Treatment of Relapsed or Refractory Multiple Myeloma in the Era of Novel Agents

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Abstract

The introduction of highly effective novel agents has resulted in a significant improvement in the outcomes of patients with multiple myeloma. These agents, namely thalidomide, bortezomib and lenalidomide, have been extensively studied in the relapsed or refractory multiple myeloma (RRMM) setting and are now being increasingly incorporated into upfront treatment strategies. Second-generation novel agents such as carfilzomib and pomalidomide are being tested in early-phase studies, and preliminary results are encouraging. However, to date, there are no practical guidelines to help physicians choose the best approach for the treatment of RRMM, and direct comparisons between therapies at relapse are warranted. Moreover, despite the recent steps forward in the treatment of multiple myeloma, this disease remains incurable. This article provides an overview of the main studies incorporating novel agents as well as second-generation new drugs for the treatment of RRMM, and may guide physicians in the choice of the most appropriate treatment, associated with prolonged duration of remission and enhanced survival.

Keywords

Multiple myeloma, novel agents, relapse, refractory, carfilzomib, pomalidomide, bendamustine

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Multiple myeloma (MM) is a neoplastic plasma cell disorder characterised by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine and associated organ dysfunction.[1] MM accounts for 13 % of all haematological malignancies. According to the European Network of Cancer Registries, it affects approximately 21,500 people every year in Europe, with 15,000 dying from it.[2] MM is typically a disease of the elderly, with a median age at diagnosis of approximately 70 years.[3] Although novel agents, such as the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide and the proteasome inhibitor bortezomib, have substantially improved outcomes, patients eventually relapse.[1]

The definition of relapsed and refractory multiple myeloma (RRMM) is linked to disease progression. Based on the European Group for Blood and Marrow Transplantation criteria,[4] as well as according to the International Myeloma Working Group (IMWG),[5] relapse from a complete response (CR) occurs when at least one of the following is present:

- reappearance of the serum or urinary paraprotein;
- ≥5 % bone marrow plasma cells;
- new lytic bone lesions and/or soft tissue plasmacytoma;
- increase in the size of residual bone lesions; and/or
- disease-related hypercalcaemia.

When a CR has not been achieved, the criteria for disease progression are:

- appearance or expansion of bone lesions;
- hypercalcaemia;
- >25 % increase in serum monoclonal paraprotein concentration;
- light chain excretion in the 24-hour urine; and/or
- plasma cells within the bone marrow.

Relapsed patients are patients who experience disease progression after achieving maximal response to induction treatment, whereas refractory patients are patients who either do not respond to therapy or progress within 60 days of the last treatment. Patients who fail to achieve at least a minimal response (MR) to induction treatment and progress on therapy are defined as primary refractory MM patients.[6]

The resistance of malignant plasma cells to treatment is partly dependent on the interaction between the bone marrow microenvironment and the clonal plasma cells themselves. The bone marrow microenvironment supports the growth of myeloma by secreting growth and antiapoptotic cytokines such as interleukin 6, tumour necrosis factor alpha, insulin-like growth factor 1 and vascular endothelial growth factor.[7] Moreover, direct interaction of the bone marrow microenvironment with MM through integrins and cell adhesion molecules promotes growth, inhibits

apoptosis and is responsible for resistance to conventional chemotherapy and corticosteroids.[8]

The benefits associated with novel agents, which target both MM cells and bone–microenvironment interaction,[9] have been confirmed in RRMM patients. Before their introduction, the treatment of RRMM was similar to first-line therapy, resulting in shorter response durations and often leading to drug resistance. Today, patients who relapse can instead benefit from new drugs and different therapeutic approaches.

The benefits of novel agents in RRMM were evident in a study of 387 patients who relapsed after stem cell transplantation.[10] Indeed, a clear improvement in overall survival (OS) from the time of relapse was seen in patients relapsing after the year 2000, that is, when new drugs started entering clinical practice. These patients had a median OS of 23.9 months, compared with 11.8 months in patients relapsing before the year 2000 ($p<0.001$). Consistently, patients treated with one or more of the newer drugs had longer survival from the time of relapse (30.9 versus 14.8 months; $p>0.001$), independently of disease status, time of autologous stem cell transplant (ASCT), treatment regimens before ASCT and response duration after ASCT.[10]

No precise guideline is available to define the treatment goals and best therapeutic approaches in RRMM. To date, the choice of treatment in this setting is mainly based on prior treatment, duration of remission, toxicity profile of the drug and patients' co-morbidities and disease characteristics. Direct comparative trials may enable physicians to better characterise RRMM and thus provide guidelines to help them choose the most appropriate treatments for patients.

Prognostic Factors

In the RRMM setting, the goal is to select the best approach for each patient while balancing efficacy and toxicity. The novel agents have been shown to induce high-quality response, particularly CR, not only in newly diagnosed patients but also in RRMM patients. In the latter, the impact of CR on survival is still controversial. Nevertheless, several recent trials suggested that RRMM patients who achieve deeper response have a better outcome, at least in terms of progression-free survival (PFS).[11–13] The choice of optimal treatment also depends on principal prognostic factors, such as the presence of extramedullary disease, cytogenetic abnormalities and resistance to novel agents.

Extramedullary Multiple Myeloma

MM is typically confined to the bone marrow and skeleton. However, a number of patients may develop extramedullary disease, defined as plasmocytomas extending to soft tissue, lymph nodes, skin, muscles and other organs, or as plasma cell leukaemia. Only a few trial have evaluated the incidence of extramedullary disease; the available data show that it is uncommon at the time of first diagnosis and more typical in the context of RRMM,[14] with an incidence of 7–18 % in patients newly diagnosed with MM and of up to 20 % in relapsed patients.[15–18] So far, no control studies have been performed, but there is some evidence showing a possible increase of extramedullary disease with the use of novels agents and high-dose chemotherapy.[14,16,17,19–22] Extramedullary disease is generally associated with significantly shorter PFS and OS[14,16] despite the use of combination therapies or novel agents, and there remains an unmet need in this particular setting.

Impact of Cytogenetic Abnormalities

The prognostic value of chromosomal abnormalities such as del(13), t(4;14) or del(17p) has not been assessed in RRMM patients treated with novel therapies, as no prospective, randomised studies have yet been performed. Retrospective analyses of Phase II/III trials of single agents or drug combinations showed conflicting data regarding the prognostic value of del(13) and t(4;14).

Avet-Loiseau et al. evaluated the impact of del(13) and t(4;14) on outcomes in 207 heavily pre-treated RRMM patients given drug combinations, including lenalidomide plus dexamethasone (RD).[23] They reported lower overall response rate (ORR) and shorter median PFS and OS in patients with del(13) and t(4;14) compared with patients who did not have these abnormalities. However, in the MM-016 study, Reece et al. reported that the advantage in time to progression (TTP) and OS conferred by the addition of lenalidomide to dexamethasone was independent of del(13) and t(4;14) – although both del(13) and t(4;14) were associated with shorter TTP in an univariate analysis.[24]

Jagannath et al. investigated the impact of del(13) on response and outcome in patients treated with bortezomib in the SUMMIT and APEX (Assessment of proteasome inhibition for extending remissions) trials.[25] They showed that del(13) was not associated with adverse prognostic impact (but the number of patients included was very small). A Korean study assessing a combination of four drugs (bortezomib plus cyclophosphamide plus thalidomide plus dexamethasone) showed a significant shorter PFS in patients with del(13) compared with patients with normal karyotypes.[26] Chang et al reported that bortezomib seems to be effective in patients with t(4;14).[27] Neither bortezomib- or lenalidomide-based combinations seem to be able to overcome poor prognosis conferred by del(17p) abnormality.[24,27,28]

The trials described above are very small, hence no definitive conclusions can be drawn from their results.

Impact of Previous Treatment

Most RRMM patients will have already been treated with combinations containing at least one of the newer drugs. Unfortunately, only few data about the impact of previous treatment on response and outcomes are currently available.

Results from studies on the impact of previous exposure to thalidomide are conflicting. Vogl et al. reported worse response and outcomes in patients treated with bortezomib alone as salvage therapy after previous therapy with thalidomide,[29] while Sonneveld et al. found no differences in terms of ORR and TTP in patients previously exposed or not to thalidomide and treated with bortezomib plus pegylated liposomal doxorubicin.[30]

Despite the hypothesis of a cross-resistance between thalidomide and lenalidomide showed in the MM009 and MM010 trials,[31] the retrospective analysis by Avet-Loiseau et al. of patients treated with RD reported that prior thalidomide did not significantly impact PFS or OS, although progression on thalidomide negatively affected both.[23] A recent retrospective Italian study also showed that previous therapy with thalidomide did not seem to affect salvage therapy with lenalidomide.[32]

Patients receiving more complex salvage therapies, such as combinations of bortezomib, lenalidomide and dexamethasone

(VRD),[13,33] bortezomib, thalidomide and dexamethasone (VTD)[34] and bortezomib, dexamethasone and cyclophosphamide (VCD),[35] showed better response if they had not received previous treatment with thalidomide or if they were not resistant to it.

Data regarding the impact of previous therapy with bortezomib are also conflicting. Avet-Loiseau et al. reported that patients previously treated with bortezomib who received salvage therapy with RD had shorter median PFS and OS.[23] Similar results were demonstrated in a multivariate analysis of the MM016 study, in which previous bortezomib induced lower PFS and OS.[24] However, in a study by Weber and colleagues, previous bortezomib did not affect ORR.[36] Two other studies found no negative impact of previous bortezomib exposure on ORR in patients treated with a PAD (bortezomib [PS-341], doxorubicin and dexamethasone) regimen[37] or a ThaDD-V (thalidomide, dexamethasone, Doxil® and Velcade®) combination.[38] These results were confirmed in the recent update analysis of the VISTA (Velcade as initial standard therapy in multiple myeloma) trial,[39] in which bortezomib administered as first-line treatment did not negatively affect the response to lenalidomide-, thalidomide- or bortezomib-based regimens given at relapse.

Previous treatment with lenalidomide did not seem to negatively affect response in patients treated with bortezomib-based regimens as salvage therapy, with the rate of partial response (PR) or better ranging from 43–57 %.[40,41] In a small study, Young and colleagues concluded that thalidomide-based regimens as salvage therapy did not exert a substantial activity in patients previously treated with lenalidomide.[42]

Finally, a previous ASCT does not seem to adversely affect response and outcomes in RRMM patients receiving combinations of new drugs.[29,33,43]

Overview of First-generation New Drugs and Approved Regimens

Thalidomide

Thalidomide has been extensively evaluated in many pilot studies and retrospective analyses, but no Phase III trials have been performed in the RRMM setting. Thalidomide alone produced a PR or better in 30 % of RRMM patients, with a one-year survival rate of 60 % and a median survival of 14 months.[44] Other studies have demonstrated that ORR can be significantly enhanced (to 50 %) by the addition of concomitant dexamethasone.[45]

Therapies combining thalidomide and conventional cytotoxic drugs[46–50] as well as bortezomib[51,52] were evaluated in small early Phase I/II studies. The combination regimens were clearly active and resulted in ORRs of 60–75 % with CR rates of approximately 10–20 %. Adverse events associated with thalidomide include sedation, constipation and increased risk of venous thromboembolism (VTE), as well as peripheral neuropathy (which occurs more frequently if the daily dose exceeds 200 mg). Thalidomide combinations with chemotherapy, specifically anthracyclines, carry an increased risk of VTE complications, which often requires more intense prophylaxis than is used when patients receive thalidomide plus dexamethasone or bortezomib. The IMWG has published guidelines on the basis of a risk assessment model; specifically, low molecular weight heparin has been recommended in patients with more than one risk factor, whereas aspirin can be considered in those with lower risk profiles.[53]

Bortezomib

The proteasome inhibitor bortezomib has shown potent anti-myeloma activity as a single agent.[54] In the large randomised APEX trial, bortezomib given intravenously on Day 1, 4, 8 and 11 showed superiority over pulsed dexamethasone in RRMM patients who had received no more than three prior treatment regimens.[55] After an extended follow-up, the ORR was 43 % with bortezomib, with a median OS of 29.8 months versus 23.7 months in the dexamethasone arm, despite substantial cross-over from dexamethasone to bortezomib.[56]

The addition of dexamethasone to bortezomib alone in patients with a suboptimal response or progression improved the degree of response in 18–39 % of patients,[57] while the use of bortezomib plus dexamethasone from the onset of therapy resulted in ORRs ranging from 54–74 %.[58,59]

Many Phase I/II trials evaluating bortezomib combinations have shown high ORRs (50–80 %) with encouraging duration of response and OS.[52,60–64] A large randomised trial comparing bortezomib alone with bortezomib plus pegylated liposomal doxorubicin showed an improved TTP (9.3 versus 6.5 months) and OS with the combination.[65]

The results of the randomised trials led the US Food and Drug Administration and European Medicines Agency to approve the use of bortezomib as a single agent or in combination with pegylated liposomal doxorubicin in the RRMM setting.

Adverse events related to bortezomib include nausea, diarrhoea, cyclic reversible thrombocytopenia, fatigue and peripheral neuropathy.[54,55,66–68] Peripheral neuropathy can be painful; in that case, it requires dose modification or discontinuation of the drug. It usually improves or resolves in affected patients following dose modification or discontinuation, although often over several months.[68]

Lenalidomide

Lenalidomide is the most recent novel agent approved for RRMM in the US and Europe. The approval was based on the results from two parallel, randomised registration trials (MM-009 and MM-010) in which RD was compared with dexamethasone alone in patients with progressive myeloma who had received one to three prior treatment regimens. The two trials had similar results: the ORRs were 60 % and 61 % with RD, compared with 20% and 24% with dexamethasone alone. The median TTP was significantly longer in patients receiving RD than in patients receiving dexamethasone alone (approximately 11 months versus 5 months, respectively, in both trials). The median OS with the drug combination was 29.6 months in the European trial (MM-010);[69] it had not yet been reached in the US trial (MM-090).[36] A pooled analysis of the trials confirmed the significant improvements in median TTP (13.4 versus 4.6 months), ORRs (60.6 % versus 21.9 %), median duration of response (15.8 versus 7 months) and median PFS (11.1 versus 4.6 months) in RD-treated patients.[70] The benefit of RD was apparent despite extensive cross-over of patients from the dexamethasone to the RD arm, similar to what had been seen in the APEX trial.

Lenalidomide has been combined with cytotoxic drugs such as doxorubicin or pegylated liposomal doxorubicin[28,71] and cyclophosphamide.[72,73] Based on preclinical models, studies of combinations of lenalidomide with the histone deacetylase inhibitors vorinostat and panobinostat, as well as with monoclonal antibodies and proteasome inhibitors, are ongoing.

Lenalidomide is associated with fewer and different adverse events than thalidomide, with less somnolence, constipation and peripheral neuropathy. However, similarly to thalidomide, the risk of VTE is increased and thus thromboprophylaxis is required.[53] Lenalidomide is also associated with myelosuppression.[36,69] If significant neutropenia occurs, either the dose of lenalidomide can be reduced, or granulocyte-colony stimulating factor can be given while the full lenalidomide dose is maintained. Experience with lenalidomide in patients with renal impairment is relatively limited, but, based on the available data, myelosuppression may be the main side effect.[74]

Overview of Second-generation New Drugs

New proteasome inhibitors, third-generation IMiDs and alkylating agents have been recently evaluated in Phase I and II clinical trials, showing encouraging results both in terms of efficacy and toxicity. Novel proteasome inhibitors, such as carfilzomib (CFZ, PR-171),[75] salinosporamide A (NPI-0052)[76] and CEP-18770,[77] are under evaluation. Preliminary clinical data on CFZ have been reported; less information is currently available on NPI-0052 and CEP-18770.

Carfilzomib

CFZ is a tetrapeptide epoxyketone and a selective proteasome inhibitor.[75] It irreversibly binds to and inhibits the chymotrypsin-like activity of the 20S proteasome.[75,78] Preclinical studies showed that CFZ resulted in a higher induction of caspase-8 and -9 than bortezomib and could overcome bortezomib-resistance in cell lines and primary plasma cell models.[75] Several Phase I/II studies investigated the role of CFZ in patients with RRMM.

PX-171-003-A0 was an open-label, single-arm Phase IIb trial in patients with advanced MM who had been refractory to at least two prior therapies (bortezomib, either thalidomide or lenalidomide, and an alkylator). CFZ was given on Day 1, 2, 8, 9, 15 and 16 of 28-day cycles (20 mg/m^2 in Cycle 1; 27 mg/m^2 in Cycles 2–12). Single-agent CFZ achieved a TTP of 6.2 months. Twenty-six percent of patients had an MR or better, with a median duration 7.4 months.[79] The median TTP was similar to that observed with bortezomib in both the SUMMIT trial conducted in RRMM patients (in which the median TTP was 7 months) and the APEX trial conducted in relapsed patients (in which the median TTP was 6.2 months).

These encouraging results led to PX-171-003-A1, an open-label, Phase IIb trial conducted by the Multiple Myeloma Research Consortium (MMRC).[80] Two hundred and sixty-six patients with refractory multiple myeloma, who had received at least two prior therapies (including bortezomib and either thalidomide or lenalidomide, plus an alkylating agent) were enrolled. These patients had received a median of five prior lines of therapy (range one to 20) and a median of 13 anti-myeloma agents. The majority had failed at least two prior bortezomib-containing regimens. Patients received CFZ at the same dose and schedule than in the PX-171-003-A0 trial. An ORR of 24 % with a median duration of response of 7.4 months (range 6.2–10.3) was observed. One CR (0.4 %), 12 very good partial responses (VGPRs) (4.7 %), 48 PRs (19 %) and 32 MRs (12 %) were achieved. An additional 83 (32 %) patients achieved stable disease (SD) for at least six weeks.

A second parallel Phase II multicentre study of CFZ (PX-171-004) was conducted by the MMRC to determine the efficacy of CFZ in bortezomib-naive RRMM patients.[81] Fifty-four patients received CFZ at a dose of 20 mg/m^2 intravenously on Days 1, 2, 8, 9, 15 and 16 of 28-day cycles for up to 12 cycles, while 19 patients received an escalated dose of 27 mg/m^2 following the same schedule. At the 20 mg/m^2 dose, the ORR was 46 % (25 of 54 patients), which included one CR, five VGPRs and 19 PRs. In addition, nine patients experienced an MR and 10 patients had SD. At the 27 mg/m^2 dose, the ORR was 53 %, with one VGPR and nine PRs. The median duration of response was 8.8 months and the median TTP was 7.6 months.

CFZ was generally well tolerated and adverse events were manageable. An analysis of 136 patients indicated that peripheral neuropathy occurred in 15 % of patients and was attributed to CFZ in 9 %.[82] Grade 3 or higher peripheral neuropathy occurred in 2 %, and grade 1 or 2 paraesthesia and dysaesthesia occurred in 7 %. None of the patients required discontinuation or dose adjustments due to neurotoxicity. These data confirm the favourable toxicity profile of CFZ with regard to neuropathy; no major dose modifications seem to be required, even in patients with pre-existing neuropathy.

Another analysis found an increase in alkaline phosphatase from baseline, most evident during the second cycle of CFZ treatment, which appeared to be associated with response to treatment.[83] Constitutional symptoms, such as fatigue, were seen in 57–66 % of patients treated with CFZ, although the majority of these events were primarily lower than grade 2 (with grade 3 or 4 fatigue occurring in about 9 % of patients). Grade 3/4 haematological events were comparable to those reported with bortezomib, and included anaemia (29–65 %), thrombocytopenia (25–46 %) and febrile neutropenia (20–42 %). Grade 3 or 4 haematologic toxicity was seen in approximately 9–10 % of the patients. Two cases of tumour lysis syndrome were observed, but no further cases have been seen since prophylaxis was routinely introduced.

Recent studies have reported encouraging preliminary safety and efficacy results with CFZ in patients with renal impairment[84,85] and cytogenetic abnormalities.[86] A Phase Ib dose-escalation study evaluated the safety, activity and maximum recommended dose of CFZ in association with lenalidomide plus low-dose dexamethasone (CRd) in 40 heavily pre-treated RRMM patients. The ORR for the 29 evaluable patients was 59 % and 72 % of patients achieved at least MR. Initial responses improved with continued therapy (up to 18 cycles). The median follow-up being 5.2 months, the median duration of response has not yet been reached. No dose-limiting toxicities or deaths attributed to therapy have been observed. The most common grade 3 adverse events were haematological (thrombocytopenia [n=6], anaemia [n=4] and neutropenia [n=6]) and all were reversible. No treatment-related neuropathy or grade 3 thrombotic events were observed.[87]

CFZ is currently being evaluated in two Phase III clinical trials. The ASPIRE (Carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma) trial is an international trial evaluating the safety and efficacy of CRd versus RD in patients with RRMM. The FOCUS (Carfilzomib for advanced refractory multiple myeloma European study) trial is a study of single-agent CFZ in RRMM designed to support a regulatory filing in Europe.

Pomalidomide

Pomalidomide (POM, CC-4047) is a third-generation IMiD currently considered the most potent of IMiDs.[88–90] The drug exerts anti-MM

Table 1: Regimens Approved for Relapsed or Refractory Multiple Myeloma and Respective Dose Schedules

Regimen	Schedule
V[55]	V: 1.3 mg/m² IV on Days 1, 4, 8 and 11 of Cycles 1–8 (21-day cycles). For extended therapy, V can be further administered on Days 1, 8, 15 and 22 of Cycles 9–11 (35-day cycles)*
Peg+V[65]	Peg: 30 mg per m² of body surface area on Day 4 V: 1.3 mg/m² IV on Days 1, 4, 8 and 11 of Cycles 1–8 (21-day cycles)
R+D[69]	R: 25 mg/d given orally on Days 1–21 of a 4-week cycle until progression or intolerance D: 40 mg on Days 1–4 of Cycles 1–4 until progression or intolerance

D = dexamethasone; IV = intravenous; Peg = pegylated liposomal doxorubicin; R = lenalidomide; V = bortezomib.
** In patients with suboptimal response after two cycles, 40 mg dexamethasone could be administered on Days 1–4 of Cycles 5–9 (28-day cycles) or on Days 1–4, 9–12 and 17–20 of Cycles 1–4 (35-day cycles).*

Table 2: Selected Thalidomide, Bortezomib and Lenalidomide Combinations in Relapsed or Refractory Multiple Myeloma

	Regimen	Number of patients	ORR (%)	Median PFS (months)	Median OS (months)
Thalidomide	C+D+T[46]	60	72	11.0*	19.0
	C+T+D[48]	71	57	NA	NA
	Peg+T+D[51]	50	76	22.0	NR
	M+P+T[49]	24	42	9.0	14.0
Bortezomib	V+T+D[52]	85	63	NA	22.0
	V+Dox+D[60]	20	56	NA	NA
	Peg+V[61]	22	63	9.3§	38.3
	V+M+T+D[63]	60	59	9.5	NA
	V+C+P[64]	13	85	>12.0	>12.0
Lenalidomide	R+C+D[72]	31	81#	NA	NA
	C+P+R[64]	15	74	NA	NA
	R+V±D[41]	35	60¥	7.7§	37.0
	V+R+D[54]	62	69	12.0§	29.0

C = cyclophosphamide; D = dexamethasone; Dox = doxorubicin; M = melphalan; NA = not available; NR = not reached; ORR = overall response rate; OS = overall survival; P = prednisone; Peg = pegylated liposomal doxorubicin; PFS = progression-free survival; R = lenalidomide; T = thalidomide; V = bortezomib.
*# Very good partial response; ¥ At least minimal response; * Event-free survival; § Time to progression.*

effects through multiple mechanisms, including inhibition of Wnt signalling, blocking signalling through nuclear factor-kappa B, pro-apoptotic properties via the caspase-8/death receptor pathway, antiangiogenic effects, downregulation of tumour necrosis factor, augmentation of natural killer cell activity and stimulation of cytotoxic T-cells.[88–95] In a Phase I study, POM was given at four dose levels (2, 3, 4 and 5 mg) on Days 1–21 of a 28-day cycle to 32 patients. The median number of previously received regimens was seven (range two to 18). The maximum tolerated dose was not reached. Overall, eight (38 %) of 21 patients treated with POM alone achieved a response (one CR, two PRs and five MRs), with a mean TTP of 8.3 weeks (range two to 36). Dexamethasone was added in 13 patients and the responses (two PRs, two MRs, one SD) improved in five (38 %) of them.[96]

Another Phase I trial evaluated alternate-day POM given at four dose levels (1, 2, 5 and 10 mg), establishing 5 mg as the maximum tolerated dose. The ORR to POM alone was 50 %, including CR (10 %), VGPR (30 %) and PR (10 %).[97]

Two subsequent studies evaluating the combination of POM with low-dose dexamethasone (POM/dex) in patients with RRMM have been performed.[98,99] In both studies, POM was given orally at a daily dose of 2 mg on Days 1–28 of a 28-day cycle and dexamethasone was given orally at a daily dose of 40 mg on Day 1, 8, 15 and 22 of each cycle. In the first trial, 38 patients achieved an overall response (OR) (63 %), including CR in three patients (5 %), VGPR in 17 patients (28 %) and PR in 18 patients (30 %). Responses were observed in eight of 20 lenalidomide-refractory patients (40 %), six of 16 thalidomide-refractory patients (37 %) and six of 10 bortezomib-refractory patients (60 %).[98] In the second trial, the treatment was administered in a cohort of patients who were refractory to lenalidomide. The ORR was 32 %, with a median time to response of 2 months and response duration of 9.1 months.[99] These results suggested a lack of cross-resistance between lenalidomide and POM.

In two sequential Phase II trials, Lacy et al. evaluated the efficacy of two different doses of POM in patients who were refractory to both lenalidomide and bortezomib.[100] Thirty-five patients who had received a median of six prior therapies (range two to 11) were enrolled in each cohort. POM was given continuously at a daily dose of either 4 mg or 2 mg during 28-day cycles, along with 40 mg of dexamethasone on Day 1, 8, 15 and 22 of each cycle. The rates of at least MR in the 4 mg and 2 mg cohorts were 49 % and 43 %, respectively, including VGPR and PR rates of 28.5 % and 26 %, respectively. These responses were fast (from one to two months) and durable. These data confirm the activity of the drug in a more heavily pre-treated population. The median follow-up being 14 months, the median duration of response has not been reached in the 2 mg cohort. Although a longer follow-up is required, the six-month overall survival rates of 78 % and 67 % reported in the 2 mg and 4 mg cohorts, respectively, are promising.

The toxicity profile of POM consisted primarily of myelosuppression, which was more pronounced in the last study, reflecting the effects of extensive prior treatments. Grade 3–4 haematologic toxicity such as neutropenia was observed in 66 % and 51 % of patients in the 4 mg and 2 mg cohorts, respectively, and the rate of thrombocytopenia was 30.5 % in both cohorts. The most common non-haematologic toxicity was fatigue. Thromboprophylaxis with aspirin was given in most of the studies evaluating POM/dex and the rate of VTE was low (from 3–6 %). An international study (MM-003) is currently evaluating POM in combination with low-dose dexamethasone versus high-dose dexamethasone in RRMM.

Bendamustine

Bendamustine is an alkylating agent that is structurally similar to both alkylating agents and purine analogues; it is not cross-resistant with alkylating agents and other drugs *in vitro*.[101] Bendamustine has shown strong activity in RRMM patients as well as in untreated patients.[102,103] In a recent Phase I study, bendamustine was combined with lenalidomide and dexamethasone in patients with RRMM.[104] Seven (67 %) of the nine patients who could be evaluated achieved a response, including one VGPR and five PRs. The maximum tolerated dose of bendamustine and lenalidomide has not been identified at this point.

Bendamustine was also evaluated in the French compassionate use programme in 110 patients with RRMM who had previously received alkylators, steroids, IMiDs and bortezomib. The initial dose of bendamustine varied between 60 and 150 mg/m² given on Day 1 and 2 of 4-week cycles. The median number of administered bendamustine cycles was four (range one to 13), with an ORR of 30 %,

including CR (2 %). The median PFS was 9.3 months and the median OS was 12.4 months. The toxicity profile of bendamustine was comparable to other alkylating agents and included mostly reversible haematologic toxicity, while the most commonly reported non-haematologic side effects were nausea, fatigue, vomiting, fever, diarrhoea, constipation and headache. Further evaluation of bendamustine in MM is warranted and this agent is currently being tested in combination with other active agents, such as bortezomib.

Other Agents

Many ongoing studies are currently assessing the role of other agents targeting novel molecular mechanisms, such as the inhibitors of heat shock proteins (HSPs), histone deacetylase inhibitors and phosphoinositide 3-kinase (PI3K)/Akt inhibitors. Results are still preliminary, as some of the drugs investigated seem to have more cytostatic than cytotoxic effect. Thus further study is needed to assess the real efficacy of these agents. Recent Phase Ib and II trials are currently investigating the advantages associated with these novel drugs when used in combination with bortezomib or lenalidomide. In addition, early-phase studies are investigating the role of several other agents – for instance, monoclonal antibodies against CD40 (SGN-40) and CS1 (elotuzumab).

Conclusions

In the RRMM setting, the major challenge is to select the best approach for each patient while balancing efficacy and toxicity. To date, few studies have specifically addressed the retreatment and sequencing issues to guide physicians in the choice of therapy. The decision mainly depends on prior treatment, duration of remission, toxicity profile of the drug and patients' co-morbidities and disease characteristics. Regarding the type of previous treatment, conflicting data on the impact of previous treatment with novel agents have been reported. To date, there is not sufficient evidence to base therapy on disease characteristics such as extramedullary disease and cytogenetic abnormalities.

Young and compliant patients at their first or second relapse, who have shown a good response to multidrug combination regimens or who have not received any, should be treated with a combination therapy containing bortezomib, one IMiD, dexamethasone and possibly one chemotherapeutic agent. By contrast, elderly and younger patients with a suboptimal response to multidrug combination regimens or at advanced relapse stage should be treated with sequential therapy based on pre-existing toxicity and type of previous therapy.

Preliminary results of second-generation new drugs, such as CFZ, POM and bendamustine, seem favourable. However, further testing is needed to completely establish the safety and efficacy of these new agents and expand the spectrum of multidrug combinations. Schedules of regimens approved for RRMM are reported in *Table 1* and selected combinations including first-generation novel agents for RRMM are detailed in *Table 2*. ■

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