Journal of Geriatric Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

The impact of age and comorbidities on practice patterns and outcomes in patients with relapsed/refractory multiple myeloma in the era of novel therapies

Parameswaran Hari [a,*], Dorothy Romanus [b], Katarina Luptakova [b], Marlo Blazer [c], Candice Yong [b], Aditya Raju [c], Eileen Farrelly [c], Richard Labotka [b], Vicki A. Morrison [d]

[a] Dept of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA
[b] Millennium Pharmaceuticals, Inc., Cambridge, MA, USA [1]
[c] Xcenda, Palm Harbor, FL, USA
[d] University of Minnesota, Hennepin County Medical Center, Minneapolis, MN, USA

ARTICLE INFO

Article history:
Received 1 May 2017
Received in revised form 29 August 2017
Accepted 28 September 2017
Available online xxxx

Keywords:
Relapsed/refractory multiple myeloma
Age
Elderly
Comorbidities
Retrospective analysis
Renal insufficiency
Cardiovascular disease
Treatment

ABSTRACT

Objectives: One-third of patients with multiple myeloma (MM) are diagnosed at age ≥ 75 years. Older patients have increased incidence of cardiovascular disease (CVD) and renal insufficiency (RI), hallmark complications of MM. We examined cumulative incidence of CVD and RI in relapsed/refractory MM (RRMM) and outcomes by age and RI/CVD.

Materials and Methods: Retrospective cohort study using a large US electronic medical records database of adult patients with RRMM initiating first- and second-line therapy (2LT) between 1/2008–06/2015. RI and CVD comorbidities were based on diagnosis codes and/or lab values.

Results: Among 628 patients, 37.1% were ≥ 75 years. Cumulative incidence of CVD and/or RI increased from 47.7% at MM diagnosis to 67.8% at first relapse. Age ≥ 75 years had a trend toward higher risk of relapse post 2LT, proxied by time to next treatment (TTNT), (adjusted HR: 1.28; 95% CI: 1.00, 1.65; $P = 0.05$). TTNT was significantly higher with comorbid CVD + RI (adjusted HR: 1.50; 95% CI: 1.11, 2.02; $P < 0.01$). Age ≥ 75 years, RI, CVD, and CVD + RI were associated with increased mortality risk from 2LT initiation; adjusted HR: 1.66 (95% CI: 1.19, 2.33; $P < 0.01$), 1.51 (95% CI: 1.01, 2.26; $P = 0.04$), 1.75 (95% CI: 1.03, 2.96; $P = 0.04$), and 1.95 (95% CI: 1.29, 2.93; $P < 0.01$), respectively.

Conclusion: Despite treatment with novel agents for RRMM in 86% of patients, an outcome gap persists for older patients and those with RI and/or CVD. Personalized treatment approaches that account for age and comorbidities, and further evaluation of innovative regimens and dosing schedules, are needed to improve outcomes for these patients.

1. Introduction

Multiple myeloma (MM) is predominantly a disease of the older population, with median age at diagnosis of 69 years and one-third of patients diagnosed at age ≥ 75 years [1]. MM remains incurable in the vast majority of patients, with relapsed patients receiving multiple lines of therapy [2,3]. Among newly diagnosed patients with MM, 20% to 50% have renal impairment (RI) at the time of diagnosis [4–7]. Older age is associated with higher rates of renal impairment in patients with MM [8]. In addition, older patients have an increased incidence of cardiovascular disease (CVD) [9]. Unfortunately, older patients are underrepresented in clinical trials, and those with concomitant comorbidities are frequently excluded [10,11].

Information regarding prescribing patterns and clinical outcomes in patients managed in routine care who are older or who have concomitant comorbidities is limited [2]. Available observational evidence points to mixed improvements in overall survival (OS) in older patients with newly diagnosed multiple myeloma (NDMM), with the majority of data limited to the first-line treatment setting [12–16]. Progression-free survival (PFS) and OS data beyond first line treatment in relapsed and refractory multiple myeloma (RRMM) are limited for patients treated with newer therapies such as non-cytotoxic chemotherapeutic agents including thalidomide, lenalidomide, and bortezomib.

The objective of our retrospective study was to describe the cumulative incidence over time of RI and CVD in a cohort of patients with MM

* Corresponding author at: Department of Medicine, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, Milwaukee, WI 53226, USA.
E-mail address: phari@mcw.edu (P. Hari).
[1] A wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

https://doi.org/10.1016/j.jgo.2017.09.007

treated in routine care. Secondly, we evaluated the variation in prescribing patterns and clinical outcomes by age and comorbidities in patients with RRMM initiating second-line therapy.

2. Methods

2.1. Patients and Data

A large, national electronic medical record (EMR) database, Humedica, was used to identify adult patients with MM. Humedica represents a large group of integrated delivery networks (IDNs) within the United States (US). Each IDN in Humedica is a comprehensive healthcare delivery system that offers patients a multitude of services across the clinical care spectrum, including acute inpatient and outpatient care. These organizations provide care for patients from all 50 states and account for over 140,000 providers, 6500 clinics, and 600 hospitals. The Humedica EMR dataset contains deidentified data for use in clinical research. The Chesapeake Institutional Review Board approved this study.

The cohort included adult patients newly diagnosed with MM who initiated first-line therapy (see Appendix) between January 1, 2008 and June 30, 2015. Patients were followed longitudinally to identify subsequent lines of therapy (Supplemental Fig. 1). Eligible patients had to have continuous care for 12 months prior to diagnosis of NDMM (washout period) through at least initiation of second-line treatment for RRMM. Patients were excluded if they had evidence of amyloidosis or plasma-cell leukemia; had evidence of MM-specific anti-cancer systemic therapy or stem cell transplant (SCT) during the washout period; underwent delayed SCT (defined as SCT date >300 days after initiation of first line therapy); had another primary cancer anytime time during the study period; did not have treatment with an MM-specific anti-cancer agent beyond first line treatment or were treated with a steroid (monotherapy with prednisone or short-term [<90 days] dexamethasone); or had treatment outside of an IDN due to risk of incomplete information.

2.2. Study Variables

The outcomes of interest were PFS and OS from start of second-line therapy. The time from the start of second line and third line therapy to the next line of therapy or death, whichever occurred first (i.e., time to next treatment [TTNT]), was used as a surrogate measure of PFS. Observations were censored at time of loss to follow-up or end of study period, which was June 30, 2015.

Cumulative incidence of comorbidities (RI and CVD) was obtained from medical records and/or provider notes in the 12 months prior to the start of first line therapy through the initiation of second line therapy (see Appendix). RI was identified via International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes or a lab value indicating creatinine clearance <40 mL/min or serum creatinine >2 mg/dL. CVD was identified via ICD-9 codes for conditions including acute myocardial infarction, coronary heart disease, and congestive heart failure. We developed a natural language processing (NLP) algorithm to identify cytogenetic results that may have been reported in free text in the EMR. High cytogenetic risk was defined as the presence of del[17p], t[4;14], or t[14;16] [2]. Front-line SCT was identified for SCT procedures that occurred within 300 days of diagnosis date.

2.3. Statistical Analyses

Chi-square tests for categorical variables and *t*-tests for continuous variables were used to compare patient demographic and clinical characteristics. The Kaplan–Meier method was used to estimate OS and TTNT, and the log-rank test was used to compare groups in univariate analyses. Age was dichotomized at <75 years vs ≥75 years (see Appendix). Multivariate Cox proportional hazard (PH) regression was used to estimate the impact of age, RI, and CVD on OS and TTNT from start of second line therapy, after controlling for other covariates of clinical relevance (see Appendix).

3. Results

3.1. Patient Characteristics

Among 628 patients who met the inclusion criteria for the study, 37.1% were aged ≥75 years, 51.0% were male, and 79.9% were Caucasian. A significantly higher proportion of the older patients (age ≥ 75 years) suffered from RI (with our without CVD) (67.4% vs 54.2%; $P < 0.01$) and CVD (with or without RI) (45.1% vs 31.4%; $P < 0.01$) compared to younger patients at time of initiation of second line therapy. Significantly more patients in the younger cohort (11.6% vs 6.0%; $P = 0.02$) had MM with a high-risk cytogenetic signature; however, the younger subgroup was more likely to have a cytogenetic test result documented in the medical record (28.9%) compared to older patients (19.3%). Younger patients were significantly more likely to have undergone a previous SCT (29.9% vs 2.2%, $P < 0.01$). There were more African American patients in the younger vs the older group (17.0% vs 7.7%). A significant difference in geographic region distribution by age was also noted in univariate analyses (Table 1). The median follow-up from start of second line therapy was 13 months (interquartile range [IQR]: 5.2, 23.3).

3.2. Cumulative Incidence of RI and CVD

At initiation of first-line therapy, 27.4% (n = 172) had comorbid RI without CVD, 7.6% (n = 48) had comorbid CVD without RI, 12.6% (n = 79) had both RI and CVD, and 52.3% (n = 329) of patients presented without either comorbidity. However, by initiation of second line therapy, the proportion of patients with no evidence of CVD or RI dropped to 32.2% (n = 220), while the proportion of patients with both comorbidities more than doubled to 27.7% (n = 174), and those with comorbid RI alone or CVD alone increased to 31.4% (n = 197) and 8.8% (n = 55), respectively (Fig. 1).

3.3. Treatment Patterns

A majority of patients received a novel agent in both first and second line treatment. The distribution of treatment regimens by age is shown in Table 2. Older patients were significantly less likely to receive triplet combination therapy in first line therapy (44.6% vs 24.9%; P < 0.01) and second line therapy (24.3% vs 15.0%; P < 0.01). A significantly higher proportion of younger patients also received the triplet backbone of a proteasome inhibitor (PI) combined with an immunomodulatory drug (IMID) compared to those aged ≥75 years: first-line therapy (21.8% vs 10.7%; P < 0.01); second-line therapy (11.1% vs 5.2%; P < 0.01). Older patients were more likely to receive an IMID-based therapy without a PI than younger counterparts in first line therapy (41.2% vs 28.9%, respectively; P < 0.01).

Treatment patterns based on presence or absence of comorbidities (Table 3) revealed that only a minority of patients with no pre-existing RI ± CVD received a PI plus an IMID combination in first line therapy (19.8%) and in second line therapy (8.4%). PI-based therapies predominated in first line therapy for patients with RI ± CVD, and IMID-based therapies predominated for those patients with CVD only. In second line therapy, however, patients with comorbid RI ± CVD were more likely to be treated with an IMID-based regimen (43.2%, patients with RI only; 44.3%, patients with RI and CVD). In patients with CVD, approximately one-third of patients received a PI-based or an IMID-based regimen in second line therapy (34.6% and 32.7%, respectively). The use of non-IMID and non-PI therapies increased among patients with RI or CVD in second line therapy. Descriptions of specific therapies used in second-line treatment and frequencies in the overall study population can be found in Supplemental Table 1.

Please cite this article as: Hari P, et al, The impact of age and comorbidities on practice patterns and outcomes in patients with relapsed/refractory multiple myeloma in the era of novel therapies, J Geriatr Oncol (2017), https://doi.org/10.1016/j.jgo.2017.09.007