

Multiple myeloma affects African Americans two to three times more often than their Caucasian counterparts (Landgren et al., 2006). Thus, a genome-wide association study (GWAS) for African American patients diagnosed with multiple myeloma is very well suited for further investigation. Spearheaded by Dr. Cozen and her colleagues at the University of Southern California, the GWAS study for African American patients was successfully launched in 2010 with more than 12 clinical trial participation sites across the United States. To date, no specific genetic abnormality has been found to explain the excess risk of multiple myeloma in the African American patient population. However, preliminary epidemiologic analysis drawn from this GWAS study showed that an increasing body mass index at age 20 is associated with younger age at diagnosis for both men and women ($p = 0.0004$), and a similar trend was seen in men only at five years prior to diagnosis (Hwang et al., 2013). Final analysis of this GWAS study in African American patients with multiple myeloma is greatly anticipated and is expected to be published in 2015.

Welcoming the Era of Novel Therapeutics

The discovery of the antitumor activity of thalidomide in relapsed, refractory multiple myeloma (Singhal et al., 1999) marked a new era of novel therapeutic options for patients with multiple myeloma. From 2003 to 2013, five drugs, namely bortezomib, lenalidomide, pegylated liposomal doxorubicin, carfilzomib, and pomalidomide, were approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients diagnosed with multiple myeloma (Anderson et al., 2013; National Comprehensive Cancer Network®, 2014). Another drug, panobinostat, was approved by FDA in February 2015 (U.S. FDA, 2015). The advent of these novel agents unequivocally improved the treatment response rate (RR), duration of remissions, event-free survival (EFS), and overall survival (OS) in patients with multiple myeloma. A recent retrospective analysis of treatment outcomes involving 1,038 patients with multiple myeloma diagnosed between 2001 and 2010 showed significant improvement in six-year OS primarily among patients older than 65 years who were diagnosed in 2006–2010, improving from 31% to 56% ($p < 0.001$) (Kumar et al., 2014). The researchers of this study greatly attributed the improved outcomes to patients' access to novel therapies and the successful completion of the prescribed length of therapy.

Patients with multiple myeloma also are reporting good global quality of life (QOL) outcomes with the use of novel agents such as bortezomib therapy during a long-term follow-up study (Delforge et al., 2012). However, more health-related QOL outcomes should be incorporated in randomized clinical drug trials in multiple myeloma to help physicians and patients choose the best possible therapy with consideration of QOL (Kvam, Fayers, Hjermstad, Gulbrandsen, & Wisloff, 2009). Oncology nurses must continue to advocate for the inclusion of QOL study endpoints in randomized clinical trials of novel drugs and should advise patients with multiple myeloma in considering QOL when making treatment decisions.

Building Lifelong Partnerships and Collaboration

The International Myeloma Foundation (IMF), a nonprofit organization dedicated to improving the lives of patients diagnosed with multiple myeloma, has been building lifelong partnerships and collaboration with the medical and nursing scientific communities. Because of the leadership of Susie Novis and Dr. Brian Durie, IMF has been instrumental in establishing and disseminating information related to the standard of care for multiple myeloma based on strong clinical research evidence through its various journal publications, patient and family seminars, and patient educational materials and handouts. When science is lacking or controversies exist in the care and treatment of patients with multiple myeloma, IMF has been proactive in developing best practice guidelines based on consensus among myeloma experts (Chng et al., 2013; Giralt et al., 2009; Kyle et al., 2010).

In 2007, IMF created and supported the Nurse Leadership Board (NLB) with its flagship project that addressed the need for publishing nursing care guidelines related to the management of side effects associated with novel therapies (Durie, 2008). NLB successfully published nursing care guidelines for the management of peripheral neuropathy (Tariman, Love, McCullagh, Sandifer, & the IMF Nurse Leadership Board, 2008), myelosuppression (Miceli, Colson, Gavino, Lilleby, & the IMF Nurse Leadership Board, 2008), deep vein thrombosis (Rome, Doss, Miller, Westphal, & the IMF Nurse Leadership Board, 2008), steroid-related side effects (Faiman, Bilotti, Mangan, Rogers, & the IMF Nurse Leadership Board, 2008), and gastrointestinal side effects (Smith, Bertolotti, Curran, Jenkins, & the IMF Nurse Leadership Board, 2008). Since the publication of the first edition of this book, NLB has added more publications related to routine health maintenance (Bilotti, Gleason, McNeill, & the IMF Nurse Leadership Board, 2011) and overall survivorship care guidelines for patients with multiple myeloma (Bilotti, Faiman, et al., 2011). Most recently, NLB published nursing guidelines for the care of patients following hematopoietic stem cell transplantation in community practice settings

(Faiman, Miceli, Noonan, & Lilleby, 2013; Mangan, Gleason, & Miceli, 2013; Miceli et al., 2013) and relative to the management of new agents in multiple myeloma (Faiman & Richards, 2014; Kurtin & Bilotti, 2013). IMF has consistently sponsored continuing nursing education programs related to multiple myeloma during regional and national meetings, including a myeloma symposium at the Oncology Nursing Society's annual conference (IMF, 2014). The IMF NLB research team is anticipating the completion and publication of its inaugural nursing research effort aimed at describing the current routine health practices of patients with multiple myeloma. The findings from this study will inform oncology nurses and other oncology clinicians on the strengths and weaknesses related to healthcare maintenance and may provide the framework for the development of an intervention study that will address healthcare maintenance issues in patients with multiple myeloma.

Finding a New Path to a Cure

One of the major recent breakthroughs in cancer care includes molecular classifications of various cancer types, and some researchers are now proposing molecular instead of organ-based cancer classifications (Cortés et al., 2014). In the field of multiple myeloma, researchers are now uncovering new molecular subgroups of multiple myeloma with prognostic significance using a micro-RNA–based classifier leading to an improved OS predictive power when compared to International Staging System/fluorescence in situ hybridization–based and gene expression profiling (GEP)-based models of multiple myeloma risk stratification. In the area of multiple myeloma therapeutics, molecular mechanisms such as the cereblon and one of its downstream targets, interferon regulatory factor 4, are now identified as specific cellular targets explaining the antitumor activities of immune modulator drugs (IMiDs) thalidomide, lenalidomide, and pomalidomide (Zhu, Kortuem, & Stewart, 2013). Cereblon is now being considered as a predictive marker for response or resistance to IMiDs (Gandhi et al., 2014). Discoveries like these could lead to improved therapeutic approaches and eventually forge a new pathway to cure myeloma.

IMF recently launched the Black Swan Research Initiative (BSRI), which focuses on eliminating minimal residual disease (MRD). Armed with a new understanding of myeloma at the cellular and molecular levels, IMF and its team of myeloma experts from the United States and Europe are developing ultra-sensitive tests to accurately measure MRD and define its absence as a cure. The tests that are being proposed to achieve MRD-zero include multiparameter flow cytometry, DNA testing of myeloma bone marrow cells, and combined positron-emission tomography–computed tomography to detect focal myeloma lesions. If all three tests are negative after the completion of ther-

apy, this will be considered MRD-zero, which is a new proposed definition of best treatment response beyond the traditional International Myeloma Working Group (IMWG) complete response criteria. These concepts mentioned in BSRI also are echoed in a recent published paper that suggests a new pathway to cure "early stage" myeloma (Roschewski, Korde, Wu, & Landgren, 2013). An international multicenter clinical trial is expected to be launched very soon to validate the prognostic significance of MRD-zero (IMF, 2013).

Promoting Nursing Research to Support Evidence-Based Myeloma Nursing Care

Significant research relative to the diagnosis, monitoring, and treatment of multiple myeloma has been conducted in the past 20 years. The research has led to an advanced understanding of multiple myeloma science and the underlying pathways in which multiple myeloma develops, yet the preponderance of research has been conducted by physicians. Medical research is highly important, but merit exists in advancing nursing science and finding ways to enhance nursing knowledge in support of multiple myeloma patient care. It remains a sad fact that nursing research to support evidence-based practice in the care of patients with multiple myeloma and ways to manage symptoms remains conspicuously absent. A lack of qualified researchers and sufficient funding for nursing research are two common reasons why multiple myeloma nursing science has not progressed as rapidly as the medical and pathobiological science. The lack of progress with nursing management of multiple myeloma symptoms is disturbing, as effective management of multiple myeloma symptoms, which is secondary to treatment or the disease, is one of the keys to successful patient outcomes.

Symptom research in multiple myeloma is particularly challenging for several reasons. First, longitudinal data are needed to understand and intervene with symptoms (Dodd et al., 2001; Dodd, Miaskowski, & Lee, 2004; 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 occur in clusters and be related to the disease, treatment, or other comorbidities. The symptoms are difficult to delineate or address, as patients often are too frail to adhere to scheduled appointments required for symptom monitoring or study procedures if enrolled in a clinical trial (Jones et al., 2013). Symptom research also often lacks objective measures to quantify symptom burden, given the subjective nature of symptoms and heavy emotional connection of cancer.

Yet, symptom research is especially important in multiple myeloma for several reasons. First, the symptom burden of disease and treatments in multiple myeloma can be substantial and primarily includes bone pain, fatigue, muscle weakness, diarrhea, and peripheral neuropathy (Jones et al., 2013). Cumulative physiologic and psychological effects of these symptoms on individuals can lead to poor QOL and limit patient access to new and yet-undiscovered drugs to treat multiple myeloma. Multiple myeloma also is a chronic illness, with many patients living in excess of 10 years (Kumar et al., 2014). 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). These challenges to conduct symptom management and end-of-life research in patients with multiple myeloma are present but are not insurmountable.

Overcoming Clinical Challenges

Nurses are the critical link to successfully identify and intervene for disease- and treatment-related symptoms. The IMF NLB plans to address the gap in scientific multiple myeloma nursing research with current and future studies. Members of the NLB seek to mentor future researchers with an interest in multiple myeloma in the coming years. Better understanding and measurement of symptoms and the underlying pathology of symptoms are not only necessary but also can lead to targeted and personalized treatment interventions. Future development of new instruments to measure symptom burden and psychometric evaluation of the new instruments are an appropriate priority and will provide an opportunity to better understand the burden of symptoms in multiple myeloma. The symptom science of multiple myeloma is an appropriate priority in nursing research. Thus, NLB is charged with the task to build evidence for the safe care of patients with multiple myeloma and improve the state of the knowledge of multiple myeloma nursing care science.

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