Cancer Treatment Reviews 41 (2015) 827–835

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Tumour Review

Clinical characteristics of patients with relapsed multiple myeloma ☆

Meletios A. Dimopoulos [a,*], Evangelos Terpos [a], Ruben Niesvizky [b], Antonio Palumbo [c]

[a] National and Kapodistrian University of Athens, School of Medicine, 80 Vas. Sofias Avenue, Athens 11528, Greece
[b] Weill Cornell Medical College/New York Presbyterian Hospital, Myeloma Center, 428 East 72nd Street, Oxford 300, New York, NY 10021, United States
[c] Department of Hematology, University of Torino, Via Genova 3, 10126 Torino, Italy

ARTICLE INFO

Article history:
Received 9 March 2015
Received in revised form 13 July 2015
Accepted 26 July 2015

Keywords:
Multiple myeloma
Immunomodulatory drug
Proteasome inhibitor

ABSTRACT

Although survival outcomes have improved over the last decade for patients with multiple myeloma (MM), few patients remain free of disease and most inevitably relapse. Selecting a treatment for patients with relapsed MM is challenging given the number and diversity of regimens patients may have previously received, which can affect subsequent therapeutic choices. Importantly, a number of patient- and disease-related factors can also have an effect on treatment choice, treatment efficacy, and tolerability; thus, an understanding of the heterogeneity of patients in the setting of relapsed MM is important for appropriate treatment selection. Here, we review select patient and disease characteristics reported in key interventional and observational studies in relapsed MM (including age, sex, race, and the presence of high-risk disease, renal impairment, or peripheral neuropathy at baseline) to examine common and disparate features of patients with relapsed MM. As therapeutic regimens can have varying efficacy and/or tolerability in patients depending on these factors, we also provide treatment recommendations for patients with select baseline characteristics.

Introduction

Multiple myeloma (MM) is a common hematologic malignancy, with an estimated 24,050 new cases (13,500 in men and 10,550 in women) diagnosed in the United States in 2014, leading to approximately 11,090 deaths [1]. Survival prospects in MM have improved during the last decade [2] with the introduction of new drug regimens, including immunomodulatory drugs (IMiDs; such as lenalidomide, thalidomide, and pomalidomide), proteasome inhibitors (such as bortezomib and carfilzomib), and pegylated liposomal doxorubicin. However, despite these modern therapeutic advances, most patients relapse [3,4].

Precise definitions of "relapsed" and "refractory" MM may differ across studies. Among patients who have already received initial treatment for MM, the term "relapsed" typically refers to cases where the malignancy recurs after a remission or to patients who respond to salvage therapy but go on to experience disease progression while they are being followed with or without maintenance treatment. In contrast, patients with "refractory" MM are typically those who fail to respond (or have limited response) to salvage therapy or who progress within 60 days of their last regimen [5,6].

Selecting treatment for patients with relapsed MM is a clinical challenge that requires careful consideration of the balance between maximizing efficacy and ensuring acceptable tolerability. Patients who experience only a biochemical relapse (in which disease progression, as defined by a $\geqslant$25% increase in serum or urine M-protein, is asymptomatic [7]) may be followed closely without treatment. However, patients with high-risk disease (e.g. patients with unfavorable cytogenetics, suboptimal response to prior treatment or aggressive disease at diagnosis [8]), or who demonstrate a rapid increase in serum or urine M-protein levels (e.g. a doubling time of 2 months or less), should receive immediate treatment [9].

This review article examines the disease characteristics and demographics of patients with relapsed MM, focusing predominantly on those who have relapsed early in their treatment course (i.e. after 1–3 prior lines of treatment) and who were enrolled in phase II or III interventional trials or observational studies. This topic is of particular interest in the era of novel therapeutics, as a number of patient- and disease-related factors may affect treatment efficacy and/or tolerability, such as age, sex, race, baseline organ function, and comorbidities, performance status,

Role of the funding source: Medical writing support was provided by BlueMomentum, a division of KnowledgePoint360 Group, an Ashfield Company, and funded by Onyx Pharmaceuticals, Inc., an Amgen subsidiary. Onyx Pharmaceuticals, Inc. reviewed a final draft of the manuscript for clinical and scientific accuracy; all authors contributed in writing the manuscript and the decision to submit the manuscript for publication.

* Corresponding author. Tel.: +30 (210) 3381541; fax: +30 (210) 3381511.
E-mail addresses: mdimop@med.uoa.gr (M.A. Dimopoulos), eterpos@hotmail.com (E. Terpos), run9001@med.cornell.edu (R. Niesvizky), appalumbo@yahoo.com (A. Palumbo).

http://dx.doi.org/10.1016/j.ctrv.2015.07.005
0305-7372/

the presence of high-risk cytogenetics, International Staging System (ISS) MM stage, β_2-microglobulin level, and the degree of bone marrow involvement. It should be noted that while most demographic data specifically for patients with relapsed MM is found in the setting of clinical trials, patients enrolled in clinical trials are likely to be more uniform than those in the population seen in clinical practice, as they are carefully selected using predefined inclusion and exclusion criteria. However, keeping these caveats in mind, understanding the heterogeneity of relapsed MM patients may also provide opportunities for the personalization of treatment, and we have provided treatment recommendations for patients with select baseline characteristics.

Select baseline patient and disease characteristics

Age/frailty

Patient age is a significant prognostic factor for patients with MM, with patients who are $\geqslant$50 years of age at diagnosis displaying significantly shorter median survival times than younger patients [10]. While new treatment options have improved survival, these benefits were largely confined to the subset of patients aged <70 years [11,12], and it is only recently that survival advantages have also become evident in older patients [13].

Since older patients typically present with multiple comorbidities and treatment-related toxicities at relapse, patient populations with relapsed MM in clinical trials, which are screened with select inclusion and exclusion criteria, may largely skew toward younger and fitter patients. While the median age of patients with MM at diagnosis is ~70 years at diagnosis [14], the median patient age in interventional clinical trials in relapsed MM is frequently around 60–65 years [6,15–34], and the median time since diagnosis for these patients typically ranges from 2 to 4 years (Table 1) [6,16,18–26,28,29,33,34]. Observational studies following patients with at least one prior relapse have reported slightly higher median ages (66–69 years) [16,35], with similar median times since diagnosis (about 3–4 years) [16] compared with patients enrolled in interventional clinical trials (Table 2).

Even among patients within the same age group, physical and cognitive functions can vary widely. Measures of performance status, such as the Eastern Cooperative Oncology Group (ECOG) scale, are simple assessments of disability and have been reported to predict poor prognoses [36]. Clinical trials in MM typically exclude patients with ECOG performance status greater than 2. In the trials of patients with relapsed MM summarized in Table 1, the proportion with an ECOG performance status of 1 or 2 ranged from 34% to 61% [6,21–23,25,27–30,33,34,37,38].

Frailty indices specifically designed to include elderly patients have also been developed to assess the biological age of patients in conjunction with their chronological age in order to guide treatment decisions [39–41]. While frailty has been found to be a significant prognostic factor for patients with MM [41] and these assessments are gaining in usage, they have not yet been routinely implemented in clinical trials in the relapsed setting.

Treatment recommendations

In elderly patients with relapsed myeloma, a geriatric assessment should be performed. Patients who are fit (e.g. active patients who do not require assistance for household tasks) should receive treatments at doses and intervals similar to that of younger patients. Patients who are unfit (e.g. those who can perform limited activities) should be treated with reduced doses and longer intervals. For frail patients (e.g. patients who need help from others for household tasks or personal care), supportive care with or without attenuated anti-myeloma therapy should be considered [3,8,42,43].

Sex

MM occurs at a slightly higher incidence rate in males compared with females (7.7 new cases per 100,000 males *vs.* 4.9 new cases per 100,000 females in the United States) [14], and this is reflected in the enrollment profile of interventional and observational studies, where males make up more than half of patients enrolled (trials have reported anywhere from 51% to 73% male patients enrolled) [6,16–19,21–30,33–35,37,44,45]. However, treatment recommendations are similar for male and female patients.

Race

While MM is approximately twofold more common in blacks (14.8 new cases per 100,000 males and 10.5 new cases per 100,000 females in the United States) than in whites (7.2 new cases per 100,000 males and 4.3 new cases per 100,000 females) [14], blacks are persistently underrepresented in clinical trials. For example, in a phase III study examining vorinostat plus bortezomib versus placebo plus bortezomib in relapsed patients who had received 1–3 prior treatment regimens, 56.0% of patients were white, while only 3.3% of patients were black; patients were enrolled from 31 countries around the world [30]. Similar rates were reported in two phase III studies examining lenalidomide plus dexamethasone versus dexamethasone alone in relapsed patients: the MM-009 study patient population was 82.1% white and 11.9% black (enrolled from Europe, Israel, and Australia), while the MM-010 study patient population was 98.3% white and 0.6% black (enrolled from the United States and Canada) [46]. The phase III study ASPIRE, which evaluated carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone in patients with relapsed MM (1–3 prior regimens) from North America, Europe, and the Middle East, also enrolled a patient population that was largely white (95.2%); 2.9% of patients were black[34]. In the PX-171-004 study examining carfilzomib in patients with relapsed MM from the United States and Canada, among patients without prior bortezomib exposure, 76.0% of patients were white and 14.0% of patients were black [21]. Interestingly, similar rates of enrollment have also been reported in the ongoing real-world observational PREAMBLE study, which is examining patients who have received one or more prior regimens: 80.2% of enrolled patients are white and 16.2% are black [16].

Evidence suggests that differences exist in the clinical features of MM in blacks versus whites, such as differences in age at diagnosis, monoclonal immunoglobulin (Ig) concentrations, IgM isotype, and abnormal serum free light chain ratios [47–49]. Disease-specific survival has been reported to vary based on race, but racial and socioeconomic disparities in treatment and outcome may also play roles in these findings, as the use of transplantation and novel agents also varies based on race and health insurance [50,51]. Overall, adequately powered studies of ethnically diverse populations are needed in MM to investigate biological differences among different racial and ethnic groups in order to understand whether treatment can be optimized for these patients.

High-risk disease

High-risk chromosomal abnormalities, such as deletion of 17p13 (del17p), or chromosomal translocations t(4;14), t(14;16), and t(14;20) are associated with reduced response rates and shorter survival times [52,53]. Among patients in clinical trials of