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Multiple Myeloma – Treatments, Economic Burden, And End Of Life Care

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MULTIPLE MYELOMA – TREATMENTS, ECONOMIC BURDEN, AND END OF LIFE CARE

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Abstract

This dissertation aimed at filling the gaps in the body of multiple myeloma (MM) literature by comparing overall survival and safety of first line maintenance or continuous treatment, and assessing disease lifetime costs, phase-specific costs and its drivers among elderly newly diagnosed (NDMM) patients. Moreover, it aimed to assess trends in EOL care and the impact of PCC on EOL care outcomes among elderly MM patients.

First, this study assessed the comparative safety and effectiveness among those who received first line LEN-based treatment versus those who received first line BORT-based treatment. The results from the study demonstrates an overall survival benefit and similar toxicity risk for patients receiving first line LEN-based continuous or maintenance treatment over those who received first line BORT-based treatment.

Further, the study results highlighted the substantial economic burden associated with MM care, in spite of the disease having low prevalence as compared to some of the other cancers. The incremental phase-specific costs were highest for the initial care phase, followed by the terminal phase, with costs being slightly lower for the continuing care phase, and lowest for the pre-diagnosis phase. Inpatient and outpatient costs were the major drivers of costs in all the four phases. Pharmacy costs were a significant driver of costs in the initial and terminal phases, and were the biggest cost driver in the continuing care phase.

Last, it assessed trends in aggressiveness of EOL care outcomes over time. While certain indicators of aggressive EOL care remained stable over time, we observed an increasing trend

for multiple ED visits and ICU stays. Moreover, this study assessed the impact of palliative care consultations on receiving aggressive EOL care, and healthcare resource use and costs at EOL. Results indicate that early palliative care consultations have the potential to reduce aggressive EOL care, and curtail healthcare resource use and costs at EOL.

Study findings about clinical and economic outcomes will help inform clinicians' treatment decisions, aid policy discussions regarding MM care and coverage, and help design interventions to integrate early palliative care into routine care among elderly MM patients.

Dedication

This dissertation is dedicated to my mother, grandparents, and Sushmitha for their unconditional love, support, and encouragement.

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CHAPTER 1

INTRODUCTION

Multiple myeloma

Overview of multiple myeloma

Multiple myeloma (MM) is a hematologic malignancy characterized by abnormal clonal growth of the plasma cells. It results from an asymptomatic premalignant growth of monoclonal plasma cells originating from post-germinal-center B cells (Palumbo and Anderson 2011). MM most commonly evolves from monoclonal gammopathy of undetermined clinical significance (MGUS). In over half of all MM patients, primary translocations involving immunoglobulin heavy chain (IgH) locus on chromosome 14q32 drives the clonal plasma cell proliferation in MGUS (Kuehl and Bergsagel 2002; Bergsagel and Kuehl 2001; Rafael Fonseca et al. 2002; Seidl, Kaufmann, and Drach 2003). Even though the exact mechanism for evolution of MGUS into MM is unknown, genetic abnormalities and bone marrow microenvironment changes like angiogenesis, cell-mediated immunity suppression, and alterations in various cytokines play an important role in the process (Kuehl and Bergsagel 2002; Bergsagel and Kuehl 2001; Rafael Fonseca et al. 2002; Hideshima and Anderson 2002; Rajkumar et al. 2002). The course of MM usually starts with a diagnosis phase, followed by a prolonged treatment phase aimed at extending overall survival (OS) and progression-free survival (PFS). MM treatment usually consists of an induction phase, followed by stem cell transplant (SCT) and a long maintenance phase post SCT for SCT eligible MM patients (McCarthy et al. 2017; Attal et al. 2017), or

continuous maintenance phase, typically a low dose extension of induction phase for SCT-ineligible MM patients (Musto and Montefusco 2016).

Diagnosis

MM is defined as either asymptomatic (SMM or smoldering multiple myeloma) or symptomatic based on the absence or presence of hypercalcemia, renal insufficiency, anemia, and bone disease, which is also known as the CRAB criteria (B. G. Durie et al. 2003; B. G. M. Durie et al. 2006; Kyle and Rajkumar 2009). As per the International Myeloma Working Group (IMWG), MGUS is defined as presence of less than 3g/dL of serum M-protein and < 10% monoclonal plasma cells in the bone marrow. MM is defined as SMM if serum M-protein levels are ≥3 mg/dL, or if there are ≥10% monoclonal plasma cells in the bone marrow. Symptomatic MM is defined as presence of end organ damage (CRAB criteria) in addition to ≥3 mg/dL serum M-protein levels or presence of ≥10% monoclonal plasma cells in the bone marrow (International Myeloma Working Group 2003; Kyle et al. 2010). In 2014, the IMWG defined "ultra-high risk" SMM as SMM with ≥ 80% risk of progressing to symptomatic MM within two years, based on presence of ≥ 60% bone marrow plasma cell burden, an involved to uninvolved light chain ratio of ≥ 100, and 2 or more lytic lesions detected from spine MRI (Rajkumar et al. 2014). According to the International Staging System (ISS), symptomatic MM is categorized into three risk groups (stages I, II, and III) based on the levels of serum β_2-microglobulin and albumin levels (Greipp et al. 2005).

In addition to detailed physical examination and review of medical history, MM diagnosis is made through tests for complete blood count, chemical analysis, serum and urine protein electrophoresis with immunofixation, quantification of monoclonal protein, and bone marrow examination (R. Fonseca et al. 2009; Kyle and Rajkumar 2009). Myeloma-related bone

lesions are usually identified through conventional radiography and MRI of the spine, skull, chest, pelvis, humeri, and femora (Kyle and Rajkumar 2009; Dimopoulos et al. 2009).

Epidemiology

MM is the most common blood cancer after lymphoma and leukemia, accounting for approximately 1.6% of all new cancer cases in the United States (US) in 2015 (Chen et al. 2017). According to data from the American Cancer Society (ACS), MM has a lifetime risk of 1 in 132 (0.8%) in the US. An estimated 30,770 new cases of MM (16,400 men and 14,370 women) were diagnosed and 12,770 patients (6,830 men and 5,940 women) died from MM in the US in 2018 (American Cancer Society 2018). According to data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program, the estimated 5-year survival rate for MM is 51%, and depends on individual patient characteristics such as age and stage at diagnosis among others (National Cancer Institute, Surveillance, Epidemiology and End Results Program. 2019). MM has a higher prevalence in men, among individuals of African American origin, and amongst the elderly. The median age at diagnosis of MM is 69 years, with majority of the individuals diagnosed at an age of 65 or greater (Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) 2018).

Treatments

MM treatment has seen a paradigm shift in the past few decades, first with the development of autologous stem cell transplant (ASCT), and then with the approval of novel agents, such as immunomodulatory drugs (IMIDs) - thalidomide and lenalidomide, and proteasome inhibitor (PI) bortezomib in the 2000s. The introduction of ASCT and novel agents

have led to drastic changes in MM management, and prolonged overall survival (Brenner, Gondos, and Pulte 2008; Kristinsson et al. 2007; S. K. Kumar et al. 2008). The last few years have seen even more modifications in the treatment landscape for MM with approvals of IMID pomalidomide in 2013, PIs carfilzomib and ixazomib in 2012 and 2015 respectively, and monoclonal antibodies daratumumab and elotuzumab in 2015 (R. Fonseca et al. 2017). MM treatment varies by patient's age and other clinical characteristics such as frailty, comorbidities, and disability status (Weisel et al. 2017). The recommended treatment for patients younger than 70 years and of good health status includes induction therapy with novel agents, followed by ASCT and maintenance therapy (McCarthy et al. 2017; Attal et al. 2017b). The standard treatment for ASCT-ineligible patients is continuous maintenance therapy with IMID or PI, which is typically a prolonged course of the induction therapy (Musto and Montefusco 2016).

Maintenance therapy aims to prolong the length of disease remission through continuous treatment, with several studies reporting maintenance and continuous therapy to have led to significant improvements in both PFS and OS (Sonneveld et al. 2012; Bahlis et al. 2017; S. Kumar et al. 2017; Richardson et al. 2017). Lenalidomide (LEN) or bortezomib (BORT) maintenance therapy are recommended as first-line for both ASCT-eligible and ASCT-ineligible MM patients, according to the National Comprehensive Cancer Network Clinical Practice Guidelines (S. K. Kumar et al. 2017). Furthermore, while there are clinical benefits of maintenance or continuous treatment with LEN- and BORT-based regimens, toxicities associated with the use of these agents, such as neuropathy, cardiac toxicity, thrombocytopenia, neutropenia, and tumor lysis syndrome, can limit their sustained use (Bringhen et al. 2017; Wang, Li, and Yan 2016; Ludwig et al. 2017; Burnette et al. 2013).

Economic burden

Cost associated with cancer treatment poses a significant burden to patients and their family members, payers, and society in general. The estimated total direct medical costs attributable to cancer treatment in the US was around $125 billion in 2010 (Roy et al. 2015). Even though MM accounts for a small proportion of patients with cancer, healthcare costs associated with treatment of MM are higher than treatment of most other types of cancer (Cook 2008). Studies that have incremental costs associated with MM have reported a significant increase in costs in the past decade, with outpatient costs, hospitalizations, and drug costs identified as drivers of increase in costs (R. Fonseca et al. 2017; Petrucci et al. 2013).

Most of the studies that have assessed disease-related costs in MM have used a prevalence-based approach. It is important to assess healthcare expenditures across phases of MM care. This is due to the fact that as disease progresses, treatments differ and thus, costs differ by each phase of MM care (de Oliveira et al. 2016). Extant literature on healthcare costs among cancer patients suggest that healthcare expenditures across the disease continuum follows a U-shaped curve, with greater expenditure happened around the time of diagnosis (initial care phase) and death (terminal phase), and lower expenditures incurred in the continuing care phase between the initial care phase and the terminal phase. These studies have also shown that such phase-based cost estimates in combination with survival estimates yield reliable estimates of long-term disease burden (Brown et al. 1999, 2002; de Oliveira et al. 2013; Krahn et al. 2010; Yabroff et al. 2008). However, there is very limited literature on disease lifetime costs of MM. One study, conducted using data from the Ontario Cancer Registry reported that the costs of MM patients were higher in the initial care phase and terminal phase, and lower in the continuing care

phase and pre-diagnosis period. This study also found that MM has the highest disease lifetime costs among of all types of cancer (de Oliveira et al. 2016).

End of life care

End of life (EOL) care is defined as "comprehensive care for life-limiting illnesses that meets the patient's medical, physical, psychological, spiritual, and social needs" (National Quality Forum 2012). It is very important to appropriately manage EOL care in order to ensure that patients receive medical care that is of high quality and cost-effective at the same time. A Medicare analysis revealed that even though around 5% of the beneficiaries die each year, they account for around 30% of total Medicare expenditures, and around 33% of costs incurred in the last year of life are attributable to the last month before death (Emanuel et al. 2002). Aggressive medical care before death is neither beneficial from a clinical perspective nor from a humanistic point of view. A study conducted across several cancer care centers across the US revealed that higher treatment costs in the last week of death was associated with poorer quality of life among patients with advanced cancer (Zhang et al. 2009). It has been reported that patients with hematological malignancies, including MM, receive more aggressive cancer-related care near death and have lower use of palliative care and hospice services as compared to patients with solid tumors (Earle et al. 2008; Ho et al. 2011; Hui et al. 2012; Sexauer et al. 2014; Tang et al. 2009; Cheng et al. 2005). The difference in quality of EOL care between hematologic cancers and solid cancers can be attributed to a variety of reasons. One of the major barriers towards inception of EOL care among patients with hematologic cancers is lack of clarity on onset of EOL. This problem is compounded by the availability of treatments in advanced stages and the rapid decline of patient's health near death (Fadul et al. 2008). Other factors that have been reported as barriers to quality of EOL care among patients with hematologic cancers include

unrealistic patient expectations and difficulties in conducting EOL discussions with patients (Odejide et al. 2014). Another key consideration in EOL care is variations in regional practice patterns. Previous studies have reported regional clinic practice norms, including physician's beliefs, and availability of medical resources to be predictors of EOL care decisions (Barnato et al. 2012; Keating et al. 2018). Studies have also reported regional practice patterns to be drivers of geographical variation in healthcare utilization and costs (B. E. Sirovich et al. 2005; B. Sirovich et al. 2008).

The treatment landscape in MM has seen a drastic change in the past two decades with the advent of stem cell transplant and novel agents. While patients with MM are living longer, the burden of the disease and side effects of the treatments often lead to high symptom burden. Studies have reported high prevalence of pain, fatigue and drowsiness among MM patients (Snowden et al. 2011; Porta-Sales et al. 2015; Niscola et al. 2007). This underlines the need for holistic assessment of MM patients and compliment cancer-directed treatment with palliative care, as evidenced by supportive care guidelines in MM (Snowden et al. 2011).

Need for the Study

Even though there is significant evidence for the clinical benefit of maintenance therapy and both LEN- and BORT- based regimens can be used as first line treatment, there is no clear consensus on the superiority of one treatment over the other due to the lack of direct comparisons. Moreover, most of the data regarding the clinical benefits of various treatment regimens are from clinical trials, with very limited real world evidence available. It is important to assess the effectiveness of maintenance therapies in real-world settings since MM is typically a disease of the elderly, who are underrepresented in RCTs, as comorbidities, frailty, and disability often lead to elderly patients being excluded from clinical trials (Hutchins et al. 1999). Additionally, there is very limited real world evidence on the comparative safety of LEN-based and BORT-based therapies, especially in a population of elderly newly diagnosed MM (NDMM) patients. An assessment of comparative safety and effectiveness of LEN-and BORT-based maintenance and continuous treatments would help clinicians in selecting the most appropriate therapy for elderly NDMM patients.

While real-world studies have assessed healthcare expenditures among MM patients, most of these studies have been limited to assessment of healthcare costs in various lines of treatment (e.g., first-line vs second-line) or examination of treatment-related costs (novel agent use versus other therapy) (MacEwan et al. 2018; Arikian et al. 2015; Teitelbaum et al. 2013). Given that majority of the MM patients in the US are diagnosed at an age of 65 or greater, and that Medicare is the primary payer for this population, and taking into consideration the changing landscape of MM treatment with introduction of several novel agents, it is important to assess the disease lifetime costs of MM from Medicare's perspective. However, no study in the US has yet evaluated the disease lifetime costs of MM from Medicare's perspective. A better understanding

of healthcare costs attributable to MM over the disease lifetime and across various phases of cancer care, and the drivers of these costs would help plan interventions and policy decisions targeted towards improving quality of cancer care while controlling costs (Kaye et al. 2018).

While a few studies have assessed trends in EOL care in hematologic malignancies in general, no study has yet assessed trends in EOL care among MM patients. Similarly, there is very limited evidence on the impact of palliative care services on quality of care, healthcare utilization, and costs at EOL. Given the changing landscape of MM treatment and the significant symptom burden associated with the disease, assessing trends in quality of EOL care among MM patients will help policy makers and medical decision makers aim tailored intervention programs to improve quality of EOL care. Moreover, evidence regarding the impact of palliative care consultation on quality of EOL care, healthcare utilization and costs could be used by clinicians and policy makers to better integrate palliative care with routine cancer care among MM patients.

Specific Aims and Objectives

The aim of this study is to assess the comparative effectiveness and safety of LEN-based versus BORT-based maintenance and continuous treatments, estimate phase-specific costs attributable to MM and its drivers as well as the disease lifetime costs of MM, and to assess trends in quality of EOL care in MM and effect of palliative care consultations on quality of EOL care, healthcare utilization at EOL, and costs at EOL among elderly NDMM patients enrolled in Medicare using SEER-linked Medicare administrative claims data. The specific study aims and objectives are as follows:

1. To assess the comparative effectiveness and safety of first-line maintenance and continuous treatment with LEN-based vs BORT-based therapies among elderly patients with NDMM
    a. To assess treatment patterns and duration of first-line LEN-based vs BORT-based maintenance and continuous treatment among elderly NDMM patients enrolled in Medicare
    b. To compare the effectiveness of first-line LEN-based vs BORT-based maintenance and continuous treatment among elderly NDMM patients enrolled in Medicare
    c. To compare safety of first-line LEN-based vs BORT-based maintenance and continuous treatment among elderly NDMM patients enrolled in Medicare
2. To assess disease lifetime costs and its predictors among elderly patients with NDMM
    a. To identify duration of initial care phase and terminal care phase among elderly patients with NDMM using Joinpoint regression

b. To assess phase-specific costs and drivers of phase-specific costs among elderly patients with NDMM
c. To assess disease lifetime costs among elderly patients with NDMM

3. To assess trends in EOL care and the impact of palliative care consultations on EOL care outcomes among elderly patients with NDMM
    a. To assess trends in quality of EOL care among elderly patients with NDMM
    b. To assess the impact of palliative care consultations on quality of EOL care, accounting for variations in regional practice patterns, among elderly newly diagnosed MM patients
    c. To assess the impact of palliative care consultations on healthcare resource utilization and costs at EOL, accounting for variations in regional practice patterns, among elderly newly diagnosed MM patients

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CHAPTER 2: PAPER 1

Comparative Effectiveness and Safety of Lenalidomide-based and Bortezomib-based Maintenance and Continuous Treatment among Elderly Patients with Newly Diagnosed Multiple Myeloma

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by abnormal clonal growth of the plasma cells. It is associated with significant mortality and morbidity, especially due to end organ damage such as renal impairment, hypercalcemia, bone lesions, and anemia.(Cowan et al. 2018) MM is the most common blood cancer after lymphoma and leukemia, accounting for approximately 1.6% of all new cancer cases in the United States (US) in 2015.(Y. Chen et al. 2017) According to data from the American Cancer Society (ACS), MM has a lifetime risk of 1 in 132 (0.8%) in the US. An estimated 30,770 new cases of MM (16,400 men and 14,370 women) were diagnosed and 12,770 patients (6,830 men and 5,940 women) died from MM in the US in 2018.(American Cancer Society 2018) According to data from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program, the estimated 5-year survival rate for MM is 51%, and depends on individual patient characteristics such as age and stage at diagnosis among others.(National Cancer Institute, Surveillance, Epidemiology and End Results Program. 2019) MM has a higher prevalence in men, among individuals of African American origin, and amongst the elderly. The median age at diagnosis of MM is 69 years, with majority of the individuals diagnosed at an age of 65 or greater.(Noone AM, Howlader N,

Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds) 2018)

MM treatment has changed drastically over the past few decades. The first major breakthrough in MM treatment came with the development of autologous stem cell transplant (ASCT), followed by introduction of novel agents such as immunomodulatory imide drugs (IMIDs) and proteasome inhibitors.(Cowan et al. 2018) The introduction of these novel agents, along with ASCT and high-dose chemotherapy, has led to substantial improvements in clinical outcomes of MM patients.(Lehners et al. 2018) The median survival of a newly diagnosed MM (NDMM) patient has increased from 2.5 years to 5-7 years.(Donk and Lokhorst 2013) MM treatment varies by patient's age and other clinical characteristics such as frailty, comorbidities, and disability status.(Weisel et al. 2017) The recommended treatment for patients younger than 70 years and of good health status includes induction therapy with novel agents, followed by ASCT and maintenance therapy with IMID or proteasome inhibitor (PI) (Attal et al. 2017; McCarthy et al. 2017). The standard treatment for ASCT-ineligible patients is continuous maintenance therapy with IMID or PI, which is typically a prolonged course of the induction therapy (Musto and Montefusco 2016).

Maintenance therapy aims to prolong the length of disease remission through continuous treatment, improving progression-free survival (PFS) and overall survival (OS).(Anderson et al. 2008) Several studies have shown maintenance and continuous therapy to lead to significant improvements in both PFS and OS.(Sonneveld et al. 2012; Richardson et al. 2017; S. Kumar et al. 2017; Bahlis et al. 2017) Lenalidomide (LEN) or bortezomib (BORT) maintenance therapy are recommended as first-line for both ASCT-eligible and ASCT-ineligible MM patients, according to the National Comprehensive Cancer Network Clinical Practice Guidelines.(S. K.

Kumar et al. 2017) Several studies have shown LEN or BORT maintenance to have a beneficial impact on MM patients' clinical outcomes, in both transplant-eligible and transplant-ineligible settings. Among patients that undergo transplant, randomized clinical trials assessing impact of LEN maintenance treatment post-ASCT have found benefits in PFS among most of the patients, except for those with stage III cancer at diagnosis and high-risk cytogenetics.(McCarthy et al. 2012; Attal et al. 2012; Palumbo et al. 2014) Similarly, evidence for improved PFS and OS with BORT-based induction and maintenance therapy has been obtained from the phase 3 HOVON-65/GMMG-HD4 trial.(Sonneveld et al. 2012; Neben et al. 2012) Previous studies evaluating the effect of maintenance therapy have also reported improved clinical outcomes with both LEN-based(Stewart et al. 2015; Dimopoulos et al. 2015; Bringhen et al. 2017; Benboubker et al. 2014; Facon et al. 2018) and BORT-based(Palumbo et al. 2010; Mateos et al. 2010; 2012; Niesvizky et al. 2015) maintenance regimens among MM patients who are ineligible for transplant.

Even though there is significant evidence for the clinical benefit of maintenance therapy and both LEN- and BORT- based regimens can be used as first line treatment, there is no clear consensus on the superiority of one treatment over the other due to the lack of direct comparisons. Moreover, most of the data regarding the clinical benefits of various treatment regimens are from clinical trials, with very limited real world evidence available. It is important to assess the effectiveness of maintenance therapies in real-world settings since MM is typically a disease of the elderly, who are underrepresented in RCTs, due to the fact that comorbidities, frailty, and disability often lead to elderly patients being excluded from clinical trials.(Hutchins et al. 1999) A real-world single center study in the US compared LEN maintenance and BORT maintenance vs no maintenance among MM patients who had undergone early ASCT. It found LEN-based maintenance has superior PFS (37 months vs 28 months) as compared to no

maintenance irrespective of patient's cancer stage and cytogenesis at diagnosis. While BORT-based maintenance did not show significantly better PFS for the entire cohort, it had superior PFS (28 months vs 16 months) for the high-risk cytogenetic patient subgroup (Chakraborty et al. 2018). Only one real-world study has assessed the comparative effectiveness of LEN vs BORT maintenance therapy among MM patients post stem cell transplant in the US. It did not find any significant differences in OS or PFS between LEN and BORT maintenance treatments. However, the study was limited by its small sample size and generalizability.(Huang et al. 2018)

While maintenance or continuous treatment with LEN- and BORT-based regimens have been associated with clinical benefits among MM patients, toxicities associated with the use of these agents can limit their sustained use.(Bringhen et al. 2017) A meta-analysis of RCTs on novel agent based treatments in MM patients reported LEN-based treatment were statistically significantly associated with neutropenia, anemia, thrombocytopenia, gastrointestinal (GI) events, and thrombosis, while BORT-based regimens were significantly associated with peripheral neuropathy (PN), and thrombocytopenia.(Wang, Li, and Yan 2016) Toxicities common to both LEN- and BORT-based treatments include neuropathy, cardiac toxicity, thrombocytopenia, neutropenia, and tumor lysis syndrome.(Ludwig et al. 2017) The toxicity burden of maintenance therapies also influences patient preference for these treatments. A survey of 1,159 MM patients in the US found toxicity to be associated with reduction in proportion of patients willing to opt for maintenance therapy.(Burnette et al. 2013) A real-world study of LEN-based and BORT-based maintenance treatments reported 17% and 7% discontinuation rate due to toxicity for LEN-based and BORT-based maintenance respectively. (Chakraborty et al. 2018)

Even though it is important to assess the comparative safety of LEN- and BORT-based therapies, very few real world studies have done that. A US single center comparison of LEN-

based vs BORT based maintenance regimens among NDMM patients post-transplant reported 9 patients (9.8% of all patients receiving LEN maintenance) in the LEN group discontinued treatment due to a serious adverse event as compared to 8 patients (12.5% of all patients receiving BORT maintenance) in the BORT group.(Huang et al. 2018) A retrospective analysis of administrative claims data among MM patients with private insurance and Medicare Advantage plans found similar cardiotoxicity risk among those who used BORT-based regimens versus those who used LEN-based regimens.(Reneau et al. 2017) However, this study only included cardiac toxicity associated with BORT or LEN use but not the other toxicities. In the current study, we aim to assess the treatment patterns and to compare the clinical effectiveness and safety of LEN- and BORT-based treatments among elderly NDMM patients using real-world data. This information, of direct comparison of LEN-based and BORT-based maintenance or continuous treatments, could be used by clinicians to select the most appropriate therapy for NDMM patients.

Methods

Data Source and Study Design

A retrospective analysis was conducted using National Cancer Institute's (NCI) SEER database linked with Medicare administrative claims database. The NCI's SEER program is an epidemiologic surveillance system that contains data collected from population-based tumor registries and was designed to track cancer incidence and mortality in the US. It includes clinical and demographic information in addition to information on cause of death for people with cancer, and is collected from 18 participating cancer registries across the US. Medicare is a federally administered health insurance program which covers elderly Americans who are 65 years of age or older, as well as younger patients with disabilities and end-stage renal disease

(ESRD). The Medicare administrative claims database provides information on claims for covered healthcare services for beneficiaries enrolled in Medicare. The SEER-linked Medicare claims database provides patient-level data for Medicare beneficiaries with cancer.(Warren et al. 2002)

The current study utilized 2007-2015 SEER data linked with 2006-2016 Medicare claims data. The SEER data consists of the Patient Entitlement and Diagnosis Summary File (PEDSF) that includes clinical, demographic, and Medicare enrollment information for individuals with cancer. The Medicare claims data consists of the Medicare Provider Analysis and Review (MEDPAR), National Claims History (NCH), Outpatient (OUTPT), Home Health Agency (HHA), Hospice, Durable Medical Equipment (DME), and Prescription Drug Event (PDE) files. The MEDPAR file contains all Medicare Part A claims indication short stay, long stay, skilled nursing facility (SNF) stays as well as ICD-9/10 diagnoses and procedures performed during each stay. The NCH file contains all Medicare Part B claims generated due to physician or supplier services in clinics and hospitals, whereas the OUTPT file contains all Medicare Part B claims outpatient providers. Both NCH and OUTPT files were used to obtain information such as procedural Healthcare Common Procedure Coding System (HCPCS) codes, diagnoses, date of claims, treatment administration, and reimbursement amounts. The HHA file contains claims for all home health care services such as number and types of visits and diagnoses. The hospice file contains claims submitted by hospice providers, and has details on type of care (inpatient care, routine home care) as well as terminal diagnosis associated with that care. The DME file contains claims with information on use of oral and intravenous chemotherapy, and infusion pumps used. The PDE file contains information about drug utilization such as, date of prescription fill, drug dispensed, quantity dispensed, days supplied, total cost, and out-of-pocket

cost. The Institutional Review Board (IRB) at the University of Mississippi has approved the study.

Study sample

This study included Medicare beneficiaries who entered the SEER registry from 2007 through 2015, and were diagnosed with MM as their primary cancer. All beneficiaries with primary MM were identified based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) code of MM (9732). Additionally, patients needed to be 66 years of age or older at the time of MM diagnosis and be continuously enrolled in Medicare Parts A and B in the 12 months prior to the month of MM diagnosis to be included in the study. The 12-month pre-diagnosis baseline period was used to obtain clinical information on comorbidities. Furthermore, patients needed to have continuous enrollment in Medicare Parts A, B, and D for at least 2 months post-MM diagnosis to be included. Patients were excluded from the study sample if they had an unknown diagnosis month or year, or if MM diagnosis was made at the time of death. Moreover, MM patients were excluded from the study sample if they had any cancer in the 5 years prior to MM diagnosis, or if they were enrolled in a health maintenance organization (HMO) in the 12-month pre- and post- MM diagnosis period.

Study Variables

Treatment patterns for continuous or maintenance treatment were assessed for all elderly NDMM patients included in the study sample. For each line of therapy, Duration of treatment was defined as the number of days between the index date (start date for the specific line of therapy) and treatment discontinuation (switch to a different line of therapy or no treatment) or end of study period. Time spent in each line of therapy was calculated using the time-to-next-treatment

approach (TTNT). TTNT was defined as the number of days spent on a particular therapy regimen until a new treatment was added to the current line of therapy or switch to a new drug regimen, or a gap in therapy of 90 or more days in current therapy. This is consistent with previous studies that have assessed treatment patterns among MM patients (C.-C. Chen et al. 2017).

Patients were assigned to LEN-based or BORT-based maintenance or continuous treatment cohorts based on index claims for first-line LEN or BORT treatment in the follow-up period post stem cell transplant (SCT) for those who underwent SCT, or follow-up period post MM diagnosis for those who did not undergo SCT respectively. Claims for LEN and BORT were identified using HCPCS codes and National Drug Codes (NDCs) respectively. The first claim date for LEN or BORT treatment were referred to as index treatment date.

For patients in both the cohorts (LEN maintenance and BORT maintenance), outcome variables assessed included duration of therapy, survival, and safety. Duration of therapy was defined as the number of days from index treatment date until a gap in treatment of greater than 90 days, a measure that has been previously used in SEER-Medicare analyses evaluating duration of cancer therapy.(Griffiths et al. 2011) Furthermore, treatment switch was defined as treatment discontinuation or initiation of a new treatment after a gap of greater than 90 days for previous treatment. Survival was operationalized as time from index treatment date to all-cause death. The date of death was obtained from the Medicare date. SEER date of death was used in case Medicare death date is missing.(Griffiths et al. 2011) The safety events included peripheral neuropathy, thrombocytopenia, neutropenia, tumor lysis syndrome, cardiac toxicity. A composite outcome measure of any of these safety events was also assessed. Cardiac toxicity for MM treatments included heart failure (HF), myocardial infarction (MI), and arrhythmia. Medical

claims for the 12-month pre index treatment period will be evaluated to control for prior history these events. Safety outcomes were binary events indicating whether a patient had a safety event. Time to safety events were assessed by calculating number of days between index treatment date and date of first safety event.

Baseline demographic covariates included age (at MM diagnosis), gender, race/ethnicity, region, rural/urban status, and marital status. Baseline clinical covariates included comorbidity, disability status, and receipt of SCT (using 5 digit HCPCS code for SCT). Comorbidity was assessed using the Deyo adaption of the Charlson Comorbidity Index (CCI).(Deyo, Cherkin, and Ciol 1992) Disability status, which is a proxy measure for performance status, was calculated using a validated, claim-based algorithm during the 12-month baseline period prior to MM diagnosis.(Davidoff et al. 2013)

Data Analysis

Propensity score matching was employed to account for covariate imbalance at baseline between the LEN and BORT treatment cohorts. A 1:1 match without replacement was performed based on the patients' propensity to be treated with LEN. Logistic regression was employed to obtain the propensity scores, and will be modeled based on age, gender, race, region, rural/urban status, marital status, receipt of SCT, disability status, and CCI score. Mean standardized differences were used to assess covariate imbalance between the two groups post propensity score matching. A standardized difference less than 0.1 was considered to be negligible (Austin 2011).

Summary of baseline clinical and demographic characteristics of the study sample was presented. For categorical variables, frequency and percentage distributions were reported. Descriptive statistics were used to depict baseline patient characteristics, treatment patterns,

survival, safety, and duration of therapy. For categorical variables, frequency and percentage distributions were reported. Statistical comparisons between the two groups were conducted using McNemar's test or Cochrane-Mantel-Haenszel test, to account for the matched data. For continuous variables, mean, standard deviation (SD), median, and range were reported. Statistical comparisons for continuous variables were conducted using paired t-tests. Descriptive summary for survival, duration of therapy, and time to safety events were conducted using unadjusted Kaplan-Meier survival analysis.

Cox Proportional Hazards models were used to compare the LEN and BORT treatment cohorts on survival, duration of therapy and safety, adjusting for demographic and clinical covariates. For each of the models, a robust variance estimator was used to account for clustering within matched pairs. For survival, patients were censored at death, treatment switch, or loss of Medicare eligibility or end of study period, whichever occurred first. For duration of therapy, patients were censored at treatment switch, loss of Medicare eligibility, end of study period, or death, whichever occurred first. For safety, patients were censored at first safety event, treatment switch, loss of Medicare eligibility, or end of study period whichever occurred first. Moreover, for each of the safety outcomes, any prior history of the safety events were controlled for in the analysis. For each of the Cox Proportional Hazards models, the proportional hazards assumption was assessed using Schoenfeld residuals and interactions with time for each of the model predictors. Significant results ($p<0.05$) indicated a violation of the proportional hazards assumption. In such cases, Stratified Cox Proportional Hazards models with robust variance estimators were employed, stratified on the variable that violated the proportional hazards assumption.

All data management and analysis will be done using SAS version 9.4.(SAS. (2015), n.d.)

Results

6,343 elderly NDMM patients met the study inclusion and exclusion criteria. The demographic and clinical characteristics of the study sample are presented in Table 1.1. Most of the elderly MM patients in the sample lived in urban areas (88.4%), were white (74.2%), did not have disability at baseline (76.8%), and did not undergo SCT (92.1%). Additionally, majority of the elderly NDMM patients in the sample were female (53.1%), 75 years old or older at baseline (54.9%), had a CCI score of 2 or more at baseline (56.3%), and resided in the western or southern (67.1%) region of the US. Moreover, majority of the MM patients in the sample were either married (48.9%) or widowed (25.5%) at the time of MM diagnosis. Furthermore, 17.3% of the elderly NDMM patients did not receive any continuous or maintenance therapy, 35.3% received one line of continuous or maintenance therapy, 20.9% received two lines of continuous or maintenance therapy, 12.4% received three lines of continuous or maintenance therapy, and 14.1% received four or more lines of continuous or maintenance therapy.

Table 1.2 depicts the patterns of continuous or maintenance treatment among elderly NDMM patients. Of all the elderly NDMM patients in the study sample, 82.7% had at least one line, 47.4% had two or more lines, and 26.5% had three or more lines of continuous or maintenance treatment. For those who received first line of continuous or maintenance treatment, 33.1% received BORT-based treatment, 22.4% received LEN-based treatment, and 6.2% received thalidomide (THAL)-based treatment. Moreover, 13.7% and 24.6% of the elderly NDMM patients who received first line treatment received combination anti-MM drug regimens and other drug regimens (chemotherapy and/or corticosteroids only) respectively. For those who received second line treatment, 25.1% received BORT-based treatment, 20.9% received LEN-based treatment, and 3.8% received THAL-based treatment. Additionally, 24.2% and 26.0% of

the elderly NDMM patients who received second line treatment received combination anti-MM drug regimens and other drug regimens respectively. For third line treatment, 24.6% received BORT-based treatment, 17.9% received LEN-based treatment, and 2.1% received THAL-based treatment. Furthermore, 24.1% and 31.3% of the elderly NDMM patients who received third line treatment received combination anti-MM drug regimens and other drug regimens respectively. Moreover, the median duration of first line treatment was 195 days [interquartile range (IQR): 118-360 days], median duration of second line treatment was 194 days [IQR: 113-352 days], and median duration of third line treatment was 168 days [IQR: 109-303 days].

To assess the comparative effectiveness and safety of first line LEN-based vs BORT-based continuous or maintenance treatment, 1,022 elderly NDMM patients with first line LEN-based regimen were matched on age, urban residency, geographical region, gender, race, marital status, disability status, receipt of SCT, and CCI score to 1,022 elderly NDMM patients with first line BORT-based regimen. As seen in Table 1.3, the standardized mean difference was negligible between the two groups for all covariates included in the propensity score (P-S) matched model.

Results from unadjusted Kaplan-Meier (K-M) survival analysis show that the median duration of first line therapy was 185 days for BORT-based treatment and 250 days for LEN-based treatment. Log-rank test results indicate that the duration of treatment for first line LEN-based treatment was significantly greater than that for first line BORT-based treatment ($p<0.001$). The median all-cause survival was 1,558 days for the BORT-based treatment group and 1,545 days for the LEN-based treatment group. There were no significant differences in overall survival between the two groups (log-rank test: $p > 0.050$). Furthermore, median time to cardiotoxicity for the BORT-based treatment group was 609 days, and that for the LEN-based

treatment group was 516 days. There were no significant differences in time to cardiotoxicity between the two groups (log-rank test: $p = 0.648$). Additionally, median time to any adverse event for the BORT-based treatment group was 486 days, and that for the LEN-based group was 417 days. There were no significant differences in time to any adverse event between the two groups (log-rank test: $p = 0.813$). Median time to thrombocytopenia and neutropenia could not be assessed for the two groups, since less than 25% of the patients in the two groups had these events. However, the mean time to event for these events were not significantly different between the two groups (thrombocytopenia: $p = 0.989$; neutropenia: $p = 0.470$).

Table 1.4 provides a descriptive summary of adverse events experienced by elderly NDMM patients while on first line LEN- and BORT-based treatment. 36.5% of the patients on BORT-based treatment had cardiotoxicity as compared to 42.2% of those on LEN-based treatment. 3.9% and 4.7% of the patients had thrombocytopenia while on BORT- and LEN-based treatment respectively. The proportion of patients having neutropenia was 4% and 5.5% among those who received BORT- and LEN-based treatment respectively. Nearly 41% of the patients in BORT-based treatment group had any adverse event as compared to 46% of the patients in LEN-based treatment group. No patients, in either of the two treatment groups, had tumor lysis syndrome while on first line treatment.

For each of the Cox proportional hazards regression models to compare survival and safety between first line LEN-based and BORT-based treatments, we tested the validity of the proportional hazards assumption by checking interactions with time and Schoenfeld residuals. Results of the validity of proportional hazards assumption are presented in Table 1.5. Statistically significant results imply violation of the proportional hazards assumption. As we can see, the proportional hazards assumption was violated for models for cardiotoxicity and the

composite any adverse event outcome. For both these models, the proportional hazards assumption was violated for the prior history of cardiotoxicity variable. For these two models, stratified Cox proportional hazards regression models with robust variance estimators were employed, stratified on the prior cardiotoxicity variable.

Results of the Cox proportional hazards models comparing survival and safety outcomes between the first line LEN-based and BORT-based treatment groups are presented in Table 1.6. As compared to first line LEN-based treatment, first line BORT-based treatment was associated with significantly greater hazard for all-cause death [hazard ratio (HR): 1.21, 95% Confidence Interval (CI): 1.01-1.47, p = 0.046]. There were no statistically significant differences between the two groups on any of the safety outcomes [cardiotoxicity: HR=0.94, 95% CI: 0.81-1.08; thrombocytopenia: HR=0.79, 95% CI=0.51-1.22; neutropenia: HR: 0.87, 95% CI=0.57-1.30; composite any adverse event: HR=0.93, 95% CI=0.82-1.06].

Discussion

In this study, we assessed the treatment patterns of continuous or maintenance treatment among elderly NDMM patients and compared the effective and safety of first line LEN-based vs BORT-based continuous or maintenance treatment. To our knowledge, this is the first study to have assessed patterns of continuous or maintenance therapy in a population-based sample of elderly NDMM patients enrolled in fee-for-service Medicare. Moreover, while evidence from both clinical trials and observational studies have demonstrated clinical benefit of first line treatment with both LEN- and BORT-based regimens, this is the first head-to-head comparison between first line LEN- vs BORT-based continuous or maintenance treatment regimens in elderly NDMM patients. These results could help clinicians choose the most appropriate first line treatment for elderly NDMM patients.

We found that 55.5% of the elderly MM patients receive first line LEN- or BORT-based treatments. The proportion of patients receiving BORT-based or LEN-based treatments as second line and third line therapies decreased to 46.0% and 42.5% respectively. Use of treatment regimens containing two or more novel anti-MM agents increased from 13.7% in the first line to around 24% in the second and third lines of treatment. These findings are similar to those of previous studies. A study that assessed treatment patterns among commercially insured MM patients found that nearly 60% of the patients received first line treatment with an IMID (lenalidomide or thalidomide) or PI (bortezomib) (MacEwan et al. 2018). As seen in our study, use of combination products of two or more novel anti-MM treatments increased as patients progressed from receiving only first line treatment to subsequent lines of treatment (second or third line of treatment). This is potentially because, as disease progresses, patients advance to next line of treatment, combination treatment regimens may be beneficial by targeting multiple pathways simultaneously without increasing the toxicity risk (Song, Cong, and Wilson 2016).

Additionally, we found that elderly NDMM patients who received first line LEN-based treatment had a longer TTNT as compared to those who received first line BORT-based treatment. While the median TTNT observed for our study sample was much shorter than those reported in clinical trials for first line LEN treatment (FIRST) and first line BORT treatment (VISTA), our findings were directionally consistent with that of the clinical trials (Benboubker et al. 2014; San Miguel et al. 2013). The shorter median TTNT for the two treatment groups in our study could possibly be explained by the fact that our study sample consisted of older and sicker patients with more frailty and worse functional status as compared to those in clinical trials. It has been seen that patients in clinical trials are often healthier than those in the real world, as

elderly patients with multi-morbidity, frailty and disability are often excluded from clinical trials (Hutchins et al. 1999; Huang et al. 2018).

In this study, we also found that compared to elderly NDMM patients who received first line LEN-based treatment, those who received first line BORT-based had significantly greater hazards for all-cause mortality. This finding is similar to the results of a recent network meta-analysis making direct comparisons between MM patients receiving LEN- and BORT-based maintenance therapy (Gay et al. 2018). Subgroup analysis among patients receiving SCT and taking prognostic factors (cytogenetic risk) also yielded similar results (Gay et al. 2018). On the other hand, one real-world study showed that the overall survival between LEN- and BORT-based maintenance treatment was not significantly different (Huang et al. 2018). But this was a single center study with a low sample size (Huang et al. 2018) Moreover, this retrospective study had a relatively short follow-up period, which may explain the lack of significant differences between the two groups (Huang et al. 2018). In terms of comparative safety, we did not find significant differences between MM patients receiving first line LEN- and BORT-based continuous or maintenance therapy on any of the adverse events of interest or the composite adverse event outcome. These findings are consistent with results of a previous study comparing the risk of cardiotoxicity among commercially insured and Medicare Advantage MM patients receiving LEN- and BORT-based treatment. (Reneau et al. 2017). No other study has directly compared the occurrence of adverse events common to both treatments.

Out study has several strengths. First, we used a population-based cohort of elderly NDMM patients to assess treatment patterns, and compared the overall survival and safety of the two treatment options that are approved for as first line continuous or maintenance therapy of

elderly MM patients. Additionally, the rich information such as MM diagnosis data in the SEER registry made it possible for us depict patients' clinical journey from their initial MM diagnosis

Our study has a number of limitations. First, our study sample consisted of elderly NDMM patients enrolled in fee-for-service Medicare. Hence, the results from our may not be generalizable to NDMM patients who are younger or elderly patients enrolled in Medicare Advantage plans. Second, as with other analysis involving administrative claims data, coding errors in the data might bias our study results. Third, we measured treatment duration using the TTNT approach, which was based on the addition or change of treatment, and pre-defined treatment gap. This approach may lead to misclassification of treatment duration for patients who may have long drug holiday or who had inadequate response to prior treatment but without showing signs of disease progression (Arikian et al. 2015). Fourth, when clinical decisions are made for treatment choice, several clinical factors including cancer stage, disease prognosis, and functional status will be taken into consideration However, these factors are not available in the SEER-linked Medicare data used in this study. Future studies should take cancer staging, disease prognosis, and functional status into account while comparing safety and survival between various treatments.

Conclusion

This study used a population-based cohort of elderly NDMM patients to depict treatment patterns and assess the comparative safety and effectiveness among those who received first line LEN-based treatment versus those who received first line BORT-based treatment. Our study results corroborated that with several novel MM agents coming onto the market in the past 10 years, MM treatment has seen a dynamic shift, with novel agents firmly established as the standard of care. We have found that the majority of the elderly NDMM patients received first

line novel agent-based therapy, and the uptake of combination MM agents in subsequent lines of therapy has been rising. Additionally, our study demonstrates an overall survival benefit and similar toxicity risk for patients receiving first line LEN-based continuous or maintenance treatment over those who received first line BORT-based treatment. This information is valuable for clinicians to make treatment decisions for elderly MM patients.

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APPENDIX A

Table 1.1 Demographic and clinical characteristics of elderly NDMM patients, 2007-2016

Demographic and Clinical Characteristics	Category	All Subjects	
		n = 6,343	
Living in urban areas (n, %)	No	733	11.6%
	Yes	5,610	88.4%
Geographical region (n, %)	Northeast	1,272	20.1%
	South	1,743	27.5%
	Midwest	814	12.8%
	West	2,514	39.6%
Gender (n, %)	Male	2,978	46.9%
	Female	3,365	53.1%
Race (n, %)	White	4,709	74.2%
	African American	1,009	15.9%
	Hispanic	190	3.0%
	Other	435	6.9%
Charlson Comorbidity Index score category (n, %)	0	1,475	23.2%
	1	1,298	20.5%
	2	945	14.9%
	3+	2,625	41.4%
Age category (n, %)	66-69	1,198	18.9%
	70-74	1,659	26.2%
	75-79	1,410	22.2%
	80-84	1,104	17.4%
	85+	972	15.3%
Disability status (n, %)	No	4,871	76.8%
	Yes	1,472	23.2%
Marital Status at diagnosis (n, %)	Single	588	9.3%
	Married	3,103	48.9%
	Separated/Divorced	567	8.9%
	Widowed	1,615	25.5%
	Other	470	7.4%
	No	5,842	92.1%

Received Stem Cell Transplant (n, %)	Yes	501	7.9%
Treatment Line of Therapy (n, %)	0	1,095	17.3%
	1	2,240	35.3%
	2	1,326	20.9%
	3	789	12.4%
	4 or more	893	14.1%

Table 1.2 Patterns of continuous or maintenance treatment among elderly NDMM patients, 2007-2016

Variable	Line of Therapy 1 (n = 5,248)			Line of Therapy 2 (n = 3,008)			Line of Therapy 3 (n = 1,682)		
	Regimen	n	%	Regimen	n	%	Regimen	n	%
Treatment	BORT-based only	1,737	33.1%	BORT-based only	755	25.1%	BORT-based only	414	24.6%
	LEN-based only	1,173	22.4%	LEN-based only	629	20.9%	LEN-based only	301	17.9%
	THAL-based only	325	6.2%	THAL-based only	114	3.8%	THAL-based only	36	2.1%
	Combination drugs	718	13.7%	Combination drugs	728	24.2%	Combination drugs	406	24.1%
	Other	1,295	24.6%	Other	782	26.0%	Other	525	31.3%
Duration of Therapy (Median, IQR), in days		195	118, 360		194	113, 352		168	109, 303

Table 1.3 Clinical and sociodemographic characteristics of elderly NDMM patients receiving first line BORT-based treatment matched with elderly NDMM patients receiving first line LEN-based treatment, 2007-2016

Demographic and Clinical Characteristics	Category	BORT group (n = 1,022)		LEN group (n = 1,022)		Standardized Mean Difference	p
Living in urban areas (n, %)	No	114	11.2%	110	10.8%	0.013	0.747
	Yes	908	88.8%	912	89.2%		
Geographical region (n, %)	Northeast	179	17.5%	194	19.0%	0.041	0.653
	South	273	26.7%	264	25.8%		
	Midwest	128	12.5%	123	12.0%		
	West	442	43.3%	441	43.2%		
Gender (n, %)	Male	475	46.5%	466	45.6%	0.018	0.554
	Female	547	53.5%	556	54.4%		
Race (n, %)	White	791	77.4%	775	75.8%	0.077	0.259
	African American	138	13.5%	144	14.1%		
	Hispanic	17	1.7%	28	2.7%		
	Other	76	7.4%	75	7.4%		
Charlson Comorbidity Index score category (n, %)	0	263	25.7%	258	25.2%	0.033	0.735
	1	234	22.9%	223	21.8%		
	2	140	13.7%	144	14.1%		
	3+	385	37.7%	397	38.9%		
Age category (n, %)	66-69	159	15.6%	148	14.5%	0.047	0.64
	70-74	285	27.9%	276	27.0%		
	75-79	244	23.9%	244	23.9%		
	80-84	199	19.5%	212	20.7%		
	85+	135	13.1%	142	13.9%		
Disability status (n, %)	No	816	79.8%	798	78.1%	0.043	0.221
	Yes	206	20.2%	224	21.9%		
Marital Status (n, %)	Single	93	9.1%	99	9.7%	0.04	0.831

	Married	542	53.0%	522	51.1%		
	Separated/Divorced	70	6.9%	73	7.1%		
	Widowed	241	23.6%	248	24.3%		
	Other	76	7.4%	80	7.8%		
Received Stem Cell Transplant (n, %)	No	985	96.4%	985	96.4%	<0.001	> 0.999
	Yes	37	3.6%	37	3.6%		

Table 1.4 Summary of adverse events for patients receiving first line BORT-based vs first line LEN-based treatment among elderly NDMM patients, 2007-2016

Adverse Events	Category	BORT group (n = 1,022)		LEN group (n = 1,022)	
Cardiotoxicity (n, %)	No	649	63.5%	591	57.8%
	Yes	373	36.5%	431	42.2%
Thrombocytopenia (n, %)	No	982	96.1%	974	95.3%
	Yes	40	3.9%	48	4.7%
Neutropenia (n, %)	No	981	96.0%	966	94.5%
	Yes	41	4.0%	56	5.5%
Tumor Lysis Syndrome (n, %)	No	1,022	100.0%	1,022	100.0%
	Yes	0	0.0%	0	0.0%
Any Adverse Event (n, %)	No	607	59.4%	549	53.7%
	Yes	415	40.6%	473	46.3%

Table 1.5 Tests for validity of proportional hazards assumption for overall survival and adverse event outcomes

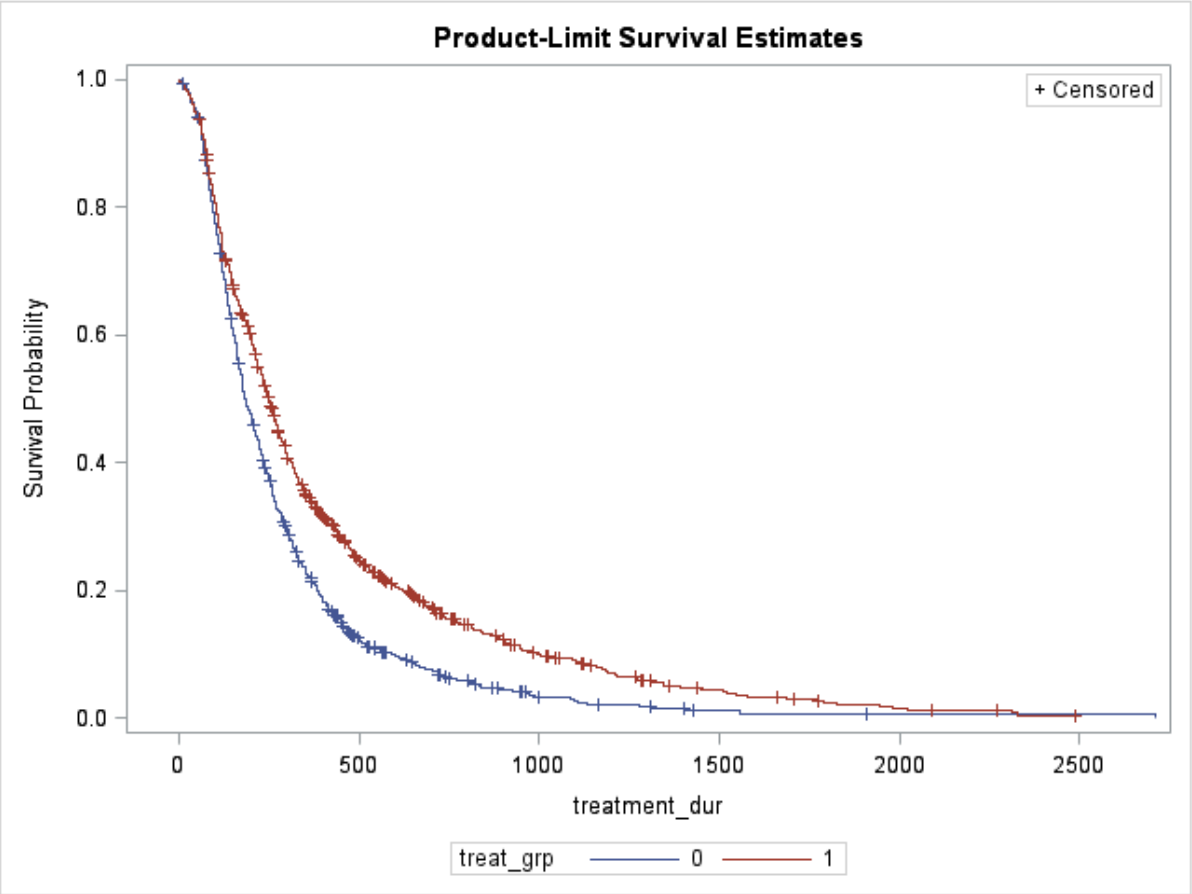
Outcome	Variable	Interaction with time	Schoenfeld Residual		
			time	log(time)	time*time
All-cause death	Treatment Group	0.659	0.521	0.146	0.832
Cardiotoxicity	Treatment Group	0.243	0.241	0.06	0.562
	Prior Cardiac Toxicity	<0.001	<0.001	<0.001	0.003
Thrombocytopenia	Treatment Group	0.729	0.994	0.465	0.941
	Prior Thrombocytopenia	0.262	0.292	0.135	0.385
Neutropenia	Treatment Group	0.686	0.729	0.096	0.846
	Prior Neutropenia	0.221	0.239	0.162	0.249
Any adverse event (composite)	Treatment Group	0.287	0.218	0.105	0.555
	Prior Cardiac Toxicity	<0.001	<0.001	<0.001	0.003
	Prior Thrombocytopenia	0.742	0.244	0.237	0.243
	Prior Neutropenia	0.746	0.348	0.128	0.681

Table 1.6 Cox proportional hazards regression analysis comparing overall survival and safety between first line BORT-based and LEN-based treatments among elderly NDMM patients, 2007-2016

Outcome	Treatment Group	Hazard Ratio	95% LCL	95% UCL	p
All-cause Death	BORT	1.21	1.01	1.47	0.046
	LEN	Ref	Ref	Ref	
Cardiotoxicity	BORT	0.94	0.81	1.08	0.361
	LEN	Ref	Ref	Ref	
Thrombocytopenia	BORT	0.79	0.51	1.22	0.289
	LEN	Ref	Ref	Ref	
Neutropenia	BORT	0.87	0.57	1.3	0.488
	LEN	Ref	Ref	Ref	
Any adverse event (composite)	BORT	0.93	0.82	1.06	0.291
	LEN	Ref	Ref	Ref	

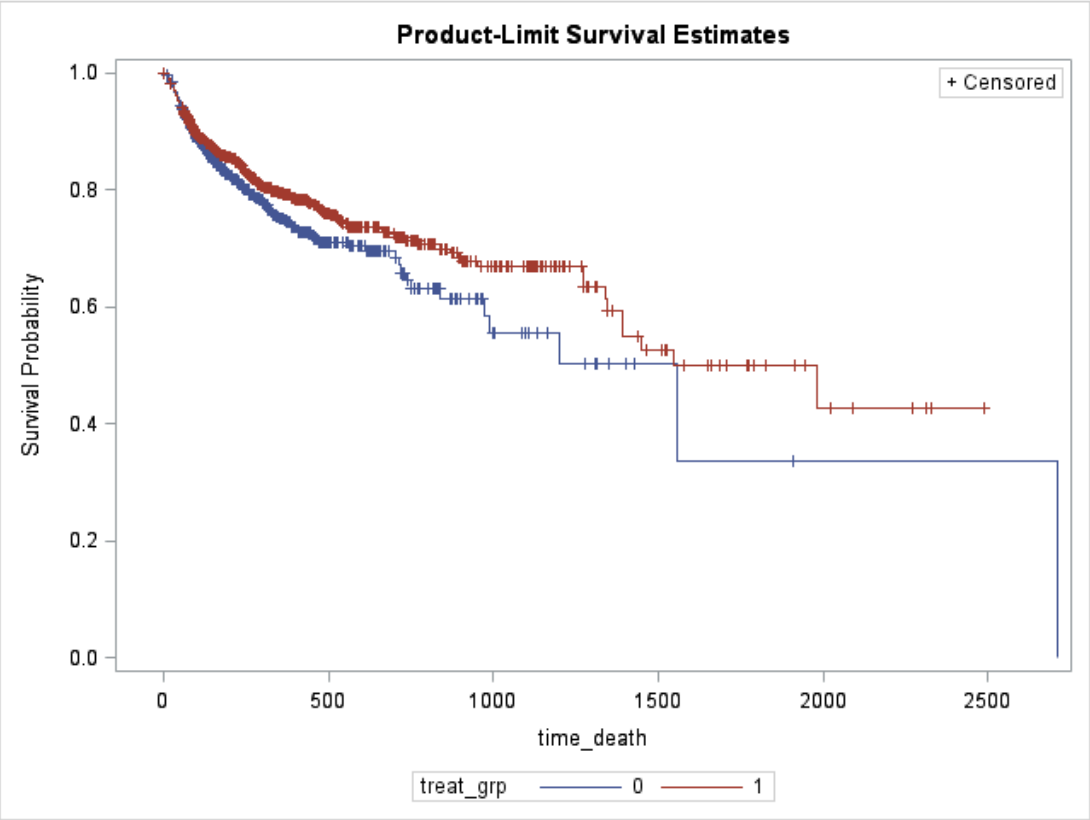
APPENDIX B

Figure 1.1 Kaplan-Meier survival plot for treatment duration for elderly NDMM patients receiving first line BORT-based vs LEN-based treatment



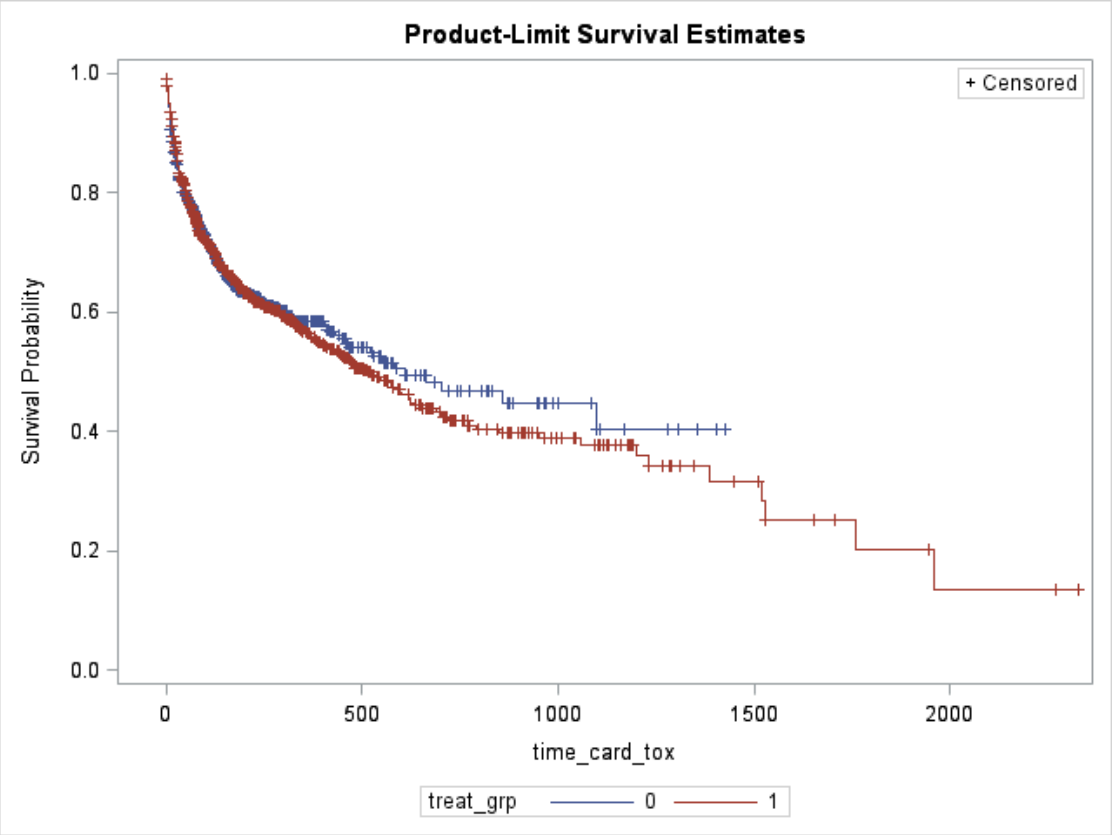
Treat_grp: 0 indicates BORT-based treatment; 1 indicates LEN-based treatment

Figure 1.2 Kaplan-Meier survival plot for overall survival for elderly NDMM patients receiving first line BORT-based vs LEN-based treatment



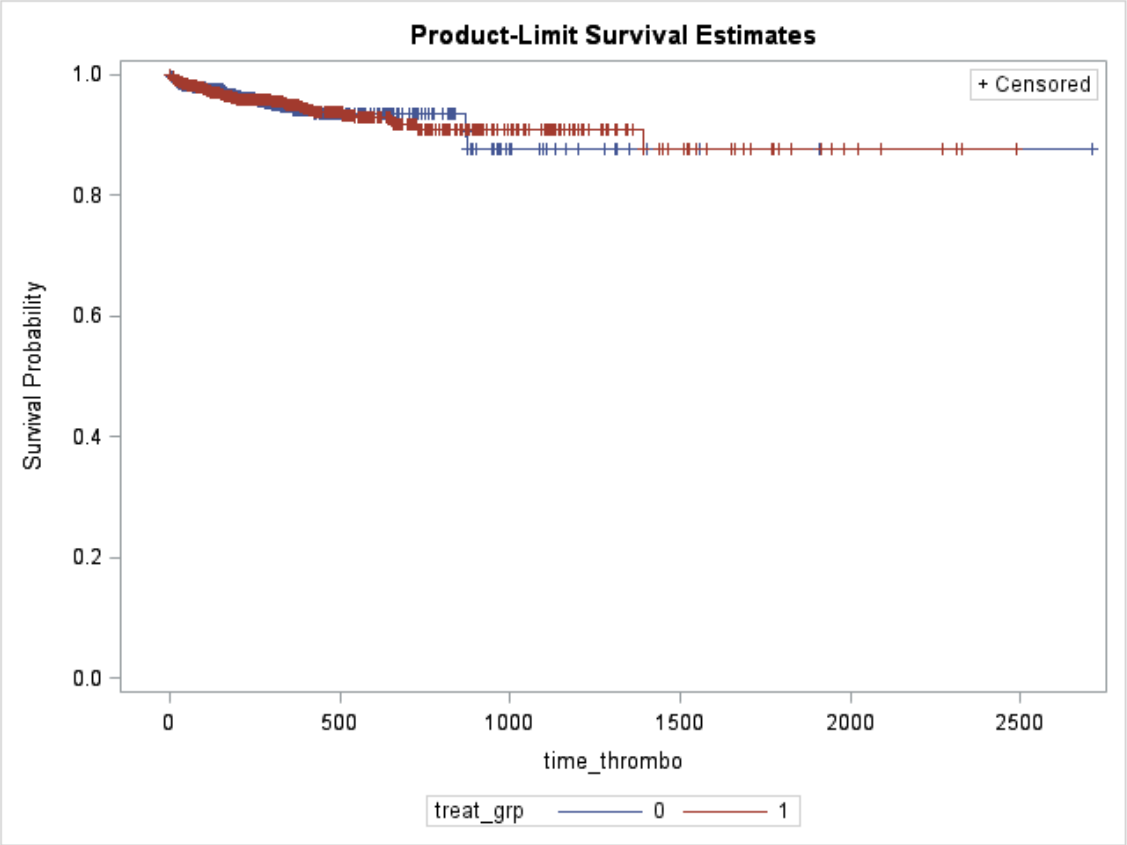
Treat_grp: 0 indicates BORT-based treatment; 1 indicates LEN-based treatment

Figure 1.3 Kaplan-Meier survival plot for cardiotoxicity for elderly NDMM patients receiving first line BORT-based vs LEN-based treatment



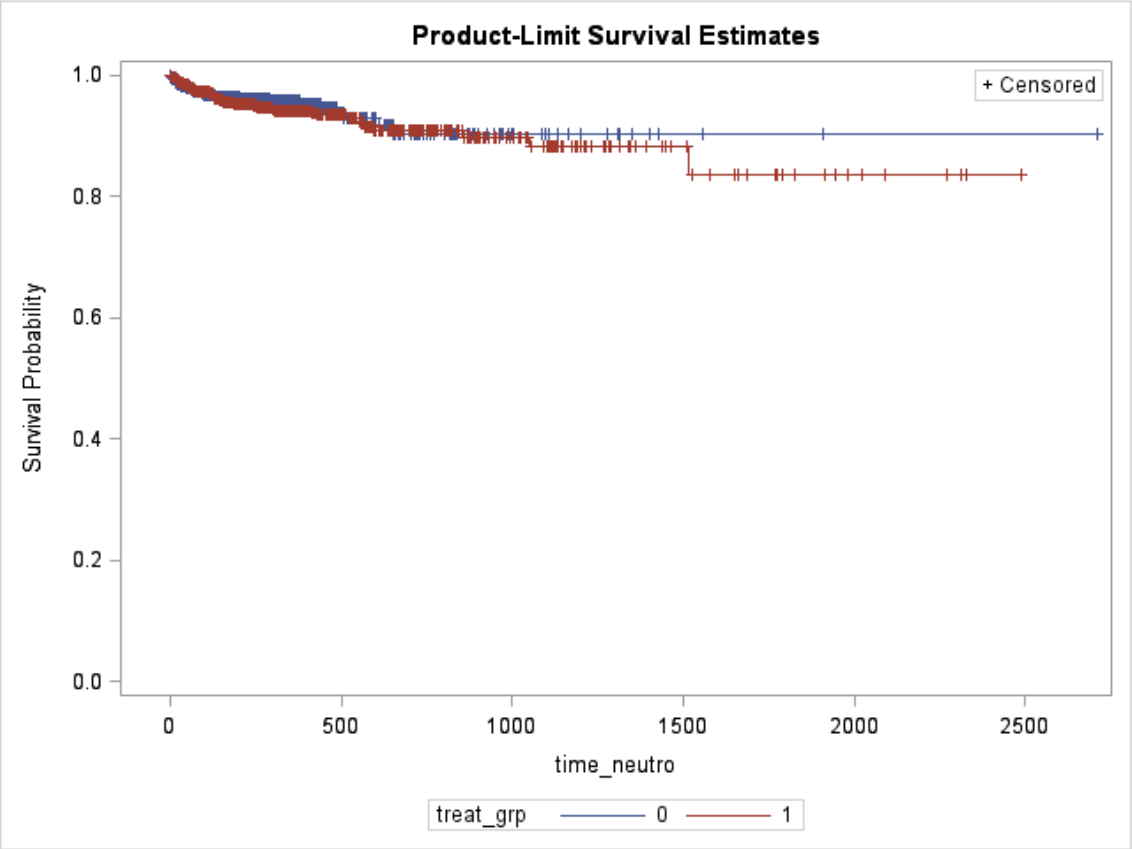
Treat_grp: 0 indicates BORT-based treatment; 1 indicates LEN-based treatment

Figure 1.4 Kaplan-Meier survival plot for thrombocytopenia for elderly NDMM patients receiving first line BORT-based vs LEN-based treatment



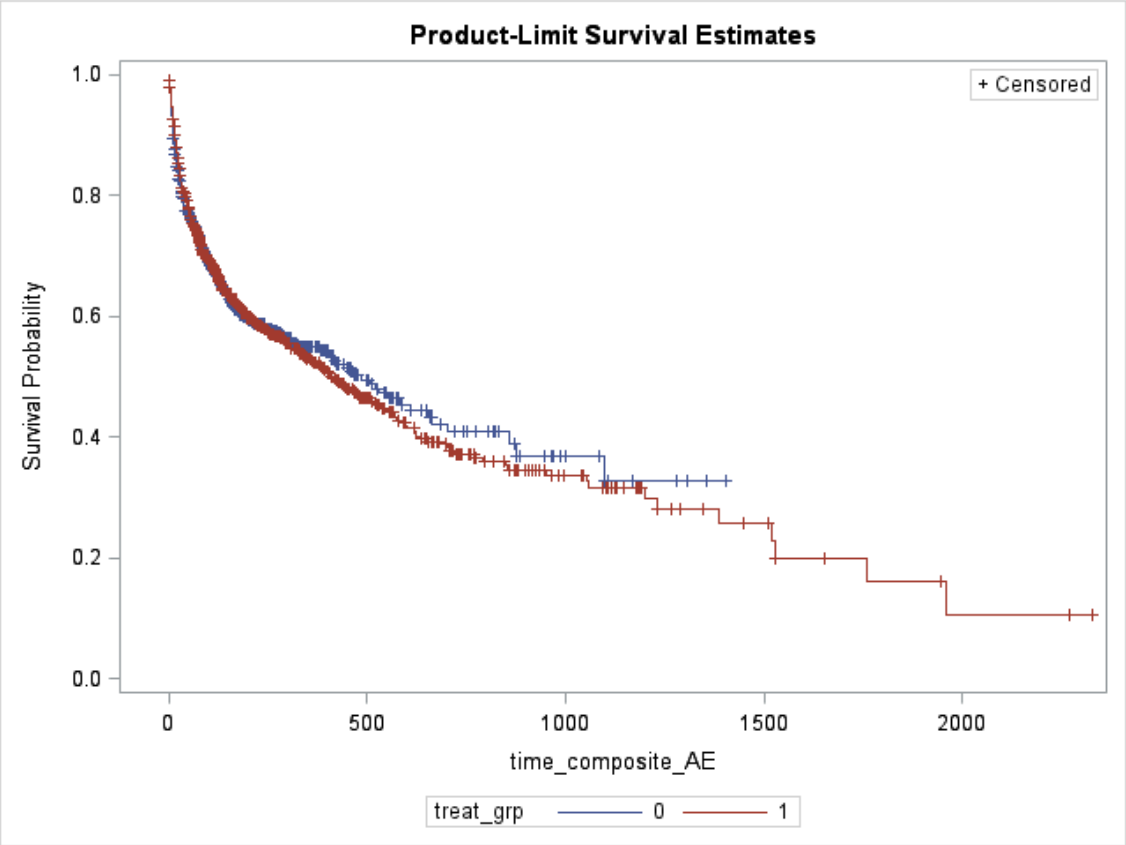
Treat_grp: 0 indicates BORT-based treatment; 1 indicates LEN-based treatment

Figure 1.5 Kaplan-Meier survival plot for neutropenia for elderly NDMM patients receiving first line BORT-based vs LEN-based treatment



Treat_grp: 0 indicates BORT-based treatment; 1 indicates LEN-based treatment

Figure 1.6 Kaplan-Meier survival plot for the composite any adverse event outcome for elderly NDMM patients receiving first line BORT-based vs LEN-based treatment



Treat_grp: 0 indicates BORT-based treatment; 1 indicates LEN-based treatment

CHAPTER 3: PAPER 2

Disease Lifetime Costs and its Predictors among Elderly Patients Newly Diagnosed with Multiple Myeloma

Introduction

Multiple Myeloma (MM) is a hematologic malignancy characterized by abnormal growth of clonal plasma cells. It is diagnosed based on presence of 10% or more clonal plasma cells on bone marrow examination, and monoclonal protein in serum or urine. Diagnosis of symptomatic MM requires proof of end organ damage, and is defined as presence of one or more of the following diseases – hypercalcemia, renal insufficiency, anemia, and bone disease (Palumbo 2012; International Myeloma Working Group 2003). In the United States (US), around 1.6% of all new cancer cases can be attributed to MM, and it has a lifetime risk of 1 in 132 (Chen et al. 2017; American Cancer Society 2018). As per the latest incidence and mortality statistics, an estimated 30,770 new cases of MM and 12,770 deaths from MM were reported in the US in 2018 (Siegel, Miller, and Jemal 2018). The median age at MM diagnosis is approximately 66-70 years, with 63% of the diagnosed patients being 65 years of age or older (Kazandjian 2016).

MM treatment has seen a paradigm shift in the past few decades, first with the development of autologous stem cell transplant (ASCT), and then with the approval of novel agents, such as immunomodulatory drugs (IMIDs) - thalidomide and lenalidomide, and proteasome inhibitor (PI) bortezomib in the 2000s. The introduction of ASCT and novel agents have led to drastic changes in MM management, and prolonged overall survival (Kristinsson et

al. 2007; Brenner, Gondos, and Pulte 2008; Kumar et al. 2008). Moreover, the last few years have seen even more modifications in the treatment landscape for MM with approvals of IMID pomalidomide in 2013, PIs carfilzomib and ixazomib in 2012 and 2015 respectively, and monoclonal antibodies daratumumab and elotuzumab in 2015 (Fonseca et al. 2017).

Cost associated with cancer treatment poses a significant burden to patients and their family members, payers, and society in general. The estimated total direct medical costs attributable to cancer treatment in the US was around $125 billion in 2010 (Roy et al. 2015). Even though MM accounts for a small proportion of patients with cancer, healthcare costs associated with treatment of MM are higher than treatment of most other types of cancer (Cook 2008). While real-world studies have assessed healthcare expenditures among MM patients, most of these studies have been limited to assessment of healthcare costs in various lines of treatment (e.g., first-line vs second-line) or examination of treatment-related costs (novel agent use versus other therapy) (MacEwan et al. 2018; Arikian et al. 2015; Teitelbaum et al. 2013). Very few studies have assessed disease-related costs. One such study that assessed trends in healthcare expenditure among newly diagnosed multiple myeloma (NDMM) patients with commercial insurance and private Medicare supplemental coverage between 2000 and 2014 in the US found that there was a three-fold increase in total per patient per month (PPPM) healthcare costs between 2000 and 2014 ($3,263 in 2000 vs $14,656 in 2014). Outpatient services and hospitalizations were reported to be the major drivers of the increase in costs. The study also compared total all-cause costs among MM patients and matched controls between 2000 and 2014, and found that the PPPM all-cause costs increased 476% for MM patients as compared to 182% for the matched controls (Fonseca et al. 2017). A cost of illness (COI) analysis among MM patients during one year of disease management in Italy, reported a total COI of €19,267,

with drug costs and hospital admissions being the primary drivers of total COI (Petrucci et al. 2013). Another analysis of healthcare costs among MM patients, conducted in Italy from a hospital perspective, reported annual costs of €14,053 (Koleva et al. 2011), whereas a Swedish chart review study conducted over a period of 5 years reported a mean PPPM cost of €2,770 for MM patients (Ghatnekar et al. 2008).

Most of the studies that have assessed disease-related costs in MM have used a prevalence-based approach. It is important to assess healthcare expenditures across phases of MM care. This is due to the fact that as disease progresses, treatments differ and thus, costs differ by each phase of MM care (de Oliveira et al. 2016). Extant literature on healthcare costs among cancer patients suggest that healthcare expenditures across the disease continuum follows a U-shaped curve, with greater expenditure incurred around the time of diagnosis (initial care phase) and death (terminal phase), and lower expenditures incurred in the continuing care phase between the initial care phase and the terminal phase. These studies have also shown that such phase-based cost estimates in combination with survival estimates yield reliable estimates of long-term disease burden (Brown et al. 1999; 2002; de Oliveira et al. 2013; Krahn et al. 2010; Yabroff et al. 2008). Assessment of phase-specific costs provides a natural framework for analysis of disease lifetime costs across the entire care continuum among cancer patients. While the initial phase costs reflect the costs of initial course of diagnosis and therapy, continuing care phase costs provide an estimate of the economic burden of surveillance and maintenance costs post the initial care phase. Terminal phase costs are reflective of costs incurred at the end of life (R. Etzioni et al. 2002). A better understanding of healthcare costs across various phases of cancer care and the drivers of these costs would help plan interventions and policy decisions targeted towards improving quality of cancer care while controlling costs (Kaye et al. 2018).

However, there is very limited literature on disease lifetime costs of MM. One study, conducted using data from the Ontario Cancer Registry reported that the costs of MM patients were higher in the initial care phase ($24,447 for males, and $24,052 for females) and terminal phase ($43,989 for males, and $45,871 for females), and lower in the continuing care phase ($15,153 for males, and $15,255 for females) and pre-diagnosis period ($3,142 for males, and $2,609 for females). This study also found that MM has the highest disease lifetime costs among of all types of cancer (de Oliveira et al. 2016). Given that majority of the MM patients in the US are diagnosed at an age of 65 or greater, and that Medicare is the primary payer for this population, and taking into consideration the changing landscape of MM treatment with introduction of several novel agents, it is important to assess the disease lifetime costs of MM from Medicare's perspective. However, no study in the US has yet evaluated the disease lifetime costs of MM from Medicare's perspective.

One difficulty in the assessment of disease lifetime costs is defining the duration of the various phases of care, which varies based on the type of cancer and cancer stage at diagnosis. While studies among patients with breast cancer and pancreatic cancer have defined duration of the terminal phase as 12 months prior to death, for patients with metastatic colorectal cancer, it has been defined as 3 months prior to death (Brown et al. 2002; Seidler et al. 2010; Chang et al. 2006; Paramore et al. 2006). In majority of incidence-based approaches for cost estimation, the first 6 months post diagnosis is defined as the initial phase of care, and the last 12 months before death as the terminal phase, with the time between the first 6 months and the last 12 months defined as the continuous phase. However such an assignment of phases of care is mostly arbitrary. Thus, it would be ideal to establish a data-driven approach that, in conjunction with clinical judgement, to establish a benchmark for defining phases of MM care, consistent with

extant phase-based net cost and disease lifetime cost literature in other cancers (Atkins et al. 2018).

In the current study, we aimed to determine the duration of initial phase and terminal phase for elderly NDMM patients using a data driven approach, assess phase-specific costs and disease lifetime costs of MM compared to matched non-cancer group, and to identify drivers of MM costs for each phase among elderly newly diagnosed MM patients.

Methods

Study Design and Data Source

A retrospective analysis was conducted using National Cancer Institute's (NCI) SEER database linked with Medicare administrative claims database. The NCI's SEER program is an epidemiologic surveillance system that contains data collected from population-based tumor registries and was designed to track cancer incidence and mortality in the US. It includes clinical and demographic information in addition to information on cause of death for people with cancer, and is collected from 18 participating cancer registries across the US. Medicare is a federally administered health insurance program which covers elderly Americans who are 65 years of age or older, as well as younger patients with disabilities and end-stage renal disease (ESRD). The Medicare administrative claims database provides information on claims for covered healthcare services for beneficiaries enrolled in Medicare. The SEER-linked Medicare claims database provides patient-level data for Medicare beneficiaries with cancer (Warren et al. 2002).

The current study has been approved by the University of Mississippi's Institutional Review Board (IRB), and utilized 2007-2015 SEER data linked with 2006-2016 Medicare claims

data. The SEER data consists of the Patient Entitlement and Diagnosis Summary File (PEDSF) that includes clinical, demographic, and Medicare enrollment information for individuals with cancer. The Medicare claims data consists of the Medicare Provider Analysis and Review (MEDPAR), National Claims History (NCH), Outpatient (OUTPT), Home Health Agency (HHA), Hospice, Durable Medical Equipment (DME), and Prescription Drug Event (PDE) files. The MEDPAR file contains all Medicare Part A claims indication short stay, long stay, skilled nursing facility (SNF) stays as well as ICD-9/10 diagnoses and procedures performed during each stay. The NCH file contains all Medicare Part B claims generated due to physician or supplier services in clinics and hospitals, whereas the OUTPT file contains all Medicare Part B claims outpatient providers. Both NCH and OUTPT files was used to obtain information such as procedural Healthcare Common Procedure Coding System (HCPCS) codes, diagnoses, date of claims, treatment administration, and reimbursement amounts. The HHA file contains claims for all home health care services such as number and types of visits and diagnoses. The hospice file contains claims submitted by hospice providers, and has details on type of care (inpatient care, routine home care) as well as terminal diagnosis associated with that care. The DME file contains claims with information on use of oral and intravenous chemotherapy, and infusion pumps used. The PDE file contains information about drug utilization such as, date of prescription fill, drug dispensed, quantity dispensed, days supplied, total cost, and out-of-pocket cost.

Study sample

This study included Medicare beneficiaries who entered the SEER registry from 2007 through 2015, and were diagnosed with MM as primary cancer. All beneficiaries with primary MM were identified based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-

O-3) code of MM (9732). MM patients needed to be 66 years of age or older at the time of MM diagnosis and have continuous enrollment in Medicare Parts A, B, and D for at least two months post-MM diagnosis or until death to be included in the study. Non-cancer Medicare beneficiaries in the 5% random sample were included as the control group. Non-cancer controls were included if they were 65 years of age or older and were continuously enrolled in Medicare Parts A, B, and D for at least 14 months from the month of start of Medicare eligibility or until death. MM patients were excluded from the study sample if they had an unknown diagnosis month or year, if MM diagnosis was made at the time of death, if they had any cancer in the 5 years prior to MM diagnosis, and if they were enrolled in a health maintenance organization (HMO) at any time between 12 months prior to MM diagnosis and death or end of study period. Beneficiaries in the non-cancer group will also be excluded if they were enrolled in a HMO at any time during the study period.

Medicare beneficiaries in the MM group and non-cancer group were matched 1:1 on months of Medicare eligibility and death date (for those who died) / date of loss of Medicare eligibility or end of study (for those who did not die during the follow-up period), using a greedy matching algorithm. Beneficiaries in the non-cancer cohort were assigned the MM-diagnosis date of the matched MM beneficiary.

Study variables

The outcome variable of interest is all-cause healthcare cost. We used payments made by Medicare (as opposed to all sources of payments or any charge variables) when making monetary comparisons. All cost estimates were adjusted to 2016 US dollars using the Medical Care Component of the Consumer Price Index.

For assessment of disease lifetime costs, ideally all beneficiaries (cases and controls) should be followed until death. However, due to short study horizons, death may not be observed for all beneficiaries. For those who did not die during the study observation period, a portion of their healthcare costs remain unobserved, leading to right censoring of healthcare costs due to which their observed costs underrepresent their actual costs (Huang 2009). For such an analysis, we can either use a full-sample estimator (irrespective of whether the beneficiary died or was censored) or use an uncensored case estimator (which only considers those beneficiaries that died during the observation period). Since the full sample estimator would only include a portion of the costs for censored beneficiaries, it would lead to an underestimation of the actual costs (Bang 2005). For the uncensored case estimator, only those beneficiaries that died during the study observation period is considered. However, the probability of remaining uncensored is not the same at all time points. As time increase, the probability of being uncensored decreases. Hence, the uncensored case estimator would be biased towards those beneficiaries that died early (Bang 2005; Raikou and McGuire 2004).

Reweighted estimators can be used to estimate mean healthcare costs for censored data. Various reweighted estimators (Lin 1997 estimator, simple IPW estimator, partitioned extension of the simple IPW estimator) have been developed over time using Kaplan-Meier (K-M) techniques (Wijeysundera et al. 2012). But use of these estimators to estimate lifetime costs may lead to biased estimates (Huang 2009; Austin, Ghali, and Tu 2003; R. D. Etzioni et al. 1999; Lipscomb et al. 1998). Since independent censoring is a requirement for K-M survival curves, it require time to censoring to be independent of time to death. But the lifetime cost to censoring for a beneficiary will not independent from their lifetime cost to death, since both are related to

the beneficiary's cost accumulation pattern (Huang 2009; Austin, Ghali, and Tu 2003; R. D. Etzioni et al. 1999; Lipscomb et al. 1998).

In light of the limitations associated with use of reweighted estimators, phase-based modeling approach is an alternative method for estimating lifetime costs. Since actual lifetime costs for the cohort does not need to be observed in the phase-based modeling approach, it does not suffer from the limitations that affect the IPW methods (Brown et al. 1999; R. Etzioni et al. 2002; Wijeysundera et al. 2010; Yabroff et al. 2009). This method has been used by several studies to estimate lifetime costs of cancer (Yabroff et al. 2009; 2005).

Consistent with previous studies that have employed a phase-based approach to model healthcare costs, costs were divided into four phases – 1) pre-diagnosis phase, which is defined as 3 months prior to diagnosis (Christensen et al. 2012; Hornbrook et al. 2013), 2) initial phase, 3) continuing phase, and 4) terminal phase (Brown et al. 1999; Yabroff et al. 2008; Baker et al. 1991; Taplin et al. 1995). Duration of the initial phase and terminal phase was determined using a data driven approach (joinpoint analysis) (Atkins et al. 2018; Kim et al. 2000). For each phase-specific cost, cost attributable to MM was calculated by subtracting the costs incurred by cases from those incurred by matched controls, using the net cost method (de Oliveira et al. 2016; Brown et al. 1999; Taplin et al. 1995).

Baseline demographic covariates included age (at MM diagnosis), sex, race, geographic location, and urban residency. Baseline clinical covariates included comorbidity, and disability status. Comorbidity was assessed using the Deyo adaption of the Charlson Comorbidity Index (CCI) (Deyo, Cherkin, and Ciol 1992). Disability status, which is a proxy measure for performance status, was calculated using a validated, claim-based algorithm during the 12-month baseline period prior to MM diagnosis (Davidoff et al. 2013).

Analysis

Descriptive statistics were used to depict baseline patient characteristics, and costs. For categorical variables, frequency and percentage distributions were reported. Statistical comparisons were conducted between the groups using McNemar's test or Cochrane-Mantel-Haenszel test, to account for the matched data. For continuous variables, mean, standard deviation (SD), median, and range were reported. Statistical comparisons for continuous variables were conducted using paired t-tests. For unadjusted healthcare costs, Wilcoxon signed rank tests were used to test for significant differences between the groups.

Determination of duration of initial phase and terminal phase

Joinpoint regression analysis was performed using Joinpoint regression software, developed by the Surveillance Research Program of the National Cancer Institute to identify duration of initial and terminal phases for MM patients. For this analysis, all MM patients in the sample who died before the end of study period were considered.

Joinpoint regression is a piecewise linear regression used to identify the best-fitting points where statistically significant changes in the trends of monthly costs occur. Separate models were estimated for the initial phase and the terminal phase. The model selection parameters for the Joinpoint regression analyses were based on diagnostic tests for heteroscedasticity – using the Cook-Weisberg test for heteroscedasticity, and autocorrelation - using the Breusch-Godfrey LM test for autocorrelation. For the initial phase model, average monthly costs were modeled from MM diagnosis to death, and for the terminal phase model, costs were modeled backward from death to MM diagnosis. The study used a minimum of 0 joinpoints to a maximum of 4 joinpoints to identify best fit of data (Kim et al. 2000). Joinpoints

were defined as points of inflection in the trend of monthly costs. The joinpoints were then used to estimate the duration of the initial and terminal phases. The months in between the initial and terminal phase were assigned to the continuing phase (Atkins et al. 2018).

Estimation of Phase-based costs

To estimate lifetime costs for MM using the phase-based approach, the cohort was divided into four phases – pre-diagnosis phase, initial phase, continuing phase, and terminal phase. Once the duration of the various phases have been determined, time (in months) spent and costs in each phase were calculated for the entire cohort. Upon calculation of monthly costs for the entire cohort, mean cost per phase were assessed, and then disease lifetime costs were assessed using phase-specific cost data and time to death data. Mean cost per phase were estimated by multiplying the phase-specific costs to the survival function estimates (Wijeysundera et al. 2012).

Beneficiaries, who died during the post-diagnosis observation period, were first be assigned to the terminal phase. Once they had been assigned to the terminal phase, any remaining time spent was first assigned to the initial phase, and then to the continuing phase. Beneficiaries, who did not die during the post-diagnosis observation period, were first assigned to the initial phase and then to the continuing phase (Wijeysundera et al. 2012).

All costs attributable to MM (lifetime, phase-specific, and individual medical service component costs within each phase) were estimated controlling for clinical and socio-demographic characteristics at baseline. Generalized linear models with log link and gamma distribution were used to assess incremental MM costs, due to their advantage over other models with regards to re-transformation bias and heteroscedasticity (Gregori et al. 2011; Mihaylova et

al., n.d.). In order to account for covariate imbalance, recycled prediction technique was used to assess the incremental impact of MM for all the cost outcomes (A. Basu and Rathouz 2005; Anirban Basu, Polsky, and Manning 2011). For this technique, the outcome was first predicted assuming every recipient to be in the non-cancer group, and then the outcome was again predicted assuming every recipient to be in the MM group. The incremental impact was then assessed by calculating the difference between the predicted outcomes for the MM and non-cancer groups. Percentile bootstrapping with 2000 replications was conducted to compute the 95% Confidence Interval (CI) for each outcome. All statistical analyses were conducted using NCI's Joinpoint regression software, SAS version 9.4, and STATA 15.

Results

6,151 NDMM patients and 111,736 non-cancer beneficiaries met the study inclusion and exclusion criteria. Of the 6,151 beneficiaries in the MM group, 3,651 died during the study period. Monthly cost data for these 3,651 NDMM patients was utilized for the Joinpoint regression analyses to determine the duration of the initial and terminal care phases. Based on the results of the Cook-Weisberg test for heteroscedasticity and Breusch-Godfrey LM test for autocorrelation, a heteroscedastic, autocorrelated model was used for estimating duration of both initial and terminal phases. As mentioned in the study methodology, the 3 months prior to MM diagnosis was considered as the pre-diagnosis phase, and any time spent by the beneficiaries between the initial and terminal phases was assigned to the continuing care phase.

Joinpoint regression result for identifying duration of the initial phase showed statistically significant inflection points in monthly cost trends at month 4 [monthly percent change (MPC): -15.0%, 95% Confidence Interval (CI): (-17.7%) - (-12.2%)] and month 14 [monthly percent change (MPC): -2.7%, 95% CI: (-3.4%) – (-2.0%)]. Most of the studies that have assessed

lifetime and phase-specific costs in cancer have conventionally considered the first 6 months or 12 months after diagnosis as the initial care phase (Banegas et al. 2018; Aly et al. 2018; Barlow 2009; Deshmukh et al. 2018; Kaye et al. 2018; Lang et al. 2009). It is unlikely for the initial phase to span across the first 14 months after diagnosis, and no previous study has considered the initial phase to be more than 12 months. Furthermore, results of the Joinpoint regression analysis reported a comparatively small MPC for the inflection point at month 14. Considering all the information, the duration of the initial phase among elderly NDMM patients was identified as the 4-month period post MM-diagnosis.

Joinpoint regression analysis result for identifying duration of the terminal phase showed statistically significant inflection points in monthly trend costs at month 3 prior to death [monthly percent change (MPC): 20.8%, 95% Confidence Interval: 17.3% - 24.1%], and month 8 prior to death [monthly percent change (MPC): 6.9%, 95% Confidence Interval: 5.4% - 8.4%]. Based on these results, the duration of the terminal phase was identified as the 3-month period prior to death. In addition, sensitivity analysis was conducted using the 8-month period prior to death as the terminal phase.

For assessing the incremental lifetime and phase-specific costs of MM, 4,533 elderly, NDMM patients were matched to 4,533 non-cancer Medicare beneficiaries. As compared to the non-cancer group, a greater percentage of MM patients lived in a rural area (93.1% for the MM group vs 88.4% for the non-cancer group, $p<0.001$) and were males (47.6% for the MM group vs 40.5% for the non-cancer group, $p<0.001$). A lower percentage of beneficiaries in the MM group were considered to have disability in the 12-month baseline period as compared to the non-cancer group (19.1% vs 23.7%, $p<0.001$). Moreover, statistically significant differences were

seen between the MM group and non-cancer group on their geographical region of residence ($p<0.001$), race ($p<0.001$), CCI score categories ($p<0.001$), and age at baseline ($p<0.001$).

The bivariate analysis results (Table 2.2) depict the significantly greater mean lifetime costs ($212,474 vs $54,086, $p<0.001$) for the MM group as compared to the matched non-cancer group. Moreover, beneficiaries in the MM group had significantly greater mean per member per month (PMPM) pre-diagnosis phase costs ($2,081 vs $1,567, $p<0.001$), initial phase costs ($10,384 vs $1,618, $p<0.001$), continuing care phase costs ($6,083 vs $1,495, $p<0.001$), and terminal phase costs ($14,417 vs $8,853, $p<0.001$) as compared to the matched non-cancer group.

In the pre-diagnosis phase (3 month prior to diagnosis), beneficiaries in the MM group had greater mean PMPM outpatient ($791 vs $396, $p<0.001$) and inpatient costs ($896 vs $733, $p<0.001$) as compared to their matched non-cancer counterparts. In the initial care phase, beneficiaries in the MM group had greater mean PMPM outpatient ($3,977 vs $432, $p<0.001$), inpatient ($3,685 vs $692, $p<0.001$), pharmacy ($2,369 vs $285, $p<0.001$), and other costs ($353 vs $209, $p<0.001$) as compared to those in the non-cancer group. In the continuing care phase, beneficiaries in the MM group had greater mean PMPM outpatient ($1,998 vs $383, $p<0.001$), inpatient ($1,270 vs $667, $p<0.001$), pharmacy ($2,567 vs $237, $p<0.001$), and other costs ($248 vs $207, $p<0.001$) as compared to their non-cancer counterparts. In the terminal phase, beneficiaries in the MM group had greater mean PMPM outpatient ($3,424 vs $1,404, $p<0.001$), inpatient ($7,845 vs $6,129, $p<0.001$), pharmacy ($1,847 vs $331, $p<0.001$), and other costs (home health agency, hospice, durable medical equipments) ($1,301 vs $989, $p<0.001$) as compared to those in the non-cancer group. As seen in Table 2.3, results of the sensitivity analysis using the 8-month period prior to death as terminal phase produced similar results.

Results of the multivariable analysis for assessing the incremental MM lifetime, phase-specific, and medical service component (inpatient, outpatient, pharmacy, and other) costs within each phase controlling for clinical and sociodemographic covariates are presented in Table 2.4. The mean adjusted lifetime cost for the MM group ($234,002; 95% Confidence Interval [CI]: $232,232-$235,870) was significantly greater than that for the non-cancer group ($49,507, 95% CI: $49,133-$49,902), with an incremental expenditure of $184,495 (95% CI: $183,099-$185,968).

The mean adjusted pre-diagnosis phase PMPM cost for the MM group ($2,588, 95% CI: $2,531-$2,647) was significantly greater than that of their matched non-cancer counterparts ($1,344, 95% CI: $1,314-$1,375), resulting in an incremental expenditure of $1,244 (95% CI: $1,216-$1,272). Within the pre-diagnosis phase, the incremental PMPM outpatient cost was $508 (95% CI: $501-$515), incremental PMPM inpatient cost was $704 (95% CI: $696-$713), incremental PMPM pharmacy cost was $21 (95% CI: $20-$21), and incremental PMPM other cost was $29 (95% CI: $28-$31).

The mean adjusted initial phase PMPM cost for the MM group ($12,556, 95% CI: $12,412-$12,700) was significantly greater than that for the non-cancer group ($1,375, 95% CI: $1,360-$1,391), an incremental expenditure of $11,181 (95% CI: $11,052-$11,309). Within the initial phase, the incremental PMPM outpatient cost was $3,973 (95% CI: $3,943-$4,005), incremental PMPM inpatient cost was $4,275 (95% CI: $4,199-$4,350), incremental PMPM pharmacy cost was $2,237 (95% CI: $2,224-$2,252), and incremental PMPM other cost was $721 (95% CI: $697-$744).

The mean adjusted continuing care phase PMPM cost for the MM group ($6,968, 95% CI: $6,897-$7,042) was significantly greater than that of their matched non-cancer counterparts

($1,334, 95% CI: $1,320-$1,348), an incremental expenditure of $5,634 (95% CI: $5,577-$5,694). Within the continuing care phase, the incremental PMPM outpatient cost was $1,802 (95% CI: $1,788-$1,816), incremental PMPM inpatient cost was $1,087 (95% CI: $1,074-$1,101), incremental PMPM pharmacy cost was $2,526 (95% CI: $2,513-$2,540), and incremental PMPM other cost was $214 (95% CI: $208-$220).

The mean adjusted terminal phase PMPM cost for the MM group ($15,364, 95% CI: $15,286-$15,447) was significantly greater than that for the non-cancer group ($9,084, 95% CI: $9,038-$9,133), an incremental expenditure of $6,280 (95% CI: $6,248-$6,314). Within the terminal phase, the incremental PMPM outpatient cost was $2,181 (95% CI: $2,168-$2,194), incremental PMPM inpatient cost was $2,060 (95% CI: $2,046-$2,075), incremental PMPM pharmacy cost was $1,600 (95% CI: $1,593-$1,608), and incremental PMPM other cost was $461 (95% CI: $457-$464).

Results of the sensitivity analyses using the 8-month period prior to death as the terminal phase are presented in Table 2.5. As depicted in Table 2.5, the results for the sensitivity analyses are similar to that of the base case (3-month terminal phase).

Discussion

To the best of our knowledge, this is the first study to have used a data-driven approach to estimate the duration of initial and terminal care phases among elderly patients newly diagnosed with MM. It is also the first study to estimate the disease lifetime cost of MM from Medicare's perspective. In the US, patients newly diagnosed with MM have a median age at diagnosis of around 69 years, and about 65% of the diagnosed MM patients are 65 years of age or older at the time of diagnosis (Kazandjian 2016). Since, Medicare is the primary payer for those who are 65

years or older, it is important to estimate the cost burden of MM from Medicare's perspective. Furthermore, this study used a phase-based costing approach to estimate incremental costs for each phase of MM care – pre-diagnosis, initial, continuing care, and terminal, and drivers of these phase-specific costs were also identified. This information will inform resource allocation decisions, and aid policy makers and payers in devising innovative interventions targeted towards improving quality of MM care while staying within their budgets (Kaye et al. 2018).

Using a data-driven approach (Joinpoint regression), we determined the duration of the initial phase to be 4 months post MM diagnosis among Medicare beneficiaries. This is the first study to have assessed the duration of the initial care phase in a real-world cohort of MM patients. The convention in majority of the studies that have employed the phase-based costing approach to assess phase-specific costs among cancer patients, in general, is to consider the first 6 or 12 months after diagnosis to be the initial phase (Banegas et al. 2018; Aly et al. 2018; Barlow 2009; Deshmukh et al. 2018; Kaye et al. 2018; Lang et al. 2009). However, such an allocation is often arbitrary and does not take into account the differences in care patterns for different cancer types. Some studies of phase-based estimates of costs of medical care in other cancer types have used similar data driven approaches to identify the duration of the initial phase. One such study, among metastatic melanoma patients, determined the duration of the initial phase to be 5 months post diagnosis of metastasis (Atkins et al. 2018). Another study, among newly diagnosed elderly melanoma patients in the US, estimated the duration of the initial phase to be the first 4 months post diagnosis (Seidler et al. 2010).

For the terminal phase, we found a significant change in the monthly cost trends at the 3-month and 8-month periods prior to death. No previous study has determined the duration of the terminal care phase in a real-world cohort of MM patients. The convention in most phase-based

costing studies in oncology has been to consider the last 12 months prior to death as the terminal phase (Banegas et al. 2018; Aly et al. 2018; Brown et al. 1999; Barlow 2009; Deshmukh et al. 2018; Kaye et al. 2018; Lang et al. 2009). However, such an approach does not take into account variations in disease-specific care patterns in different cancer types. A few other studies have used data driven approaches, similar to ours, to identify duration of the terminal phase in various other cancer types. A study among metastatic melanoma patients estimated the duration of the terminal phase to be the last 5 months prior to death (Atkins et al. 2018). Another study, among elderly newly diagnosed melanoma patients assessed the duration of the terminal phase to be the last 6 months prior to death (Seidler et al. 2010). Moreover, the duration of the terminal phase was estimated to be the last 3 months prior to death in a cohort of newly diagnosed metastatic colorectal cancer patients (Paramore et al. 2006).

Our study estimated the incremental disease lifetime cost of MM to be $184,494 for the base case, i.e., considering the 3-month period prior to death as the terminal phase. Sensitivity analysis with the terminal phase being the last 8 months prior to death produced similar results, with the estimated the incremental disease lifetime cost of MM to be $187,548. This highlights the substantial cost burden associated with MM care. Our study findings are consistent with that of extant literature. A study that estimated phase-specific and lifetime costs of various cancers in Canada reported the lifetime cost of MM to be around $120,000 (in 2009 dollars) (de Oliveira et al. 2016). The previous study was limited to patients from a cancer registry in Canada, and only included those who had been diagnosed with MM up until 2007. With the approval of several anti-MM drugs since 2007, and the paradigm shift seen in MM care along with increased survival for MM patients, our study presents a more recent estimate of costs associated with MM care.

We estimated the incremental phase-specific costs of MM for each of the four phases of care – pre-diagnosis, initial, continuing care, and terminal, standardized in PMPM units. The incremental phase-specific costs were highest for the initial care phase, followed by the terminal phase, with costs being slightly lower for the continuing care phase, and lowest for the pre-diagnosis phase. Our findings are consistent with that of a previous study, conducted in Canada, which assessed phase-specific costs in MM, among other cancers. They reported costs to be highest in the initial and terminal phase, and much lower in the continuing care phase and pre-diagnosis phase (de Oliveira et al. 2016). Our study shows that following MM diagnosis, cost trends followed a U-shaped curve in the sense that higher costs were seen in the initial phase, which then dipped in the continuing care phase, before increasing again in the terminal phase. This is similar to that seen in studies of other cancer types that have assessed phase-specific costs (Brown et al. 2002; Atkins et al. 2018). While incremental costs for the continuing phase in our study was lower than that for the terminal phase, it was only slightly lower than the terminal phase costs, and much higher than that for the pre-diagnosis phase. The continuous care phase cost is in contrast to that found in the previous study conducted in Canada (de Oliveira et al. 2016). This is possibly due to the increased survival for MM patients with the approval and uptake of expensive, anti-MM immunotherapies in recent years (Kumar et al. 2008; Fonseca et al. 2017). Increasing continuing phase costs over the course of time have also been reported by phase-based cost assessments in other cancer types (Kaye et al. 2018). Since continuing phase costs primarily include costs of maintenance therapy following initial treatment and/or cancer relapse (R. Etzioni et al. 2002), the higher than expected continuous phase cost in our study is suggestive of chronic use of expensive immunotherapy drugs which are often used to prolong survival in patients (Kaye et al. 2018).

Moreover, we also identified cost drivers for each phase of MM care. For the base scenario (3 month terminal phase), inpatient and outpatient costs were the major drivers of costs in all the four phases. Pharmacy costs were a significant driver of costs in the initial and terminal phases, and were the biggest cost driver in the continuing care phase. Outpatient costs accounted for around 41%, 36%, 32%, and 35% of the incremental pre-diagnosis, initial, continuing care, and terminal phase MM costs respectively. Inpatient costs accounted for 57%, 38%, 19%, and 33% of the incremental pre-diagnosis, initial, continuing care, and terminal phase MM costs respectively. Pharmacy costs accounted for 20%, 45%, and 25% of the incremental initial, continuing care, and terminal phase MM costs respectively. Trends in cost drivers seen in our study are consistent with that of a previous study that assessed drivers of phase-specific costs among commercially insured MM patients in the US (Aly et al. 2018). While though new treatments have prolonged survival in MM, it remains incurable. However, with the paradigm shift in MM treatment over the past couple of decades, MM care has been largely limited to the outpatient setting. This can be a possible explanation for the high outpatient cost across all phases. Another study, that assessed trends in costs among commercially insured MM patients, reported inpatient and outpatient services to be the biggest drivers of MM costs (Fonseca et al. 2017). The high pharmacy cost, especially in the continuing care phase is possibly due to use of expensive, immunotherapy regimens that have been approved in the past decade or so.

Our study has several strengths. First, we used a data-driven approach to identify duration of various phases of MM care. Second, since the study used SEER data, reporting of the MM diagnosis is likely to be more accurate as compared to studies that may have used claims-based algorithms to identify MM diagnosis. This is due to the fact that SEER registry data is subject to stringent data quality checks, in accordance with North American Association of Central Cancer

Registries standards, and is deemed to have 98% accuracy (Warren et al. 2002). Third, since a majority of NDMM patients are 65 years of age or older and Medicare is the primary payer for such patients, the lifetime and phase-specific cost estimates in the Medicare population help provide an estimate of the burden to Medicare of MM care. Moreover, the costs estimated in the study can be potentially used in studies evaluating the impact of interventions directed towards MM prevention and treatment. Furthermore, findings from our study can inform policy decisions, and aid evaluation of alternative payment models in MM. Information on the phase-specific costs and cost drivers in each phase may help shape implementation of bundled payment models, such as Oncology Care Model, in the context of MM (Kline et al. 2017).

The study has a few limitations. Similar to other claims analyses, coding errors can bias study estimates. Additionally, the study was limited to MM patients enrolled in fee-for-service Medicare who were 66 years of age or older at the time of their diagnosis. Hence, our findings are not generalizable to other populations. Moreover, the SEER registry lacked information to inform MM staging. Hence, our analyses could not be stratified by cancer stage. Future studies should estimate MM lifetime and phase-specific costs stratified by cancer stage to see if the cost patterns vary by cancer stage.

Conclusion

Our study used a data-driven approach to identify the duration of initial and terminal phases of care along MM care continuum. We also highlighted the substantial economic burden associated with MM care, in spite of the disease having low prevalence as compared to some of the other cancers. Findings on the economic burden of MM, its lifetime and phase-specific costs, and drivers of cost in each phase of MM care can aid policy discussions regarding MM care and

coverage. It can also be used to help design bundled payment models specific to MM (Kline et al. 2017).

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APPENDIX A

Table 2.1 – Clinical and sociodemographic characteristics of elderly NDMM patients and matched elderly non-cancer beneficiaries enrolled in Medicare, 2006-2016

Demographic and Clinical Characteristics	Category	Non-cancer group		MM group		p
		N = 4,533		N = 4,533		
Living in urban areas (n, %)	No	313	6.9%	524	11.6%	<0.001
	Yes	4,220	93.1%	4,009	88.4%	
Geographical region (n, %)	Northeast	768	16.9%	954	21.0%	<0.001
	South	941	20.8%	1,231	27.2%	
	Midwest	424	9.3%	575	12.7%	
	West	2,400	53.0%	1,773	39.1%	
Gender (n, %)	Male	1,837	40.5%	2,159	47.6%	<0.001
	Female	2,696	59.5%	2,374	52.4%	
Race (n, %)	White	3,253	71.8%	3,418	75.4%	<0.001
	African American	332	7.3%	663	14.6%	
	Hispanic	230	5.1%	130	2.9%	
	Other	718	15.8%	322	7.1%	
Charlson Comorbidity Index score category (n, %)	0	1,567	34.6%	1,156	25.5%	<0.001
	1	937	20.7%	964	21.3%	
	2	586	12.9%	709	15.6%	
	3+	1,443	31.8%	1,704	37.6%	
Age category (n, %)	66-69	2,046	45.1%	942	20.8%	<0.001
	70-74	793	17.5%	1,278	28.2%	
	75-79	504	11.1%	983	21.7%	
	80-84	424	9.4%	740	16.3%	
	85+	766	16.9%	590	13.0%	
Disability status (n, %)	No	3,460	76.3%	3,668	80.9%	<0.001
	Yes	1,073	23.7%	865	19.1%	
Death (n, %)	No	2,460	54.3%	2,460	54.3%	-
	Yes	2,073	45.7%	2,073	45.7%	

Table 2.2 – Unadjusted comparisons between elderly NDMM and non-cancer Medicare beneficiaries on lifetime costs, and phase-specific costs (3 month terminal phase), 2007-2016

Cost Type (PMPM)	MM group (in US $)		Non-cancer group (in US$)		p
	Mean	Std. Dev	Mean	Std. Dev	
Disease Lifetime	212,474.7	149,539.6	54,085.6	78,265.3	<0.001
Pre-diagnosis Phase	2,080.9	3,971.0	1,566.8	4,601.3	<0.001
Outpatient	790.6	1,022.6	395.6	821.6	<0.001
Inpatient	896.0	3,244.4	733.4	3,946.9	<0.001
Part D	292.2	658.2	268.6	465.6	0.124
Other	102.1	416.4	169.3	696.9	0.643
Initial Phase	10,384.5	9,108.2	1,618.2	4,177.1	<0.001
Outpatient	3,976.7	3,122.5	431.8	953.1	<0.001
Inpatient	3,685.2	6,936.0	692.5	3,365.9	<0.001
Part D	2,369.3	3,259.9	284.6	590.0	<0.001
Other	353.3	726.2	209.4	831.9	<0.001
Continuing Care Phase	6,082.8	5,582.0	1,495.0	3,096.5	<0.001
Outpatient	1,997.7	2,045.7	383.2	784.7	<0.001
Inpatient	1,270.1	3,315.8	667.4	2,305.8	<0.001
Part D	2,566.9	3,141.5	237.1	436.2	<0.001
Other	248.1	655.7	207.4	690.1	<0.001
Terminal Phase	14,417.0	11,572.1	8,853.1	13,575.5	<0.001
Outpatient	3,424.2	3,180.1	1,404.0	2,021.7	<0.001
Inpatient	7,845.3	9,572.2	6,128.9	12,248.5	<0.001
Part D	1,846.8	3,207.5	331.2	498.4	<0.001
Other	1,300.8	1,606.8	989.0	1,641.4	<0.001

Table 2.3 - Unadjusted comparisons between elderly NDMM and non-cancer Medicare beneficiaries on lifetime costs, and phase-specific costs (8 month terminal phase), 2007-2016

Cost Type (PMPM)	MM group (in US $)		Non-cancer group (in US$)		p
	Mean	Std. Dev	Mean	Std. Dev	
Disease Lifetime	217,039.2	153,819.4	56,008.0	81,928.1	<0.001
Pre-diagnosis Phase	2,080.9	3,971.0	1,566.8	4,601.3	<0.001
Outpatient	790.6	1,022.6	395.6	821.6	<0.001
Inpatient	896.0	3,244.4	733.4	3,946.9	<0.001
Part D	292.2	658.2	268.6	465.6	0.124
Other	102.1	416.4	169.3	696.9	0.643
Initial Phase	10,023.4	8,591.0	1,443.5	4,362.3	<0.001
Outpatient	3,962.4	3,106.7	399.6	885.0	<0.001
Inpatient	3,306.9	6,276.3	606.8	3,616.4	<0.001
Part D	2,434.6	3,308.0	274.7	594.4	<0.001
Other	319.6	668.7	162.5	696.8	<0.001
Continuing Care Phase	5,787.4	4,848.5	1,220.9	2,539.2	<0.001
Outpatient	1,933.3	1,955.3	344.7	709.6	<0.001
Inpatient	1,039.8	2,311.9	487.3	1,792.8	<0.001
Part D	2,607.4	3,149.6	230.7	444.1	<0.001
Other	206.9	584.7	158.1	569.4	<0.001
Terminal Phase	11,685.1	8,243.3	5,919.0	7,431.9	<0.001
Outpatient	3,241.3	2,739.2	1,061.7	1,529.4	<0.001
Inpatient	5,354.1	6,263.5	3,679.0	6,397.3	<0.001
Part D	2,205.7	3,153.8	374.4	480.3	<0.001
Other	883.9	1,155.4	803.9	1,386.1	<0.001

Table 2.4 – Multivariable analysis between elderly NDMM and non-cancer Medicare beneficiaries on disease lifetime and phase-specific costs (3 month terminal phase), 2007-2016

Cost Type (PMPM)	MM group (mean, in US $)			Non-cancer group (mean, in US$)			Attributable to MM (mean, in US$)		
	Estimate	95% LCL	95% UCL	Estimate	95% LCL	95% UCL	Estimate	95% LCL	95% UCL
Disease Lifetime	234,001.7	232,231.7	235,870.3	49,507.2	49,132.7	49,902.5	184,494.5	183,098.9	185,967.7
Pre-diagnosis Phase	2,588.5	2,530.7	2,647.4	1,344.4	1,314.3	1,375.0	1,244.1	1,216.3	1,272.4
Outpatient	872.8	861.6	884.9	365.2	360.5	370.2	507.6	501.1	514.7
Inpatient	1,247.3	1,218.7	1,277.6	543.3	522.8	564.6	704.0	695.5	712.9
Part D	291.7	288.7	294.8	270.5	267.7	273.4	21.2	20.9	21.4
Other	182.1	174.5	189.5	152.7	146.4	158.9	29.4	28.2	30.5
Initial Phase	12,556.7	12,411.8	12,699.7	1,375.4	1,359.6	1,391.1	11,181.3	11,052.2	11,308.6
Outpatient	4,368.8	4,335.6	4,403.9	395.8	392.8	399.0	3,973.0	3,942.8	4,004.9
Inpatient	4,820.9	4,735.7	4,904.7	545.9	536.7	555.0	4,275.0	4,199.0	4,349.7
Part D	2,507.7	2,493.0	2,523.9	270.3	268.8	272.1	2,237.4	2,224.2	2,251.8
Other	867.8	839.3	894.9	146.9	142.0	151.4	720.9	697.2	743.5
Continuing Care Phase	6,967.5	6,896.9	7,041.9	1,333.5	1,320.0	1,347.7	5,634.0	5,576.9	5,694.1
Outpatient	2,165.5	2,148.7	2,183.4	364.0	361.1	367.0	1,801.5	1,787.6	1,816.4
Inpatient	1,644.7	1,623.4	1,667.5	558.0	549.6	566.9	1,086.8	1,073.8	1,100.6
Part D	2,750.6	2,736.3	2,766.1	224.8	223.6	226.1	2,525.8	2,512.6	2,540.1
Other	410.4	399.0	421.4	196.0	190.6	201.3	214.4	208.4	220.1
Terminal Phase	15,364.4	15,285.6	15,447.1	9,084.3	9,037.7	9,133.2	6,280.1	6,247.9	6,313.9
Outpatient	3,699.3	3,676.5	3,722.3	1,518.4	1,509.1	1,527.9	2,180.9	2,167.5	2,194.4
Inpatient	8,411.2	8,353.0	8,472.1	6,350.9	6,306.9	6,396.9	2,060.3	2,046.1	2,075.2
Part D	1,946.5	1,937.5	1,955.7	346.2	344.6	347.8	1,600.3	1,592.9	1,607.9
Other	1,266.9	1,257.2	1,276.0	806.2	800.0	811.9	460.7	457.3	464.1

Table 2.5 - Multivariable analysis between elderly NDMM and non-cancer Medicare beneficiaries on disease lifetime and phase-specific costs (8 month terminal phase), 2007-2016

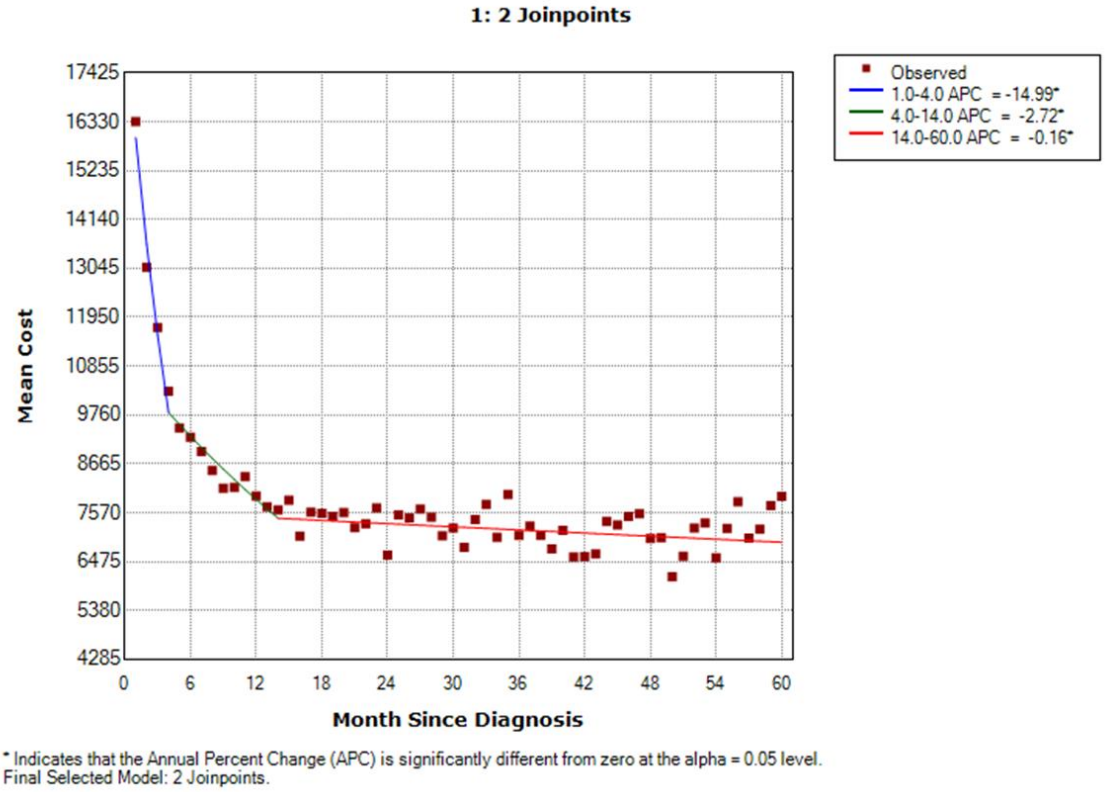
Cost Type (PMPM)	MM group (mean, in US $)			Non-cancer group (mean, in US$)			Attributable to MM (mean, in US$)		
	Estimate	95% LCL	95% UCL	Estimate	95% LCL	95% UCL	Estimate	95% LCL	95% UCL
Disease Lifetime	238,860.4	237,049.2	240,767.4	51,312.7	50,923.6	51,722.3	187,547.7	186,125.6	189,045.0
Pre-diagnosis Phase	2,588.5	2,530.7	2,647.4	1,344.4	1,314.3	1,375.0	1,244.1	1,216.3	1,272.4
Outpatient	872.8	861.6	884.9	365.2	360.5	370.2	507.6	501.1	514.7
Inpatient	1,247.3	1,218.7	1,277.6	543.3	522.8	564.6	704.0	695.5	712.9
Part D	291.7	288.7	294.8	270.5	267.7	273.4	21.2	20.9	21.4
Other	182.1	174.5	189.5	152.7	146.4	158.9	29.4	28.2	30.5
Initial Phase	12,179.4	12,045.4	12,314.1	1,282.5	1,268.4	1,296.7	10,896.9	10,777.0	11,017.4
Outpatient	4,354.4	4,322.5	4,388.5	375.6	372.9	378.6	3,978.8	3,949.6	4,009.9
Inpatient	4,378.2	4,300.5	4,453.7	503.5	495.1	511.6	3,874.7	3,805.3	3,942.1
Part D	2,584.1	2,568.3	2,601.0	264.0	262.4	265.7	2,320.1	2,305.9	2,335.3
Other	875.2	846.2	903.3	121.9	117.8	125.8	753.3	728.3	777.4
Continuing Care Phase	6,597.5	6,527.3	6,668.8	1,091.5	1,079.9	1,103.3	5,506.0	5,447.4	5,565.5
Outpatient	2,106.1	2,090.0	2,122.9	332.6	330.0	335.2	1,773.5	1,760.0	1,787.7
Inpatient	1,321.9	1,302.2	1,342.5	351.7	344.9	358.7	970.2	957.3	983.8
Part D	2,830.2	2,814.4	2,846.7	218.7	217.5	220.0	2,611.5	2,596.9	2,626.8
Other	351.7	342.5	360.8	156.0	151.9	160.0	195.7	190.6	200.8
Terminal Phase	12,362.5	12,304.2	12,422.4	5,927.8	5,899.8	5,956.5	6,434.8	6,404.4	6,465.9
Outpatient	3,481.7	3,460.7	3,503.4	1,108.1	1,101.5	1,115.0	2,373.6	2,359.2	2,388.3
Inpatient	5,720.6	5,682.9	5,759.0	3,792.6	3,768.2	3,817.4	1,928.0	1,914.6	1,941.6
Part D	2,315.2	2,305.1	2,325.9	393.2	391.4	395.0	1,922.0	1,913.7	1,930.9
Other	852.9	844.8	860.3	617.0	611.2	622.4	235.9	233.6	237.9

Table 2.6 Joinpoint regression estimates for identifying duration of initial and terminal phases of care among elderly NDMM patients who died during 2007-2016

Outcome	Joinpoint	Estimate	95% LCL	95% UCL	MPC (95% CI)	p
Initial Phase	1	4	3	6	15.0 (12.2-17.7)	<0.001
	2	14	10	19	2.7 (2.0-3.4)	<0.001
Terminal Phase	1	3	3	5	20.8 (17.3-24.1)	<0.001
	2	8	7	11	6.9 (5.4-8.4)	<0.001
	3	34	26	45	1.2 (1.1-1.4)	<0.001

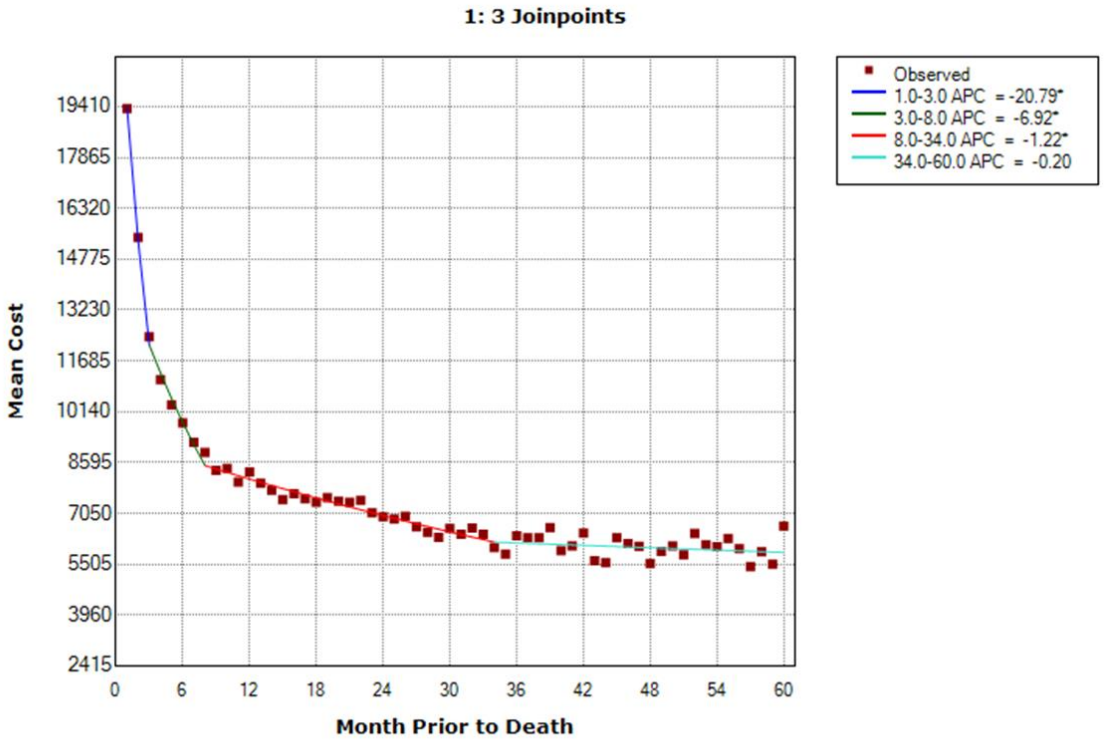
APPENDIX B

Figure 2.1 – Joinpoint regression for initial phase



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 2 Joinpoints.

Figure 2.2 – Joinpoint regression for terminal phase



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 3 Joinpoints.

CHAPTER 4: PAPER 3

End-of-Life Care in Multiple Myeloma – Trends, and Impact of Palliative Care

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by abnormal growth of clonal plasma cells. More than 10,000 people die from MM each year in the United States (US), with an estimated 12,770 deaths reported in 2018 (Siegel, Miller, and Jemal 2018). Even though MM treatment has advanced significantly in the past two decades, MM still remains incurable. With deaths from MM rising every year, an increasing number of MM patients find themselves at the end of their life each year. As per the National Quality Forum (NQF), end-of-life (EOL) care is defined as "comprehensive care for life-limiting illnesses that meets the patient's medical, physical, psychological, spiritual, and social needs" (National Quality Forum 2012).

EOL costs impose a significant burden on payers, patients, and society. It is very important to appropriately manage EOL care in order to ensure that patients receive medical care that is of high quality and cost-effective at the same time. A Medicare analysis revealed that even though around 5% of the beneficiaries die each year, they account for around 30% of total Medicare expenditures, and around 33% of costs incurred in the last year of life are attributable to the last month before death (Emanuel et al. 2002). Empirical evidence suggests that cancer patients often receive cost-intensive aggressive medical care before death, even when it may be

of little clinical value and can negatively affect their quality of life (Bekelman et al. 2016; Tangka et al. 2015; Langton et al. 2016; Zhang et al. 2009; Garrido et al. 2015); and cancer patients who die from cancer incur greater healthcare expenditures at EOL as compared to non-cancer patients or cancer patients who die from other reasons (Tangka et al. 2015; Langton et al. 2016). However, aggressive medical care before death is neither beneficial from a clinical perspective nor from a humanistic point of view. A study conducted across several cancer care centers across the US revealed that higher treatment costs in the last week of death was associated with poorer quality of life among patients with advanced cancer (Zhang et al. 2009). Incorporating palliative care into clinical disease management of cancer patients nearing their EOL is an effective technique for providing high quality, cost-effective care and has been shown to improve EOL cancer care outcomes, such as overall survival and quality of life, and early palliative care has been associated with use of less aggressive medical care at EOL (Perone, Riall, and Olino 2016; Temel et al. 2010; Howie and Peppercorn 2013; Schenker and Arnold 2017; Ferrell et al. 2017).

However, it has been reported that patients with hematological malignancies, including MM, receive aggressive cancer-related care near death and have lower use of palliative care and hospice services as compared to patients with solid tumors (Earle et al. 2008; Ho et al. 2011; Hui et al. 2012; Sexauer et al. 2014; Tang et al. 2009; Cheng et al. 2005). For example, one study reported that the proportion of patients receiving palliative care was only 18% for hematologic malignancies as compared to 44% for solid tumors (Hui et al. 2012). A retrospective cohort study that compared patients with hematologic and solid cancers on a NQF and American Society of Clinical Oncology (ASCO) endorsed measure of quality of EOL care for aggressiveness of care found that patients with hematologic cancers have significantly higher

rates for all aggressiveness of care indicators than patients with solid cancers. It also reported hematologic cancer patients to have higher targeted therapy use and lower use of palliative care services as compared to solid cancer patients (Hui et al. 2014). The difference in quality of EOL care between hematologic cancers and solid cancers can be attributed to a variety of reasons. One of the major barriers towards inception of EOL care among patients with hematologic cancers is lack of clarity on onset of EOL. This problem is compounded by the availability of treatments in advanced stages and the rapid decline of patient's health near death (Fadul et al. 2008). Other factors that have been reported as barriers to quality of EOL care among patients with hematologic cancers include unrealistic patient expectations and difficulties in conducting EOL discussions with patients (Odejide et al. 2014).

The treatment landscape in MM has seen a drastic change for the past two decades with the advent of stem cell transplant and novel agents. While patients with MM are living longer, the burden of the disease and side effects of the treatments often lead to high symptom burden. Studies have reported high prevalence of pain, fatigue and drowsiness among MM patients (Snowden et al. 2011; Porta-Sales et al. 2015; Niscola et al. 2007). This underlines the need for holistic assessment of MM patients and compliment cancer-directed treatment with palliative care, as evidenced by supportive care guidelines in MM (Snowden et al. 2011). A retrospective study that assessed the effectiveness of early palliative care among MM patients demonstrated significant improvements in pain control, in addition to reduction in physical and emotional symptom burden (Porta-Sales et al. 2017).

While a few studies have assessed trends in EOL care in hematologic malignancies in general, no study has yet assessed trends in EOL care among MM patients. Similarly, there is very limited evidence on the impact of palliative care services on quality of care, healthcare

utilization, and costs at EOL. Given the changing landscape of MM treatment and the significant symptom burden associated with the disease, assessing trends in quality of EOL care among MM patients will significantly contribute to the body of literature in MM, and help policy makers and medical decision makers aim tailored intervention programs to improve quality of EOL care. Moreover, an assessment of impact of palliative care consultation on quality of EOL care, healthcare utilization and costs will add to the evidence base on palliative care in MM, and could be used by clinicians and policy makers to better integrate palliative with routine MM care. In the current study, we aimed to assess trends in EOL care, and the impact of palliative care consultations on quality of care, healthcare utilization and costs at EOL among elderly newly diagnosed MM patients.

Methods

Data Source and Study Design

A retrospective analysis was conducted using National Cancer Institute's (NCI) SEER database linked with Medicare administrative claims database. The NCI's SEER program is an epidemiologic surveillance system that contains data collected from population-based tumor registries and was designed to track cancer incidence and mortality in the US. It includes clinical and demographic information in addition to information on cause of death for people with cancer, and is collected from 18 participating cancer registries across the US. Medicare is a federally administered health insurance program which covers elderly Americans who are 65 years of age or older, as well as younger patients with disabilities and end-stage renal disease (ESRD). The Medicare administrative claims database provides information on claims for covered healthcare services for beneficiaries enrolled in Medicare. The SEER-linked Medicare

claims database provides patient-level data for Medicare beneficiaries with cancer (Warren et al. 2002).

The current study utilized 2007-2015 SEER data linked with 2006-2016 Medicare claims data. The SEER data consists of the Patient Entitlement and Diagnosis Summary File (PEDSF) that includes clinical, demographic, and Medicare enrollment information for individuals with cancer. The Medicare claims data consists of the Medicare Provider Analysis and Review (MEDPAR), National Claims History (NCH), Outpatient (OUTPT), Home Health Agency (HHA), Hospice, Durable Medical Equipment (DME), and Prescription Drug Event (PDE) files. The MEDPAR file contains all Medicare Part A claims indication short stay, long stay, skilled nursing facility (SNF) stays as well as International Classification of Diseases, ninth revision (ICD-9) or International Classification of Diseases, tenth revision (ICD-10) diagnoses and procedures performed during each stay. The NCH file contains all Medicare Part B claims generated due to physician or supplier services in clinics and hospitals, whereas the OUTPT file contains all Medicare Part B claims outpatient providers. Both NCH and OUTPT files were used to obtain information such as procedural Healthcare Common Procedure Coding System (HCPCS) codes, diagnoses, date of claims, treatment administration, and reimbursement amounts. The HHA file contains claims for all home health care services such as number and types of visits and diagnoses. The hospice file contains claims submitted by hospice providers, and has details on type of care (inpatient care, routine home care) as well as terminal diagnosis associated with that care. The DME file contains claims with information on use of oral and intravenous chemotherapy, and infusion pumps used. The PDE file contains information about drug utilization such as, date of prescription fill, drug dispensed, quantity dispensed, days

supplied, total cost, and out-of-pocket cost. The Institutional Review Board (IRB) at the University of Mississippi has approved the study.

Study sample

This study included Medicare beneficiaries who entered the SEER registry from 2007 through 2015, and were diagnosed with MM as their primary cancer. All beneficiaries with primary MM will be identified based on the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) code of MM (9732). The last month of a MM patient's life was considered as the EOL period. MM patients needed to be 66 years of age or older at the time of death, died during the study period (2007-2016), and have continuous enrollment in Medicare Parts A, B and D in the 12 months prior to the EOL period to be included in the study. MM patients were excluded from the study sample if they had an unknown diagnosis month or year, had a missing date of death, or if MM diagnosis was made at the time of death or within 30 days of date of death. Moreover, MM patients were excluded from the study sample if they ever had a diagnosis for any other type of cancer, or if they were enrolled in a health maintenance organization (HMO) in the 12-month period prior to the EOL period.

All MM patients included in the study sample were assigned to the palliative care consultation (PCC) cohort or non-PCC cohort based on whether they had a consultation for palliative care in the 12-month period prior to death. PCC visits were identified using the ICD-9 and ICD-10 codes of V66.7 and Z51.5 respectively. For MM patients with multiple PCC visits, the first such visit was considered and, was referred to as index PCC.

Outcome Measures

The key outcomes of interest were EOL care outcomes, healthcare resource utilization, and healthcare costs during EOL. EOL care outcomes included the following 6 NQF/ASCO indicators (Hui et al. 2014; Earle et al. 2003) in the EOL period: > 1 emergency department visit, > 1 hospital admission, > 14 days of hospitalization, an intensive care unit (ICU) admission, death in a hospital, and use of chemotherapy in the last 14 days of life. Additionally, we assessed a composite aggressiveness of EOL care measure, which was determined based on the presence of at least one of the 6 NQF/ASCO indicators. Consistent with previous research, ICU admission will be defined as presence of one or more of the following in the EOL period: ICU indicator code, intensive care day count of 1 or more, and procedure codes for continuous invasive mechanical ventilation, or cardiopulmonary resuscitation, or insertion of feeding tubes (Accordino et al. 2016; Quan, Parsons, and Ghali 2004; Cooke et al. 2014; Morden et al. 2012).

Furthermore, we assessed all-cause healthcare resource utilization and healthcare costs at the EOL. Resource utilization included number of ICU admissions and ER visits. We considered payments made by Medicare when calculating healthcare costs. All cost estimates were adjusted to 2016 US dollars.

Covariates

Study covariates included patient demographic and clinical characteristics at baseline (i.e., prior to beginning of the EOL period). Baseline demographic covariates included age, sex, race, urban residency, geographical region, and marital status. Baseline clinical covariates included comorbidity, and disability status. Comorbidity was assessed using the Deyo adaption of the Charlson Comorbidity Index (CCI) (Deyo, Cherkin, and Ciol 1992). Disability status was

defined as a binary variable based on a claim-based algorithm during the 12-month baseline period prior to beginning of the EOL period (Davidoff et al. 2010; Griffiths et al. 2011; Williams et al. 2015). It was based on claims for one or more of the following – hospice care, home health agency, skilled nursing facility, oxygen use, wheelchair use, and walking aid, and was combined into a score of 0 (none) or 1 (use of any service). Moreover, months of survival post MM diagnosis was included as a covariate in the study.

Data Analysis

Propensity score matching was employed to account for covariate imbalance at baseline between the PCC and no PCC cohorts. A 1:1 match without replacement was performed based on the patients' propensity to have a PCC visit. Logistic regression was employed to obtain the propensity scores, and was modeled on age, urban residency, geographical region, gender, race, marital status, disability status, and CCI score. Mean standardized differences were used to assess covariate imbalance between the two cohorts post propensity score matching. A standardized difference less than 0.1 indicates negligible differences between the cohorts (Austin 2011).

Descriptive statistics were used to depict baseline patient characteristics, aggressiveness of EOL care outcomes, healthcare resource utilization and costs at EOL. For categorical variables, frequency and percentage distributions were reported. Statistical comparisons were conducted between cohorts using McNemar's test or Cochrane-Mantel-Haenszel test, to account for the matched data. For continuous variables, mean, standard deviation (SD), median, and range were reported. Statistical comparisons for continuous variables were conducted using paired t-tests. For unadjusted healthcare costs at EOL, Wilcoxon signed rank test were used to test for significance between the cohorts.

The Cochran-Armitage trend test were employed to evaluate the change in proportion of elderly MM patients over time (2007 – 2016) for the following outcomes - 6 ASCO/NQF quality of EOL care indicators, and composite aggressiveness of EOL care outcome. Results from the trend test were confirmed with Joinpoint regression analysis (Kim et al. 2000) for each of the ASCO/NQF quality of EOL care indicators and the composite aggressiveness of EOL care outcome. Separate conditional logistic regression models were used to compare the ASCO/NQF EOL quality of care indicators and the composite aggressiveness of EOL care outcome between the PCC and no PCC cohorts, accounting for matching between the cohorts. All of the models were run controlling for months of survival post MM diagnosis and any other covariate that had a non-negligible mean standardized difference (greater than 0.1).

Generalized linear models with log link and poisson distribution was employed to compare all-cause healthcare resource utilization at EOL between the PCC and no PCC cohorts, controlling for months of survival post MM diagnosis and any covariate with a non-negligible standardized mean difference. Generalized linear models with log link and gamma distribution was employed to compare all-cause healthcare cost at EOL between the PCC and no PCC cohorts, controlling for months of survival post MM diagnosis and any covariate with a non-negligible standardized mean difference. For all the cost and count models, recycled prediction technique was used to assess the incremental impact of PCC on healthcare use and costs, to account for covariate imbalance (A. Basu and Rathouz 2005; Anirban Basu, Polsky, and Manning 2011). For this technique, the outcome was first predicted assuming every recipient to be in the no PCC group, and then the outcome was again predicted assuming every recipient to be in the PCC group. The incremental impact was then assessed by calculating the difference

between the predicted outcomes for the PCC and no PCC groups. Percentile bootstrapping with 1000 replications was conducted to compute the 95% Confidence Interval (CI) for each outcome.

Separate subgroup analyses were conducted for all multivariable analyses – one for MM patients that had their first PCC visit prior to EOL period (early PCC) compared to those without any PCC visits, and another for MM patients that had their first PCC visit in the EOL period (late PCC) versus those who did not have any PCC visits. All data management and analysis were done using National Cancer Institute's Joinpoint regression software, SAS version 9.4, and STATA 15.

Results

5,151 elderly MM patients who died during the study period met the study inclusion and exclusion criteria. The sample characteristics are presented in Table 3.1. Most of the elderly MM patients in the sample lived in urban areas (89.1%), were white (73.7%), had a CCI score of 3 or more (72.4%), had disability (70.7%), and did not have any PCC visits (68.8%). Additionally, majority of the MM patients in the sample were female (51.2%), 75 years old or older (66.8%), and resided in the western or southern (67.2%) region of the US. Moreover, majority of the MM patients in the sample were either married (47.4%) or widowed (27.2%) at the time of MM diagnosis.

Tables 3.2.1-3.2.4 depicts results of the univariate trend analysis for proportion of elderly MM patients that had greater than one ED visit, greater than 14 days of inpatient stay, greater than one inpatient admission, and ICU stay in the EOL period respectively, from 2007 to 2016. Additionally, results of the univariate trend analysis for proportion of elderly MM patients that had death in hospital, chemotherapy use in the last 14 days of life, and any aggressive EOL care

in the EOL period from 2007 to 2016 are presented in Table 3.2.5, Table 3.2.6, and Table 3.2.7, respectively. As per results of the Cochrane-Armitage trend test, there was statistically significant increase in the proportion of elderly MM patients with greater than one ED visits in the EOL period ($p = 0.017$), and ICU stay in the EOL period ($p = 0.005$), between 2007 and 2016. Moreover, statistically significant decrease was seen in the proportion of elderly MM patients with greater than 14 days of inpatient stay in the EOL period ($p = 0.004$), and death in hospital ($p<0.001$) between 2007 and 2016. No statistically significant change was observed in the proportion of elderly MM patients with greater than one inpatient admission in the EOL period ($p=0.113$), chemotherapy use in the last 14 days of life ($p=0.060$), and any aggressive EOL care ($p=0.703$) between 2007 and 2016.

Trend analysis results obtained from the Cochrane-Armitage trend tests were confirmed using Joinpoint regression analysis. Table 3.2.8 presents trend test results from the Joinpoint regression analysis, and Figures 3.1-3.6 depict the trends in proportion of elderly MM patients with greater than one ED visit, greater than 14 days of inpatient stay, greater than one inpatient admission, ICU stay, death in hospital, and any aggressive EOL care in the EOL period between 2007 and 2016 respectively. As we can see, the linear trends reported in the Cochrane-Armitage trend tests were confirmed by the Joinpoint regression analysis. We could not conduct a Joinpoint regression analysis to confirm the results of the Cochrane-Armitage trend test for the proportion of elderly MM patients that had chemotherapy use in the last 14 days of life over time, since there were no patients with chemotherapy use in the last 14 days of life in certain years.

For assessing the impact of PCC on aggressiveness of EOL care outcomes, healthcare resource utilization at EOL, and costs at EOL, 1,588 elderly MM patients with any PCC prior to

death were matched on age, urban residency, geographical region, gender, race, marital status, disability status, and CCI score to 1,588 elderly MM patients without any PCC. Table 3.3.1 presents the descriptive characteristics for the any PCC and no PCC cohorts. As seen in Table 3.3.1, the standardized mean difference was negligible between the two cohorts for all covariates included in the propensity score (P-S) matched model. The two cohorts were significantly different on months of survival post MM diagnosis [27 months (median) of survival post MM diagnosis in the any PCC group vs 18 months (median) of survival post MM diagnosis in the no PCC group; $p < 0.001$].

For the subgroup analysis between the late PCC and no PCC cohorts, 1,074 elderly MM patients with late PCC (first PCC visit in the EOL period) were matched to 1,074 elderly MM patients without any PCC. Table 3.3.2 presents the descriptive characteristics for the late PCC and no PCC cohorts. As seen in Table 3.3.2, the standardized mean difference was negligible between the two cohorts for all covariates included in the P-S matched model. The two cohorts were significantly different on months of survival post MM diagnosis [27 months (median) of survival post MM diagnosis in the late PCC group vs 18 months (median) of survival post MM diagnosis in the no PCC group; $p < 0.001$]. Additionally, the two cohorts were significantly different on disability at baseline (64% in the late PCC group vs 67% in the no PCC group, $p = 0.046$).

For the subgroup analysis between the early PCC and no PCC cohorts, 514 elderly MM patients with early PCC (first PCC visit prior to beginning of the EOL period) were matched to 514 elderly MM patients without any PCC. Table 3.3.3 presents the descriptive characteristics for the early PCC and no PCC cohorts. As seen in Table 3.3.3, the standardized mean difference was negligible between the two cohorts for all the covariates included in the P-S matched model,

except for disability at baseline (standardized mean difference = 0.113). The two cohorts were significantly different on months of survival post MM diagnosis [26 months (median) of survival post MM diagnosis in the early PCC group vs 18 months (median) of survival post MM diagnosis in the no PCC group; p = 0.001]. Additionally, the two cohorts were significantly different on disability at baseline (88% in the early PCC group vs 84% in the no PCC group, p = 0.003).

Results of the unadjusted analysis between the any PCC and no PCC cohorts on aggressiveness of EOL care outcomes, healthcare resource utilization at EOL, and costs at EOL is presented in Table 3.4.1. As compared to the no PCC group, the any PCC group had significantly greater proportion of patients with greater than 1 ED visits (p<0.001), greater than 14 days of inpatient stay (p = 0.005), greater than 1 inpatient admission (p<0.001), ICU stay (p<0.001), death in hospital (p<0.001), and any aggressive EOL care (p<0.001). Moreover, as compared to the no PCC group, the any PCC group had higher healthcare resource utilization at EOL (p<0.001), and higher cost at EOL (p<0.001).

Results of the unadjusted analysis between the late PCC and no PCC cohorts on aggressiveness of EOL care outcomes, healthcare resource utilization at EOL, and costs at EOL is presented in Table 3.4.2. As compared to the no PCC group, the late PCC group had significantly greater proportion of patients with greater than 1 ED visits (p<0.001), greater than 14 days of inpatient stay (p<0.001), greater than 1 inpatient admission (p<0.001), ICU stay (p<0.001), death in hospital (p<0.001), and any aggressive EOL care (p<0.001). Moreover, as compared to the no PCC group, the any PCC group had higher healthcare resource utilization at EOL (p<0.001), and higher cost at EOL (p<0.001).

Results of the unadjusted analysis between the early PCC and no PCC cohorts on aggressiveness of EOL care outcomes, healthcare resource utilization at EOL, and costs at EOL is presented in Table 3.4.3. As compared to the no PCC group, the early PCC group had significantly lower proportion of patients with greater than 1 ED visits ($p=0.022$), greater than 14 days of inpatient stay ($p=0.002$), greater than 1 inpatient admission ($p=0.001$), ICU stay ($p<0.001$), death in hospital ($p<0.001$), and any aggressive EOL care ($p<0.001$). Moreover, as compared to the no PCC group, the any PCC group had lower healthcare resource utilization at EOL ($p<0.001$), and lower cost at EOL ($p<0.001$).

Table 3.5 depicts results of the conditional logistic regression analysis between the any PCC and no PCC groups on aggressiveness of EOL care outcomes (>1 ED visit, inpatient LOS > 14 days, >1 inpatient admission, ICU stay, death in hospital, any aggressive EOL care), controlling for months of survival post MM diagnosis. As compared to the no PCC group, MM patients in the any PCC group had greater odds for all the aggressiveness of EOL care outcome [>1 ED visits: Odds Ratio (OR):1.4, 95% Confidence Interval (CI): 1.2-1.7; inpatient LOS >14 days: OR: 1.3, 95% CI: 1.1-1.5; >1 inpatient admissions: OR: 1.5, 95% CI: 1.3-1.8; ICU stay: OR: 1.7, 95% CI: 1.5-2.0; and death in hospital: OR: 1.5, 95% CI:1.3-1.8], and the composite outcome of any aggressive care in EOL [OR: 1.9, 95% CI: 1.6-2.2]. Subgroup analyses showed that, after controlling for months of survival post MM diagnosis and disability at baseline, MM patients in the late PCC group had greater odds for all aggressiveness of EOL care outcomes [>1 ED visits: OR:1.9, 95% CI: 1.5-2.3; inpatient LOS >14 days: OR: 1.7, 95% CI: 1.4-2.1; >1 inpatient admissions: OR: 2.0, 95% CI: 1.7-2.5; ICU stay: OR: 2.8, 95% CI: 2.2-3.3; and death in hospital: OR: 2.2, 95% CI:1.8-2.7], and the composite outcome of any aggressive EOL care [OR: 4.2, 95% CI: 3.3-5.3] than their matched no PCC group counterparts. However, MM patients in

the early PCC group had lower odds for all aggressiveness of EOL care outcomes [>1 ED visits: OR:0.7, 95% CI: 0.5-0.9; inpatient LOS >14 days: OR: 0.6, 95% CI: 0.4-0.8; >1 inpatient admissions: OR: 0.6, 95% CI: 0.4-0.8; ICU stay: OR: 0.5, 95% CI: 0.4-0.7; and death in hospital: OR: 0.6, 95% CI:0.4-0.8], and the composite aggressive EOL care outcome [OR: 0.5, 95% CI: 0.4-0.6] than those in no PCC group. Conditional logistic regression models could not be run for the chemotherapy use in the last 14 days of life outcome, due to low event rate and model convergence issues.

Results of the multivariable analysis for assessing incremental healthcare resource use at EOL and costs at EOL are presented in Table 3.6. After controlling for months of survival post MM diagnosis, the any PCC group had significantly greater healthcare resource utilization at EOL (incremental difference: 0.33, 95% CI: 0.33, 0.34) and costs at EOL (incremental difference: $5,315, 95% CI: $5,309, $5,323) as compared to the no PCC group. Subgroup analyses showed that, after controlling for months of survival post MM diagnosis and disability, the late PCC group had significantly greater healthcare resource utilization at EOL (incremental difference: 0.66, 95% CI: 0.65, 0.67) and costs at EOL (incremental difference: $10,272, 95% CI: $10,230, $10,311) than the no PCC group. However, controlling for months of survival post MM diagnosis and disability, the early PCC group had significantly lower healthcare resource utilization at EOL (incremental difference: 0.35, 95% CI: 0.34, 0.35) and costs at EOL (incremental difference: $4,846, 95% CI: $4,818, $4,872) than the no PCC group.

Discussion

MM treatment has seen a paradigm shift in the past few decades, and the availability of several immunotherapies has prolonged survival among patients with MM (Cowan et al. 2018; Lehners et al. 2018; Donk and Lokhorst 2013). This is the first study to assess trends in EOL care using a

population-based cohort of elderly MM patients. Results from this study will help understand the general trend of EOL care among elderly MM patients, and inform intervention programs designed to improve quality of EOL care. Additionally, this is also the first study to assess the impact of palliative care consultations on the aggressiveness of EOL care, healthcare resource utilization and healthcare costs at EOL. This information could help clinicians and policy makers in developing policies and interventions aimed towards improving integration of early palliative care with routine MM care.

Our findings about the trends in aggressive EOL care, among elderly MM patients, from 2007 to 2016 are consistent with previous studies that have assessed trends in the aggressiveness of EOL care in other cancer types. A SEER-Medicare analysis of elderly uterine cancer patients reported that there was no significant difference in trend of any aggressive EOL care, inpatient admission in the EOL period, and chemotherapy use over time (Margolis et al. 2017). Another study that examined trends in aggressiveness of EOL among Medicare beneficiaries with cancer found that there was a significant increase in the proportion of beneficiaries with more than one ED visit at EOL and at least one ICU stay over time (Wang et al. 2016). Similar to our findings, it also reported a decrease in proportion of beneficiaries that died in hospital over time, and did not find any significant difference in trends of chemotherapy in the EOL period over time (Wang et al. 2016). A Canadian analysis of trends in aggressiveness of EOL care among cancer patients also reported similar results, with there being a decline in proportion of patients with multiple inpatient admission at EOL over time, and an increasing trend for proportion of patients with multiple ED visits at EOL, and EOL ICU admissions (Ho et al. 2011).

Additionally, we found that compared to MM patients who had no PCC visits, having PCC at any time prior to death is associated with greater odds of receiving aggressive EOL care

(41% to 86% greater odds), higher healthcare resource utilization at EOL, and higher costs at EOL. While these results may seem to contradict with our expectations, it is not surprising considering the fact that almost 70% of the patients in our sample that had a PCC visit had late PCC (i.e., in the last 30 days prior to death). Our subgroup analysis found that those who had a late PCC visit had even greater odds of receiving aggressive EOL care (89% to 317% greater odds) than those who did not have a PCC visit. Furthermore, MM patients who had a late PCC visit had much higher healthcare resource use and costs at EOL (the incremental difference being twice as high as that for the any PCC vs no PCC comparison) as compared to those who did not have a PCC visit. This is potentially because patients who had a late PCC visit were sicker than those that did not have a PCC visit and are more likely to be cared for in the ED and ICU (Bhulani et al. 2018) where PCC may have been preferentially made to these patients who were sicker and had higher symptom burden. Previous studies have found that patients with hematologic malignancies are usually referred for PCC later than those with solid tumors (Boyce, McHugh, and Lyon 2003; Delgado-Guay et al. 2009; Zimmermann et al. 2013), and symptom relief is usually the major reason for PCC referrals in patients with hematologic cancers (Corbett et al. 2013; Auret, Bulsara, and Joske 2003; Albrecht and Rosenzweig 2012). Our findings are similar to that of a previous study that assessed the impact of PCC on healthcare resource use and costs among elderly pancreatic cancer patients in the US, and reported that having a PCC was not associated with reduced healthcare resource use and costs at EOL (Bhulani et al. 2018).

However, we found from our subgroup analysis between those who had early PCC visits (i.e, first PCC visit prior to beginning of the EOL period) and no PCC visits that having an early PCC visit was associated with significantly lower odds for all aggressiveness of EOL care

outcomes than those who did not have a PCC visit. Moreover, those who had an early PCC visit had significantly lower healthcare resource use and costs at EOL as compared to those who did not have a PCC visit. These results highlight the benefits of early palliative care consultation among elderly MM patients, and its potential to help avoid unnecessary treatment and inappropriate care at EOL. Our findings are consistent with that of previous studies. Controlled, prospective studies have reported reduced healthcare resource utilization and costs for patients that have undergone early palliative care (Brumley et al. 2007; Siderow, Silvers, and Meier 2016). Another study, among women with gynecologic cancers, reported early palliative care to be associated with a reduction in aggressive EOL care and costs (Nevadunsky et al. 2014). Additionally, other studies have found early palliative care to be associated with lower likelihood of dying in hospital (Poulose, Do, and Neo 2013) and aggressive treatment in the EOL period (Jang et al. 2015). An early palliative care intervention program for MM patients, conducted in Spain, found it to improve patient's general activity, sleep, mood, in addition to reductions in their symptom burden (Porta-Sales et al. 2017).

Our study has several strengths. First, we used a population-based cohort of elderly MM patients to assess trends in receiving aggressive EOL care over time. Several studies have reported cancer patients to receive high cost, aggressive care in the period prior to death, even though current evidence suggests that such care does not provide much clinical value and often affects their quality of life negatively (Bekelman et al. 2016; Tangka et al. 2015; Langton et al. 2016; Zhang et al. 2009; Garrido et al. 2015). These real-world results can help inform interventions targeted towards reducing aggressive EOL care among MM patients. Additionally, this is the first study to assess the impact of PCC on aggressive EOL care outcomes, and healthcare resource use and costs at EOL. Results from this study can help policy makers design

interventions targeted towards incorporating early palliative care among MM patients, in order to help reduce unnecessary healthcare resource use and costs at EOL.

However, our study results need to be considered in light of certain limitations. First, this study only included MM patients who were 66 years old or older at the time of death. Thus, our results may not be generalizable to younger people. Nevertheless, since the median age at diagnosis of MM is 69, and around 2/3rd of all MM patients are diagnosed at the age of 65 or older, our study sample is likely to be representative of the population of MM patients. Second, the analysis was limited to MM patients enrolled in fee-for-service Medicare. Hence, our results are not generalizable to elderly MM patients enrolled in Medicare managed care organizations. Future studies should examine whether MM patients enrolled in Medicare managed care plans had similar results. Third, coding errors in claims data might bias our study results. Fourth, we lack information on patient functional status, and their symptom burden, namely, pain and fatigue, which are very common amongst MM patients as they approach end of life (Snowden et al. 2011; Porta-Sales et al. 2015; Niscola et al. 2007). Future studies should consider accounting for patients' performance and symptom burden, if possible, to assess the impact of palliative care consultations on receiving aggressive EOL care, and healthcare resource use and costs at EOL.

Conclusion

Our study used a population-based cohort of elderly MM patients to assess trends in aggressiveness of EOL care outcomes over time. While certain indicators of aggressive EOL care remained stable over time, we observed an increasing trend for multiple ED visits and ICU stays. Moreover, this study assessed the impact of palliative care consultations on receiving aggressive EOL care, and healthcare resource use and costs at EOL. Results indicate that early palliative care consultations have the potential to reduce aggressive EOL care, and curtail

healthcare resource use and costs at EOL. Findings from this study can aid policy discussions and help plan interventions aimed to decreasing aggressive EOL care, and aid development and integration of early palliative care consultations in routine MM care.

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APPENDIX A

Table 3.1 Characteristics of elderly MM patients who died during 2007-2016

Demographic and Clinical Characteristics	Category	N = 5,151	
Living in urban areas (n, %)	No	564	10.9%
	Yes	4,587	89.1%
Geographical region (n, %)	Northeast	1,041	20.2%
	South	1,410	27.4%
	Midwest	647	12.6%
	West	2,053	39.8%
Gender (n, %)	Male	2,515	48.8%
	Female	2,636	51.2%
Race (n, %)	White	3,798	73.7%
	African American	848	16.5%
	Hispanic	178	3.5%
	Other	327	6.3%
Charlson Comorbidity Index score category (n, %)	0	339	6.6%
	1	476	9.2%
	2	607	11.8%
	3+	3,729	72.4%

Age category (n, %)	66-69	618	12.0%
	70-74	1,091	21.2%
	75-79	1,103	21.4%
	80-84	1,054	20.5%
	85+	1,285	24.9%
Disability status (n, %)	No	1,511	29.3%
	Yes	3,640	70.7%
Marital Status (n, %)	Single	505	9.8%
	Married	2,443	47.4%
	Separated/Divorced	477	9.3%
	Widowed	1,402	27.2%
	Other	324	6.3%
Year of Death (n, %)	2007	136	2.6%
	2008	246	4.8%
	2009	342	6.6%
	2010	418	8.1%
	2011	479	9.3%
	2012	600	11.7%
	2013	622	12.1%
	2014	784	15.2%
	2015	809	15.7%
	2016	715	13.9%
Palliative Care Consultation	No	3,542	68.8%

	Yes	1,609	31.2%
Survival Months (median, Q1-Q3)		21	6,43

Table 3.2.1 Trend in multiple ED visits during EOL among elderly MM patients who died, 2007-2016

Year of Death	> 1 ED visit (n, %)	
	No	Yes
2007	103 (75.7%)	33 (24.3%)
2008	200 (81.3%)	46 (18.7%)
2009	269 (78.7%)	73 (21.3%)
2010	336 (80.4%)	82 (19.6%)
2011	372 (77.7%)	107 (22.3%)
2012	457 (76.2%)	143 (23.8%)
2013	493 (79.3%)	129 (20.7%)
2014	602 (76.8%)	182 (23.2%)
2015	618 (76.4%)	191 (23.6%)
2016	529 (74.0%)	186 (26.0%)
Cochrane Armitage trend test: p = 0.017		

Table 3.2.2 Trend in greater than 14 days of inpatient stay during EOL among elderly MM patients who died, 2007-2016

Year of Death	> 14 days inpatient LOS (n, %)	
	No	Yes
2007	94 (69.1%)	42 (30.9%)
2008	186 (75.6%)	60 (24.4%)
2009	260 (76.0%)	82 (24.0%)
2010	319 (76.3%)	99 (23.7%)
2011	359 (75.0%)	120 (25.0%)
2012	464 (77.3%)	136 (22.7%)
2013	503 (80.9%)	119 (19.1%)
2014	601 (76.7%)	183 (23.3%)
2015	640 (79.1%)	169 (20.9%)
2016	569 (79.6%)	146 (20.4%)
Cochrane-Armitage trend test: p =0.004		

Table 3.2.3 Trend in multiple inpatient admissions during EOL among elderly MM patients who died, 2007-2016

Year of Death	> 1 inpatient admission (n, %)	
	No	Yes
2007	97 (71.3%)	39 (28.7%)
2008	189(76.8%)	57 (23.2%)
2009	261 (76.3%)	81 (23.7%)
2010	319 (76.3%)	99 (23.7%)
2011	358 (74.7%)	121 (25.3%)
2012	453 (75.5%)	147 (24.5%)
2013	491 (78.9%)	131 (21.1%)
2014	589 (75.1%)	195 (24.9%)
2015	627 (77.5%)	182 (22.5%)
2016	562 (78.6%)	153 (21.4%)
Cochrane-Armitage trend test: p = 0.113		

Table 3.2.4 Trend in ICU stay during EOL among elderly MM patients who died, 2007-2016

Year of Death	ICU stay (n, %)	
	No	Yes
2007	98 (72.1%)	38 (27.9%)
2008	178 (72.4%)	68 (27.6%)
2009	243 (71.1%)	99 (28.9%)
2010	280 (67.0%)	138 (33.0%)
2011	338 (70.6%)	141 (29.4%)
2012	417 (69.5%)	183 (30.5%)
2013	437 (70.3%)	185 (29.7%)
2014	542 (69.1%)	242 (30.9%)
2015	526 (65.0%)	283 (35.0%)
2016	467 (65.3%)	248 (34.7%)
Cochrane-Armitage trend test: p = 0.005		

Table 3.2.5 Trend in death in hospital among elderly MM patients who died, 2007-2016

Year of Death	Death in hospital (n, %)	
	No	Yes
2007	78 (57.3%)	58 (42.7%)
2008	166 (67.5%)	80 (32.5%)
2009	228 (66.7%)	114 (33.3%)
2010	274 (65.6%)	144 (34.4%)
2011	318 (66.4%)	161 (33.6%)
2012	396 (66.0%)	204 (34.0%)
2013	438 (70.4%)	184 (29.6%)
2014	534 (68.1%)	250 (31.9%)
2015	587 (72.6%)	222 (27.4%)
2016	503 (70.4%)	212 (29.6%)
Cochrane-Armitage trend test: $p < 0.001$		

Table 3.2.6 Trend in chemotherapy use in the last 14 days of life among elderly MM patients who died, 2007-2016

Year of Death	Chemo use in last 14 days of life (n, %)	
	No	Yes
2007	135 (99.3%)	1 (0.7%)
2008	246 (100%)	0 (0%)
2009	340 (99.4%)	2 (0.6%)
2010	418 (100%)	0 (0%)
2011	475 (99.2%)	4 (0.8%)
2012	592 (98.7%)	8 (1.3%)
2013	613 (98.6%)	9 (1.4%)
2014	777 (99.1%)	7 (0.9%)
2015	798 (98.6%)	11 (1.4%)
2016	709 (99.2%)	6 (0.8%)
Cochrane-Armitage trend test: p=0.060		

Table 3.2.7 Trend in any aggressive EOL care among elderly MM patients who died, 2007-2016

Year of Death	Any aggressive EOL care (n, %)	
	No	Yes
2007	54 (39.7%)	82 (60.3%)
2008	114 (46.3%)	132 (53.7%)
2009	144 (42.1%)	198 (57.9%)
2010	191 (45.7%)	227 (54.3%)
2011	217 (45.3%)	262 (54.7%)
2012	267 (44.5%)	333 (55.5%)
2013	291 (46.8%)	331 (53.2%)
2014	349 (44.5%)	435 (55.5%)
2015	366 (45.2%)	443 (54.8%)
2016	315 (44.1%)	400 (55.9%)
Cochrane-Armitage trend test: p=0.703		

Table 3.2.8 Joinpoint regression analysis for trends in aggressive EOL care outcomes among elderly MM patients who died, 2007-2016

Outcome	Model Selected	p (linear trend)
> 1 ED visits	Joinpoints: 0	0.029
Inpatient LOS > 14 days	Joinpoints: 0	0.014
> 1 Inpatient admissions	Joinpoints: 0	0.104
ICU stay	Joinpoints: 0	0.011
Death in hospital	Joinpoints: 0	0.006
Any aggressive EOL care	Joinpoints: 0	0.515

Table 3.3.1 Clinical and sociodemographic characteristics of elderly MM patients who died during 2007-2016, with and without PCC visits

Demographic and Clinical Characteristics	Category	No PCC group (n = 1,588)		PCC group (n = 1,588)		Standardized Mean Difference	p
Living in urban areas (n, %)	No	135	8.5%	146	9.2%	-0.024	0.278
	Yes	1,453	91.5%	1,442	90.8%		
Geographical region (n, %)	Northeast	362	22.8%	343	21.6%	0.044	0.173
	South	337	21.2%	347	21.8%		
	Midwest	185	11.7%	203	12.8%		
	West	704	44.3%	695	43.8%		
Gender (n, %)	Male	770	48.5%	754	47.5%	0.02	0.294
	Female	818	51.5%	834	52.5%		
Race (n, %)	White	1,187	74.7%	1,170	73.7%	0.028	0.683
	African American	251	15.8%	263	16.6%		
	Hispanic	38	2.4%	42	2.6%		
	Other	112	7.1%	113	7.1%		
Charlson Comorbidity Index score category (n, %)	0	98	6.2%	109	6.9%	0.039	0.476
	1	125	7.9%	132	8.3%		
	2	182	11.5%	189	11.9%		
	3+	1,183	74.4%	1,158	72.9%		
Age category (n, %)	66-69	210	13.2%	216	13.6%	0.041	0.228
	70-74	365	23.0%	355	22.4%		
	75-79	342	21.5%	366	23.0%		
	80-84	319	20.1%	307	19.3%		
	85+	352	22.2%	344	21.7%		
Disability status (n, %)	No	440	27.7%	444	28.0%	-0.001	0.771
	Yes	1,148	72.3%	1,144	72.0%		
Marital Status (n, %)	Single	147	9.3%	156	9.8%	0.052	0.203

	Married	797	50.2%	772	48.6%		
	Separated/Divorced	138	8.7%	155	9.8%		
	Widowed	407	25.6%	397	25.0%		
	Other	99	6.2%	108	6.8%		
Survival Months (median, Q1-Q3)		18	5,39	27	9,50	-	<0.001

Table 3.3.2 Clinical and sociodemographic characteristics of elderly MM patients who died during 2007-2016, with late PCC visit and without PCC visits

Demographic and Clinical Characteristics	Category	No PCC group (n = 1,074)		PCC group (n = 1,074)		Standardized Mean Difference	p
Living in urban areas (n, %)	No	102	9.5%	107	10.0%	-0.016	0.553
	Yes	972	90.5%	967	90.0%		
Geographical region (n, %)	Northeast	258	24.0%	234	21.8%	0.063	0.098
	South	234	21.8%	244	22.7%		
	Midwest	126	11.7%	140	13.0%		
	West	456	42.5%	456	42.5%		
Gender (n, %)	Male	551	51.3%	544	50.7%	0.013	0.581
	Female	523	48.7%	530	49.3%		
Race (n, %)	White	818	76.2%	806	75.1%	0.035	0.698
	African American	150	14.0%	163	15.2%		
	Hispanic	27	2.5%	26	2.4%		
	Other	79	7.3%	79	7.3%		
Charlson Comorbidity Index score category (n, %)	0	65	6.1%	77	7.2%	0.063	0.192
	1	96	8.9%	100	9.3%		
	2	128	11.9%	140	13.0%		
	3+	785	73.1%	757	70.5%		
Age category (n, %)	66-69	134	12.5%	145	13.5%	0.053	0.23
	70-74	255	23.7%	244	22.7%		
	75-79	246	22.9%	262	24.4%		
	80-84	222	20.7%	214	19.9%		
	85+	217	20.2%	209	19.5%		
Disability status (n, %)	No	359	33.4%	383	35.7%	-0.047	0.046
	Yes	715	66.6%	691	64.3%		
Marital Status (n, %)	Single	84	7.8%	93	8.7%	0.057	0.344

	Married	576	53.6%	553	51.5%		
	Separated/Divorced	88	8.2%	97	9.0%		
	Widowed	259	24.1%	257	23.9%		
	Other	67	6.3%	74	6.9%		
Survival Months (median, Q1-Q3)		18	5,38	27	8,50	-	<0.001

Table 3.3.3 Clinical and sociodemographic characteristics of elderly MM patients who died during 2007-2016, with early PCC visit and without PCC visits

Demographic and Clinical Characteristics	Category	No PCC group (n = 514)		PCC group (n = 514)		Standardized Mean Difference	p
Living in urban areas (n, %)	No	33	6.4%	39	7.6%	-0.046	0.289
	Yes	481	93.6%	475	92.4%		
Geographical region (n, %)	Northeast	104	20.2%	109	21.2%	0.04	0.578
	South	103	20.0%	103	20.0%		
	Midwest	59	11.5%	63	12.3%		
	West	248	48.3%	239	46.5%		
Gender (n, %)	Male	219	42.6%	210	40.9%	0.036	0.286
	Female	295	57.4%	304	59.1%		
Race (n, %)	White	369	71.8%	364	70.8%	0.062	0.511
	African American	101	19.7%	100	19.5%		
	Hispanic	11	2.1%	16	3.1%		
	Other	33	6.4%	34	6.6%		
Charlson Comorbidity Index score category (n, %)	0	33	6.4%	32	6.2%	0.04	0.874
	1	29	5.6%	32	6.2%		
	2	54	10.5%	49	9.5%		
	3+	398	77.5%	401	78.1%		
Age category (n, %)	66-69	76	14.8%	71	13.8%	0.048	0.803
	70-74	110	21.4%	111	21.6%		
	75-79	96	18.7%	104	20.2%		
	80-84	97	18.9%	93	18.1%		
	85+	135	26.2%	135	26.3%		
Disability status (n, %)	No	81	15.8%	61	11.9%	0.113	0.003
	Yes	433	84.2%	453	88.1%		
Marital Status (n, %)	Single	63	12.3%	63	12.3%	0.059	0.592

	Married	221	43.0%	219	42.6%		
	Separated/Divorced	50	9.7%	58	11.3%		
	Widowed	148	28.8%	140	27.2%		
	Other	32	6.2%	34	6.6%		
Survival Months (median, Q1-Q3)		18	6,41	26	10,50	-	0.001

Table 3.4.1 Unadjusted comparisons between any PCC and no PCC groups on aggressive EOL care, healthcare resource utilization and costs

Outcomes	Category	No PCC group (n=1,588)		PCC group (n=1,588)		p
> 1 ED visits (n, %)	No	1,262	79.5%	1,163	73.2%	<0.001
	Yes	326	20.5%	425	26.8%	
Inpatient LOS > 14 days (n, %)	No	1,254	79.0%	1,187	74.8%	0.005
	Yes	334	21.0%	401	25.2%	
> 1 Inpatient admissions (n, %)	No	1,263	79.5%	1,155	72.7%	<0.001
	Yes	325	20.5%	433	27.3%	
ICU stay (n, %)	No	1,139	71.7%	974	61.3%	<0.001
	Yes	449	28.3%	614	38.7%	
Death in hospital (n, %)	No	1,139	71.7%	1,008	63.5%	<0.001
	Yes	449	28.3%	580	36.5%	
Chemotherapy use in last 14 days (n, %)	No	1,572	99.0%	1,571	98.9%	0.858
	Yes	16	1.0%	17	1.1%	
Any aggressive EOL care (n, %)	No	784	49.4%	562	35.4%	<0.001
	Yes	804	50.6%	1,026	64.6%	
HCRU in EOL (mean, sd)		1.17	1.32	1.49	1.3	<0.001
EOL costs (mean, sd)		$19,997.6	20,375.5	$25,055.8	20,365.4	<0.001

Table 3.4.2 Unadjusted comparisons between late PCC and no PCC groups on aggressive EOL care, healthcare resource utilization and costs

Outcomes	Category	No PCC group (n=1,074)		PCC group (n=1,074)		p
> 1 ED visits (n, %)	No	850	79.1%	723	67.3%	<0.001
	Yes	224	20.9%	351	32.7%	
Inpatient LOS > 14 days (n, %)	No	837	77.9%	734	68.3%	<0.001
	Yes	237	22.1%	340	31.6%	
> 1 Inpatient admissions (n, %)	No	845	78.7%	700	65.2%	<0.001
	Yes	229	21.3%	374	34.8%	
ICU stay (n, %)	No	763	71.0%	542	50.5%	<0.001
	Yes	311	29.0%	532	49.5%	
Death in hospital (n, %)	No	760	70.8%	583	54.3%	<0.001
	Yes	314	29.2%	491	45.7%	
Chemotherapy use in last 14 days (n, %)	No	1,061	98.8%	1,058	98.5%	0.564
	Yes	13	1.2%	16	1.5%	
Any aggressive EOL care (n, %)	No	521	48.5%	212	19.7%	<0.001
	Yes	553	51.5%	862	80.3%	
HCRU in EOL (mean, sd)		1.18	1.32	1.84	1.21	<0.001
EOL costs (mean, sd)		$20,785.7	21151.9	$30,646.3	19411.4	<0.001

Table 3.4.3 Unadjusted comparisons between early PCC and no PCC groups on aggressive EOL care, healthcare resource utilization and costs

Outcomes	Category	No PCC group (n=514)		PCC group (n=514)		p
> 1 ED visits (n, %)	No	412	80.2%	440	85.6%	0.022
	Yes	102	19.8%	74	14.4%	
Inpatient LOS > 14 days (n, %)	No	417	81.1%	453	88.1%	0.002
	Yes	97	18.9%	61	11.9%	
> 1 Inpatient admissions (n, %)	No	418	81.3%	455	88.5%	0.001
	Yes	96	18.7%	59	11.5%	
ICU stay (n, %)	No	376	73.2%	432	84.1%	<0.001
	Yes	138	26.5%	82	15.9%	
Death in hospital (n, %)	No	379	73.7%	425	82.7%	<0.001
	Yes	135	26.3%	89	17.3%	
Chemotherapy use in last 14 days (n, %)	No	511	99.4%	513	99.8%	0.317
	Yes	3	0.6%	1	0.2%	
Any aggressive EOL care (n, %)	No	263	51.2%	350	68.1%	<0.001
	Yes	251	48.8%	164	31.9%	
HCRU in EOL (mean, sd)		1.13	1.31	0.77	1.17	<0.001
EOL costs (mean, sd)		$18,350.9	18561.0	$13,374.7	17110.8	<0.001

Table 3.5 Multivariable analysis for aggressive EOL care between the PCC and no PCC groups

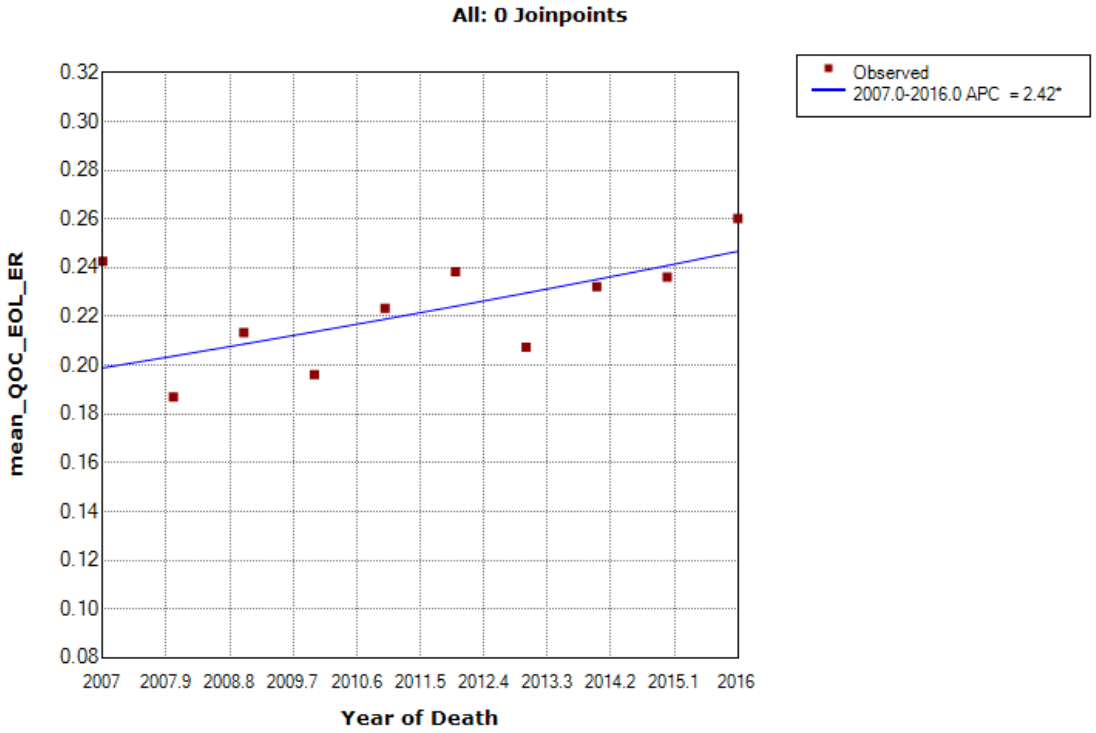
Outcomes	No PCC group			PCC group		
	Odds Ratio	95% Confidence Interval		Odds Ratio	95% Confidence Interval	
	no PCC (n=1,588)			Any PCC (n=1,588)		
> 1 ED visits	Reference	Reference	Reference	1.41	1.18	1.67
Inpatient LOS > 14 days	Reference	Reference	Reference	1.30	1.10	1.54
> 1 Inpatient admissions	Reference	Reference	Reference	1.49	1.25	1.75
ICU stay	Reference	Reference	Reference	1.69	1.45	2.00
Death in hospital	Reference	Reference	Reference	1.54	1.30	1.79
Any aggressive EOL care	Reference	Reference	Reference	1.86	1.59	2.16
	no PCC (n=1,074)			PCC in EOL (n=1,074)		
> 1 ED visits	Reference	Reference	Reference	1.89	1.52	2.33
Inpatient LOS > 14 days	Reference	Reference	Reference	1.72	1.41	2.13
> 1 Inpatient admissions	Reference	Reference	Reference	2.04	1.67	2.50
ICU stay	Reference	Reference	Reference	2.78	2.22	3.33
Death in hospital	Reference	Reference	Reference	2.22	1.82	2.70
Any aggressive EOL care	Reference	Reference	Reference	4.17	3.33	5.26
	no PCC (n=514)			PCC prior to EOL (n=514)		
> 1 ED visits	Reference	Reference	Reference	0.70	0.50	0.98
Inpatient LOS > 14 days	Reference	Reference	Reference	0.59	0.42	0.84
> 1 Inpatient admissions	Reference	Reference	Reference	0.57	0.40	0.82
ICU stay	Reference	Reference	Reference	0.52	0.38	0.71
Death in hospital	Reference	Reference	Reference	0.58	0.42	0.79
Any aggressive EOL care	Reference	Reference	Reference	0.47	0.35	0.61

Table 3.6 Multivariable analysis for healthcare resource utilization (HCRU) and costs at EOL between the PCC and no PCC groups

Outcomes	No PCC group	PCC group	Incremental Difference		
	Mean	Mean	Mean	95% Confidence Interval	
	No PCC (n = 1,588)	Any PCC (n=1,588)			
HCRU in EOL	1.17	1.50	0.33	0.33	0.34
EOL cost (in US $)	19,883.7	25,199.4	5,315.7	5,308.8	5,323.1
	No PCC (n = 1,074)	PCC in EOL (n = 1,074)			
HCRU in EOL	1.18	1.84	0.66	0.65	0.67
EOL cost (in US $)	20,618.0	30,890.4	10,272.4	10,229.6	10,311.4
	No PCC (n = 514)	PCC prior to EOL (n = 514)			
HCRU in EOL	1.12	0.77	0.35	0.34	0.35
EOL cost (in US $)	18,281.6	13,435.4	4,846.2	4,818.4	4,872.3

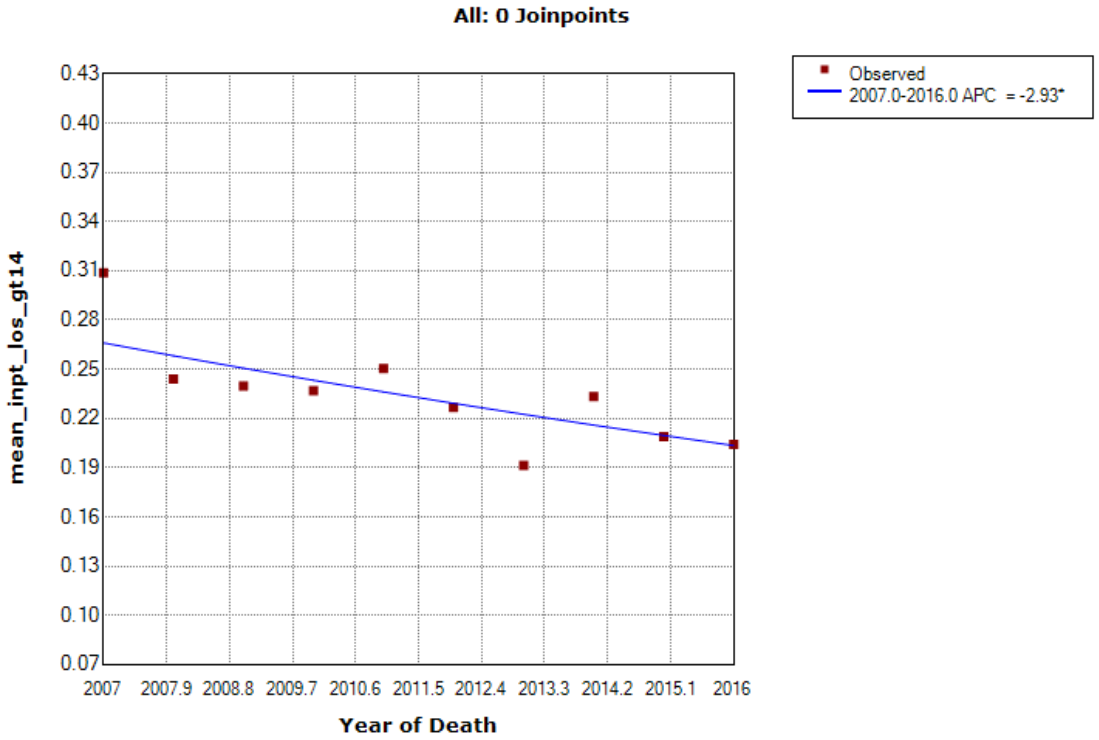
APPENDIX B

Figure 3.1 Joinpoint regression for trend in multiple ED visits during EOL among elderly MM patients who died, 2007-2016



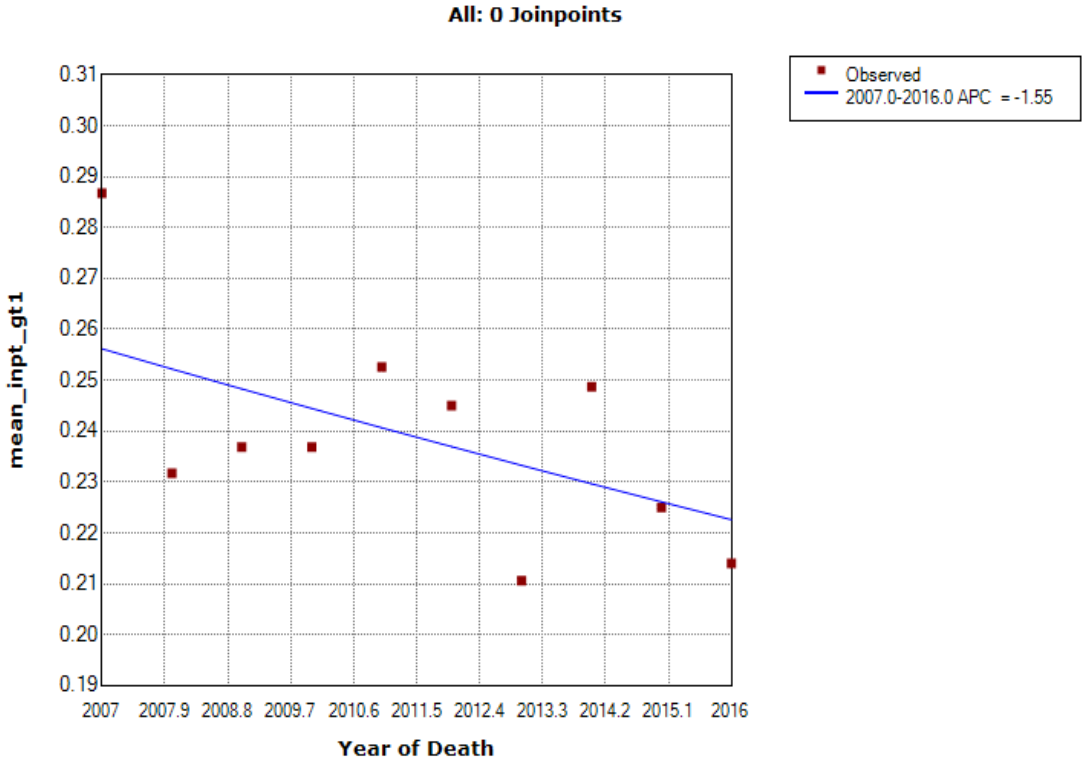
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Figure 3.2 Joinpoint regression for trend in greater than 14 days of inpatient stay during EOL among elderly MM patients who died, 2007-2016



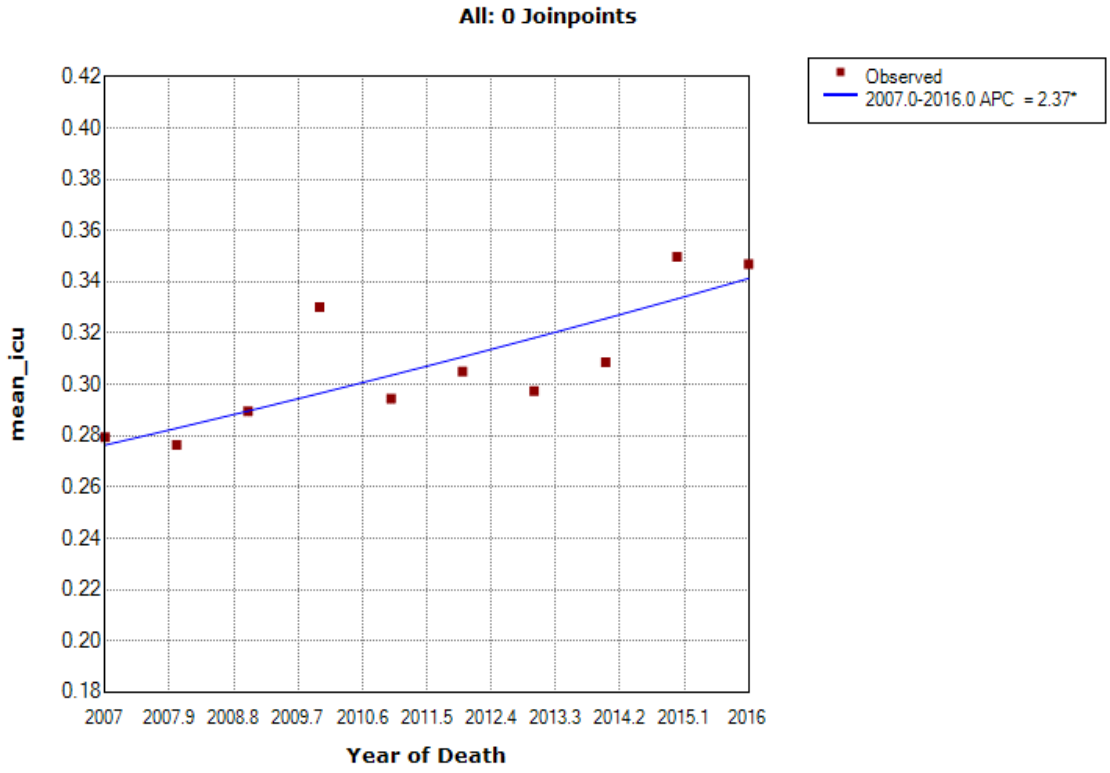
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Figure 3.3 Joinpoint regression for trend in multiple inpatient admissions during EOL among elderly MM patients who died, 2007-2016



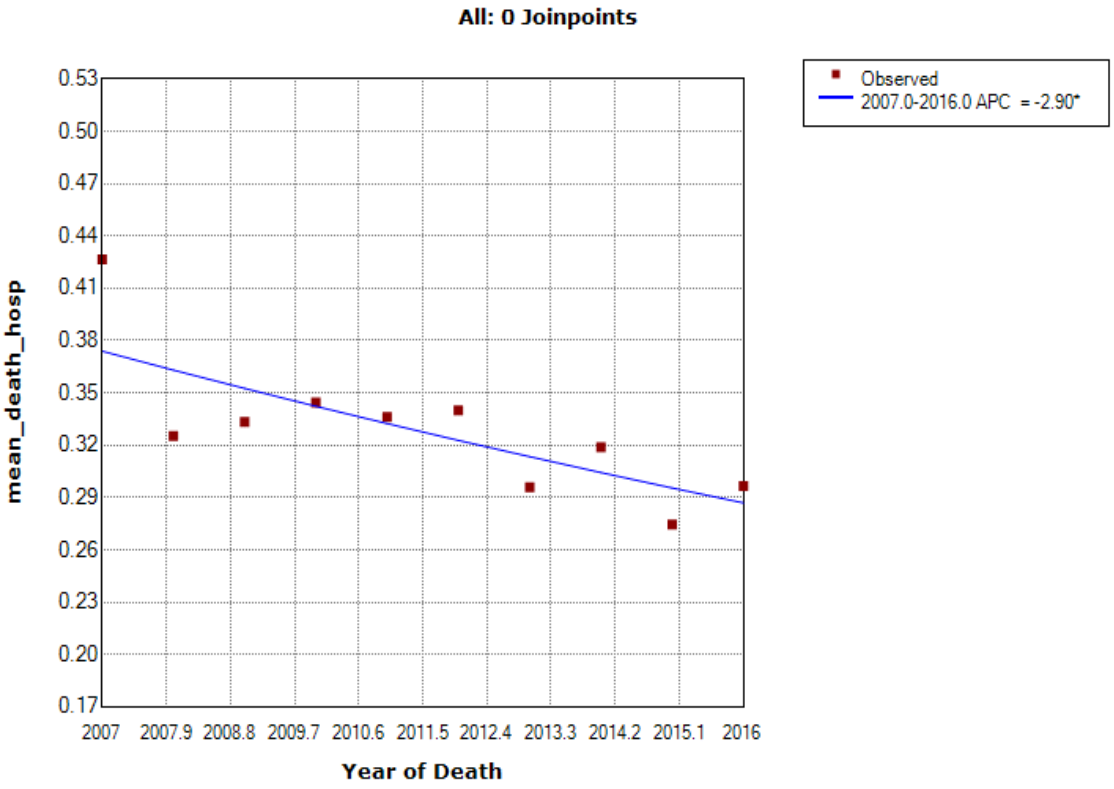
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Figure 3.4 Joinpoint regression for trend in ICU stay during EOL among elderly MM patients who died, 2007-2016



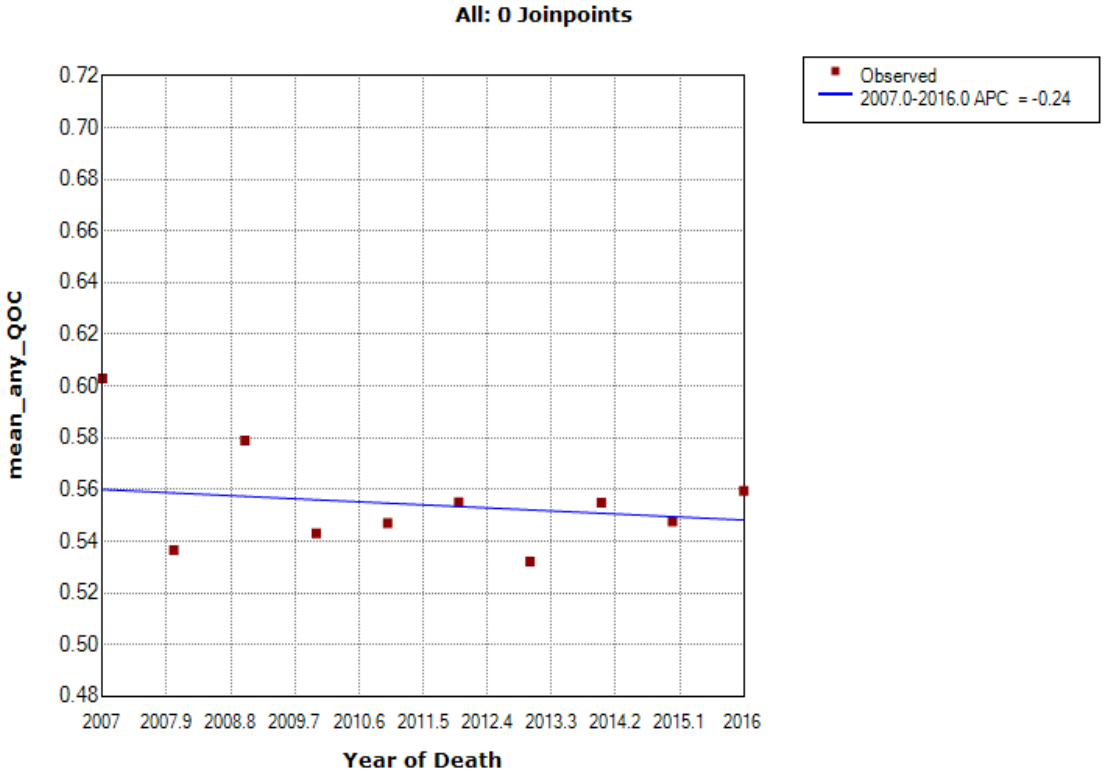
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Figure 3.5 Joinpoint regression for trend in death in hospital among elderly MM patients who died, 2007-2016



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Figure 3.6 Joinpoint regression for trend in any aggressive EOL care during EOL among elderly MM patients who died, 2007-2016



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

CHAPTER 5

Dissertation Summary and Future Research

Summary

This study used a population-based cohort of elderly NDMM patients to depict treatment patterns and assess the comparative safety and effectiveness among those who received first line LEN-based treatment versus those who received first line BORT-based treatment. Our study results corroborated that with several novel MM agents coming onto the market in the past 10 years, MM treatment has seen a dynamic shift, with novel agents firmly established as the standard of care. We have found that the majority of the elderly NDMM patients received first line novel agent-based therapy, and the uptake of combination MM agents in subsequent lines of therapy has been rising. Additionally, our study demonstrates an overall survival benefit and similar toxicity risk for patients receiving first line LEN-based continuous or maintenance treatment over those who received first line BORT-based treatment.

Using a data-driven approach (Joinpoint regression), it determined the duration of the initial phase to be 4 months post MM diagnosis among Medicare beneficiaries. For the terminal phase, it found a significant change in the monthly cost trends at the 3-month and 8-month periods prior to death. The results highlighted the substantial economic burden associated with MM care, in spite of the disease having low prevalence as compared to some of the other cancers. The incremental phase-specific costs were highest for the initial care phase, followed by the terminal phase, with costs being slightly lower for the continuing care phase, and lowest for

the pre-diagnosis phase. Inpatient and outpatient costs were the major drivers of costs in all the four phases. Pharmacy costs were a significant driver of costs in the initial and terminal phases, and were the biggest cost driver in the continuing care phase.

Moreover, it assessed trends in aggressiveness of EOL care outcomes over time. While certain indicators of aggressive EOL care remained stable over time, we observed an increasing trend for multiple ED visits and ICU stays. Moreover, this study assessed the impact of palliative care consultations on receiving aggressive EOL care, and healthcare resource use and costs at EOL. Results indicate that early palliative care consultations have the potential to reduce aggressive EOL care, and curtail healthcare resource use and costs at EOL.

Future Directions

First, our study sample consisted of elderly NDMM patients enrolled in fee-for-service Medicare. Hence, the results from our may not be generalizable to NDMM patients who are younger or elderly patients enrolled in Medicare Advantage plans. Future studies should investigate this relationship among younger or elderly patients enrolled in Medicare Advantage plan to assess its generalizability in other populations. Second, when clinical decisions are made for treatment choice, several clinical factors including cancer stage, disease prognosis, and functional status will be taking into consideration However, these factors are not available in the SEER-linked Medicare data used in this study. Future studies should take cancer staging and disease prognosis into account while comparing safety and survival between various treatments. Third, our analyses on incremental lifetime and phase-specific costs of MM could not be stratified by cancer stage. Future studies should estimate MM lifetime and phase-specific costs stratified by cancer stage to see if the cost patterns vary by cancer stage. Fourth, we lack information on patient functional status, and their symptom burden, namely, pain and fatigue,

which are very common amongst MM patients as they approach end of life. Future studies should consider accounting for patients' performance and symptom burden, if possible, to assess the impact of palliative care consultations on receiving aggressive EOL care, and healthcare resource use and costs at EOL.

CURRICULUM VITAE

KAUSTUV BHATTACHARYA

SUMMARY

- Expertise in retrospective analysis of complex survey databases and administrative claims data
- Proficient in various primary data collection and analysis techniques, and economic analysis and decision analysis modeling
- Advanced knowledge of statistical techniques
- Well versed with various statistical analysis software (SAS, STATA, SPSS), economic modeling software (TreeAge Pro 2015), and survey design software (Qualtrics)
- Knowledge of US Health Care system

EDUCATION

University of Mississippi, University, MS
PhD in Pharmaceutical Sciences **(**August 2014 – February 2020)
Emphasis: Pharmacy Administration (Track: Health Outcomes Research)
Dissertation: Multiple Myeloma: Treatments, Economic Burden, and Quality of End-of-Life Care
Advisor: Dr. Yi Yang

MS in Pharmaceutical Sciences **(**August 2014 - May 2017)
Emphasis: Pharmacy Administration (Track: Health Outcomes Research)
MS Thesis: Economic Burden of Depression among individuals with Irritable Bowel Syndrome in the National Medicaid Population
Thesis Advisor: Dr. Donna West-Strum

Jadavpur University, Kolkata, India
Bachelors in Pharmaceutical Sciences (July 2008-June 2012)

RESEARCH EXPERIENCE

Pharmerit International, Bethesda, MD
Summer Intern, Health Economics and Outcomes Research (June 2018 – August 2018)

- Real-world evidence generation using administrative claims, complex survey data, and review of medical chart data
- Clinical Trial Analysis and Reporting
- Protocol development for various projects
- Systematic Literature Review and Reporting

Bristol-Myers Squibb, Plainsboro, NJ
Summer Intern, Medical Affairs (June 2016 – August 2016)

- Responsible for writing AMCP dossier and updating the PVP document
- Involved in identifying studies for Medicaid summaries and incorporating them
- Reviewed ICER RA scoping document
- Devised a systematic search algorithm to generate the full body of clinical and economic evidence for the product

University of Mississippi, University, MS
Graduate Research Assistant, Center for Pharmaceutical Marketing and Management,
Department of Pharmacy Administration
Advisor: Dr. Benjamin F. Banahan III

- **Research analyst, MS-DUR (**June 2015-February 2020)
    - Responsible for study design and analysis of various research projects under MS-Evidence based Drug Utilization Review to help shape state Medicaid policy decisions
    - Responsible for designing SAS programs for creation of weekly research files, monthly resource utilization reports, annual drug exceptions monitoring reports

- **Research Lead, MS-DUR (**March 2019 – February 2020)
    - Led various research projects under MS-Evidence based Drug Utilization Review; responsibilities include assisting other Research Assistants operationalize and develop analysis plans for various research projects

TEACHING EXPERIENCE

University of Mississippi, University, MS

- Data Management and Statistical Software: PHAD 690
    - Guest Lecturer, Summer 2019
    - Lectured and demonstrated certain data management techniques in SAS

- Pharmacoeconomics, Pharmacoepidemiology, and Medication Safety**:** PHAD 494
    - Co-Instructor, Spring 2019

- Delivered lectures covering topics: Cost-of-illness analysis, Cost-minimization analysis, Cost-benefit analysis, Cost-effectiveness analysis, and Health-related quality of life

- Introduction to Pharmacy and U.S. Health Care System: PHAD 392
  - Graduate Teaching Assistant, Department of Pharmacy Administration Spring 2015

- Social and Behavioral Aspects of Pharmacy Practice: PHAD 391
  - Graduate Teaching Assistant, Department of Pharmacy Administration Fall 2014

PUBLICATIONS

PEER-REVIEWED JOURNALS

Hu EY, Ramachandran S, **Bhattacharya K**, Nunna S. Obesity Among High School Students in the United States: Risk Factors and Their Population Attributable Fraction. Prev Chronic Dis 2018;15:180122. DOI: https://doi.org/10.5888/pcd15.180122.

Bhattacharya, K., Joshi, N., Shah, R., & Nahar, V. K. (2019). Impact of Depression on Health-Related Quality of Life among Skin Cancer Survivors. SKIN The Journal of Cutaneous Medicine, 3(6), 381-394

Ramachandran S, Young J, **Bhattacharya K,** Elkin D, Sattler A. Impact of a Coordinated Care Program on Costs and Outcomes of Children with Mental Illnesses in Mississippi Medicaid. Manuscript in preparation for submission to *JMCP*.

Bhattacharya K, Yang Y, Khanna R, West-Strum D. Impact of Depression on Healthcare utilization and Costs among Individuals with Irritable Bowel Syndrome in Multi-state Medicaid Population. Manuscript in preparation for submission to *Journal of Medical Economics.*

Bhattacharya K, Inguva S, Shah R. Financial Toxicity of Cancer Care and its Effect on Caregiver Burden, Access to Medical Care, Health-related Quality of Life and Other Patient Reported Outcomes. Manuscript in preparation for submission to *Cancer*.

PEER-REVIEWED CONFERENCE PRESENTATIONS

Bhattacharya K, Banahan BF III. Medication Adherence as a Predictor of Switching Oral Antipsychotic Users to Long-term injectables. Academy of Managed Care Pharmacy (AMCP) Spring Meeting, April 19-22, 2016, San Francisco, CA.

Bhattacharya K, Noori W, Khanna R. Impact of Depression on Health-Related Quality of Life among Survivors of Skin Cancer. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 21st Annual International Meeting, May 21-25, 2016, Washington, DC.

Bhattacharya K, Yang Y. A Cost-effectiveness analysis of Palbociclib and other Aromatase Inhibitors for Treatment of Advanced Breast Cancer. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 21st Annual International Meeting, May 21-25, 2016, Washington, DC.

Bhattacharya K, Banahan BF III. Comparison of the CMS Chronic Conditions Data Warehouse (CCW) Algorithms and the Condition-Based and Prescription-Based Comorbidity Scores as Predictors of Ambulatory Healthcare Utilization Using Mississippi Medicaid Claims Data. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 22nd Annual International Meeting, May 20-24, 2017, Boston, MA.

Bhattacharya K, Ramachandran S, Young J, Elkin D. Impact of a Coordinated Care Program on Costs and Outcomes of Children with Mental Illnesses in Mississippi Medicaid ***(Awarded Bronze medal for best poster)***. Academy of Managed Care Pharmacy (AMCP) Nexus 2017 Meeting, October 16-19, 2017, Dallas, TX.

Bhattacharya K, Banahan BF III, Pittman E, Noble C. Comparison of Long-acting vs Short-acting Anti-psychotics on Hospitalization and Healthcare Costs among Patients with Schizophrenia Enrolled in Mississippi Medicaid. Academy of Managed Care Pharmacy (AMCP) Annual Meeting 2018, April 24-26, Boston, MA.

Bhattacharya K, Yang Y, Khanna R, West-Strum D. Impact of Depression on Healthcare utilization and Costs among Individuals with Irritable Bowel Syndrome in Multi-state Medicaid Population ***(Awarded Top 10% for the Best Research Poster).*** International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD**.**

Hu E, **Bhattacharya K,** Ramachandran S, Nunna S. Modifiable Risk Factors and Population Attributable Risk of Obesity among High School Students in the United States ***(Awarded Top 10% for the Best Research Poster)***. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD.

Axon R, **Bhattacharya K,** Adilgozhina G, Milky G, Jiang R. Findings from the 2018 ISPOR Student Interest Survey. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 23rd Annual International Meeting, May 19-23, 2018, Baltimore, MD.

Rong Y, **Bhattacharya K,** Pittman E, Zhang Y, Noble S, Kirby T, Banahan BF III. Comparison Study of Current Global Initiative for Chronic Obstructive Lung Disease (GOLD)

Recommendations with COPD Exacerbation Treatments in Mississippi Medicaid. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 24th Annual International Meeting, May 18-22, 2019, New Orleans, LA.

Bhattacharya K, Banahan BF III, Pittman E, Noble S, Kirby T. Prevalence of Adverse Events among Children Taking Multiple vs Single Antipsychotics. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 24th Annual International Meeting, May 18-22, 2019, New Orleans, LA.

Bhattacharya K, Yang Y, Bentley JP, Ramachandran S, Banahan BF III, Chang Y, Bhakta N, Shah R. Phase-specific and lifetime costs of multiple myeloma (MM) among elderly patients in the United States (US). International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 25th Annual International Meeting, May 16-20, 2020, Orlando, FL.

PROJECTS

COMPLETED PROJECTS

- Impact of Depression on Health-Related Quality of Life among Survivors of Skin Cancer
- Medication Adherence as a Predictor of Switching Oral Antipsychotic Users to Long-term Injectables
- Cost-effectiveness Analysis of Palbociclib and other Aromatase Inhibitors for the Treatment of Advanced Breast Cancer
- Impact of a Coordinated Care Program on Costs and Outcomes of Children with Mental Illnesses in Mississippi Medicaid
- Comparison of Long-acting vs Short-acting Antipsychotics on Hospitalization and Healthcare Costs among Patients with Schizophrenia Enrolled in Mississippi Medicaid
- Impact of Intravenous Acetaminophen on Duration of Opioid Use among Patients Undergoing Outpatient Surgical Procedures in Mississippi
- Modifiable Risk Factors and Population Attributable Risk of Obesity among High School Students in the United States
- Economic and Humanistic Burden of Depression and Anxiety among Patients with Chronic Comorbidities
- Financial Toxicity of Cancer Care and its Effect on Caregiver Burden, Access to Medical Care, Health-related Quality of Life and Other Patient Reported Outcomes

PROJECTS IN PROGRESS

- Comparative effectiveness of Coronary Artery Bypass Grafting (CABG) versus Percutaneous Coronary Intervention (PCI) on clinical and economic outcomes among elderly chronic kidney disease patients
- Health-related quality of life and health utility among children and adolescents with hemophilia and its impact on care-givers
- Comparative effectiveness and safety of maintenance and continuous treatment with novel agent-based therapies among elderly patients newly diagnosed with multiple myeloma
- Disease lifetime costs and its predictors among elderly patients newly diagnosed with multiple myeloma
- Trends in quality of end of life care and impact of palliative care consultations on quality of end of life care among elderly patients with multiple myeloma

GRANTS/FELLOWSHIPS AWARDED

Title: Health Utility and its Determinants among Children and Adolescents with Hemophilia

- Agency: Bayer Hemophilia Awards Program
- Role: Co-Investigator
- Involved with submission of grant proposal, development of the survey, data collection, and analysis, and development of manuscripts
- Amount awarded: $25,000

Title: Medical Marketing Economics Fellowship 2018

- Competitive Fellowship awarded by the Fellowship Selection Committee based on academic performance, research, and service
- Amount awarded: $5,000

MANUSCRIPT REVIEWS

- Pharmacotherapy
- Pediatrics
- Methods of Information in Medicine
- Journal of Pharmaceutical Health Services Research
- Journal of General Internal Medicine
- International Journal of Women's Dermatology
- Preventing Chronic Diseases

CONFERENCE RESEARCH REVIEWS

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual Meeting 2020
- Pharmacy Quality Alliance (PQA) Annual Meeting 2020

HONORS AND AWARDS

- Awarded Farlow Fellowship, Department of Pharmacy Administration, University of Mississippi, September 2019
- ISPOR Travel Grant recipient for attending the 23rd Annual International ISPOR meeting, May 19-23, 2018, Baltimore, MD
- Graduate Student Achievement Award in Pharmacy Administration, University of Mississippi, April 2018
- Winner of the PMRG case study competition and was awarded a travel grant by the PMRG Institute to attend the 9th Annual PMRG Institute meeting, October 4-6, 2015, Philadelphia, PA
- Winner of the University of Mississippi ISPOR Chapter Research Grant, 2015

LEADERSHIP EXPERIENCES AND PROFESSIONAL MEMBERSHIPS

- President, ISPOR Student Chapter at the University of Mississippi (2017-2018)
- Member, ISPOR Survey Committee, responsible for fielding and analyzing the ISPOR student member interest survey (2017 – 2018)
- Member, ISPOR Statistical Methods and Oncology Special Interest Groups (2017 – Present)
- Secretary, Rho Chi – The Academic Honor Society in Pharmacy (2016 – 2018)

DATABASES USED IN RESEARCH

- Behavioral Risk Factor Surveillance System (BRFSS)
- National Medicaid Administrative claims data
- Mississippi Medicaid Administrative claims data
- 5% National Medicare Administrative claims data
- Surveillance, Epidemiology, and End Results (SEER)-linked Medicare claims data
- Youth Risk Behavior Surveillance System (YRBSS)
- Medical Expenditure Panel Survey (MEPS)
- IPSOS Global Oncology Monitor

CERTIFICATIONS

- SAS® certified Base Programmer for SAS® 9
- SAS® certified Advanced Programmer for SAS® 9
- Interdisciplinary Certificate in Applied Statistics (ICAS), University of Mississippi (Graduate Minor in Applied Statistics)