Current treatment landscape for relapsed and/or refractory multiple myeloma

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Abstract | Recent developments in the treatment of multiple myeloma have led to improvements in response rates and to increased survival; however, relapse is inevitable in almost all patients. Recurrence of myeloma is typically more aggressive with each relapse, leading to the development of treatment-refractory disease, which is associated with a shorter survival. Several phase II and III trials have demonstrated the efficacy of recently approved agents in the setting of relapsed and/or refractory multiple myeloma, including immunomodulatory agents, such as lenalidomide and pomalidomide, and proteasome inhibitors, such as bortezomib and carfilzomib. Currently, however, there is no standard treatment for patients with relapsed and/or refractory disease. This Review discusses the current treatment landscape for patients with relapsed and/or refractory multiple myeloma and highlights disease-related and patient-related factors—such as pre-existing comorbidities or toxicities—that are important considerations for clinicians when selecting an appropriate treatment regimen.

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Introduction

Multiple myeloma (MM), the second most common haematological malignancy in the USA and Europe,[1,2] is caused by the uncontrolled proliferation of monoclonal plasma cells, resulting in the production of monoclonal immunoglobulin (also known as 'M-protein') and substantial immunosuppression and end-organ damage, including direct and indirect effects on the blood, skeleton, and kidneys.[3] Despite the fact that recent treatment options for this disease have led to improved response rates and increased survival, most patients with MM will ultimately relapse.[4] Although second and later remissions can be achieved with additional treatment, tumours typically recur more aggressively after each relapse, leading to decreased duration of response (DOR) and ultimately culminating in the development of treatment-refractory disease, which is associated with shortened survival times (median survival of 9 months).[3,5]

In patients with MM, the amount of M-protein in the serum or urine is used to measure disease progression and response to therapy. Some patients who initially respond to treatment have an early 'biochemical relapse' when disease progression occurs, which is defined as a ≥25% increase of serum and/or urine M-protein from its lowest value, that is asymptomatic and occurs without evidence of end-organ damage.[6] Such patients might not need immediate treatment but instead require close follow-up, provided they are carefully restaged to ensure the absence of more-widespread disease. However, in patients who experience a rapid increase of M-protein while in biochemical relapse (doubling time of 2 months or less), treatment is recommended to avoid an imminent complication. Patients whose disease progression is associated with not only an increase in M-protein level but also with other symptoms and/or end-organ dysfunction (such as development of new lytic bone lesions and/or soft plasmacytomas, increase in size of residual bone lesions, development of hypercalcaemia, decreasing haemoglobin, and worsening renal function) are considered to have clinical relapse and are to be treated promptly.[7]

In patients with relapsed and/or refractory disease, although multiple therapeutic options exist, there is no uniform standard treatment.[8] Disease-related and patient-related factors must be considered when evaluating treatment choices. In this Review, we provide an overview of the current treatment landscape for patients with relapsed and/or refractory MM, focusing on results from phase II and III trials, and critically discuss treatment options in determining optimal regimens of approved agents.

Definitions

The three patient populations included in studies of relapsed and/or refractory MM include the relapsed but not refractory group, the primary refractory group, and the relapsed-and-refractory group. The relapsed MM group consists of patients with active disease who have received one or more prior therapies and whose disease is

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Competing interests
M.A.D. has served as a consultant for Celgene, Centocor Ortho Biotech, Inc., and Onyx Pharmaceuticals, Inc. P.G.R. has served as a member of advisory committees for Bristol–Myers Squibb, Celgene, Genmab, Johnson & Johnson, Millennium Pharmaceuticals, Novartis and Onyx, and has received research funding from Celgene and Millennium Pharmaceuticals. P.M. has served as a consultant and as a member of a speakers bureau for Celgene, Millennium Pharmaceuticals, Inc., and Onyx Pharmaceuticals, Inc. K.C.A. has received compensation as a member of the scientific advisory boards of Celgene, Gilead, Onyx Pharmaceuticals, Inc., and Sanofi-Aventis, and is one of the scientific founders of Acetylon and Oncopep.

Key points

- There is currently no uniform standard of care for the treatment of patients with relapsed and/or refractory multiple myeloma (MM), but combination regimens are generally preferred over monotherapy
- Incorporation of immunomodulatory drugs and proteasome inhibitors into anti-MM treatment regimens has improved survival rates in these difficult-to-treat patients
- Each anti-MM agent is associated with a distinct safety profile that can impact treatment selection and its use in combination with other agents
- An understanding of disease-related and patient-related factors, as well as treatment-related toxicities, is critical for evaluating appropriate therapeutic options for each patient

not refractory to the most recent treatment. Patients within the relapsed-and-refractory MM group are defined as patients with disease relapse who have achieved minimal response (a reduction in serum or urinary M-protein >25%) or with progressive disease while on salvage therapy or disease progression within 60 days of last therapy. The primary refractory group consists of patients who have failed to achieve minimal response or better, including 'non-responding but non-progressing' patients who have no significant change in M-protein levels and no evidence of clinical progression and patients with primary refractory progressive disease. For the purposes of this Review, we have specifically focused our discussion on studies of patients in the relapsed or relapsed-and-refractory setting, as trials enrolling patients in these settings often exclude patients with primary refractory disease.

Treatment of relapsed MM

A number of treatment options are available for patients with relapsed disease, which include the use of salvage autologous stem-cell transplantation (ASCT), targeted agents (such as immunomodulatory drugs [IMiDs] or proteasome inhibitors), chemotherapy (including cyclophosphamide, bendamustine, doxorubicin, vincristine, cisplatin, etoposide, and melphalan), and corticosteroids.

Salvage ASCT

In Europe and the USA, high-dose therapy followed by ASCT is a standard of care for patients with newly diagnosed MM who are transplant-eligible, with ongoing studies evaluating the optimal timing of early versus late ASCT in the setting of novel agents.[9] A second ASCT has been shown to be beneficial and safe for some patients who relapse following an initial ASCT, with reported overall response rates (ORRs) ranging from 80–93%.[10,11] Patients who achieve a durable response (at least ≥18–24 months) after their initial ASCT seem to benefit the most from a second transplantation, particularly if the progression-free interval is 3 years or longer.[11,12] Other factors associated with improved progression-free survival (PFS) and overall survival include disease sensitive to reinduction before the use of salvage ASCT; stage I disease before receipt of salvage ASCT, according to the International Staging System; and use of bortezomib-containing or lenalidomide-containing regimens for reinduction.[11] These findings suggest that the use of novel agents and salvage ASCT might represent complementary rather than alternative approaches for the treatment of patients with MM.

Thalidomide

Thalidomide was the first IMiD evaluated in patients with MM; although used widely to treat patients with relapsed MM, it is not approved for this indication in Europe or the USA (Table 1).[13] A meta-analysis by Glasmacher *et al.*[14] examining 42 phase II trials of thalidomide monotherapy

Table 1 | Regional indications for immunomodulatory drugs and proteasome inhibitors for MM

Agent	Europe (http://www.emea.europe.eu)	USA (http://www.fda.gov)
Thalidomide	Combination with melphalan and prednisone to treat patients ≥65 years of age with newly diagnosed MM or who cannot be treated with high-dose chemotherapy	Combination with dexamethasone for patients with newly diagnosed MM
Lenalidomide	Combination with dexamethasone for patients with relapsed MM (≥1 prior therapy)	Combination with dexamethasone for patients with relapsed MM (≥1 prior therapy)
Pomalidomide	Combination with dexamethasone for patients with relapsed and refractory MM (≥2 prior therapies, including lenalidomide and bortezomib, with disease progression on the last treatment)	Combination with low-dose dexamethasone for relapsed and refractory MM (≥2 prior therapies, including lenalidomide and bortezomib, with disease progression ≤60 days after completion of the last treatment)
Bortezomib	Combination with melphalan and prednisone for patients with newly diagnosed MM who cannot be treated with high-dose chemotherapy or with a bone marrow transplant Combination with dexamethasone or with dexamethasone with thalidomide for patients with newly diagnosed MM who are eligible for bone marrow transplant As a single agent or in combination with pegylated liposomal doxorubicin or dexamethasone for patients who failed to respond to ≥1 prior therapy and who have already had or cannot undergo a bone marrow transplant	Treatment of patients with MM
Carfilzomib	Not yet approved in Europe for MM	Treatment of patients with relapsed and refractory MM (≥2 prior therapies, including an immunomodulatory agent and a proteasome inhibitor, with disease progression ≤60 days after completion of the last treatment)

Abbreviation: MM, multiple myeloma.

Table 2 | Results from select trials in relapsed MM

Reference	Patients (*n*)	Dose and schedule	ORR % (CR %)	Median overall survival
Glasmacher *et al.* (2006)[14]	1,674	THAL: 50–800 mg/d	29 (1.6)	14.0 months 60% at 1 year
Palumbo *et al.* (2004)[16]	120	THAL: 100 mg/d DEX: 40 mg/d (days 1–4 of each month)	46–56	19.0 months–not reached
Dimopoulos *et al.* (2009)[23]	704	LEN: 25 mg/d (days 1–21 of 28-day cycle) DEX: 40 mg/d (days 1–4, 9–12, 17–20 cycles 1–4; days 1–4 cycles 5+)	61 (15)	38.0 months
Richardson *et al.* (2005)[27]	669	BTZ: 1.3 mg/m^2 days 1, 4, 8, 11 for eight 21-day cycles, then days 1, 8, 15, 22 for three 35-day cycles	38 (6)	80% at 1 year
Dimopoulos *et al.* (2013)[32]	384	21-day cycles: BTZ: 1.3 mg/m^2 days 1, 4, 8, 11 DEX: 20 mg days 1, 2, 4, 5, 8, 9, 11, 12	75	Not reached 79% at 1 year
Garderet *et al.* (2012)[33]	269	THAL: 200 mg daily DEX: 40 mg for 4 days every 3 weeks BTZ: 1.3 mg/m^2 days 1, 4, 8, 11 for eight 21-day cycles, then days 1, 8, 15, 22 for four 42-day cycles	86 (25)	71% at 2 years
Dimopoulos *et al.* (2004)[36]	53	28-day cycles: CYC: 150 mg/m^2 days 1–5 THAL: 400 mg days 1–5, 14–18 DEX: 20 mg/m^2 days 1–5, 14–18	60 (5)	17.5 months
Schey *et al.* (2010)[37]	31	28-day cycles: CYC: 300–700 mg on days 1, 8 LEN: 25 mg, days 1–21 DEX: 20 mg, days 1–4, 8–11	81 (29)	80% projected for 30 months
Kropff *et al.* (2007)[38]	54	BTZ: 1.3 mg/m^2 days 1, 4, 8, 11 for eight 21-day cycles, then days 1, 8, 15, 22 for three 35-day cycles DEX: 20 mg on day of and day after BTZ CYC: 50 mg/d	82 (16)	22.0 months
Lentzsch *et al.* (2012)[34]	29	28-day cycles: BEN: 75–100 mg/m^2 days 1, 2 LEN: 5–10 mg days 1–21 DEX: 40 mg weekly	52 (0)	93% at 1 year
Ludwig *et al.* (2013)[35]	79	28-day cycles: BEN: 70 mg/m^2 days 1, 4 BTZ: 1.3 mg/m^2 days 1, 4, 8, 11 DEX: 20 mg days 1, 4, 8	61 (15)	25.6 months
Orlowski *et al.* (2007)[40]	646	21-day cycles: BTZ: 1.3 mg/m^2 days 1, 4, 8, 11 PLD: 30 mg/m^2 day 4	44 (4)	76% at 15 months
Palumbo *et al.* (2008)[41]	64	28-day cycles: BTZ: 1.3 mg/m^2 days 1, 4, 8, 11 DEX: 40 mg days 1–4 DOX: 20 mg/m^2 days 1, 4 or PLD: 30 mg/m^2 day 1	67 (9)	66% at 1 year
Baz *et al.* (2006)[42]	62	28-day cycles: PLD: 40 mg/m^2 day 1 VIN: 2 mg day 1 DEX: 40 mg days 1–4 LEN: 5–15 mg days 1–24	75	Not yet reached
Lee *et al.* (2003)[39]	236	DEX: 40 mg/day for 4 days THAL: 400 mg/day CIS: 10 mg/m^2 for 4 days DOX: 10 mg/m^2 for 4 days CYC: 400 mg/m^2 for 4 days ETOP: 40 mg/m^2 for 4 days	40 (31)	NR

Abbreviations: BEN, bendamustine; BTZ, bortezomib; CIS, cisplatin; CR, complete response; CYC, cyclophosphamide; DEX, dexamethasone; DOX, doxorubicin; ETOP, etoposide; LEN, lenalidomide; MM, multiple myeloma; NR, not reported; ORR, overall response rate; PLD, pegylated liposomal doxorubicin; THAL, thalidomide; VIN, vincristine.

in patients with relapsed and/or refractory MM showed an ORR (partial response or better) of 29%, 1-year overall survival rate of 60%, and median overall survival of 14 months (Table 2). In this analysis, a wide range of thalidomide doses are included, with intermediate thalidomide doses ranging from 200–800 mg/day.[14] The optimal dose of thalidomide can vary from patient to patient; however, higher doses and longer treatment

duration have been associated with increased frequency and severity of thalidomide-related adverse events, particularly that of peripheral neuropathy.[15] The addition of dexamethasone to thalidomide has improved outcomes, resulting in an increased ORR of approximately 55% in patients with relapsed MM, including patients refractory to single-agent thalidomide.[16,17] These findings indicated that the anti-MM activities of the two agents act synergistically, possibly through the induction of dual apoptotic cascades, as suggested by preclinical data demonstrating that caspase-8 and caspase-9 are activated by IMiDs and dexamethasone, respectively.[18–21]

Lenalidomide

The thalidomide derivative lenalidomide was developed to be a more-potent drug while minimizing some of the toxicity that has been associated with thalidomide use, including decreased incidence of peripheral neuropathy.[22] Regulatory approval of lenalidomide in Europe and the USA was based on the pivotal phase III studies MM-009 and MM-010, which showed that the combination of lenalidomide and dexamethasone greatly improved response rates compared with dexamethasone alone in patients with relapsed MM. A pooled analysis of both studies ($n = 704$) demonstrated that treatment with dexamethasone combined with lenalidomide led to superior ORR (60.6% versus 21.9%; $P < 0.001$), median time-to-progression (TTP; 13.4 months versus 4.6 months; $P < 0.001$), and median overall survival (38.0 months versus 31.6 months; $P = 0.045$) compared with dexamethasone plus placebo.[23] When the dexamethasone plus lenalidomide combination was administered as second-line therapy in patients with relapsed or refractory MM, ORR was 66.9%, median TTP was 17.1 months, and median overall survival was 42 months.[24] Following its regulatory approval, lenalidomide is now commonly used in the relapsed setting in Europe and the USA.

Bortezomib

The proteasome inhibitor bortezomib was initially approved for use in treating MM in both Europe and the USA based on results from the SUMMIT trial.[25] Both regions have approved bortezomib across broad indications in MM, although the specific labelling language describing the therapeutic indications differs somewhat in each region due to differences in the regulatory approval processes.[26] In Europe, bortezomib is approved for use in combination with melphalan and prednisone for patients with newly diagnosed MM who are ineligible for stem cell transplantation, or in combination with dexamethasone with or without thalidomide in patients who are eligible for stem cell transplantation, or as a single agent or in combination with pegylated liposomal doxorubicin or dexamethasone in patients who failed to respond to at least one other treatment and who have already had a transplant or who are ineligible for transplant. In the USA, bortezomib is broadly approved for use in the treatment of patients with MM, and it is specifically approved for use with melphalan and prednisone in patients with previously untreated MM. Bortezomib has also been recently approved in the USA for re-treatment in patients who had previously responded to bortezomib treatment and who relapsed at least 6 months after completing their bortezomib treatment.

Approvals of bortezomib in both regions were also based on the results of the phase III study APEX, which examined bortezomib given intravenously in patients with relapsed MM ($n = 669$).[27] In this trial, bortezomib treatment improved ORR (38% versus 18%, $P < 0.001$), median TTP (6.2 months versus 3.5 months, $P < 0.001$), and 1-year survival rates (80% versus 66%, $P = 0.003$) relative to high-dose dexamethasone.[27] Following further follow-up, patients in the bortezomib arm had a longer median overall survival than patients in the high-dose dexamethasone arm (29.8 months versus 23.7 months; $P = 0.027$), despite more than 60% of patients in the dexamethasone arm crossing over to receive bortezomib.[28]

As observed with thalidomide and lenalidomide, the addition of dexamethasone to bortezomib led to improved response rates in comparison with patients who received bortezomib alone.[29–31] A retrospective study across three clinical trials ($n = 384$) also demonstrated significantly higher ORR (75% versus 41%, $P < 0.001$) and longer median PFS (11.9 months versus 6.4 months) and median TTP (13.6 months versus 7.0 months) in patients with MM treated at first relapse with bortezomib and dexamethasone compared with treatment with bortezomib alone.[32]

Combination regimens

Three-drug regimens are frequently used to treat patients with relapsed MM, and data indicate that these combinations might demonstrate superior efficacy in terms of response rates, whereas their effect on PFS and overall survival are not as clear. Common triplet combination regimens use thalidomide, bortezomib, and/or lenalidomide as backbone agents, in addition to an alkylator and/or corticosteroid. However, most of these triplet combinations have only been evaluated in phase II studies in the relapsed MM setting. There has been only one phase III prospective study to date reporting on a triplet combination (bortezomib, thalidomide, and dexamethasone [VTD]) compared with a two-drug combination (thalidomide and dexamethasone) in patients who relapsed after receiving ASCT.[33] The investigators found that PFS was superior in the triplet arm (18.3 months versus 13.6 months; $P = 0.001$) and that there was a trend towards improved overall survival in patients receiving VTD (Table 2).

The addition of the alkylating agents bendamustine or cyclophosphamide to dexamethasone plus an IMiD (that is, lenalidomide or thalidomide) or bortezomib was effective and well tolerated.[34–39] For example, the combination of bendamustine and dexamethasone has resulted in an ORR of 52% when combined with lenalidomide[34] and of 61–75% when combined with bortezomib in patients with relapsed MM.[35] Furthermore, cyclophosphamide and dexamethasone combined with thalidomide yielded an ORR of 60% in a single-arm

Table 3 | Treatment recommendations for patients with relapsed MM

Patient characteristics	Lenalidomide	Thalidomide	Bortezomib
Renal impairment	±	+	+
Prior history of cancer	±	+	+
VTE risk	–	–	+
Pre-existing peripheral neuropathy	+	–	–
Poor-risk cytogenetics	–	–	+

Abbreviations: –, not recommended; +, recommended; ±, may be considered; MM, multiple myeloma; VTE, venous thromboembolism.

phase II study in patients with relapsed MM,[36] whereas higher ORRs have been reported when the two agents are combined with lenalidomide (81%) in patients with relapsed/refractory MM[37] or bortezomib (82%) in patients with relapsed MM.[38] The combination of thalidomide with dexamethasone and infusional chemotherapy, such as cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE), is effective in patients with relapsed MM, with a reported ORR of 40%.[39]

Regulatory agencies in Europe and the USA have approved the combination of bortezomib with pegylated liposomal doxorubicin (PLD) for bortezomib-naive patients who have received at least one prior therapy. This approval is based on the results from a phase III trial (DOXIL-MMY-3001; $n = 646$), which demonstrated that this combination resulted in a longer median TTP (9.3 months versus 6.5 months, respectively), a longer median DOR (10.2 months versus 7.0 months, respectively), and a similar ORR (44% versus 41%) when compared with bortezomib monotherapy.[40] Dexamethasone added to bortezomib and doxorubicin or PLD have also been found to be effective combination regimens.[41] PLD combined with lenalidomide, dexamethasone, and vincristine (DVd-R) resulted in high response rates (75%) in a phase I/II trial,[42] with lower rates of peripheral neuropathy relative to those previously reported with the combination of PLD, thalidomide, dexamethasone, and vincristine (DVd-T) (5% grade 3/4 peripheral neuropathy with DVd-R versus 20% with DVd-T).[43]

Finally, combinations of both an IMiD and a proteasome inhibitor are being examined based on the rationale that the two classes of agents might have synergistic effects when used together. Such combinations include VTD; lenalidomide, bortezomib, and dexamethasone[44,45] or lenalidomide, bortezomib, dexamethasone, and PLD,[46] with very promising activity and favourable tolerability reported with these regimens. Specifically, ORRs of 50–70% and encouraging median overall survival of ≥25 months have been reported with these combinations.[44–46] The addition of bortezomib and thalidomide to melphalan and prednisone or dexamethasone has been shown to be effective in patients with relapsed MM,[47,48] as has the combination of melphalan and prednisone with lenalidomide and thalidomide.[49]

Treatment recommendations

At relapse, patients with MM can either repeat the therapy they received initially or switch to a different treatment regimen. This decision can be influenced by a wide range of factors, including drug availability in the specific country, patient age, comorbidities, performance status, prior treatment received, the duration of remission to the frontline regimen, and toxicities that could have developed from prior treatment.

While anti-MM treatments have proved efficacious in patients with relapsed MM, their use is associated with significant adverse effects that can affect treatment choice. For this reason, elderly and frail patients are usually treated with mild, low-dose regimens, typically thalidomide or bortezomib combined with either melphalan and prednisone or cyclophosphamide and dexamethasone.[50–52]

Because of the nature of the disease, anti-MM treatments are frequently associated with some degree of myelosuppression (including neutropenia and thrombocytopenia).[53–56] In addition, thalidomide and lenalidomide, either alone or in combination, have been associated with an increased risk of venous thromboembolism (VTE).[14,57] Patients at risk for VTE, therefore, should avoid an IMiD-based regimen (Table 3),[52] although a retrospective analysis of the MM-009 and MM-010 trials with lenalidomide and dexamethasone suggested that the development of VTE did not adversely affect survival.[58]

As lenalidomide is predominantly excreted via the kidneys, dose adjustment may be needed in patients with moderate or severe renal impairment or patients on dialysis.[52,59,60] Therefore, in the presence of renal dysfunction, the use of another agent, such as bortezomib, might be preferable. Patients with relapsed MM receiving lenalidomide with dexamethasone are also at an increased risk of developing second primary malignancies; overall, this risk is low, with an overall incidence rate of 3.62 events per 100 patient-years.[61] Treatment with thalidomide or intravenous bortezomib is associated with the development of neurological complications, particularly treatment-emergent peripheral neuropathy. Patients with significant pre-existing peripheral neuropathy should be spared additional exposure to intravenous bortezomib or thalidomide,[52] and a reasonable alternative could be lenalidomide or subcutaneous bortezomib. In a phase III study, reductions in the rates of peripheral neuropathy were observed with subcutaneous versus intravenous bortezomib (38% versus 53% all-grade peripheral neuropathy [$P = 0.044$], 6% versus 16% grade ≥3 peripheral neuropathy [$P = 0.026$], respectively), suggesting that the different pharmacokinetics associated with subcutaneous and intravenous administration might significantly reduce the neuropathic toxicity of bortezomib (Table 4).[59,62–67]

In addition, treatment with bortezomib has been associated with an increased incidence in herpes zoster reactivation (reported in 13% of patients).[27,38,68,69] Routine antiviral prophylaxis is effective in preventing herpes zoster virus reactivation and should be considered in patients receiving bortezomib-based treatment, particularly those who have a history of herpes zoster infection.[70,71]

Table 4 | Incidence rates of peripheral neuropathy

Treatment	Any peripheral neuropathy (%)	Grade ≥3 peripheral neuropathy (%)	Patient population
Thalidomide[63]	25–81	6–20	Relapsed or refractory MM
Lenalidomide[59,63]	3	1–2	Relapsed or refractory MM
Bortezomib, intravenous[64,65]	53	16	Relapsed MM
Bortezomib, subcutaneous[64,65]	38	6	Relapsed MM
Pomalidomide[66]	15	1	Relapsed and refractory MM
Carfilzomib[67]	14	1	Relapsed and/or refractory MM

Abbreviation: MM, multiple myeloma.

Although bortezomib treatment has been only rarely linked to reports of cardiac dysfunction,[72] some caution should be exercised in its use to treat patients with pre-existing cardiac conditions. Further studies are needed to fully characterize these complications, their relationship to bortezomib therapy, and their impact on treatment paradigms. A recent meta-analysis of cardiac complications following bortezomib-based treatment has presented reassuring results in this regard, with a low rate of grade ≥3 heart failure (1.9%) reported in patients with relapsed and/or refractory MM.[73]

As a general guideline, a good response (partial response or better) to earlier treatment and a long remission (≥12 months) with acceptable adverse events may advocate for re-treatment with the initial regimen or at least components thereof.[52,60,74,75] However, repeat administration of lenalidomide has been associated with better response rates than re-treatment with thalidomide, possibly due to differences in mode of action between the two agents that can result in different levels of cross-resistance.[75] For patients who relapse within 6 months of completion of their initial treatment, a switch in class of agent is indicated, such as switching from use of an IMiD to a proteasome inhibitor, as a short remission duration is indicative of rapid progression or aggressive relapse, which might be associated with development of class resistance.[76] Contrasting results have been observed in relation to the efficacy of lenalidomide following bortezomib-based treatment. In the MM-009 trial, response rates for the combination treatment of lenalidomide plus dexamethasone were similar among patients who had or had not undergone previous bortezomib treatment,[63] but other studies have demonstrated shorter TTP, PFS, and overall survival for that combination in patients who were previously treated with bortezomib.[77,78] As per the current practice in Europe, the combination of thalidomide and dexamethasone with or without cyclophosphamide is often used in the salvage setting as third-line treatment after patients have become refractory to lenalidomide and bortezomib.

Certain cytogenetic abnormalities, such as translocation t(4;14) and deletion del17p, are associated with poor outcome,[79] and more-aggressive therapy (such as triplet combinations instead of doublet or single-agent treatment) may be needed for patients harbouring such alterations. The use of thalidomide and lenalidomide has shown limited success in overcoming the poor prognosis associated with high-risk chromosomal aberrations.[77,80] Bortezomib treatment, however, seems to reduce the prognostic significance of high-risk chromosomal aberrations in patients with relapsed MM[81] and can be recommended for treatment of these patients.[52]

In summary, there are currently several treatment options available for patients with relapsed myeloma. In our experience, for patients who develop an asymptomatic biochemical relapse, we recommend adding corticosteroids (if previously discontinued) to the current agent (bortezomib or lenalidomide), as well as an alkylating agent such as cyclophosphamide.

For patients who experience a symptomatic relapse from an unmaintained remission, our recommendation is to repeat the previous regimen if the duration of unmaintained remission has been ≥6 months. For all other patients, a switch of class of agents is recommended. In patients with good performance status, especially when there are signs of aggressive relapse and/or adverse cytogenetics, the use of a triple combination regimen is advisable.

Treatment of relapsed and refractory MM

Patients with relapsed and refractory MM are a challenging population to treat—they are likely to have more aggressive disease and to be heavily pretreated, thus, having more pre-existing toxicities. Clinical trials remain an important option for the treatment of these patients.

Depending on the treatment to which a patient is refractory, thalidomide, lenalidomide, or bortezomib (as single agents or in combination regimens) can be used for subsequent treatment; however, response rates tend to be lower than in patients with relapsed MM owing to the more advanced state and aggressive nature of the disease and the development of treatment resistance (Table 5).[82,83] Additionally, patients with relapsed and refractory MM in late-line settings are more likely to have been previously treated with and to be refractory to thalidomide, lenalidomide, and/or bortezomib. Research has shown that patients who are refractory to bortezomib and an IMiD have a median survival of only 9 months with salvage treatment.[5] Therefore, there is an unmet need for additional treatments for MM patients who are refractory to current regimens, and this need has driven the development of new agents.

Two agents, the IMiD pomalidomide and the proteasome inhibitor carfilzomib, have recently been approved in the USA (and in the case of pomalidomide, in Europe as well) for use in patients with relapsed and refractory MM who have failed bortezomib-based and lenalidomide-based therapies.

Pomalidomide

Similar to lenalidomide, pomalidomide is based on the chemical backbone structure of thalidomide and further improves on the tolerability profile of lenalidomide, while also providing increased potency. The pivotal phase I/II

Table 5 | Results from selected trials in relapsed and refractory MM

Reference	Patients (*n*)	Dose and schedule	ORR % (CR %)	Median overall survival
Richardson *et al.* (2009)[82]	222	28-day cycles: LEN: 30 mg/day days 1–21	26 (2)	23.2 months
Jagannath *et al.* (2006)[83]	106	21-day cycles: BTZ: 1.0 or 1.3 mg/m^2 days 1, 4, 8, 11 DEX: 20 mg days 1, 2, 4, 5, 8, 9, 11, 12	NR	NR
Richardson *et al.* (2013)[84]	221	28-day cycles: POM: 4 mg days 1–21 DEX: 40 mg/week	34	16.5 months
Lacy *et al.* (2011)[85]	70	28-day cycles: POM: 2 or 4 mg days 1–28 DEX: 40 mg days 1, 8, 15, 22	2 mg 26 (0) 4 mg 28 (<1)	2 mg 78% at 6 months 4 mg 67% at 6 months
San Miguel *et al.* (2013)[66]	455	28-day cycles: POM: 4 mg days 1–21 DEX: 40 mg days 1, 8, 15, 22	31 (1)	12.7 months
Siegel *et al.* (2012)[55]	266	28-day cycles: CFZ: 20/27 mg/m^2 days 1, 2, 8, 9, 15, 16	24 (<1)	15.6 months
Vij *et al.* (2012)[88]	129	28-day cycles: CFZ: 20 or 20/27 mg/m^2 days 1, 2, 8, 9, 15, 16	48 (2)	Not yet reached
Vij *et al.* (2012)[89]	35	28-day cycles: CFZ: 20 mg/m^2 days 1, 2, 8, 9, 15, 16	17 (3)	29.9 months
Papadopoulos *et al.* (2011)[92]	33	28-day cycles: CFZ: 20/36, 20/45, 20/56 or 20/70 mg/m^2 days 1, 2, 8, 9, 15, 16	Overall: 59 20/56 mg/m^2 60 (5)	NR
Papadopoulos *et al.* (2013)[93]	22	28-day cycles: CFZ: 20/45 or 20/56 mg/m^2 days 1, 2, 8, 9, 15, 16 DEX: 20 mg days 1, 2, 8, 9, 15, 16; 40 mg day 22	55	NR
Shah *et al.* (2013)[104]	72	28-day cycles: CFZ: 20/27 mg/m^2 days 1, 2, 8, 9, 15, 16 POM: 4 mg days 1–21 DEX: 40 mg days 1, 8, 15, 22	64	16.3 months
Mark *et al.* (2013)[105]	119	28-day cycles: CLA: 500 mg twice daily POM: 4 mg days 1–21 DEX: 40 mg days 1, 8, 15, 22	61	Not yet reached

Abbreviations: BTZ, bortezomib; CFZ, carfilzomib; CLA, clarithromycin; CR, complete response; DEX, dexamethasone; LEN, lenalidomide; MM, multiple myeloma; NR, not reported; ORR, overall response rate; POM, pomalidomide.

study MM-002 ($n = 221$) found that the combination of pomalidomide with low-dose dexamethasone was more efficacious than single-agent pomalidomide in patients with relapsed and refractory MM (ORRs of 34% and 15%, respectively).[84] Interestingly, following treatment with pomalidomide and low-dose dexamethasone, similar ORRs were also reported in patients who had received prior carfilzomib treatment ($n = 50$; ORR 37%) and in patients refractory to lenalidomide ($n = 174$; ORR 30%) or refractory to both lenalidomide and bortezomib ($n = 136$; ORR 31%),[84] suggesting that pomalidomide with dexamethasone may overcome resistance to carfilzomib, bortezomib, and/or lenalidomide in some patients. The overall clinical activity of pomalidomide combined with dexamethasone and its activity in patients who are refractory to bortezomib and/or lenalidomide have been further confirmed in additional studies.[53,66,85]

In a randomized phase III study (MM-003), pomalidomide with low-dose dexamethasone ($n = 302$) was compared with high-dose dexamethasone ($n = 153$) in patients with primary refractory or relapsed and refractory MM. At 10 months' median follow-up, PFS was significantly longer in patients treated with pomalidomide and low-dose dexamethasone versus patients treated with high-dose dexamethasone alone (median PFS 4.0 months versus 1.9 months, respectively).[66] Comparable results were seen in a subgroup analysis of patients who were dual-refractory to bortezomib and lenalidomide (74% of patients in the MM-003 trial, median PFS 3.7 months; $P < 0.0001$).[66] A significant improvement in overall survival was observed in the final analysis (median overall survival 12.7 months versus 8.1 months; $P = 0.0285$).[66] Longer overall survival with pomalidomide and low-dose dexamethasone was also observed in lenalidomide-refractory patients ($P = 0.0234$), but there were no significant differences in overall survival between the groups of patients who were refractory to bortezomib or to lenalidomide and bortezomib.[66]

Based on MM-002 and MM-003 study results, pomalidomide has been approved in Europe and the USA for use with low-dose dexamethasone in patients with relapsed and refractory MM who have disease progression

Table 6 | Treatment recommendations for patients with relapsed and refractory MM

Patient characteristics	Carfilzomib	Pomalidomide
Renal impairment (CrCl <40 mL/min)	+	–
History of cancer	+	+
VTE risk	+	–
Pre-existing peripheral neuropathy	+	+
Steroid-free treatment	+	±
Poor-risk cytogenetics	±	+

Abbreviations: –, not recommended; +, recommended; ±, may be considered; CrCl, creatinine clearance; MM, multiple myeloma; VTE, venous thromboembolism.

following at least two prior therapies, including lenalidomide and bortezomib. Ongoing studies are examining pomalidomide in combination with other anti-MM treatments and its use in earlier lines of treatment.

Carfilzomib

Carfilzomib is a selective and irreversible proteasome inhibitor that has been shown to have fewer off-target effects compared with bortezomib in preclinical models.[86] Carfilzomib has been approved for single-agent use in the USA in patients who have received at least two prior therapies, including a proteasome inhibitor and an IMiD. The phase III study FOCUS[87] is currently examining single-agent carfilzomib versus low-dose corticosteroids and optional cyclophosphamide in support of regulatory approval in Europe. However, in the single-arm phase II study PX-171-003-A1, treatment of patients with relapsed and refractory MM with single-agent carfilzomib led to durable responses, resulting in an ORR of 23.7%, a median DOR of 7.8 months, and median overall survival of 15.6 months.[55] Furthermore, the phase II study PX-171-004 examined carfilzomib in patients with relapsed and/or refractory MM who had been previously treated with bortezomib ($n = 35$) and in patients who were bortezomib-naive ($n = 129$).[88,89] In patients previously treated with bortezomib, the ORR was 17.1%, with a median DOR >10.6 months and a median TTP of 4.6 months,[89] whereas in 126 response-evaluable bortezomib-naive patients, an ORR of 47.6% and median TTP of 12.0 months were noted (median DOR was not reached).[88] The lower ORR in patients previously treated with bortezomib may be attributable to a subset of patients having developed resistance to the class of proteasome inhibitors. In addition, these patients had a higher median number of prior therapies (three; range, 1–13) compared with bortezomib-naive patients (two; range, 1–4).[88,89]

Both the PX-171-003-A1 trial and the PX-171-004 trial examined a target dose of 27 mg/m^2 of carfilzomib infused over 2–10 min; however, increasing the length of time over which carfilzomib is administered might improve the tolerability of treatment and allow for higher doses to be administered.[90,91] In the phase Ib/II study PX-171-007 ($n = 33$), single-agent carfilzomib was administered by intravenous infusion over 30 min, at doses up to 70 mg/m^2 in patients with relapsed and/or refractory MM.[92] At the maximum tolerated dose (20 mg/m^2 in cycle 1 and 56 mg/m^2 in cycle 2 and beyond), an ORR of 60% was reported.[92] Furthermore, the PX-171-007 study also examined the use of carfilzomib (≤56 mg/m^2) in combination with dexamethasone ($n = 22$), which yielded an ORR of 55% and a safety profile consistent with single-agent carfilzomib at comparable doses.[93] Overall, higher doses of carfilzomib seem to be associated with an increased likelihood of achieving a clinical response,[94,95] but they might also be associated with increased cardiac and pulmonary toxicity.[96,97] Additional studies are needed to more fully define the efficacy and safety profile of carfilzomib. To this end, a target dose of 56 mg/m^2 is being further examined in the phase III study ENDEAVOR,[98] which is comparing carfilzomib with dexamethasone versus bortezomib with dexamethasone in patients with relapsed MM. In addition, higher doses of carfilzomib, up to 70 mg/m^2, administered weekly are also being explored in patients with relapsed MM in the phase I/II trial CHAMPION-1.[99] Thus far, doses higher than those recommended in the label have not been examined in patients with relapsed and refractory disease.

Combination regimens

Several triplet regimens incorporating carfilzomib and/or pomalidomide are being investigated in patients with relapsed and/or refractory MM. In the relapsed setting, combination regimens that benefit from the complementary activity of a proteasome inhibitor and an IMiD are especially promising, including carfilzomib with lenalidomide and dexamethasone[100–102] and bortezomib with pomalidomide and dexamethasone.[103]

In the relapsed and refractory setting, the combination of carfilzomib with pomalidomide and dexamethasone was examined in a phase I/II study in patients who were lenalidomide-refractory and were heavily pretreated (median of six lines of prior therapy), reporting a high response rate (ORR of 64%) and a good tolerability for the combination.[104]

Another promising triplet combination includes the antibiotic clarithromycin that is thought to enhance the antimyeloma activity of pomalidomide and dexamethasone. The combination of clarithromycin, pomalidomide, and dexamethasone (ClaPD) is being investigated in a phase II trial in heavily pretreated relapsed or refractory MM patients ($n = 119$; median of five prior lines of therapy; 68% of patients double-refractory to lenalidomide and bortezomib).[105] Promising tolerability and efficacy were observed with this regimen, with an ORR of 61% and a median PFS of 8.1 months, with similar results observed in the double-refractory patients.[105] Of note, an analysis of patients in this study treated with carfilzomib before or after the ClaPD regimen reported that the sequence of both treatments was equally effective in the salvage setting regardless of the order in which the therapies were administered.[106]

Treatment recommendations

The approvals of carfilzomib and pomalidomide represent important new treatment options for patients with dual-refractory disease, and their use should be considered for this challenging patient population (Table 6).

Patients in the relapsed and refractory setting have already been exposed to multiple lines of therapy. It is, therefore, important to consider the safety profiles of pomalidomide and carfilzomib when evaluating treatment choices. Patients with existing comorbidities or those who are at risk of developing treatment-emergent adverse events associated with either pomalidomide or carfilzomib should be carefully monitored throughout the course of treatment.

Pomalidomide and, to a lesser extent, carfilzomib have been associated with myelosuppression, similar to what has been observed with other anti-MM agents.[67,107] Specifically, in the MM-002 study, 41% of patients treated with pomalidomide and low-dose dexamethasone reported grade 3/4 neutropenia; 46% of patients received granulocyte colony-stimulating factor, and approximately 20% received erythroid growth factors as supportive care during treatment.[84] Proactive management of haematological adverse events is recommended so that patients can receive continuous treatment and derive maximal clinical benefit. Patients receiving pomalidomide or carfilzomib should be monitored throughout treatment for the appearance of haematological adverse events via regular complete blood counts, and dose interruptions can be recommended for grade 4 neutropenia or thrombocytopenia.[107,108]

Beyond the haematological adverse events, some caution is warranted for the use of such drugs in patients with progressive renal dysfunction until additional data from ongoing studies are available.[56] Although pomalidomide has not been extensively evaluated in patients with impaired renal function, the agent is excreted primarily through the kidneys. Thus, it is recommended that patients with serum creatinine >3.0 mg/dL avoid treatment with pomalidomide.[107] By contrast, carfilzomib is cleared extrarenally; thus, dose adjustments are not usually necessary in patients with impaired renal function or those on dialysis.[109]

Of note, treatment-emergent peripheral neuropathy is uncommon with either single-agent carfilzomib or with pomalidomide in combination with dexamethasone,[66,67] making both agents recommended for patients with pre-existing peripheral neuropathy or for use in combination with drugs associated with an increased risk of peripheral neuropathy, such as thalidomide (Tables 4 and 6).[56] In addition, as with other IMiDs, pomalidomide has been associated with an increased risk of VTE, warranting that an anticoagulation prophylaxis be considered in patients receiving pomalidomide treatment.[107]

The use of standard dose single-agent carfilzomib has been associated with a somewhat higher rate of cardiopulmonary adverse events as compared with other anti-MM agents in the relapsed or relapsed and refractory population.[17,67,110] Clinicians should be promptly informed about the occurrence of cardiopulmonary events, such as dyspnoea, dysrhythmia, myocardial infarction, and cardiac failure, so that these complications can be proactively managed at an early stage.[111] Patients should be evaluated for baseline cardiac risk factors, such as the use of antihypertensive or antidiabetic medication, history of anthracycline exposure, known or suspected amyloidosis, or age ≥60 years, before initiating carfilzomib treatment. When such factors are identified, a careful monitoring of the patient with regular echocardiographic measurements, frequent assessment of vital signs and pulmonary function, and serial laboratory measurements of cardiac markers (for example, troponin or brain natriuretic peptide) is recommended. In the event of cardiac complications, a possible intervention might include reducing hydration and decreasing steroid doses to minimize fluid retention. In addition, as noted earlier, longer infusion times (30 min versus 2–10 min) might be better tolerated by patients and could lead to reduced rates of cardiopulmonary adverse events. Further studies are underway to better understand the mechanisms underlying the cardiac and pulmonary toxicity reportedly associated with carfilzomib treatment.[87,112]

Jakubowiak *et al.*[113] have evaluated the outcome of patients with relapsed and refractory MM treated with single-agent carfilzomib on the basis of their cytogenetic risk (high versus standard risk). The group of patients with high cytogenetic risk included carriers of del[17p13], t[4;14], or t[14;16] chromosomal alterations. Analysis of the two groups revealed a comparable ORR (25.8% versus 24.6%), whereas median DOR and overall survival were shortened in patients in the high-risk subgroup (DOR 5.6 months versus 8.3 months; overall survival 9.3 months versus 19.0 months),[113] suggesting that carfilzomib can, at least partially, overcome the impact of high-risk cytogenetics on heavily pretreated patients. In the final analysis of the MM-003 trial, the high-risk cytogenetic group included carriers of del[17p13] and/or t[4p16/14q32] chromosomal alterations. This analysis reported that patients had significantly longer PFS and overall survival when treated with pomalidomide and low-dose dexamethasone versus high-dose dexamethasone in patients with high-risk or standard-risk cytogenetics.[114] These results were further supported by a phase II trial examining single-agent pomalidomide in relapsed and refractory MM, where activity was observed in heavily pretreated patients who had high risk defined by gene-expression profiling, elevated lactate dehydrogenase, or the presence of abnormal metaphase cytogenetics (ORR of 28%).[115] Either carfilzomib or pomalidomide could be considered for use in patients with high-risk cytogenetics. Interestingly, emerging data indicate that patients with del17p alterations might derive more clinical benefit than patients with t(4;14) alterations from treatment with pomalidomide plus low-dose dexamethasone in the relapsed MM setting; however, further follow-up is needed.[116]

The treatment of myeloma that has developed resistance and/or intolerance to lenalidomide and bortezomib is challenging, and clinicians are currently divided on the best treatment strategy for overcoming drug resistance. Strategies include switching classes of agents entirely or adding a different class of agent to the treatment regimen against which the patient has developed resistance. Promising results with the latter strategy have been observed by adding the HSP-90 inhibitor tanespimycin[117] or the histone deacetylase inhibitor panobinostat[118] to bortezomib treatment in bortezomib-refractory patients.

Carfilzomib and pomalidomide with low-dose dexamethasone, the latest additions to the proteasome inhibitor and IMiD classes, represent important new treatment options for patients with refractory disease. In general, based on our experience, we recommend carfilzomib for patients with severe renal impairment or with a history of VTE, and when corticosteroids are absolutely contraindicated. The combination of pomalidomide and low-dose dexamethasone is instead recommended for patients who prefer an outpatient regimen, who have 17p deletion, or who have failed carfilzomib treatment.

New agents in clinical development

In addition to the approved agents described previously, a number of compounds are currently in clinical development for treating patients with relapsed and/or refractory MM.

Antibodies against antigen targets that are expressed on the myeloma cell or on components of the bone marrow microenvironment are an important class of agent being developed for MM. These antibodies exert their anti-MM function by targeting immune cells to kill myeloma cells. Daratumumab, an anti-CD38 antibody in phase I/II clinical development,[119] has received 'breakthrough therapy' designation by the USA FDA for patients with MM who have received at least three prior lines of therapy (including a proteasome inhibitor and an IMiD) or who are refractory to both a proteasome inhibitor and an IMiD. The breakthrough therapy designation for daratumumab was based on results from a phase I/II clinical trial in patients with relapsed and refractory MM, in which 42% of patients who received ≥4 mg/kg daratumumab ($n = 12$) achieved a partial response.[120] Elotuzumab, an anti-CS1 monoclonal antibody, has shown particular promise in combination with lenalidomide and low-dose dexamethasone in patients with relapsed MM.[121] This combination was tested in a phase II study in patients with relapsed MM ($n = 73$) and resulted in an ORR of 84% and a median PFS of 33 months for patients treated with 10 mg/kg of elotuzumab with lenalidomide and low-dose dexamethasone.[121] For comparison, a pooled analysis of the phase III studies of lenalidomide with high-dose dexamethasone reported an ORR of 61% and a median TTP of 13 months.[23] The combination of elotuzumab, lenalidomide, and dexamethasone is being further evaluated in the phase III ELOQUENT-2 study[122] in patients with relapsed/refractory MM.

Another avenue of immunotherapy is the use of anti-MM vaccines in conjunction with other treatments such as ASCT and/or antibodies. A patient-specific vaccination approach involves the use of a hybridoma whereby patient-derived tumour cells are fused with autologous dendritic cells.[123] A phase II study investigated the combination of ASCT with hybridoma vaccination and reported that 47% of patients achieved a complete response, with 24% of complete responses occurring more than 100 days post-transplant.[123] Another phase II study is currently evaluating the combination of ASCT, hybridoma vaccine, and the novel monoclonal anti-PD-1 antibody CT-011, under the rationale that CT-011 can potentially enhance vaccine efficacy by inhibiting the immunosuppressive PDL-1/PD-1 pathway.[124,125]

Other promising new therapeutics in development include oral proteasome inhibitors such as oprozomib[126] and ixazomib,[127] selective nuclear export inhibitors such as KPT-276,[128,129] and histone deacetylase inhibitors such as panobinostat, vorinostat, and ACY-1215.[130] Recently, the phase III PANORAMA-1 study of bortezomib and dexamethasone with panobinostat or placebo demonstrated that the addition of a histone deacetylase inhibitor significantly improves PFS (median of 12.0 months versus 8.1 months, respectively) in patients with relapsed or relapsed and refractory MM.[131] Meanwhile, ARRY-520, an inhibitor of the microtubule motor protein kinesin, showed encouraging clinical activity and tolerability when combined with carfilzomib[132] or bortezomib[133] in phase I studies. While it is too early to say where these new options will fit into treatment regimens for patients with relapsed or relapsed and refractory disease, as these compounds have distinct mechanisms of action from proteasome inhibitors and IMiDs, many of them are expected to be complementary to the therapies that are currently available. Several studies are examining their use in combination with existing treatments in the hope of demonstrating that targeting multiple pathways can improve clinical outcomes and overcome tumour resistance.

Conclusions

Among patients with MM, relapsed and/or refractory patients continue to be a challenging population to treat, with no agreed-upon uniform standard of care. Since the introduction of IMiDs and proteasome inhibitors, however, survival rates for patients with relapsed and/or refractory disease have continued to rise. The development and approval of new agents, including carfilzomib and pomalidomide, offer even greater improvements in efficacy and safety in this difficult-to-treat patient group, and compounds still in development, such as monoclonal antibodies, may offer additional clinical benefit.

The appropriate selection and management of patients is crucial, particularly in the late-line treatment setting, and further studies will help to define optimal treatment regimens for relapsed or relapsed and refractory MM, and identify the optimal patient subgroups that will benefit most from their use.

Review criteria

The PubMed database and abstracts from the annual meetings of the American Society of Haematology, ASCO, and European Haematology Association were reviewed for topics regarding clinical trials in relapsed or relapsed and refractory multiple myeloma. Search terms used included, but were not limited to, "clinical trials", "thalidomide", "bortezomib", "lenalidomide", "pomalidomide", "carfilzomib", "relapsed multiple myeloma", and "relapsed and refractory myeloma" in various combinations to identify manuscripts and abstracts on approved agents in these indications. Articles were limited to those written in English, but were not limited by publication date.

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Author contributions

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