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Tumour Review

Clinical characteristics of patients with relapsed multiple myeloma ☆

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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,

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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

Table 1
Patient demographics and disease characteristics in key interventional clinical trials in relapsed MM.

Study/ reference	Patient population/treatment	*N*	Median age (range)	Median time since diagnosis	Male sex	ECOG PS	ISS stage	Cytogenetics	β_2-Microglobulin	Renal impairment	Prior therapy
[96]	Relapsed from front-line anti-MM treatment administered in the HOVON-50 trial; treated in daily practice	139	60 (34–69)	24.9 months (range, 1.9–61.4)	58%	NR	NR	NR	>2.7 μg/mL: 78%	Median CrCl: 6 mmol/L	NR
APEX [19]	Relapsed MM (1–3 prior therapies); treated with BTZ or DEX	669	BTZ arm: 62 DEX arm: 61	BTZ: 3.5 years DEX: 3.1 years	BTZ: 56% DEX: 60%	NR	NR	NR	BTZ: 3.7 mg/L DEX: 3.6 mg/L	CrCl < 30 mL/min: 4.3% 30–50 mL/min: 15.6% 51–80 mL/min: 40.3% <80 mL/min: 39.8%	1 prior: 38% 2–3 prior: 57%
CREST [20]	Relapsed or refractory to first-line anti-MM treatment regimen; treated with BTZ or BTZ + DEX	54	63	2.0 years	NR	NR	NR	Abnormal cytogenetics: 38%	⩾4 mg/L: 53%	NR	NR
NCT00813150 [38]	Relapsed and/or refractory MM (1–3 prior therapies); treated with BTZ + DEX ± cyclophosphamide	96	71 (30–85)	NR	NR	0: 59% 1: 35% 2: 6%	NR	NR	NR	NR	1 prior: 57% 2 prior: 30% 3 prior: 9%
[37]	Relapsed or refractory MM (1–3 prior therapies); treated with BTZ + DEX + cyclophosphamide (induction) and BTZ + cyclophosphamide (maintenance)	59	69 (46–86)	NR	56%	0: 65% 1: 29% 2: 5%	NR	NR	NR	NR	1 prior: 75% 2 prior: 20% 3 prior: 5%
PX-171–004 [6,21]	Relapsed and/or refractory MM (1–3 prior therapies; split into groups with prior BTZ treatment and with no prior BTZ treatment); treated with CFZ	164 (prior BTZ: 35; no prior BTZ: 129)	Prior BTZ: 63 No prior BTZ: 65	Prior BTZ: 3.6 years No prior BTZ: 3.6 years	Prior BTZ: 51% No prior BTZ: 59%	Prior BTZ, 1 or 2: 54% No prior BTZ, 1 or 2: 60%	Prior BTZ: II or III: 43% No prior BTZ, I or II, 73%	Prior BTZ: high-risk cytogenetics 26% No prior BTZ: unfavorable cytogenetics 15%	Prior BTZ: median 3.3 mg/L No prior BTZ: NR	Prior BTZ: CrCl < 50 mL/min 11% No prior BTZ: CrCl < 50 mL/min 16%	Prior BTZ: median 3 No prior BTZ: median 2
PX-171–006 [22,23]	Relapsed or progressive MM (1–3 prior therapies); treated with CFZ + LEN + DEX	84	61.5	3.1 years	57%	In phase 2 dose-expansion, 1 or 2: 61%	NR	Unfavorable cytogenetics: 26%	NR	NR	Median 2
ASPIRE [34]	Relapsed MM (1–3 prior therapies); treated with CFZ + LEN + DEX	792	64.0 (31.0–91.0)	3.1 years	56%	0: 43% 1: 48% 2: 9%	I: 17% II: 24% III: 44%	High-risk cytogenetics: 13%	<2.5 mg/L: 19% ⩾2.5 mg/L: 81%	CrCl < 30 mL/min:<1% 30–49 mL/min: 7% 50–79 mL/min: 41% ⩾80 mL/min: 51%	Median 2 1 prior: 43% 2–3 prior: 57%
NCT00558896 [24]	Relapsed/refractory MM (1–3 prior therapies); treated with POM + DEX	60	65.5	3.7 years	60%	NR	II or III: 78%	Abnormal cytogenetics: 33% High-risk FISH: 30%	3.5 μg/dL	NR	NR
NCT00908232 [26]	Relapsed/progressed MM (1 prior therapy); treated with BTZ + DEX	163	64 (34–86)	2.6 years	53%	NR	NR	NR	NR	GFR < 15 mL/min: 3% 15–29 mL/min: 10% 30–59 mL/min: 35.6% ⩾60 mL/min: 51%	NR
DOXIL-MMY-3001 [33]	Relapsed or refractory MM (at least 1 prior therapy); treated with PLD + BTZ or BTZ	646	61 (28–88)	36.7 months	56%	0: 44% 1: 56%	NR	Abnormal cytogenetics: 18%	⩽2.5 mg/L: 14% >2.5 mg/L: 86%	Median serum creatinine: 90.0 μmol/L	1 prior: 34% ⩾2 prior: 66%
MMVAR/IFM 2005–04 [18]	Relapsed or progressed MM (first relapse after at least 1 ASCT); treated with BTZ + THAL + DEX or THAL + DEX	269	61.2 (29–76)	3.1 years	63%	NR	I: 58% II: 26% III: 16%	Abnormal cytogenetics: 41%	NR	Median serum creatinine: 79.6 μmol/L	NR

(*continued on next page*)

Table 1 (*continued*)

Study/ reference	Patient population/treatment	*N*	Median age (range)	Median time since diagnosis	Male sex	ECOG PS	ISS stage	Cytogenetics	β_2-Microglobulin	Renal impairment	Prior therapy
MUK-Six [32]	Relapsed and relapsed/ refractory MM (1–4 prior therapies); treated with PAN + BTZ + THAL + DEX	48	62 (41–76)	NR	NR	NR	I 54% II: NR III: 10%	NR	NR	NR	Median 1
HOVON-86 [45]	First relapse or primary refractory MM; treated with BTZ + LEN + DEX (reinduction) + LEN (maintenance)	77	66 (46–84)	NR	64%	NR	I: NR II: 26% III: 5%	NR	NR	NR	1 prior: 100%
NCT00378209 [25]	Relapsed and refractory MM (1–3 prior therapies); treated with LEN + BTZ + DEX	64	65 (32–83)	2.8 years	66%	NR	NR	Abnormal cytogenetics: 27%	3.3 mg/L	NR	Median 2
MM-009 [28]	Relapsed or refractory MM ($\geqslant$1 prior therapy) treated with LEN + DEX or DEX	352 LEN + DEX: 176 DEX: 175	LEN + DEX: 63 (33–84) DEX: 64 (40–82)	LEN + DEX: 3.4 years DEX: 4.0 years	LEN + DEX: 59% DEX: 58.9%	0: 41% 1: 43% 2: 14% 3:<1%	NR	NR	<2.5 mg/L: 28% $\geqslant$2.5 mg/L: 72%	NR	1 prior: 32% $\geqslant$2 prior: 68%
MM-010 [29]	Progressive MM ($\geqslant$1 prior therapy); treated with LEN + DEX or DEX	353 LEN + DEX: 177 DEX: 176	LEN + DEX: 64 (36–86) DEX: 62 (37–85)	LEN + DEX: 3.1 years DEX: 3.1 years	LEN + DEX: 60% DEX: 59%	0: 44% 1: 46% 2: 6%	NR	NR	LEN:<2.5 mg/L: 29%; $\geqslant$2.5 mg/L: 71% DEX:<2.5 mg/L: 29%; $\geqslant$2.5 mg/L: 71%	NR	1 prior: 38.2% $\geqslant$2 prior: 61.8%
NCT00773747 [30]	Non-refractory progressing MM that had previously responded to treatment (1–3 prior regimens); treated with VOR + BTZ or BTZ	637 VOR + BTZ: 317 BTZ: 320	VOR + BTZ: 61 (30–85) BTZ: 63 (29–86)	$\leqslant$2 years: 32% >2 years: 68%	NR	0: 38% 1: 52% 2: 9% 3:<1%	I: 36% II: 41% III: 24%	NR	$\leqslant$2.5 mg/L: 19% >2.5 mg/L: 80%	NR	VOR + BTZ: median 2 BTZ: median 2
[54,55]	Relapsed/refractory MM ($\leqslant$4 prior therapies); treated with BEN + BTZ + DEX	75	68 (41–85)	NR	45%	NR	I-II: 74% III: 27%	High-risk cytogenetics: 22%	NR	NR	Median 1 1 prior: 53% 2 prior: 29% 3 prior: 8% 4 prior: 10%
NCT01701076 [44]	Relapsed/refractory MM (1 prior therapy); treated with BEN + LEN + DEX	50	68 (46–84)	NR	73%	NR	II or III: 49%	High-risk cytogenetics: 13%	NR	NR	1 prior: 100%
PANORAMA-1 [27]	Relapsed or relapsed and refractory MM (1–3 prior regimens); treated with PAN + BTZ + DEX or BTZ + DEX	768 PAN + BTZ + DEX: 387 BTZ + DEX: 381	PAN + BTZ + DEX: 63 (56–69) BTZ + DEX: 63 (56–68)	NR	53.0%	0: 44% 1: 49% 2: 6%	I: 40% II: 26% III: 21%	NR	NR	CrCl 60–89 mL/min: 66.9% $\geqslant$90 mL/min: 32.4%	1 prior: 51.4% 2 prior: 30.2% 3 prior: 18.1%

ASCT: autologous stem cell transplantation; BEN: bendamustine; BTZ: bortezomib; CFZ: carfilzomib; CrCl: creatinine clearance; DEX: dexamethasone; ECOG PS: Eastern Cooperative Oncology Group performance status; FISH: fluorescent in situ hybridization; GFR: glomerular filtration rate; ISS, International Staging System; LEN: lenalidomide; MM: multiple myeloma; NR: not reported; PAN: panobinostat; PLD: pegylated liposomal doxorubicin; POM: pomalidomide; THAL: thalidomide; VOR: vorinostat.

Table 2
Patient demographics and disease characteristics in select observational studies in MM.

Study/ reference	Patient population	*N*	Median age (range)	Time since diagnosis[a]	Male sex	ECOG PS	ISS stage	Cytogenetics	β2-Microglobulin	Renal impairment	Prior therapy[a]
PREAMBLE [16,90]	Relapsed or refractory MM in real-world daily practice	111	IMiD: 66 (43–87) PI: 69 (37–86) IMiD + PI: 67.5 (52–87)	IMiD: 3.6 years PI: 3.5 years IMiD + PI: 2.8 years	52.3%	NR	I: 20% II: 20% III: 25%	High-risk cytogenetics: 16%	NR	NR	1 prior: 47% 2 prior: 30% ⩾3 prior: 22%
[17]	Followed patients with newly diagnosed MM through relapse at a single institution	578	65	NR	61%	NR	NR	NR	>2.7 μg/mL: 78%	Median creatinine: 1.3 mg/dL	NR

ECOG PS: Eastern Cooperative Oncology Group performance status; IMiD: immunomodulatory agent; ISS: International Staging System; MM: multiple myeloma; NR: not reported; PI: proteasome inhibitor.
[a]Updated data presented at the 2014 Annual Meeting of the American Society for Hematology for 189 patients: time since diagnosis (all regimens), 41.0 months; 1 prior therapy, 49%, 2 prior therapies, 32%.

relapsed MM, high-risk cytogenetics have been reported in a minority of patients, although it should be noted that many trials also report a substantial number of patients with unknown cytogenetic status [6,18,20–25,34,54,55]. Different trials have utilized varying definitions for the category of high-risk cytogenetics [6,18,20–25,54]. Rates have ranged from 15% (for patients with del17p, t(4;14), t(14;16), or hypoploidy) [21] to 30% (for patients with del17 or del17p, t(4;14), or t(14;16)) [24], while abnormal cytogenetics without definition of the specific aberrations were reported in 41% of patients enrolled in a clinical trial examining patients in their first relapse [18]. The real-world observational PREAMBLE study reported that 16% of patients had high-risk cytogenetics as defined by fluorescence *in situ* hybridization (FISH) [16].

Beyond cytogenetics, other indicators of high-risk disease include tumor burden and staging [56]. β_2-Microglobulin is a serum marker of tumor burden in patients with MM and has been shown to be prognostic for patient survival [57–59]. The majority of patients with relapsed MM in clinical trials have moderately high levels of β_2-microglobulin, typically above 2.5 mg/dL. Median values of β_2-microglobulin in trials in this setting have ranged from 2.7 mg/L [15] to 3.7 mg/L [19], and 70–80% of patients were reported to have β_2-microglobulin >2.5 mg/L [28–30,34].

Serum β_2-microglobulins and albumin form the basis of ISS [50]. Between 31% and 78% of patients with relapsed MM who are enrolled in clinical trials have ISS stage II or III disease at the time of enrollment [6,18,24,25,27,30,34,44,45,60], and a somewhat similar rate of ISS stage II or III disease was reported in the observational PREAMBLE study (45%) [16].

While ISS stage and high-risk cytogenetics are each prognostic indicators in their own right, studies have shown that patients with high-risk disease determined by a combination of ISS staging (e.g. ISS stage II or III) and FISH (e.g. t(4;14) and/or del17p13) have poorer prognoses than other patients, although these studies have focused on newly diagnosed MM patients [61–63].

Patients with relapsed myeloma may present with elevated serum lactate dehydrogenase (LDH) and/or extramedullary involvement [64,65], features which indicate high-risk disease [65,66]. Elevated LDH has been found to be an adverse prognostic indicator for survival in patients with MM [67,68]. Extramedullary disease is generally associated with poor outcomes [65], while extramedullary relapses are associated with lower overall survival and increased risk of bone plasmacytomas or fractures [64].

Treatment recommendations

As secondary genetic events are present in the relapse of myeloma, patients should be checked at the time of relapse for the presence of del17p, at a minimum. This is an important consideration, as patients with relapsed myeloma and del17p may benefit from treatment with newer IMiDs (i.e. pomalidomide) [69] or more aggressive procedures. Patients with t(4;14) may benefit from the use of proteasome inhibitor-based treatment [70,71]. Patients with extramedullary disease may be candidates for treatment with infusional chemotherapy with or without novel agents (i.e. PACE, (V)DT-PACE, etc.) [72].

Renal impairment

Renal function is an important characteristic in patients with MM, as the development of renal failure is a negative prognostic factor for patient survival [73–75]. Renal dysfunction is a common comorbidity in patients with MM, as excess monoclonal light chain production associated with the disease often leads to kidney complications. In the relapsed setting, the overproduction of the involved free light chain may lead to cast nephropathy, which may or may not be present at diagnosis. A number of patients (5–15%) may present with "light chain escape" at relapse and thus may develop renal impairment which was not present at diagnosis [76]. Furthermore, amyloidosis may be another cause underlying renal impairment, typically in patients at the late stage of their disease. In addition, a number of anti-MM agents are eliminated via the kidneys (such as melphalan, prednisone, or lenalidomide), necessitating careful selection of treatment regimens for patients with renal impairment [77–81]. For this reason, clinical trials in relapsed MM typically exclude patients with poor renal function (e.g. creatinine clearance [CrCl] ⩽ 30 mL/min).

In the MM-009 and MM-010 studies, 4.1% of patients had severe (CrCl < 30 mL/min), 11.1% had moderate (30–49 mL/min), and 37.7% had mild renal impairment (50–79 mL/min); nearly half of patients (47.1%) had normal renal function (⩾80 mL/min) [82]. Using similar definitions in the APEX study, which examined patients with relapsed MM (1–3 prior therapies) receiving bortezomib versus dexamethasone, 4.3% of patients had severe renal impairment, 15.6% had moderate impairment and 40.3% had mild impairment; 39.8% of patients had normal renal function (>80 mL/min) [83]. Similar results were reported in the ASPIRE study, where 0.1% of patients had severe renal impairment, 7.1% had moderate impairment, 40.9% had moderate impairment, and more than half (51.0%) had normal renal function [34]. In a phase II study in patients receiving bortezomib and dexamethasone as second-line therapy with no eligibility restrictions based on renal function, patients with severe or moderate renal impairment were enrolled at slightly higher rates, although the investigators used different cutoff values for reporting patient renal function: 12.9% of patients had glomerular filtration rate (GFR) < 30 mL/min, 35.6% had GFR 30–59 mL/min, and 50.9% had GFR ⩾ 60 mL/min

[26]. On the other end of the spectrum, in the PX-171-004 study, severe or moderate renal impairment (CrCl < 50 mL/min) was reported in only 11.4% of patients with prior bortezomib treatment and 15.5% of patients who were bortezomib-naive [6,21].

Treatment recommendations

Patients with renal impairment should be treated with agents that are excreted extrarenally, such as proteasome inhibitors (bortezomib or carfilzomib) [84,85]. Dose adjustments may be needed in patients with moderate or severe renal impairment who are treated with agents predominantly excreted via the kidney, such as lenalidomide [81]. Pomalidomide can also be used in patients with relapsed MM [86].

Prior or existing peripheral neuropathy (PN)

PN is a common occurrence in patients with relapsed MM, resulting from complications of the disease and treatment-related toxicities. Patients who have previously received thalidomide or bortezomib may have residual PN due to the prior use of these drugs. Clinical trials in the relapsed setting often exclude patients with severe PN at baseline. For example, the PX-171-004, PX-171-006, and ASPIRE studies of carfilzomib treatment in patients with relapsed MM required that enrolled patients not have had PN that was grade 3 or 4, or grade 2 with pain at baseline. Despite these restrictions, 53% of patients in PX-171-004 and 36% of patients in ASPIRE had PN at baseline [6,21], and 70–83% of patients in the PX-171-004 and PX-171-006 studies had a history of PN [21,22]. The phase II study NCT00558896 of pomalidomide plus low-dose dexamethasone in relapsed or refractory patients also excluded patients with grade 3 or 4 PN, and 45% of enrolled patients had PN at baseline [24]. A phase II study examining bortezomib as second-line treatment (NCT00908232) excluded patients with grade 2 or higher PN, and 22% of patients had PN at baseline [26]. These findings illustrate the prevalence of PN in the relapsed MM patient population, especially considering that PN-based exclusion criteria were used.

Treatment recommendations

As thalidomide or intravenous bortezomib have been associated with the development of PN, patients with pre-existing PN should be treated with other agents [87,88]. A phase III study has demonstrated that subcutaneous bortezomib may be a suitable alternative as well, as it has been demonstrated to have reduced neuropathy toxicity relative to intravenous administration [89].

Prior therapies received

The number and type of prior therapies received can have important implications for patient treatment options and prognoses. Research has shown that the duration of patient responses decreases with each successive regimen received, which is possibly due to the development of therapeutic resistance [17]. As new agents become available, the spectrum of regimens that patients have been previously treated with evolves accordingly.

In a real-world observational study conducted between 1985 and 1998, of 578 patients followed from diagnosis, 0% received thalidomide in their first-line regimen, and only 7% received thalidomide at any point during their treatment course [17]. In contrast, latest data from 189 patients enrolled in the multi-national observational study PREAMBLE, which was initiated in 2012, show that IMiDs were administered as first-line treatment in 46% of patients (of whom 35% were from North America and 66% were from Europe), and 46% of patients received proteasome inhibitors first-line (of whom 48% were from North America and 52% were from Europe). Most patients receiving first-line treatment consisting of an IMiD combined with a proteasome inhibitor ($n = 15$) were from North America (80%) [90].

In clinical trials in which enrolled patients had received 1–3 prior regimens but which had no other restrictions on the types of prior treatment patients could have received (i.e. the PX-171-004, PX-171-006, and ASPIRE trials examining carfilzomib-based regimens, and the NCT00558896 trial examining pomalidomide-based treatment), between 21% and 77% of patients had received prior bortezomib [6,23,24,34], and between 20% and 70% of patients had received prior lenalidomide [23,24,34]. These large ranges may, in part, be indicative of the continuing evaluation of how to best use these newer anti-MM agents. While not reported in PX-171-004, rates of prior transplantation were similar in the PX-171-006 and NCT0055896 trials (65% and 65%) and slightly lower in the ASPIRE study (56%) [23,24,34]. Rates of prior thalidomide were also similar in the PX-171-006 and NCT00558896 trials (46% and 47%, respectively) [23,24].

Treatment recommendations

The specific agents and classes of treatment patients have previously received are important considerations when evaluating how to treat MM that has progressed. In patients with relapsed disease, re-treatment with agents from the initial regimen may be considered in patients who achieved a partial response or better and a remission lasting 12 months or longer following initial treatment [91–94]. Patients who relapse rapidly following initial treatment should receive a different class of agents from their original treatment [95].

Discussion

While some patient characteristics are similar across studies in relapsed MM (such as sex or median age), others vary dramatically from study to study (such as prevalence of high-risk disease or renal impairment). These variations may originate from a number of factors, the most predominant of which may be the specific clinical questions being addressed in a given trial, including the treatment regimen(s) that are being investigated. Trial enrollment criteria can vary significantly from trial to trial to select an appropriate patient population for investigation and can result in large differences in patient demographics between trials. It should also be noted that while some of the trials reviewed here focused on patients with relapsed MM only, other trials included patients with relapsed and/or refractory MM, which represents a patient population more likely to have a poorer prognosis and/or baseline comorbidities.

Observational studies tend to have less stringent eligibility criteria than interventional clinical trials and so may be expected to report a higher degree of heterogeneity across their enrolled patient populations and thus be more similar to a real-world population. Unfortunately, there have been few observational studies conducted in patients with relapsed MM, and those few have reported limited information on patient demographics and disease characteristics. Additional observational studies in relapsed MM are needed to better understand how results from interventional clinical trials may best be applied to diverse patient groups outside a clinical trial setting.

Possessing greater knowledge of the demographic and baseline disease characteristics of patients enrolled in clinical trials is important for interpreting results and practically applying clinical trial findings toward patient treatment. In this respect, data from both clinical trials and real-world studies can inform individual treatment decisions by providing an indication of how a particular patient may benefit from certain therapeutic approaches at each stage of disease, while keeping in mind the level of response

achieved with previous treatment. While patients with relapsed MM are a challenging patient population to treat, an awareness of the individual patient's unique clinical presentation can be valuable in helping to guide treatment choices to ultimately arrive at the most beneficial outcome for each patient.

Author contributions

All authors participated in the preparation of the manuscript and contributed to initial drafts, edited version, and final version. All the authors read and approved the final version before submission. M.A.D proposed the concept for the manuscript.

Conflict of interest statement

M.A.D. has served as a consultant for Celgene, Centocor Ortho Biotech, and Onyx Pharmaceuticals. E.T. has received honoraria from Onyx Pharmaceuticals, Janssen-Cilag, and Celgene, received research funding from Janssen-Cilag, and served as an advisor for Onyx Pharmaceuticals. R.N. has served as a consultant and received research funding from Celgene, Millennium, and Onyx Pharmaceuticals, and has served on speaker bureaus for Celgene, Millennium, and Onyx Pharmaceuticals. A.P. has served as a consultant or advisor for and received honoraria from Amgen, Bristol-Myers Squibb, Celgene, Janssen, Millennium, and Onyx Pharmaceuticals.

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