Original Study

Prolonged Duration of Therapy Is Associated With Improved Survival in Patients Treated for Relapsed/Refractory Multiple Myeloma in Routine Clinical Care in the United States

Parameswaran Hari,[1] Dorothy Romanus,[2] Antonio Palumbo,[2] Katarina Luptakova,[2] Robert M. Rifkin,[3] Linh Mai Tran,[4] Aditya Raju,[5] Eileen Farrelly,[5] Stephen J. Noga,[2] Marlo Blazer,[5] Ajai Chari[6]

Abstract

Despite the emerging paradigm favoring continuous therapy, we found that in routine clinical care, myeloma patients at first relapse frequently discontinue treatment before progression, resulting in a therapy duration that is significantly shorter than the interval to the next therapy. We further describe the association between the length of second-line therapy and improved overall survival for patients with relapsed/refractory multiple myeloma.

Background: In clinical trials, an extended therapy duration has been associated with better outcomes in patients with newly diagnosed multiple myeloma (NDMM). However, data on how the therapy duration affects the outcomes for patients with relapsed/refractory multiple myeloma (RRMM) are limited. We conducted a large, retrospective study in the United States to evaluate the effect of the duration of second-line therapy on overall survival. **Patients and Methods:** Adults with NDMM from January 2008 to June 2015 were followed up to identify their second-line therapy. The duration of therapy (DOT) and time to next therapy (TTNT), as a proxy for progression-free survival, were estimated using the Kaplan-Meier method. The relationship between the duration of second-line therapy and overall survival was evaluated with a logistic marginal structural model to mitigate the risk of treatment selection and survival bias. **Results:** A total of 628 NDMM patients developed a relapse after initial therapy. The median DOT for second-line therapy was 6.9 months (95% confidence interval [CI], 5.9-7.7 months), which was shorter than the corresponding TTNT (median, 15.1 months; 95% CI, 13.4-17.3 months). Each additional month of second-line therapy was associated with a reduced adjusted risk of death at 1 year (odds ratio, 0.78; 95% CI, 0.77-0.83; $P < .001$). **Conclusion:** In a large database capturing a heterogeneous patient population and varied treatment patterns reflecting routine clinical care, we found a clinical benefit for continued longer DOT at first relapse. Despite the emerging paradigm favoring continuous therapy, second-line progression-free survival (utilizing TTNT as the proxy) was more than twofold longer than the DOT. Understanding the barriers to extended DOT could help to improve the outcomes for RRMM patients.

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Introduction

Multiple myeloma (MM) is the second-most common hematologic malignancy and primarily affects the elderly population.[1] Novel therapies have been associated with a significant improvement in overall survival (OS) for patients with MM[2,3]; however, relapse will be inevitable for most patients. Consensus has been increasing that prolonged therapy for patients with newly diagnosed MM (NDMM) correlates with improved patient

[1]Department of Medicine, Medical College of Wisconsin, Milwaukee, WI
[2]Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA
[3]Rocky Mountain Cancer Centers, Denver, CO
[4]University of California, Berkeley, CA
[5]Xcenda, LLC, Palm Harbor, FL
[6]Icahn School of Medicine at Mount Sinai, New York, NY

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Address for correspondence: Parameswaran Hari, MD, Department of Medicine, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, Milwaukee, WI 53226
E-mail contact: phari@mcw.edu

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outcomes. The phase III The Front-line Investigation of Revlimid and Dexamethasone versus Standard Thalidomide (FIRST) trial demonstrated that continuous frontline therapy with lenalidomide plus dexamethasone until disease progression leads to better progression-free survival (PFS) compared with fixed-duration therapy.[4] Also, post hoc analyses of trial data that examined the effect of fixed-duration versus continuous therapy or cumulative dose on patient outcomes demonstrated a beneficial effect from prolonged frontline therapy for patients with NDMM.[5,6] Another retrospective analysis by Mateos et al[7] reported a significant benefit for PFS and time to progression (TTP), but not for OS, with less intensive prolonged therapy compared with a shorter, more intensive fixed-duration treatment with a bortezomib, melphalan, and prednisone combination in NDMM.

With second-line therapy, evaluations of the effects of the duration of therapy (DOT) on outcomes have been limited to lenalidomide and dexamethasone therapy. These were based on subgroup analyses of large prospective trials in which treatment was given until progression or, alternatively, on small single-institution experiences.[8-12] In 1 study of 50 patients, those treated for > 3 years had a longer median TTP compared with those treated for 2 to 3 years, regardless of the response rate.[10] In another small retrospective study of 67 patients, OS and the overall response rate were significantly better for patients treated with lenalidomide and dexamethasone for > 12 months compared with patients who stopped treatment at < 12 months for reasons other than progression.[11] However, these studies varied in the extent to which they controlled for patient and disease factors and treatment exposure at baseline and over time—all aspects that can affect OS. Some analyses did not account for selection[8] and/or survival[10,12] bias. Others adjusted for baseline confounders but did not account for selection bias over time or survival bias.[11] Some included landmark analyses[8] or time-dependent multivariate Cox regression models.[9] However, with these traditional regression methods, including Cox regression models with time-varying covariates and landmark analyses, the possibility exists that the results could be biased in the presence of a time-dependent exposure (continuation of therapy) and time-varying confounders.[13-15]

Larger, multi-institutional studies that encompass practice patterns outside of a clinical trial setting (ie, standard-of-care patients who tend to be older and have a greater comorbidity burden) and studies that apply robust statistical methods to account for selection and survival bias are necessary to further characterize and confirm the effects of second-line DOT on the outcomes of patients with RRMM. In the present retrospective cohort study, we examined the relationship of second-line DOT and outcomes in a large national cohort of 628 RRMM patients treated in routine care in the United States using the marginal structural model (MSM), including adjustment for patient, disease, and treatment factors.

Patients and Methods

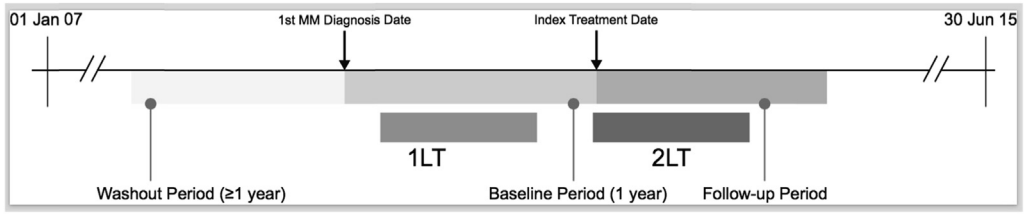
Study Design and Data Source

The present study was a retrospective observational study of de-identified Humedica electronic medical record (EMR) data from January 1, 2007 to June 30, 2015. The EMR Humedica database is a large clinical database with a broad geographic representation from all 50 states and accounts for > 140,000 providers, 6500 clinics, and 600 hospitals in the United States. The source of Humedica data is primarily from large integrated delivery networks (IDNs) in the United States. Each IDN in Humedica is a comprehensive health care delivery system that offers patients a multitude of services across the clinical care spectrum, including acute inpatient and outpatient care. The Humedica EMR data set contains de-identified data for use in clinical research. The Chesapeake institutional review board approved the present study.

Study Cohort

Adult patients with NDMM who had received care within an IDN were identified for the present study. A diagnosis of MM was defined as ≥ 2 EMRs with an MM diagnosis code (International Classification of Diseases, 9th revision, Clinical Modification [ICD-9-CM] codes 203.00, 203.01, 203.02) ≥ 60 days but ≤ 1 year apart during the identification period from January 1, 2008 to June 30, 2015. The date of the first EMR with a diagnosis code for MM was used as the diagnosis date. Patients initiating first-line therapy were followed up after the MM diagnosis to identify subsequent lines of therapy (Figure 1). Eligible patients were required to have continuous care for 12 months before the diagnosis date for NDMM (washout period) through the initiation of at least second-line therapy for RRMM. The start of second-line therapy was the index date for the analyses of outcomes. Patients with a history of frontline stem cell transplantation (SCT) before the initiation of second-line therapy were included. Those with a diagnosis of secondary cancers during the 12-month period before the diagnosis of MM or those who had undergone treatment outside the IDN (with

Figure 1 Study Period



Abbreviations: 1LT = first-line Therapy; 2LT = second-line Therapy; MM = multiple myeloma.