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Future agents and treatment directions in multiple myeloma

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Summary

The development of bortezomib and IMIDs resulted in a revolution in the treatment of MM. Moreover, second-generation proteasome inhibitors (carfilzomib) and IMIDs (pomalidomide) have recently been approved. Nevertheless, the incurability of this disease requires other drugs with different mechanisms of action to either prolong the survival of patients refractory to current therapies, or achieve cure. Active research has been done exploring the pathogenesis of MM and searching for novel druggable targets. In this regard, some of these novel agents seem promising, such as monoclonal antibodies (anti-CD38 - daratumumab or anti-CS1 - elotuzumab) or the kinesin protein inhibitor Arry-520. Other agents under investigation are kinase inhibitors, signaling pathways inhibitors or deacetylase inhibitors. With so many novel agents under investigation, future therapy in MM will probably involve the combined use of the already approved drugs with some of those newly discovered.

Keywords

Multiple Myeloma; Proteasome Inhibitors; IMIDs; Targeted Agents; Monoclonal Antibodies; Deacetylase Inhibitors; Targeted drugs

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Introduction

Treatment of Multiple myeloma (MM) has experienced a significant revolution in recent decades: alkylators such as melphalan or cyclophosphamide in combination with steroids were the standard treatment for these patients for over 30 years. However, in the last years of the past century, novel agents with more specific mechanisms of action have appeared. This fact reflects the situation not only in MM, but also for many haematological and solid tumors, in which treatment is moving from a chemotherapy-oriented approach, in which drugs were non-specifically directed against highly proliferative cells, towards an novel targeted therapy era in which drugs and their combinations target specific mechanisms of tumor cell growth and survival.[1] Particularly in MM several non-chemotherapeutic agents such as proteasome inhibitors or immunomodulatory agents (IMIDs) have been discovered, developed and approved.[2,3] The addition of these agents into the treatment armamentarium of MM has increased the median survival of MM patients from 2–3 years to at least 7 years.[4] However, despite this clear benefit, MM is still considered incurable in the vast majority of patients and virtually all MM patients will eventually relapse. In fact, if a recent retrospective analysis of the outcome of patients who are refractory to bortezomib and IMIDs has shown a quite dismal prognosis.[5].

This has opened a new avenue of research, which is the investigation of novel mechanisms that could be important for the MM plasma cell to survive and could be used as therapeutic targets.[6,7] A plethora of novel mechanisms and agents have been investigated in MM in the recent years both from a preclinical and also a clinical perspective.[8–10] These agents may be divided into two different groups: first there are second and third generation agents that are derived from the already approved and active agents (such as proteasome inhibitors, immunomodulatory agents and alkylators). But there are also many agents that target other novel pathogenetic mechanisms of the MM cells. Among this novel drugs it is worth highlighting the following ones: monoclonal antibodies, deacetylase inhibitors, PI3K/AKT/mTOR inhibitors, monoclonal antibodies or Cyclin-dependent kinases (CDK) 4/6 inhibitors. Some of these agents and mechanisms are still in preclinical or early clinical phases of development, but others have already reached phase III and are close to approval, either as single agents or in combination with the current standard of care. Parallel research is been made in order to develop biomarkers that would allow the selection of those patients that would benefit the most from a given drug or family of drugs or, most importantly, those patients that would not respond to a certain type of agents.

The present review summarizes the current understanding of pathogenesis-driven therapeutic targets currently being explored in MM and the novel agents targeting these pathways under investigation in this disease. First we will discuss the most relevant pathways or mechanisms that are investigated in MM, and then we will review the clinical data with the most promising groups of agents that are been tested in MM patients.

Pathogenesis driven therapeutic targets in MM

1. Proteasome & Unfolded Protein Response

Most tumor cells depend for their growth and survival on a correct functioning of the ubiquitin-proteasome system that is responsible for the regulation of several proteins required for the survival of normal and tumoral cells. In this regard, one of the most significant advances in the treatment of MM in the last decades was the discovery of the preclinical[11,12] and clinical[13–15] antimyeloma activity of bortezomib (PS-341),[16] the first in class proteasome inhibitor. The proteasome is an enzymatic complex responsible for the degradation of many of the intracellular proteins. Eukaryotic cells, present with the 26S proteasome, that is composed by a 20S catalytic subunit and one or two 19S regulatory subunits at either side of the 20S subunit.[17,18] The 20S catalytic core is a barrel-shaped structure composed by four stacked rings (2 α at both extremes and 2 β en the middle), each of them formed by 7 subunits.[19,20] Three subunits of the β catalytic rings have the most important enzymatic activities: the β1 (caspase-like activity), the β2 (trypsin-like activity) and β5 (chymotrypsin-like activity). A second form of the proteasome is the immunoproteasome[21], which generates antigenic peptides presented by class I major histocompatibility complex (MHC) to induce a cytotoxic immune response.[22] In this immunoproteasome the β1, β2 and β5 subunits are replaced with β1i (LMP2), β2i (MECL1 or LMP10) and β5i (LMP7) after exposure to interferon-γ (IFN-γ) or tumor necrosis factor-α (TNF-α).

The inhibition of this pathway has been associated with several biological processes that lead to an anti-myeloma effect.[23–25] Among the main consequences responsible for this antitumoral activity, it is important to highlight that several cell cycle proteins such as cyclin-inhibitors or CDK-inhibitors are known substrates of the proteasome and are degraded by this organelle, and therefore, its inhibition would result in a cell cycle arrest. The proteasome is also responsible for the degradation of several antiapoptotic and tumor suppressor proteins that, consequently, become upregulated by using proteasome inhibitors.[26] Its inhibition also prevents the clearance of misfolded proteins, inducing endoplasmic reticulum (ER) stress and activation of the unfolded protein response.[27,28] Finally, proteasome inhibitors also block the NF-κB transcription factor pathway, by preventing the degradation of the IκB (Inhibitor of NF-κB) after its poliubyquitination by IKK (IκB kinase).[29]

2. Immune system

The ability of myeloma cells to induce an immunosuppressive state in their surrounding BM microenvironment,[30–32] and the clinical success of the immunomodulatory thalidomide derivatives,[33–37] which are counteracting this immunosuppression, have led to increased interest in preclinical and potential clinical development of additional strategies to augment anti-MM immune responses. Major successes have been achieved in recent clinical trials for solid tumors with antibody-based therapies against the immune inhibitory effects of programmed death receptor 1 (PD-1) and its ligands, such as PD-ligand 1 (PD-L1).[38,39] Given this success as well as preclinical evidence supporting the role of PD-L1/PD-1 blockade in myeloma,[40–43] clinical trials have or will soon be initiated to implement this

approach for MM. As outlined elsewhere in this review, there is a major recent emphasis on monoclonal antibody-based therapies against surface antigens on MM cells, including CS1 (elotuzumab) or CD38 (daratumumab). Substantial progress has also been achieved in preclinical and/or clinical studies of cell-based immunotherapeutic efforts, including dendritic cell (DC)-based vaccines for MM immunotherapy, such as the use of DC/tumor cell fusions.[44] Anti-MM immunotherapy is also expected to further benefit from more comprehensive understanding of the molecular and cellular mechanisms whereby MM cells escape immune surveillance. In this regard, myeloid-derived suppressor cells (MDSCs) have recently emerged as important mediators of the immunosuppressive state of the local microenvironment of MM cells.[45–49] Furthermore, recent studies using high throughput scalable *in vitro* platforms to assess interactions between human effector cells and tumor cells have documented that bone marrow stromal cells are capable of suppressing the anti-myeloma activity of natural killer (NK) cells,[50] suggesting that therapeutic targeting of MM cell–BM stroma interactions may enhance the responses of MM cells to not only a small molecule inhibitor-based therapeutics, but also immune-based therapies.

3. Cell Cycle and mitotic regulators

Similarly to the situation with t(9;22) in Chronic Myeloid Leukemia, t(15;17) in acute promyelocytic leukemia or, more recently, MYD88 mutations in WM, the search for a specific oncogenic event in MM that could be target for some therapeutic intervention has been a matter of investigation. In this regard, the recently reported results of the whole genome sequencing of patient MM tumor cells did not show evidence of any unique genomic abnormality.[51] In fact, according to our knowledge, the only common oncogenic event found in MM patients to date, reported some years ago, is cyclin D deregulation by gene expression profiling.[52] Based on this, some efforts have been made to develop agents that could target the cell cycle abnormalities present in MM cells. The main focus has been the CDKs (cyclin-dependent kinases), in particular CDK 4/6, which is responsible for cyclin-D phosphorylation. Nevertheless, clinical results with the CDK 4/6 inhibitor Seleciclib in combination with bortezomib and dexamethasone have been discouraging.[53]

Other compounds involved in cell cycle regulation are inhibitors of proteins required for the spindle formation and its correct functioning. In this regard, two proteins have been specifically targeted: One is the aurora Kinase A, against which a specific inhibitor (MLN8237) has been developed. It is in early stages of development in combination with bortezomib.[54] A second protein that has been targeted is the kinesin spindle protein (KSP), that is a member of the kinesin superfamily of microtubule-based motors, which is responsible for centrosome separation and bipolar spindle assembly and maintenance. A KSP inhibitor (Arry-520) blocks this protein, arrests cells in mitosis, and induces subsequent apoptosis. Clinical results in MM with this novel agent are really promising, and will be described in the second part of the review.

4. Interaction with Microenvironment

MM is considered a prototypical tumor type for the study of interactions between tumor cells and their microenvironment, with major focus placed over the years on the interaction of MM cells with BMSCs. Major progress has been recently achieved in terms of the

mechanistic understanding and potential therapeutic implications of this protective effect. The development of compartment specific bioluminescence imaging (CS-BLI) [55] helped determine that BMSCs confer resistance to MM cells not only to glucocorticoids, anthracyclines and alkylating agents, but also to a broader range of agents, including investigational agents of different classes[55]. Interestingly, it was also observed that BMSCs may also render MM more sensitive to certain other classes of therapeutics[55]. This phenomenon, termed “microenvironment-dependent synthetic lethality”, likely occurs in settings when the administered treatment inhibits some of the key cascades induced in MM cells by BMSCs and may have profound implications for drug development in MM and beyond, as it implies that many potentially promising therapeutics may have been excluded in the past from the preclinical pipeline, due to almost exclusive reliance of preclinical drug development on tumor cell monocultures, rather than preclinical systems which simulate the in vivo tumor-microenvironment interactions. Significant progress was made towards a more comprehensive understanding of molecular cascades triggered in MM cells by their interaction with BMSCs. For instance, BMSCs induce in MM cells increased transcriptional output of a broad range of oncogenic pathways including Ras, PI3K/Akt, NF-kappaB; MYC, IRF4, and other molecular networks which important for MM cells or malignant cells more broadly.[55]

5. Kinome and deregulated kinases

Kinase deregulation is quite frequent in hematological malignancies, and in some cases these abnormalities are the driver mechanisms responsible for the development and progression of disease. The paradigm of this situation is the bcr/abl rearrangement secondary to t(9;22) that results in the constitutive overexpression of the tyrosine kinase protein bcr in chronic myeloid leukemia (CML). Moreover, constitutive activation of some of these receptors confers adverse prognosis in other hematological malignancies, such as FLT3 mutation in AML. As a consequence, kinase inhibitors have been tested in hematological malignancies and in solid tumors, and also in MM. The first kinase inhibitors to be used in MM were cKit/PDGFR inhibitors such as imatinib[56] and dasatinib.[57,58] Several others, including VEGF-R,[59] IGF1-R,[60,61] EGF-R[62] or PKC [63] inhibitors, were subsequently tested. Nevertheless, the clinical activity of all these agents in monotherapy in MM is quite modest, and no really compelling data in combination has been shown to date.

High expectations were raised for FGFR3 inhibitors in patients with t(4;14) translocation, that induces an overexpression of this protein. However, clinical results of two small molecules[64,65] and one MoAb[66] have been disappointing. In summary, pilot studies with this group of molecules have not resulted in significant clinical activity but there are still some agents that remains promising such as dinaciclib, a CDK 1, 2, 5 and 9 inhibitor, designed based on data indicating that CDK-5 inhibition was one of the top bortezomib-sensitizing mechanisms in high-throughput RNAi screening.[67] It is in the first stages of development, both as single agent and in combination with bortezomib.

6. Deregulated Signaling pathways

Another cancer hallmark is deregulation or abnormal activation of signaling pathway, such as PI3K/AKT/mTOR, RAF/MEK/ERK, JAK/STAT and NFkB.[6,7] This leads to

uncontrolled proliferation, and increased threshold for apoptosis, leading to drug resistance. Several pathways have been specifically deregulated in MM, such as the NFkB[68] and the PI3K/AKT/mTOR pathways.[69–71] As a result, several agents that can block these proteins have been developed. Proteasome inhibitors block degradation of the inhibition of NFkB (IkB) kinase by the proteasome, thereby blocking of the NFkB translocation into the nucleus and function. There are also inhibitors of the PI3K/AKT/mTOR pathway, such as the AKT inhibitor, perifosine, that despite its lack of efficacy in monotherapy,[72] has been combined with bortezomib [73] and with lenalidomide[74] showing responses. The mTORC1 complex has also been targeted by drugs such as everolimus and temsirolimus, alone[75,76] or in combination with bortezomib[77] or lenalidomide[78–80] in more heavily treated patients.

The RAS/RAF/MEK/ERK pathway has also been targeted with farnesyl-transferase inhibitors (tipifarnib),[81], and most recently with the MEK inhibitor selumetinib (ARRY-6244)[82] that has shown some responses as single agent (8% PR in patients with five previous lines of therapy). To date, results in phase I/II stages did not demonstrate a clear benefit, and will probably be necessary to combine them with other agents to see clinical activity.

Clinical Results with the most promising novel agents under investigation

1. Novel PI: Carfilzomib, Ixazomib, Marizomib, Oprozomib

After bortezomib, several other proteasome inhibitors have been developed (Table 1) belonging to different chemical families such as the boronic acids (bortezomib and ixazomib), epoxyketones (carfilzomib and oprozomib) or salinosporamides (marizomib). Importantly, they target different catalytic subunits of the proteasome: while bortezomib and ixazomib target the chymotrypsin- and caspase-like activities, carfilzomib or oprozomib are selective for the chymotrypsin-like activity. By contrast, marizomib has a broader pattern of inhibition, targeting all three catalytic activities. Carfilzomib, oprozomib and marizomib irreversibly inhibit this activity, whereas bortezomib and ixazomib are reversible inhibitors. Finally, some novel agents are orally bioavailable, such as izaxomib or oprozomib.

Regarding the clinical activity of these agents (Table 2), carfilzomib is already FDA-approved for the treatment of MM patients who have received at least two previous therapies, including bortezomib and an immunomodulatory agent, and are refractory to their last therapy. The overall response rate (ORR) of this agent in monotherapy in bortezomib-naïve patients was 52%,[83] a figure that is slightly higher than the 43% ORR observed with bortezomib in a similar population studied in the APEX trial.[14,15] More importantly, approximately 20% of patients refractory to bortezomib responded (at least PR) to carfilzomib in two different trials (PX-171–003 and PX-171–004),[84,85] probably indicating a lack of complete cross-resistance between the two proteasome inhibitors. Based on this, a phase 3 randomized trial (FOCUS) has compared the activity of carfilzomib against best supportive care in patients with advanced MM and for whom no other therapeutic option is available.

This agent has also been combined with several anti-MM agents both in relapsed patients and also in the upfront setting. One of the most advanced studies is the combination of carfilzomib with lenalidomide and dexamethasone. The phase 2 PX-171–006 trial of 84 patients relapsing after 1 to 3 prior therapies has reported an ORR of 69% (77% at the MTD), with 4% stringent complete remission (sCR), 37% very good partial response (VGPR), and 28% partial response (PR).[86] A phase 3 randomized trial (Aspire), has evaluated the efficacy and safety of lenalidomide plus low-dose dexamethasone with or without carfilzomib. This trial has already completed enrollement, and results are pending.[87] This same combination has also been moved to the newly diagnosed settings in two trials;[88,89] with very good results in both trials: ORR superior to 95% and a CR/nCR rate of 64%. No stem cell collection problems were encountered. A similar combination is that in which lenalidomide is substituted with thalidomide. Accordingly, newly diagnosed young patients, who are candidates for ASCT received carfilzomib + thalidomide + dexamethasone in the induction and consolidation after transplant. This schema resulted in an ORR of 88% (including 18% CR) after induction and 90% (with 35% CR) after ASCT and consolidation.[90] The addition of cyclophosphamide to this combination (cyclone trial) in untreated patients resulted in 96% ORR, with 29% CR after four cycles of induction.[91] As MPV is one of the standards in elderly MM patients, carfilzomib has also been combined with alkylators and dexamethasone in transplant ineligible newly diagnosed patients. One combination with cyclophosphamide showed 93% PR or better, with 68% at least VGPR,[92] and another one including melphalan resulted in an ORR of 89% and 51% VGPR or better.[93] Finally, other preliminary combinations are being explored with novel drugs such as histone deacetylase inhibitors,[94–96] pomalidomide,[97] and the kinase spindle protein inhibitor Arry-520[98,99] in relapsed and refractory patients.

Regarding cytogenetic abnormalities, it seems that overall response to carfilzomib is comparable between the high and low risk FISH subgroups, while time-to-event end points showed a trend of shorter duration in high-risk patients, including median duration of response and overall survival.[100]

This drug has also proven to be quite safe. Apart from the individual safety reports of the different trials, a pooled analysis of the toxicity profile of 526 patients receiving carfilzomib in monotherapy has recently been reported.[101] The most frequent grade 3 (G3) AEs were hematological but, the incidence of any grade PN was only 14% (1% G3). Carfilzomib was also safe in patients with renal impairment in a trial specifically designed to evaluate this issue.[102] Importantly, an alert was raised due to a potential higher incidence of cardio-pulmonary toxicity in patients treated with carfilzomib with even with some sudden deaths. Although they may be related, at least partially, to the frailty of the patients, it is important to be especially cautious with this issue.

The second-generation compound oprozomib (ONX-0912; previously PR-047),[103] is a structural analog of carfilzomib that is orally bioavailable. Oprozomib capsules administered in split doses demonstrated clinical activity in a phase 1 trial in patients with hematologic malignancies (MM & CLL).[104] In order to improve gastrointestinal tolerability, a once-daily administered tablet was introduced in this phase 1b/2 trial with 16 MM and 5

Waldenström's macroglobulinemia (WM) patients already enrolled, a good safety profile and preliminary promising response data.[105]

Ixazomib (MLN9708) is the first orally bioavailable proteasome inhibitor evaluated to date in clinical studies for the treatment of MM. Two studies are exploring its activity in monotherapy in relapsed/refractory MM patients previously exposed to proteasome inhibitors, although only a low proportion of them had high-risk cytogenetic abnormalities or were bortezomib refractory. One (C16004) involves the weekly administration of the drug[106] and the other (C16003) features a biweekly schedule.[107] The MTD has already been defined for both schedules and > 10% of these refractory patients have achieved responses in the two phase I dose-escalation trials (table 2). With respect to toxicity, the most remarkable finding was the absence of significant PN, although treatment related rash has been noted. Ixazomib is also being examined in combination with melphalan and prednisone in newly diagnosed MM, with all the 15 patients evaluable for response achieving at least PR (3 CR, 6 VGPR, and 6 PR).[108] The combination with lenalidomide and low-dose dexamethasone in untreated patients also showed an ORR of 88%, including 40% at least VGPR and 18% CR.[109]

Marizomib (NPI-0052) is still in the early stages of development, but appears to have similar efficacy and toxicity to those of the afore mentioned novel proteasome inhibitors, showing minimal peripheral neuropathy and activity in heavily pretreated patients (with ORR between 15–20%) (table 2).[110]

2. Novel IMIDs: Pomalidomide

Several trials have analyzed the activity of pomalidomide alone and in combination with dexamethasone and other agents (table 3). In this regard, the addition of dexamethasone induces synergy,[111] and this combination in the initial phase 2 study induced a 62% response rate with a PFS of 13 months (table 2).[112]

Several trials have explored the activity of pomalidomide + dexamethasone in patients refractory to lenalidomide[113,114] or double refractory to lenalidomide and bortezomib.[114–116] In these trials, approximately one-third of patients achieved at least PR and the PFS ranged from 3.3 to 7.7 months (table 2). This led to the recent FDA approval of the combination of pomalidomide + dexamethasone for the treatment of relapsed/refractory MM patients for patients who have received at least 2 prior therapies, including lenalidomide and bortezomib, and were refractory to the last line of therapy.

All these studies were the bases for the phase 3 trial (MM-003) that randomized (2:1) 455 relapsed/refractory MM patients that had failed both lenalidomide and bortezomib and were refractory to their last therapy, to receive pomalidomide + low dose dexamethasone vs high dose dexamethasone. There was a significant advantage for the pomalidomide arm over dexamethasone in terms of ORR (21% vs 3%), PFS (3.6 vs 1.8 months) and OS (NR vs 7.8 months).[117]

The safety profile was quite similar to that of lenalidomide, being the hematological side effects the main source of toxicity

Several trials are already testing the activity of pomalidomide and dexamethasone in combination with several agents in relapsed/refractory patients such as proteasome inhibitors (carfilzomib[97] or bortezomib[118]), clarithromycin,[119] cyclophosphamide[120,121] and pegylated liposomal doxorubicin,[122] although results of most of these studies are only preliminary (Table 3).

3. Novel Alkylators

Alkylators have been the backbone of MM treatment for many years and in fact melphalan is still a key component in the treatment of young (with ASCT) and elderly MM patients. Based on the efficacy of this agent, several other alkylators have been explored in MM. The main one has been bendamustine, whose chemical structure combines that of an alkylator with a purine analog ring. An initial phase III trial compared bendamustine + prednisone with melphalan + prednisone in newly diagnosed patients, and showed a benefit especially in terms of TTP (14 vs. 10 months).[123] This trial supported the European approval of bendamustine in combination with prednisone for the treatment of newly diagnosed MM patients who are not candidates for ASCT and with preexisting neuropathy that prevents the use of proteasome inhibitors or thalidomide. Afterwards, this agent has been combined with several agents in pilot studies carried out in relapsed refractory MM patients (Table 4). The combination with bortezomib and steroids has produced a 50%-75% ORR, with[124–127] thalidomide (26%-86% ORR),[128–130] or, more recently, with lenalidomide (52%-76% ORR with 24%-33% VGPR).[131,132]

Another novel alkylator recently developed is the novel dipeptide prodrug of melphalan called melphalan-flufenamide (mel-flufen). It has demonstrated high preclinical activity even in melphalan resistant cells, based on a preferential delivery of melphalan to tumor cells due to the intracellular cleavage of melflufen by some peptidases overexpressed in malignant cells.[133]

4. Monoclonal Antibodies

Monoclonal antibodies are the standard of care for several haematological and solid tumors. By contrast, results in MM have been quite disappointing until recently.[8] Rituximab (anti-CD20) was the first of these agents to be tested in MM, with discouraging results.[134,135] Since then, several other MoAbs have been tested in MM.[78,79]

Elotuzumab is the best evaluated of these agents in MM. It is directed against CS1, a glycoprotein that is present on plasma cells, and may also be expressed in NK and CD8+ T cells. This agent may enhance the immune recognition of plasma cells in the immune synapse and therefore it is a perfect candidate to be combined with IMIDs, which enhance antibody-dependent cellular toxicity.. In line with this, although the results in monotherapy were modest (with stable disease as best response),[136] the combination with lenalidomide and dexamethasone has given excellent results with more than 80% durable PR in relapsed patients.[137,138] A phase III registration enabling trial in relapsed myeloma comparing lenalidomide + dexamethasone with lenalidomide + dexamethasone + elotuzumab has just been completed.

CD38, CD138, CD56, and CD40 are other antigens of the plasma cells that have been targeted by MoAbs. The most promising of them are the CD38 directed antibodies. In this regards, Daratumumab monotherapy, in a very heavily pretreated population, induced 78% of at least MR and 44% of PR or better at the higher dose levels (> 2 mg/kg).[139,140] These results are highly promising for a drug used in monotherapy in patients with a median of six previous treatments. This has prompted the development of other antiCD38 MoAbs, such as SAR650984, which has a similar profile and is already being tested in phase I clinical trials.

5. Deacetylase inhibitors

These agents have already demonstrated activity in several hematological malignancies, such as Hodgkin Lymphoma or Cutaneous T cell lymphoma, and there is a particular rationale for using these agents in MM. This is due to their role in the regulation of the unfolded protein response, through inhibition of the aggresome formation and inactivation of the chaperone system (by acetylating HSP-90). Several DACis with different chemical structures and selectivities for targeting the DAC families (vorinostat, panobinostat, romidepsin, givinostat or the HDAC6 specific inhibitor ACY1215) have been tested in MM. The results of the phase I/II trials that have analyzed the activity of DACi in relapsed/refractory MM showed that, despite their promising preclinical activity, the clinical efficacy of all these drugs in monotherapy in MM, was quite modest.[141–145]

Nevertheless, based on the simultaneous targeting of different pathways involved in the unfolded protein response, the combination of DACi + bortezomib has been extensively studied. This rationale relies in the blockade of the degradation of the ubiquitinated misfolded proteins with proteasome inhibitors, and the use of DACis to interfere with the activity of heat-shock proteins, which are necessary for the correct folding of proteins, and with aggresome formation and autophagy (through inhibition of DAC6). Overall, this would induce a toxic accumulation of misfolded proteins. The clinical results of the only phase 3 randomized trial (Vantage 088) currently available that compared bortezomib with bortezomib + vorinostat showed an improved response rate (ORR 56% vs. 41%, $P < 0.0001$) but this translated into only a minimal advantage in PFS (7.6 vs. 6.8 months. HR = 0.774 (0.64 – 0.94). $p = 0.010$) and no differences in OS.[146] Although these results were disappointing, we await the results of another phase 3 randomized trial (Panorama 1) in which panobinostat is used instead of vorinostat and that also included dexamethasone in the combination. What seems clearer is the ability of these agents to revert bortezomib resistance in two different trials in which vorinostat and panobinostat induced 20–30% responses when added to bortezomib (+/− dexamethasone) in bortezomib-refractory patients.[147,148]. Another avenue of investigation is the use of more specific DACi such as the HDAC-6-specific inhibitor (rocilinostat) in order to minimize the general toxicity associated with non-specific DACi and maintain efficacy.[145] This agent has also demonstrated promising results when combined with IMIDs.[149]

6. Kinesin Spindle Protein Inhibitors

As has already been mentioned, one of the agents with more promising results to date as a single agent is the KSP inhibitor Arry-520. This drug has produced a 16% PR or better on its

own in patients very heavily pretreated with a median of 6 prior lines of therapy.[150,151] Moreover, the addition of dexamethasone increased the response rate to 22%[151] in a much worse population of patients with a median of ten previous lines of therapy. Overall the drug is well tolerated, except for the development of neutropenia that makes it necessary to administer concomitant G-CSF when this drug is used. These promising results have led to the initiation of several trials in combinations with other agents such as bortezomib and carfilzomib.

Expert Commentary

Multiple Myeloma therapy has has experienced significant evolution in the last years. This has led to a clear improvement not only in the survival of MM patients, but also in their quality of life, as novel agents generally have a good toxicity profile and their use significantly reduces the symptoms and complications, such as anemia or bone pain, associated with MM progression. To date, four classes of agents (alkylators, steroids, proteasome inhibitors and IMIDs) have demonstrated activity in MM, have been approved for the treatment of MM patients, and are, in fact, the backbone of MM therapy. Based on the success of what we can call “old novel agents” (bortezomib, thalidomide and lenalidomide) in the last years, MM has become a paradigm for the investigation of novel agents and new mechanisms of action. In fact a plethora of novel drugs with different mechanisms of action have been explored in the last 15 years from the preclinical setting to the clinical trials. However, only a minority of these agents has reached phase III evaluation, and none of them (apart from novel proteasome inhibitors and IMIDs) has yet been approved by regulatory agencies. Nevertheless, there are some of those drugs or families that have higher promise: among them, we can specially highlight three of them. The fist two ones are two monoclonal antibodies. These type of agents will probably represent a novel avenue in the therapeutic options of MM patients. One of these MoAb is the anti-CD38 daratumumab (or the one at earlier stages of develoment SAR-650984) that have demonstrated activity in monotherapy These agents have very good safety profile and therefore are perfectly suitable for combination with other currently used agents. As an example of this, the other MoAb with activity is the one targeting CS1, elotuzumab, that in combination with lenalidomide and dexamethasone had very good efficacy through the activation of the immune anti-MM effect. Finally, Arry-520 is a kinesin spindle protein inhibitor that, by targeting this protein, induces mitotic catastrophe in tumor cells. It has activity in monotherapy and mainly when combined with dexamethasone in very heavily pretreated patients and is currently being combined with other novel agents.

Five year view

The approval of thalidomide, bortezomib and lenalidomide in the first decade of this century has been followed in the last year by the approval of two derivatives of those drugs: carfilzomib and pomalidomide. We expect that in the next five years, treatment of MM could change in different ways. It is quite ventured to predict how these novel agents will be incorporated into the future treatment armamentarium in MM. Probably, several of these novel treatments will be approved in the upcoming years, and the most possible initial indication will be for patients refractory to proteasome inhibitors and IMIDs. And

afterwards, their use will be, for sure, expanded to other settings. One possibility will be to optimize combinations including some of the just mentioned agents (daratumumab, SAR650984, elotuzumab, Arry-520, some DACi, etc.) with the current standard of care (proteasome inhibitors, IMIDs, alkylators or steroids). Some of these combinations have already been clinically tested with good results. This will provide more choices for the subsequent relapses and get nearer the objective of transforming MM into a chronic disease.

Moreover, if we adopt a more optimistic view, we could aim at the real curability of MM, similar to the situation with other hematological malignancies. One important avenue of research to achieve this purpose is the evaluation of MRD by different techniques, what has led to the concept of immunophenotypic or molecular remission. This absence of detectable tumor cells by highly sensitive techniques, if sustained, will drive to the concept of operational cure. The use of cocktails of different agents with different mechanisms of action in an earlier stage of the disease, at diagnosis or, probably earlier in an asymptomatic situation, when lower tumor burden is present and hypothetically less intraclonal variability, will probably help to obtain this high quality remissions/cure. The use of these agents in this setting may also favour the complete eradication of the tumor clone and the subsequent curability of the disease.

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Key Issues

Survival of MM has significantly increased in the last years mainly due to the development and approval of two families of novel agents: Proteasome Inhibitors and Immunomodulatory drugs (IMIDs). These agents have improved not only the survival of MM patients but also their quality of life.

These novel agents (bortezomib and IMIDs), along with alkylators and steroids currently compose the backbone of the treatment of MM patients, either young or elderly.

Second and third generation agents from these same families (carfilzomib, ixazomib, marizomib, pomalidomide) have been developed and have demonstrated similar or even higher activity in some cases to their parental drugs.

These second-generation agents have some activity even in patients refractory to the first generation drugs in their respective families. This suggests the lack of complete cross-resistance between components of the same families.

Drugs with novel mechanisms of action are currently being explored both preclinically and in the clinical setting. This includes: monoclonal antibodies, deacetylase inhibitors, kinase inhibitors, and agents interfering with different signaling pathways among others. None of them has yet reached approval from the regulatory authorities.

After active research on monoclonal antibodies for several years without clear success, two have recently demonstrated activity in relapsed refractory MM: elotuzumab (anti-CS1) in combination with lenalidomide and dexamethasone and daratumumab (anti-CD38) in monotherapy.

The activation of the immune system against MM is an atractive approach, as derived from the good results obtained with IMIDs and also with the combination with elotuzumab. Novel agents and monoclonal antibodies are currently being explored searching for this immunotherapy.

DACi had great promise some years ago. Results to date have been discouraging, but we still have to wait for data on different combinations with bortezomib + dexamethasone and also for results of more specific DACi.

Table 1

Biological features of the most relevant proteasome inhibitors in MM

Prot. Inh.	Type	Catalytic activity inhibition			Pattern of inhibition	Route	Phase of development
		CT-L	C-L	T-L			
Bortezomib (PS-241)	Boronic Acid	X	X		Reversible	iv/sc	Approved
Carfilzomib (PR-171)	Epoxyketone	X			Irreversible	iv	Approved
Ixazomib (MLN-9708)	Boronic Acid	X	X		Reversible	iv/po	Phase III
Oprozomib (ONX-0912 or PR-047)	Epoxyketone	X			Irreversible	po	Phase 1
Marizomib (NPI-0052)	Salinospore	X	X	X	Irreversible	iv	Phase 1

Table 2

Summary of the most relevant clinical trials with novel proteasome inhibitors in monotherapy in relapsed/refractory MM

Drug	Trial	Phase	n	Prior lines	ORR (≥ PR)	PFS (months)	Reference
Carfilzomib (PR-171)	PX–171–001	1	10 MM	-	10%	-	O'Connor. CCR 2009[152]
	PX–171–002	1	28	-	19%	-	Alsina. CCR 2012[153]
	PX-171-003A0	2	46	5 (2–16)	17%	3.5	Jagannath. Clin Lymph Myeloma 2012[154]
	PX–171–003A1	2	266	5 (1–20)	24%	3.7	Siegel. Blood 2012[155]
	PX–171–004	2	129 Btz naïve patients	2 (1–4)	C-1: 42% C-2: 52%	C-1: 8.2 C-2: NR	Vij Blood 2012[83]
			35 Btz treated patients	3 (1–13)	17%	4.6	Vij BJH 2012[85]
	PX-171–005	2	50 (Renal impairment)	5 (1–15)	26%	-	Badros. Leukemia 2013[102]
Ixazomib (MLN-9708)	C16004	1	60	6 (2–18)	15%	-	Kumar. ASCO 2013[106]
	C16003	1	57	4 (1–28)	13%	-	Lonial. ASCO 2012[107]
Marizomib (NPI-0052)	NPI-0052–101 NPI-0052–102	1	34	6	14%	-	Richardson. ASH 2011[110]

NR: Not reached

Table 3

Clinical trials with pomalidomide in relapsed MM patients

Phase	+/− Dex or other comb.	n	Prior lines	ORR ≥PR	PFS Months	OS Months	Reference
1	No	24	3 (1–6)	54%	9.7	22.5	Schey. JCO 2004 [156]
1	No	20	4 (1–7)	50%	10.5	33	Streetly. BJH 2008 [157]
1b	Dex&	38*	6 (2–17)	Pom: 13% + Dex: 21%	4.6	18.3	Richardson. Blood 2013[111]
2	No	108*	5 (1–13)	15%	2.6	13.6	Richardson. ASH 2011[158] & Siegel ASCO 2013[159]
	Dex	113*		34%	4.6	16.5	
2	Dex	60	2 (all ≤ 3)	65%	13	40	Lacy. JCO 2009[112] & ASH 2012[114]
2	Dex	34**	4 (1−7+)	32%	5	33	Lacy Leukemia 2010[113] & ASH 2012[114]
2	Dex	60**	2 (all ≤ 3)	38%	7.7	92%	Lacy ASH 2012[114]
2	Dex	120**	-	21%	4.3	74%	Lacy ASH 2012[114]
2	Dex	35***	6 (3–9)	26%	6.4	16	Lacy Blood 2011[115] & ASH 2012[114]
	Dex	35***	6 (2–11)	29%	3.3	9.2	
2	Dex	43***	5 (1–13)	35%	5.4	14.9	Leleu ASH 2011[116]
	Dex	41***		34%	3.7	14.8	
3	Dex	302**	5 (1–17)	21%	3.6	NR	San Miguel ASCO 2013[117]
2	Clarithromycin/ Dex	100	5 (3–15)	54%	8.2	NR	Mark ASH 2012[119]
1/2	Carfilzomib/ Dex	32**	6 (2–15)#	33%	70%	-	Shah ASH 2012[97]
2	PLD/Dex	27	5 (1–18)	22%	-	-	Hilger ASCO 2013[122]
1	Bortezomib/Dex	21**	1–4	72%	-	-	Richardson ASCO 2013[118]
1	Cyclophosphamide/Dex	10**	5 (3–10)	40%	-	-	Baz ASH 2012[120]

Phase	+/− Dex or other comb.	n	Prior lines	ORR ≥PR	PFS Months	OS Months	Reference
1/2	Cyclophospham ide /Prednisone	55	3 (1–3)	51%	10.4	-	Larocca EHA 2013[121]

Dex: Low Dose Dexamethasone (40 mg weekly) except for the trial with Cyclophosphamide + Dexamethasone that are high doses.

PLD: Pegylated liposomal doxorubicin

*Previous lenalidomide & bortezomib

**Lenalidomide-refractory patients

***Lenalidomide- & bortezomib-refractory

&Dexamethasone added in 22 non-responding patients

$OS/PFS at 6 months

#Corresponds to the 12 patients enrolled in the phase 1

Table 4

Selected clinical trials with bendamustine in relapsed MM patients

Alone/ Combination	n	Prior Lines	ORR (≥PR)		PFS (months)	Reference
Single agent	31	-*	31%	7% CR, 24% PR	26	Knop. Haematologica 2005[160]
+ Bort	40	6 (1->7)	27%	2% CR, 5% VGPR, 21%PR	8.4	Berenson. BJH 2013[161]
+ Bort-Dex	40	4 (2–10)	72%	25% VGPR, 47%PR	-	Hrusovsky. ASH 2007[126]
+ Bort-Dex	45	2 (1->4)	51%	15% CR, 6% VGPR, 30% PR	9.4	Ludwig. ASH 2011 [125]
+ Bort-Pred	78	2 (1–9)	69%	30% VGPR, 40% PR	-	Pönisch. J Cancer Res Clin Oncol 2013[162]
+ Thal-Pred	28	2 (1–6)	86%	14% CR, 18% VGPR, 50% PR	11	Pönisch. BJH 2008[128]
+ Thal-Dex	23	5 (3–7)	26%	4% CR, 22% PR	3	Grey-Davies. BJH 2012[130]
+ Len-Dex	29	3 (1–6)	52%	24% VGPR, 28% PR	6.1	Lentzsch. Blood 2012[131]
+ Len-Pred	21	2 (1–2)	76%	5% sCR, 28% VGPR, 43% PR	48% @ 18m	Pönisch. BJH 2013[132]

*All relapsing after ASCT