Original Study

Heterogeneity of Second-Line Treatment for Patients With Multiple Myeloma in the Connect MM Registry (2010-2016)

Sundar Jagannath,[1] Rafat Abonour,[2] Brian G.M. Durie,[3] Cristina Gasparetto,[4] James W. Hardin,[5] Mohit Narang,[6] Howard R. Terebelo,[7] Kathleen Toomey,[8] Lynne Wagner,[9] Shankar Srinivasan,[10] Amani Kitali,[10] Lihua Yue,[10] E.Dawn Flick,[10] Amit Agarwal,[10] Robert M. Rifkin[11]

Abstract

Connect MM is a large prospective observational US-based disease registry that was used to evaluate second-line treatment patterns in patients with relapsed or refractory multiple myeloma during a 5-year period, from 2010 to 2016. Treatment uptake was found to coincide with clinical milestones (ie, regulatory approvals, clinical study results), with growing preference for newer agents and triplet combinations over time.

Background: The treatment landscape for multiple myeloma (MM) has undergone recent changes with the regulatory approval of several new therapies indicated for second- and later-line disease. Using data from Connect MM, the largest multisite, primarily community-based, prospective, observational registry of MM patients in the United States, selection of second-line treatments was evaluated during a 5-year period from 2010 to 2016. **Patients and Methods:** Eligible patients were aged $\geq$ 18 years, had newly diagnosed MM $\leq$ 2 months before study entry, and were followed for up to 8 years. Patients who received $\geq$ 2 lines of therapy were analyzed. "Tepee" plots of stacked area graphs differentiated treatments by color to allow visualization of second-line treatment trends in MM patients. **Results:** As of February 2017, 855 of 2897 treated patients had progressed to second-line treatment. Treatment selection was heterogeneous; shifting patterns of treatment choices coincided with the approval status of newer agents. The most common treatment regimens in the early part of the decade were lenalidomide and/or bortezomib, with or without dexamethasone, with increasing use of newer agents (carfilzomib, pomalidomide, daratumumab, and elotuzumab) and triplet combinations over time. The influence of the baseline patient characteristics of age, history of diabetes, peripheral neuropathy, and renal function on treatment choice was also examined. **Conclusion:** These findings indicate that community physicians are current in their MM management practices, with uptake of new drugs and acquaintance with results of randomized clinical trials using combinations almost concurrent with their regulatory approval and publication.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■

Keywords: Community, Real-world, Refractory, Relapsed, Therapies

Introduction

Recent entry of new therapies into the multiple myeloma (MM) treatment landscape has been driven by evidence-based medicine, with continued impact from clinical trials. Although current treatment guidelines provide a list of preferred antimyeloma agents,[1] specific recommendations are lacking, resulting in wide variability in therapeutic approaches.

[1]Mount Sinai Hospital, New York, NY
[2]Indiana University Simon Cancer Center, Indianapolis, IN
[3]Cedars Sinai Samuel Oschin Cancer Center, Los Angeles, CA
[4]Division of Cellular Therapy, Duke University Medical Center, Durham, NC
[5]University of South Carolina, Columbia, SC
[6]US Oncology Research, Maryland Oncology Hematology, Columbia, MD
[7]Providence Cancer Institute, Southfield, MI
[8]Steeplechase Cancer Center, Somerville, NJ
[9]Wake Forest University School of Medicine, Winston-Salem, NC
[10]Celgene Corporation, Summit, NJ
[11]US Oncology Research, Rocky Mountain Cancer Centers, Denver, CO

Submitted: Jan 5, 2018; Revised: Apr 20, 2018; Accepted: Apr 27, 2018

Address for correspondence: Sundar Jagannath, MD, Tisch Cancer Institute Icahn School of Medicine at Mount Sinai, 1 Gustave Levy Place, New York, NY 10029 Fax: (212) 241-8608; e-mail contact: sundar.jagannath@mssm.edu

https://doi.org/10.1016/j.clml.2018.04.007

Connect MM (NCT01081028) is the largest multisite, prospective, observational cohort study in the United States, with 3011 newly diagnosed MM (NDMM) patients enrolled from September 2009 through April 2016. Because a high proportion (84%) of patients are enrolled from community sites, Connect MM is a valuable resource for characterizing treatment uptake in daily practice. Connect MM has previously been used to describe the demographic and disease characteristics of NDMM patients in clinical practice[2] and how these differ compared to patients enrolled onto clinical trials,[3] to establish the low incidence of second primary malignancies associated with lenalidomide in this community-based population,[4] and to construct a matrix to predict individual patient risk of early mortality.[5]

The objective of this study was to describe second-line treatment patterns over time for patients with relapsed or refractory MM. The long-term prospective design of the Connect MM registry makes it a useful tool for describing salvage treatment options in MM. Patients were enrolled over the course of 7 years, allowing for longitudinal analyses of treatment patterns, captured both during the induction phase and throughout each patient's journey (for up to 8 years of follow-up).

Methods

Study Design

Connect MM was designed to characterize treatment and outcomes for patients with NDMM. Patients were enrolled onto 2 cohorts from September 2009 to April 2016 and were from community, academic, and government centers across the United States. Cohort 1 enrolled patients from September 2009 through December 2011; Cohort 2 enrolled patients from December 2012 through April 2016. Eligible patients were aged $\geq$ 18 years and must have been newly diagnosed with MM within 2 months before study entry. Patients were followed for up to 8 years. This analysis was conducted for the population of treated patients who received $\geq$ 2 lines of therapy. Data, including treatment choice, were captured at baseline and quarterly thereafter until death or discontinuation. To visualize trends in second-line treatment regimens used during the 5-year period (quarter 3-4, 2010, to quarter 1-2, 2016), we used a novel "Tepee" plot approach, consisting of a stacked area graph that differentiates treatments by color, with band width representing frequency of use at a given time interval; colors with wider bands signify more frequently used regimens.[6] Horizontal lines denote each sequential 6-month interval and represent 100% of patients initiating therapy during that time period.

Results

Disposition and Patient Characteristics

A total of 3011 patients were enrolled into 2 cohorts. As of the data cutoff date (July 7 2016), 2908 patients had initiated first-line treatment. Of those, 1095 continued to receive first-line treatment, 856 progressed and initiated second-line treatment, 491 died before second-line treatment, 366 discontinued before second-line treatment, and 100 progressed and stopped first-line treatment without initiating second-line treatment by the data cutoff date. At baseline, median age was 66 years (range, 32-93 years), with 37% of patients aged $\geq$ 70 years; 58% were men, and 84% were white. Patients had International Staging System stage I (17%), II (28%), or III (29%) MM (unspecified, 26%). A total of 84% of patients were enrolled in community centers, 15% in academic centers, and 1% in government centers.

Second-Line Treatment Patterns

The initial analysis showed heterogeneity in the use of various drugs and combinations for treatment in the second-line setting (Figure 1A). The most common treatment regimens used in late 2010 and early 2011 were bortezomib and dexamethasone; lenalidomide and dexamethasone; lenalidomide, bortezomib, and dexamethasone; bortezomib alone; lenalidomide alone; and cyclophosphamide, bortezomib, and dexamethasone. Regimens shifted over time, including increased use of carfilzomib and pomalidomide from 2012, coinciding with regulatory approval of these agents and availability through expanded access programs around the time of drug approval (Figure 1B). A smaller proportion (approximately 30%) of patients were categorized as having received "other" regimens, including multiple combination regimens, with no overriding trend (Figure 1B, Supplemental Table 1 in the online version).

We also examined the use of therapies based on number of agents in a regimen and drug class. Triplet use, including combinations of chemotherapeutic agents, increased over time (Figure 2A). Use of alkylating agents and combinations such as dexamethasone, cyclophosphamide, etoposide, and cisplatin decreased after approval of pomalidomide and carfilzomib, whereas use of monoclonal antibodies increased after approval of daratumumab and elotuzumab (Figure 2B). At the most recent time point, immunomodulatory drugs and proteasome inhibitors, alone or in combination, comprised 80% of all treatments used (Figure 2B).

Factors Influencing Second-Line Treatment Choice

Treatment choices in second-line therapy were then characterized based on the presence or absence of potentially influential baseline characteristics. Age is an important factor for MM treatment decision by clinicians, because of its association with frailty, increased comorbidities, poor tolerability, and higher risk of complications.[7] Age was significantly associated with the number of drugs used ($P < .001$). Seventy-two percent (270/374) of patients aged $\geq$ 70 years received monotherapy or doublets versus 55% (264/481) of patients aged $<$ 70 years. Triplets or quadruplets (which included combinations of chemotherapeutic agents) were used more frequently in patients aged $<$ 70 years (45%, 217/481) than $\geq$ 70 years (28%, 104/374). Carfilzomib use was less frequent in patients aged $\geq$ 70 versus $<$ 70 years. Of the 148 patients who received carfilzomib, 95 (64%) were aged $<$ 70 years and 53 (36%) were aged $\geq$ 70 years. Use of novel therapy (immunomodulatory agents, proteasome inhibitors, and/or monoclonal antibodies) was similar in patients aged $<$ 70 and $\geq$ 70 years (Figure 2C and D) with approximately 80% of patients in either age group receiving these treatments. Age did not affect the use of steroids: 80% of patients aged $<$ 70 years (386/481) of patients aged $\geq$ 70 years (294/374) received steroids (Figure 2C and D). History of diabetes also did not affect the use of steroids: 79% (119/151) and 80% (554/694) of patients with and without a history of diabetes received steroids, respectively.

Peripheral neuropathy (PN) is a common complication in patients with MM and is frequently associated with certain anti-MM