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Abstract

Introduction: Novel agents and the availability of autologous stem cell transplantation have revolutionized the treatment of patients with multiple myeloma. First generation novel agents, thalidomide, lenalidomide and bortezomib have significantly improved response and survival of patients. Second generation novel agents such as pomalidomide, carfilzomib, and monoclonal antibodies are being tested both in the newly diagnosed and relapse settings, and results are promising.

Areas covered: In this review article, the main results derived from phase III trials with thalidomide, lenalidomide and bortezomib for the treatment of myeloma patients, both at diagnosis and at relapse, are summarized. Data about second generation novel agents such as pomalidomide and carfilzomib are also reported. Newer effective drugs currently under investigation and the promising results with monoclonal antibodies are described.

Expert opinion: The availability of new effective drugs has considerably increased the treatment options for myeloma patients. A sequential approach including induction, transplantation (when possible), consolidation and maintenance is an optimal strategy to achieve disease control and prolong survival. Despite these improvements, the best combination, the optimal sequence and the proper target of newer drugs need to be defined.

1. Introduction

Multiple myeloma (MM) accounts for 1.6% of all cancers, 13% of all hematologic malignancies and 1.9% of all cancer deaths[1]. The diagnosis of MM requires the presence of at least 10% clonal plasma cells on bone marrow examination and/or a biopsy-proven plasmacytoma, as well as evidence of end-organ damage based on CRAB criteria (ie, hypercalcemia, renal insufficiency, anemia, or bone lesions)[2]. Recently, clonal bone marrow plasma cell percentage of 60% or higher, involved/uninvolved serum free light chain ratio of 100 or higher, more than one focal lesion on magnetic resonance imaging studies have been considered as biomarkers associated with near inevitable development of CRAB features[3].

In the past decade, the introduction of autologous stem-cell transplantation (ASCT) and the availability of novel agents such as thalidomide, lenalidomide, and bortezomib have revolutionized the treatment paradigm of MM, with considerable improvements in responses and survival[4]. In Europe, patients <65 years with no comorbidities are considered suitable for ASCT, while conventional chemotherapy is the

option in patients ≥65 years, with gentler approaches for patients over 75 years. In both young and elderly patients, induction therapies and maintenance strategies including novel agents are commonly adopted. Yet, MM patients eventually relapse or become refractory to currently available drugs. Second-generation novel agents and new combinations are being tested in ongoing clinical trials and will further increase the treatment options for MM patients.

2. APPROVED NOVEL AGENTS

2.1 Immunomodulatory drugs

2.1.1 Thalidomide

The combination melphalan-prednisone (MP) had long been the standard of care for patients not eligible for high-dose therapy and transplantation. Thalidomide, an immunomodulatory drug (IMiD), was the first novel agent to be approved for the treatment of MM. An efficacy meta-analysis of six trials, including 1685 newly-diagnosed (ND) MM patients (Table 1)[5], showed that the addition of thalidomide to MP (MPT) significantly prolonged both progression-free survival (PFS) and overall survival (OS) compared to MP[6]. Based on these data, in Europe, MPT was adopted as a standard of care in transplant-ineligible patients until recently, when new and more effective combinations became available. The benefit obtained with thalidomide has provided the basis for the development of new generation IMiDs, lenalidomide and pomalidomide.

2.1.2 Lenalidomide

Lenalidomide is a second generation IMiD currently used for the treatment of both relapse/refractory (RR) and NDMM patients. Based on the results of two phase III trials, MM009 and MM010, conducted in RRMM patients, lenalidomide plus dexamethasone demonstrated to be superior to dexamethasone alone, both in terms of responses and outcomes (PFS and OS)[7,8]. These results led to the approval of lenalidomide for RRMM patients in USA and in Europe in 2006.
The excellent results observed in the relapse setting paved the way for the investigation of lenalidomide as part of the upfront treatment in ND patients.
In a phase III trial, lenalidomide plus high-dose dexamethasone (RD) was compared to lenalidomide plus low-dose dexamethasone (Rd) in ND patients, both eligible and ineligible for ASCT[9]. Despite a higher overall response rate (ORR) with RD (79% vs. 68.3%, p=0.008), patients treated with Rd had a significantly longer 2-year OS (75% vs. 87%, p<0.001). The survival benefit associated with Rd was particularly evident in patients older than 65 years of age (1-year OS: 83% with RD vs. 94% with Rd).

Two phase III trials in ASCT-eligible patients investigated lenalidomide administered both during induction/consolidation and maintenance; after induction treatment (Rd), patients were randomized to ASCT or conventional chemotherapy (CC). In the MPR-MEL200 trial, 402 patients were firstly randomized to either melphalan-lenalidomide-prednisone (MPR) or ASCT and then to lenalidomide maintenance or no maintenance [10]. ASCT proved to be superior to MPR both in terms of PFS (median, 43 months vs 22.4 months; p<0.001) and 4-year OS (82% vs 65%; p=0.02). In the CRD-MEL200 trial, 389 NDMM patients could receive either ASCT or CC [cyclophosphamide-lenalidomide-dexamethasone (CRD)]; after a second randomization patients were allocated to lenalidomide maintenance alone or with prednisone (RP). ASCT prolonged PFS (NR vs 28 months; p=0.03) and 3-year OS (60% vs 38%; p=0.03) as compared to CRD[11].

The phase III FIRST trial compared for the first time upfront thalidomide (MPT) and lenalidomide, given continuously (Rd) until progression or in a fixed schedule of 18 cycles (Rd-18)[12]. In 1623 ND ASCT-ineligible patients, Rd significantly prolonged median PFS (25 months) as compared to both Rd-18 (21 months; p<0.001) and MPT (21 months; p<0.001). Furthermore, Rd significantly reduced the risk of death by 22% as compared to MPT. The longer median PFS2 reported among patients treated with Rd in comparison with those who received MPT (43 months vs 36; p=0.005) showed that a prolonged lenalidomide exposure did not negatively affect the responsiveness to second-line treatment. This study demonstrated the superiority of the doublet, alkylating-free regimen Rd over MPT.

The EMN01 trial compared a 2-drug alkylator-free regimen (Rd) versus 3-drug lenalidomide-based regimens [cyclophosphamide-prednisone-lenalidomide (CPR) and MPR] in 662 NDMM elderly patients[13]. All patients received maintenance with lenalidomide alone or with prednisone (RP). No significant differences in terms of median PFS (23 vs 23 vs 27 months) and 3-year OS (73% vs 72% vs 67%) were detected among Rd, CPR and MPR arms, respectively. A slight PFS advantage was observed in patients <75 years treated with MPR, while no differences were reported between 2- and 3-drug regimens among patients >75 years. Six phase III trials explored the role of lenalidomide as a maintenance agent. In the transplant setting, three studies in which lenalidomide was compared to placebo or no maintenance showed a significant PFS benefit in favor of lenalidomide maintenance but in only one a significant OS advantage was detected[10,14,15]. In the CRD-Mel200 trial, the addition of prednisone to lenalidomide showed a PFS benefit as compared to lenalidomide alone (2-year PFS: 83% vs 64%; p=0.02)[11]. Among 459 elderly patients, MPR followed by lenalidomide (MPR-R) significantly improved median PFS in comparison with MPR and MP (31 months vs. 14 months vs. 13 months; p<0.001). This advantage was more evident in patients younger than 75 years, in whom MPR-R significantly improved PFS compared to MPR and MP. In a landmark analysis from start of maintenance, lenalidomide maintenance significantly prolonged PFS as compared to placebo, regardless of age (26 months with MPR-R vs. 7 months with MPR-placebo, p<0.001), with a 66% reduced risk of progression. A concern about second primary malignancies (SPM) with a long-term use of lenalidomide has been raised: a meta-analysis showed that the risk of developing an SPM was higher when lenalidomide was combined with alkylating agents, especially melphalan[16].

2.1.3 Pomalidomide

Pomalidomide is a third generation IMiD that demonstrated efficacy in MM patients refractory to both lenalidomide and bortezomib. Several phase I/II studies explored the activity of pomalidomide (2 to 4 mg), both alone or in combination with dexamethasone: the ORR ranged from 26% to 65% and median PFS from 3 to 13 months, based on the number of prior therapies (median 2 to 6) and the refractoriness status to bortezomib and lenalidomide. The IFM 2009-002 study explored two schedules of pomalidomide-dexamethasone: pomalidomide given for 21 days of a 28-day cycle (21/28) or continuously during a 28-day cycle (28/28). No differences in responses and outcomes were reported. The investigators recommended the 21/28 schedule for a better marrow recovery [17]. In the phase III MM-003 trial pomalidomide-dexamethasone (4 mg, 21/28) was compared to high-dose dexamethasone (HiDex) in 455 MM patients RR to both lenalidomide and bortezomib [18]. Pomalidomide-dexamethasone induced a higher ORR than HiDex (21% vs 3%; p<0.001) and significantly prolonged median PFS (4 months vs 2 months; p<0.001) and OS (not reached vs 8 months, p<0.001).

Pomalidomide was then approved by the FDA and the EMA in 2013 for use alone (USA) or in combination with dexamethasone in patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on their last therapy[19].

Promising results were achieved with the combination of pomalidomide and alkylating agents or proteasome inhibitors (PI). Pomalidomide-cyclophosphamide-prednisone (PCP), administered to 69 RRMM patients in a phase Ib/II study, led to an ORR of 51% (46% in lenalidomide-refractory patients), a median PFS of 10 months and a 1-year OS rate of 69%[20]. The addition of cyclophosphamide to pomalidomide-dexamethasone (PCD) was compared to pomalidomide-dexamethasone in a phase II study[21]; PCD lead to a higher response rate (65% vs 39%; p=0.03), and longer median PFS (9 vs 4 months; p=0.04) and OS (16 months vs 10; p=0.08). In a phase I/II trial in RR patients, pomalidomide-dexamethasone plus bortezomib (PVD) showed to be well tolerated and highly effective, with an ORR of 81% and a median PFS of 17.7 months[22]. The synergistic activity of pomalidomide and the second generation PI, Carfilzomib (KPd) is currently under investigation: preliminary results from an ongoing phase Ib/II study confirmed the role of this association, reporting an ORR of 72% (ORR 78% in PIs naïve/sensitive patients)[23].

Pomalidomide demonstrated to be safe and effective in patients with mild to moderate renal impairment (clearance creatinine > 45 ml/min). Two ongoing studies (MM-008 and MM-013) will help to determine the optimal dose of pomalidomide in patients with severe renal impairment (creatinine clearance <30 ml/min).

2.2 Proteasome Inhibitors

Proteasome inhibitors (PI) are a class of novel agents targeting the proteasome. Their activity is generally higher in neoplastic cells, thus resulting in activation of pro- and anti-proliferative signals, disruption of cell-cycle regulation, and activation of apoptotic pathways and cell death. Bortezomib is the first in class PI approved by the US FDA for the treatment of NDMM and RRMM. Second-generation PIs include carfilzomib, already licensed by the FDA for RRMM patients, and other compounds currently under development such as Oprozomib, Ixazomib and Marizomib.

2.2.1 Bortezomib

Bortezomib is the first PI introduced into MM clinical practice; it is a boronic acid derivative that reversibly inhibits the chymotrypsin- and caspase-like activities of both the constitutive proteasome and the immunoproteasome [24,25]. Bortezomib was granted approval by the FDA and EMA for the treatment of MM patients who relapsed after at least 1 prior line based on the results of the phase III APEX trial, comparing bortezomib plus dexamethasone (VD) to dexamethasone alone. VD showed longer median time-to-progression (TTP, 6 months vs 3 months; p<0.001) and OS (30 months vs 24 months; p<0.001) compared with dexamethasone.

In NDMM patients, bortezomib is currently used in pre-transplant induction regimens, in association with steroids and IMIDs and/or chemotherapy, as well as in elderly, transplant-ineligible patients.

In ASCT-eligible patients, VD induced higher response rates than vincristine-doxorubicin-prednisone (VAD), with a VGPR rate of 38% vs 15% after induction, which improved after transplantation (54% *vs* 37%). The difference between response rates translated into a PFS improvement in favor of VD (36 months vs. 30 months, p=0.064)[26]. The 3-drug regimen bortezomib, thalidomide and dexamethasone (VTD) has been compared with the 2-drug thalidomide-dexamethasone (TD) and with VD[27,28]. In a phase III study VTD,

as induction and consolidation after ASCT, resulted in higher nCR/CR rates after consolidation as compared to TD (73% vs 61%; p=0.02), with a significant increase in the nCR/CR rate in the VTD group after consolidation treatment. VTD, in comparison with TD, prolonged 3-year PFS (60% vs 42%; p=0.04. Similar results were reported in another phase III trial comparing VTD (with a reduced-dose of bortezomib) and VD as induction treatment. Better quality of responses (VGPR/CR, 49% vs 36%, P = 0.05) and longer median PFS were reported with VD induction. Nevertheless, none of the two studies found an OS advantage in favor of VD[29]. The combinations of VD plus lenalidomide (VRD) or cyclophosphamide (VCD) are adopted for the upfront treatment of ASCT-eligible patients. Data from the phase II EVOLUTION trial showed a similar activity between VCD and VRD; furthermore, the addition of lenalidomide to VCD (VCRD) did not increase the CR rate as compared to 3-drug regimens.

Bortezomib has demonstrated excellent results in elderly patients and has become a back-bone in the treatment of ASCT-ineligible patients. The randomized phase III VISTA study compared bortezomib plus MP (VMP) and MP in 682 ASCT-ineligible patients. VMP proved to be superior to MP inducing a higher ORR (71% vs 35%; p<0.001) and CR rate (30% vs 4%; p<0.001) and a longer median TTP (24 vs 17 months; p<0.001). An updated analysis confirmed the OS advantage with VMP in comparison with MP (3-year OS: 68% vs 54%)[30]. A Spanish phase III trial randomized 260 patients to receive either VMP or bortezomib-thalidomide-prednisone (VTP) as induction treatment, followed by either VP or VT maintenance. No differences were recorded in terms of PFS and OS between VMP and VTP. After the second randomization, patients who were maintained with VT had longer PFS (median, 39 vs 32 months; p=0.1) and 5-year OS (69% vs 59%;p =0.1). On the other hand, VT maintenance was more toxic than VP in terms of grade 3/4 non-hematologic adverse events (17% vs 5%; p=0.009)[31]. The phase III GIMEMA trial compared standard VMP to the 4-drug VMP plus thalidomide (VMPT) followed by VT maintenance in 511 patients over 65 years[32,33]. A significant PFS (median, 35 vs 25 months; p<0.001) and 5-year OS (61% VS 51%; P=0.01) advantage was reported with VMPT-VT as compared with VMP. This advantage was particularly evident in patients less than 75 years. Furthermore, when bortezomib schedule was changed from twice-weekly to once-weekly, the rate of grade 3/4 toxicities decreased without affecting efficacy.

A prospective randomized study in relapsed patients compared subcutaneous vs intravenous bortezomib[34]. Bortezomib administered subcutaneously showed to be as effective as intravenous bortezomib, with the advantage of a significant reduction in peripheral neuropathy. Based on these results, subcutaneous bortezomib was granted approval.

2.2.2 Carfilzomib

Carfilzomib primarily inhibits chymotripsin-like site of the proteasome, forming a stable and irreversible adduct with the proteasome excretion[35,36]. Carfilzomib has been investigated in both the relapse and the upfront settings, either alone or in combination with steroids, alkylators and novel agents.

The pivotal study that granted the FDA approval of carfilzomib for the treatment of RRMM is the phase II trial (PX-171-003-A1) that enrolled 266 patients (median of 5 prior therapies) treated with twice-weekly carfilzomib (20/27 mg/m2)[37]. The ORR was 24%, the median duration of response was 8 months and OS 16 months; a similar ORR (20%) was reported among patients who were refractory or intolerant to bortezomib and lenalidomide. Carfilzomib was then granted accelerated approval by the FDA in 2012 for the treatment of patients with MM who have received at least two prior therapies, including bortezomib and an IMiD, and who have demonstrated disease progression on or within 60 days of completion of last therapy. In the PX-171-007 study, different doses of escalated carfilzomib were tested: 36, 45, 56 or 70

mg/m2, alone or in combination with dexamethasone[38]. At the maximum tolerated dose (MTD) of carfilzomib (56 mg/m2), the ORR was 50% for patients receiving carfilzomib only and 55% for those receiving carfilzomib-dexamethasone. In the CHAMPION-1 study, a the MTD (70 mg/m2) of once-weekly carfilzomib, a 93% ORR was observed in RR patients [39].

The promising results reported in the phase Ib/II PX-171-006 trial led to the randomized, phase III ASPIRE trial that assessed the addition of carfilzomib (20/27 mg/m2) to Rd (KRd; Table 2)[40]. A total of 792 RR patients were randomized to receive either KRd or Rd. KRd induced a higher CR rate (35% vs 9%; p<0.0001) and significantly prolonged median PFS (26 vs 18 months; p=0.0001) as compared to Rd; noteworthy, a trend toward a better 2-year OS was reported in the KRd arm (73% vs 65%; p=0.04).

Data about the head-to head comparison between carfilzomib and bortezomib in the ENDEAVOUR study have been recently presented[41]. 929 RRMM patients were randomized to receive either carfilzomib or bortezomib ,plus dexamethasone. Patients in the carfilzomib arm had a higher rate of ORR, at least VGPR and CR rate, resulting into a significantly longer PFS (median, 18.7 months vs 9.4 months; HR 0.53; p<0.0001).

In the upfront setting, carfilzomib has been tested in combinations with IMiDs, alkylating agents and HDACIs. In the phase II CARTHADEX trial including ASCT-eligible patients, induction with carfilzomib combined with thalidomide and dexamethasone resulted in a 90% ORR[42]. In a phase Ib/II trial conducted in 53 patients, KRd induced an ORR of 98%, with a 68% ≥nCR rate [43]. Among 58 elderly patients enrolled in a phase II trial, the combination of carfilzomib, cyclophosphamide and dexamethasone induced an ORR of 95% after induction, with a sCR rate of 20%[44].

A formal comparison between bortezomib and carfilzomib combined with MP is currently ongoing in a randomized, phase III trial (CLARION).

2.3 Histone deacetylase inhibitors

2.3.1 Panobinostat

Histone deacetylase inhibitors (HDACis) are a new class of compounds active against MM. Deacetylases are a group of enzymes that regulate activity of proteins post-translationally by reversing protein acetylation. They play a role in many cellular processes, including gene expression and protein degradation [45], Panobinostat is a potent inhibitor of all class I, II, and IV histone deacetylase (HDACs). The synergistic activity of panobinostat, bortezomib and dexamethasone (PVD) was tested in a phase Ib trial [46]. The MTD of panobinostat was determined at the dose of 20 mg three times a week in a 21-day cycle; the results from the phase II expansion cohort led to the choice of the 2 weeks on/1 week off schedule instead of the continuous schedule, better tolerated and more effective. Results from this trial influenced the schedule adopted in the phase II PANORAMA2 and the subsequent phase III PANORAMA1 trials. In the PANORAMA2 trial, conducted in 55 RRMM bortezomib-refractory patients, PVD induced an ORR of 35%, that translated into median PFS and OS of 5 and 17 months, respectively [47]. The addition of panobinostat to VD demonstrated to be able to re-capture approximately 1/3 of bortezomib-refractory patients. Those results provided the rationale for the randomized, phase III PANORAMA1 trial in which 768 RRMM patients (not-bortezomib refractory) were randomized to either PVD or VD [48]. Despite a similar ORR, the better quality of responses obtained with PVD (nCR/CR rate 28% vs 16%; p=0.0006) induced a longer PFS (median, 12

months vs 8 months; p<0.0001), while no significant survival benefit detected between the two arms (median, 34 vs 30 months; p=0.026). The advantage reported among patients who were treated with PVD was consistent despite age (<65 vs >65 years), ISS (I vs II/III) or previous treatment with bortezomib. Based on these data, on February 2015, the FDA approved panobinostat for use in combination with bortezomib and dexamethasone for the treatment of myeloma patients who received at least 2 prior regimens, including bortezomib and IMiDs. Combinations of panobinostat with new drugs such as carfilzomib and lenalidomide are currently under evaluation.

2.3.2 Bendamustine

Bendamustine is a peculiar bi-functional alkylator used in many lymphoproliferative disorders. It has been tested in both ND and RRMM patients in combination with various drugs, showing promising activity with currently approved novel agents. In a phase II study comparing bendamustine, at two different doses (60 vs 100 mg/m2) plus thalidomide and low-dose dexamethasone, in 94 RRMM patients, a 46% ORR was reported, that translated into a median PFS of 8 months[49]. The addition of bendamustine to the second generation IMiD, lenalidomide, has been explored in different studies, showing an interesting potential. The combination of bendamustine plus Rd (6 cycles plus Rd maintenance for up to 12 cycles), administered to MM patients relapsing after first line treatment induced a VGPR+CR rate of 53%[50]. Promising results have been observed with the combination of bendamustine, bortezomib and steroids, both upfront and at relapse. In the first report investigating this combination in patients with a median of 4 prior therapies, an ORR of 85% was reported[51]. Among 75 RRMM patients, bendamustine plus VD induced a 75% ORR that translated into median PFS and OS of 13 and 24 months, respectively[52,53]. Based on the anti-myeloma activity reported in the relapse setting, bendamustine is currently under investigation also in the upfront setting, for the treatment of both ASCT-eligible and ineligible patients[54,55].

3 Novel agents under development

3.1 Proteasome Inhibitors

3.1.1 Ixazomib

Ixazomib is an orally bioavailable inhibitor of the 20S proteasome [56]. In clinical trials, ixazomib showed promising activity both as a single agent and in combination with dexamethasone [57-59]. Furthermore it exerts anti-myeloma activity in combination with IMiDs. The synergistic activity of PIs and IMiDs provided the rationale for the evaluation of the combination of a fully orally available combination: ixazomib plus Rd. In a phase I/II study enrolling NDMM patients, the recommended phase II dose (RP2D) of ixazomib administered once-weekly in combination with Rd was 2.23 mg/m2 [60]; hence the choice of a fixed dose (4 mg) for the phase II portion of the trial in which 50 patients were enrolled. Ixazomib-Rd proved to be effective, with at least a partial response (≥PR) rate of 94% and a CR rate of 19% after the first four cycles, with a CR rate improvement to 32% after eight cycles. Similar results were reported in a second phase I/II trial with ixazomib-Rd among 50 ND patients [61]. At the RP2D of ixazomib (3 mg) the ≥PR rate was 93% and the CR rate was 24%. More interestingly, 82% of CR patients were minimal residual disease (MRD) negative. Ixazomib mainly caused hematologic toxicity, in particular grade 3-4 thrombocytopenia and neutropenia. A very low rate of grade 3-4 peripheral neuropathy has been reported with ixazomib (≤5%).

Promising results from phase II studies led to the ongoing, randomized, phase III trial comparing Ixazomib-Rd to the standard Rd. Furthermore, ixazomib is currently under investigation as a maintenance agent, both alone or in combination with lenalidomide.

3.1.2 Oprozomib and Marizomib

Preliminary efficacy of oprozomib, an irreversible orally available PI, in patients with hematologic malignancies has been observed. A phase Ib/II study to determine the MTD and to evaluate safety and tolerability of oprozomib-dexamethasone is currently ongoing. The most common grade 3 toxicities observed were diarrhea, anemia and nausea. Preliminary results suggest that oprozomib-dexamethasone may reduce gastrointestinal side effects associated with oprozomib alone [62].
Marizomib is a potent, orally active inhibitor of the 20S proteasome, potentially able to overcome Bortezomib resistance *in vitro* [63,64]. Early studies suggest a synergistic activity of marizomib and IMiDs (pomalidomide and lenalidomide).

3.2 Monoclonal Antibodies

Monoclonal antibodies (MoAbs) can be directed against a large variety of antigen targets expressed on myeloma cells or on cellular and non-cellular components of the bone marrow microenvironment, such as signaling molecules, cell surface receptors or proteins, plasma cell growth factors and mediators of adhesion and invasiveness [65].

3.2.1 Anti-CS1

Elotuzumab

Elotuzumab is a fully humanized monoclonal IgG1 antibody directed against human CS1, a surface glycoprotein involved in MM cell adhesion to bone marrow stromal cells and in NK activity regulation [66]. Elotuzumab has been evaluated in combination with bortezomib and lenalidomide in two Phase I and I/II studies, demonstrating encouraging results in terms of responses; notably, prior exposure to novel agents did not affect response rate [67,68]. In a recent phase III trial (ELOQUENT-2), the addition of elotuzumab to the standard Rd has been tested in RR patients. Elotuzumab-Rd increased the ORR (79% vs 66%; $p<0.001$) and significantly prolonged median PFS (19 vs 15 months; $p<0.001$) in comparison with Rd [69].

3.2.2 Anti-CD38

Daratumumab

Daratumumab is a human IgG1κ MoAb that mediates destruction of CD38- expressing malignant plasma cells increasing the apoptosis induced by novel agents. A phase Ib study evaluated the safety, tolerability and dose of daratumumab in combination with VD, VTD, VMP, and pomalidomide-dexamethasone [70]: the addition of daratumumab did not negatively impact on safety profile. Daratumumab was also evaluated in combination with Rd in a phase I/II study: toxicities were manageable and encouraging activity was reported, as the majority of the patients achieved PR or better [71].

SAR650984

SAR650984 is the second IgG monoclonal antibody that binds to a unique epitope in the human CD38 receptor; the activity of SAR650984 was evaluated in combination with Rd in pre-treated patients; treatment was well tolerated and responses were rapid, increasing with prolonged treatment [72].

4. Conclusion

Sequential approaches based on novel agents are a sensible choice for the treatment of MM patients, for both patients eligible and ineligible for ASCT. The introduction of thalidomide, lenalidomide, and bortezomib has considerably changed the treatment paradigm of MM patients. Second-generation novel agents, such as carfilzomib and pomalidomide, are already available. Newer compounds, in particular monoclonal antibodies are currently under investigation. The results obtained so far are promising and these newer drugs will significantly enrich the treatment armamentarium for MM patients, both at diagnosis and relapse.

5. Expert Opinion

The introduction of novel agents has dramatically changed the outcome of MM patients. A better understanding of myeloma cells has brought to the identification of new targets towards the new drugs are directed. However, despite the great efficacy of novel agents, MM patients eventually relapse. A survival analysis conducted among patients relapsed after first-generation new drugs has shown poor PFS (5 months) and OS (9 months), thus highlighting the clinical need for newer compounds able to overcome myeloma cells resistance to currently approved anti-myeloma agents.

Thalidomide was the first novel agent introduced in the landscape of myeloma treatment. Today, it is currently adopted in NDMM patients, both ASCT-eligible and ineligible. Among younger patients, thalidomide can be administered in combination with bortezomib during pre-transplant induction and consolidation. In the elderly, MPT is a standard of care. The use of thalidomide as a maintenance agent is often limited by its safety profile, especially among elderly patients. Thalidomide is being replaced by the second-generation IMiD, lenalidomide, a more potent compound with a favorable safety profile. Lenalidomide is approved for both RRMM patients and, more recently, for the upfront treatment of NDMM patients. It has demonstrated efficacy as part of the induction treatment of ASCT-eligible patients in combination with bortezomib and steroids. In elderly patients, Rd administered continuously has recently proved to be superior to MPT. Toxicities associated with lenalidomide are mainly hematologic. Its safety profile and the oral administration make lenalidomide a particularly attractive compound to be used continuously during maintenance. In both young and elderly patients, lenalidomide maintenance significantly delays relapse, despite a survival advantage is yet unclear. The third-generation IMiD Pomalidomide has shown an excellent efficacy in heavily pre-treated patients, particularly in those RR after bortezomib and lenalidomide; the anti-myeloma activity of pomalidomide is enhanced by the combination with dexamethasone. The addition of a third drug - cyclophosphamide or PIs - seems to augment responses and prolong survival. The safety profile of pomalidomide is similar to that of lenalidomide: most common toxicities derive from myelosuppression. Furthermore, pomalidomide can be safely used in patients with mild to moderate renal failure.

PIs are highly active against myeloma cells. Bortezomib is a backbone of the upfront treatment of both young and elderly patients. In ASCT-eligible patients, bortezomib has been successfully combined with IMiDs (VTD and VRD), with anthracycline (PAD) and alkylators (VCD). Bortezomib-based consolidation after transplantation improves depth of response obtained with ASCT. In ASCT-ineligible patients, VMP is the treatment of choice for fit patients; moreover, bortezomib can be safely administered to patients with renal failure. The major issue observed with bortezomib is the emergence of peripheral neuropathy, a toxicity that may lead to treatment discontinuation. Data about alternative schedule (once-weekly) and

route of administration (subcutaneous) have demonstrated to reduce neuropathy. Second-generation PIs have been recently introduced in clinical studies. Carfilzomib is an irreversible PI that has shown its ability to overcome bortezomib refractoriness. In addition, no significant neuropathy has been observed with carfilzomib. The excellent activity of carfilzomib in clinical trials granted its approval by the FDA. Subsequently, the role of carfilzomib started to be investigated as upfront treatment and a formal comparison with bortezomib in ND ASCT-ineligible patients (CMP vs VMP) is currently ongoing. Other second-generation PIs such as ixazomib and oprozomib are intriguing molecules, particularly because of their oral administration. Promising results come from MoAbs, such as elotuzumab, daratumumab and SAR650984. Their combination with other novel agents will clarify their role in the treatment of MM.

The biological heterogeneity typical of MM cells and the emergent drug resistance to novel agents are a big challenge to physicians. Despite the great efficacy of newer drugs, relapse is almost inevitable. Therefore, compounds with a different mechanism of action from those of available drugs are highly needed to increase the efficacy of standard treatments and to overcome myeloma resistance to current therapies. Several molecules are currently under investigation in pre-clinical and clinical studies. Filanesib, a kinase spindle protein inhibitor able to cause an aberrant mitotic arrest and consequent cell death, has already demonstrated, its ability to act synergistically with dexamethasone and proteasome inhibitors in early phase trials in the relapse setting, with promising response rates. Selinexor, an oral selective inhibitor of nuclear export (EXPO1), is another promising compound, with a brand new target in myeloma; selinexor, showed synergistic activity with dexamethasone and is currently under investigation in combination with various backbone regimens in myeloma, such as IMiDs and PIs. Preliminary data about perifosine, a synthetic alkylophospholipid directed against cell membranes and able to prevent the activation of AKT protein, showed synergism between perifosine and dexamethasone, melphalan and bortezomib.

In the era of novel agents, the number of active compounds against myeloma cells is rapidly rising, allowing physicians to tailor treatment according not only to patient's characteristics but also to the sensibility of the disease to the different drugs available. In this regards, the identification of biomarkers, such as cereblon for IMiDs and AAG for Filanesib, able to predict tumor response to treatments, is of great interest and paves the way to personalized treatment.

Despite the availability of numerous anti-myeloma drugs, many questions still remain unanswered. The best combination, the optimal sequence and the proper target of newer drugs, are issues to be clarified in the next future.

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Article highlights box

- Novel agents have revolutionized the treatment paradigm of patients with MM
- Thalidomide, lenalidomide, bortezomib are currently used in standard approaches in both patients eligible and ineligible for transplantation
- Novel agents are today incorporated into induction and consolidation/maintenance treatment strategies
- New generation novel agents with improved efficacy and better tolerability, such as pomalidomide, carfilzomib, and also monoclonal antibodies, are under investigation and preliminary results are promising.

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Tables

1. PHASE III TRIALS IN NDMM

Regimen	Schedule	Patients	ORR	PFS-OS	AEs ≥ Grade 3
MPT Fayers [5]	**Mel-P-Thal**	815	59%	Median PFS:20,3 mo Median OS: 39,3 mo	Hematologic AEs: 32% Infection: 13% Peripheral neuropathy: 6% Deep-vein-thrombosis: 6%
RD Rajkumar [9]	**Len** 25 mg on days 1-21 **Dex** 40 mg on days 1-4, 9-12, and 17-20 of a 28-day cycle	223	79%	1-year OS: 87%	Fatigue: 15% Pneumonia: 16% Deep-vein-thrombosis: 26%
Rd Rajkumar [9]	**Len** 25 mg on days 1-21 **Dex** 40 mg on days 1, 8, 15, and 22 of a 28-day cycle	222	68%	1-year OS: 96%	Fatigue: 9% Pneumonia: 9% Deep-vein-thrombosis: 12%
Rd Benboubker [12]	**Len** 25 mg on days 1-21 **Dex** 40 mg on days 1, 8, 15, and 22 for 18 28-day cycles	541	73%	Median PFS: 20,7 mo 4-year OS: 56%	Neutropenia: 26% Infection: 22% Cardiac events: 7%
Rd Magarotto [13]	**Len** 25 mg on days 1-21 **Dex** 40 mg on days 1, 8, 15, and 22 of a 28-day cycle until PD	535	75%	Median PFS: 25,5 mo 4-year OS: 59%	Neutropenia: 28% Infection: 29% Cardiac events: 12%
CPR Magarotto [13]	**Len** 25 mg/day on days 1-21 **Cyclo** 50 mg/day or every other day on days 1-21 **P** 25 mg every other day of a 28-day cycle	222	NA	Median PFS: 23 mo 3-year OS: 72%	At least a G3- 4 hematologic events in ≤75 ys pts: 33% At least a G3- 4 hematologic events in >75 ys pts: 33%
MPR (EMN01) Magarotto [13]	**Len** 10 mg/day on days 1- 21 **Mel** 0.18-0.13 mg/Kg for 4 days **P** 1.5 mg/Kg for 4 days of a 28-	218	NA	Median PFS: 27 mo	At least a G3- 4 hematologic event in ≤75 ys pts: 66% At least a G3- 4 hematologic

	day cycle			3-year OS: 67%	events in >75 ys pts: 70%
MPR-R Palumbo [16]	**Mel** 0.18 mg/kg on days 1- 4 **P** 2 mg/kg on days 1-4 **Len** 10 mg on days 1-21; **Len maintenance**: 10 mg on days 1-21 of 28-day cycles	152	77% ≥VGPR 33%	Median PFS: 31 mo 3-year OS: 70%	Neutropenia G4: 35% Thrombocytopenia G4: 11% Infection: 10%
VTD Cavo [27]	**Bor** 1.3 mg/m2 on days 1, 4, 8, and 11 **Thal** 100 mg daily for the first 14 days and 200 mg daily thereafter **Dex** 40 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of 21 day cycles	236	97.5%	3-year PFS: 60% 3-year OS: 90%	Gastrointestinal : 2% Peripheral neuropathy: 0,6%
VD Harousseau [26]	**Bor** 1.3 mg/m2 on days 1, 4, 8, and 11 **Dex** 40 mg on days 1-4 (all cycles) and on days 9-12 (cycles 1 and 2) for four 21 day cycles	240	78.5%	Median PFS: 36 mo 3-year OS: 81,4%	Anaemia: 4% Neutropenia: 5% Infection: 9% Thrombosis:2%
VMP San Miguel [30];	**Mel** 9 mg/m2 on days 1-4 **P** 60 mg/m2 on days 1-4 **Bor** 1.3 mg/m2 on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9 of 9 6-week cycles	344	71%	2-years PFS: 50% 3-year OS: 68%	Neutropenia: 40% Thrombocytopenia: 37% Peripheral neuropathy: 13% Infections: 10%
VMPT-VT Palumbo [32,33]	**Bor** 1.3 mg/m^2 on days 1, 8, 15, 22 **Mel** 9 mg/m^2 on days 1–4 **P** 60 mg/m^2 on days 1–4 **Thal** 50 mg/d for nine 35-d cycles **Bor-T maintenance: Bor** 1.3 mg/m^2 every 14 d; **Thal** 50 mg/d for 2 years	254	89%	3-year PFS: 56% 3-year OS: 89%	Neutropenia: 38 % Thrombocytopenia: 22 % Peripheral neuropathy: 8 % Infections: 13%
VTP Mateos [31]	**Bor** 1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32 **Thal** 100 mg/day **P** 60 mg/m² on days 1-4	130	81%	Median PFS: 25 mo 3-year OS: 65%	Neutropenia: 22 % Thrombocytopenia: 12 % Peripheral neuropathy: 9% Cardiac events: 8%

ORR: overall response rate; PFS: progression free survival; OS: overall survival; AEs: adverse events. Mel: melphalan; P: prednisone; Thal: thalidomide; Len: lenalidomide; Cyclo: cyclophosphamide; Dex: dexamethasone; Bor: bortezomib; Pan: panobinostat; NA: not available

TABLE 2: PHASE III TRIALS IN RRMM

Regimen	Schedule	ORR	PFS (median)	OS (median)
Pd San Miguel [48]	**Pomalidomide** 4 mg on days 1-21 of a 28-day cycle **Dexamethasone** 40 mg on days 1, 8, 15, and 22 of of a 28-day cycle	31%	4 months	13 months
KRd Stewart [40]	**Carfilzomib**: 20/27 mg/m2 on days 1,2,8,9,15 and 16 (cycles 1-12) and 1,2,15 and 16 (cycles 13-18) of a 28-day cycle **Lenalidomide**: 25 mg ond days 1-25 of a 28-day cycle **Dexamethason**e: 40 mg on days 1,8,15 and 22 of a 28-day cycle	87%	26 months	NR (2-year OS: 73%)
PAN-Vd San Miguel [48]	**Pan** 20 mg on days 1, 3, 5, 8, 10, 12 of a21 day cycles **Bor** 1.3 mg/m2 on days 1, 4, 8, 11 of a21 day cycles **Dex** 20 mg on days 1, 2, 4, 5, 8, 9, 11, 12 of a21 day cycles	61%	12 months	34 months
Elotuzumab-Rd Lonial [68]	**Elotuzumab:** 10 mg/kg on days 1,8,15 and 22 (cycles 1-2) and on days 1 and 15 (from cycle 3) of a 28-day cycle **Lenalidomide**: 25 mg ond days 1-25 of a 28-day cycle **Dexamethason**e: 40 mg on days 1,8,15 and 22 of a 28-day cycle	79%	19 months	NA

P: pomalidomide, d:dexamethasone, K: carfilzomib, R: lenalidomide, PAN: panobinostat, V: bortezomib, ORR: overall response rate, PFS: progression-free-survival, OS. Overall survival, NA: not available