Emerging options in multiple myeloma: targeted, immune, and epigenetic therapies

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Considerable progress has been made in the treatment of multiple myeloma in the past decade with median survival for the disease improving significantly. This has come through a combination of better understanding of the disease biology and coordinated research into new treatment approaches including better supportive care. However, patients eventually become refractory to available treatments and succumb to the disease, highlighting the need to develop new treatment approaches. The genetic heterogeneity in the disease and clonal evolution under treatment pressure underlie the development of resistance, underscoring the need to develop more effective therapies that can eradicate the disease at initial treatment as well as the need for new classes of drugs with varying mechanisms of action. To this end, there has been intense focus on exploring novel approaches to therapy including small-molecule inhibitors targeting specific abnormalities, immune therapies including monoclonal antibodies and adaptive T-cell therapy, as well as epigenetic approaches. Although many of these drugs are in the early stages of clinical development, the early data appear to be very promising. Many of these drugs can be safely and effectively combined with the current treatment classes such as proteasome inhibitors and immunomodulatory drugs, further enhancing the treatment options for myeloma.

Learning Objectives

- Review new classes of therapies that are being explored for treatment of myeloma
- Discuss the mechanisms of action of the newer drugs
- Discuss the potential role of these new drugs and combinations in the management of multiple myeloma

Introduction

The past decade has witnessed tremendous progress in terms of new therapies for multiple myeloma (MM), paralleled by a deeper understanding of the disease biology and the underlying disease heterogeneity that has hampered efforts at eradicating the tumor clone and potentially curing the disease.[1-3] Unraveling the genetic landscape of MM and the mutational profile of the disease at various stages has led to identification of potential mechanisms of disease progression and development of refractoriness to currently available therapies.[4-7] Unlike disorders such as chronic myeloid leukemia, where a singular genetic defect can lead to development of a specific disease phenotype, a myriad of genetic abnormalities underlies the seemingly common phenotypic appearance of MM across patients. This has resulted in the ongoing and constant effort to identify new therapeutic targets in MM. Broadly, the therapeutic targets in MM can be grouped into those that are unique to the malignant plasma cell (MM specific) and those that are ubiquitous and reflect an altered natural process (plasma cell specific). Several novel therapies, especially those with new mechanisms of action, are currently in evaluation in clinical trials.[8] Here, we will briefly review some of the most exciting new therapies that are in various stages of clinical trials (Table 1). In addition, there are several new drugs that have been approved recently for treatment of MM; they are covered in the section on relapsed MM and will not be reviewed here.

Targeted therapies

Many of the currently used and effective therapies in MM have well-defined targets, modulation of which results in cellular alterations leading to MM cell demise.[7] These include, as examples, the proteasome subunit for the proteasome inhibitors and cereblon for the immunomodulatory drugs. More recently, several drugs with specific targets have been introduced that are anticipated to be effective in MM given the role of the target in MM cell survival and growth. These may include proteins and pathways that are intact but more relevant in the disease states or are altered in the disease states (eg, mutation driven).

ABT199 (venetoclax)

The intrinsic apoptosis pathway is regulated by a balance between antiapoptotic (eg, BCL-2, BCL-X_L, BCL-W, MCL-1) and proapoptotic (eg, BAX, BAK, BIM, BID, NOXA) proteins, with proapoptotic proteins sequestered by BCL-2, BCL-X_L, and/or MCL-1 in steady state and prevented from inducing cell death.[9] In response to various stimuli, they can be released and translocate to the mitochondrial outer membrane, leading to an increase in mitochondrial permeability and a cascade of signaling leading to cellular apoptosis. BCL-2 has been shown to be overexpressed in a subset of MM cells,

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Table 1. Results of early clinical trials of novel agents

Drug	Phase of study	Patient population	Prior lines of therapy	N	ORR, %	VGPR, %	DOR, mo	PFS, mo
Venetoclax[13]	Phase 1	Relapsed, PI and IMiD exposed	5 (1-15)	66	21	15	9.7	2.6 (TTP)
Venetoclax + bortezomib	Phase 1	Relapsed, PI and IMiD exposed	3 (1-13)	66	67	23	NA	NA
Selinexor[17]	Phase 1	Refractory to Btz, Cfz, Len, and Pom	7 (3-16)	79	21	5	5	2.3
Selinexor + bortezomib	Phase 1	≥1 line of prior therapy, not refractory to bortezomib	4 (1-11)	22	77	18	NA	NA
Afuresertib[22]	Phase 1	Refractory to available standard therapy	NA	34	9	0	NA	NA
Trametinib[25]	Phase 1	Relapsed MM, 1 cohort with Ras mutation, 1 cohort with no mutation	4 (2-8)	12/13	8 (1/12)	0	NA	NA
LGH447[24]	Phase 1	Relapsed, refractory MM	4 (1-16)	59	11	2	5.5	NA
Isatuximab[30]	Phase 1/2	Double refractory to an IMiD and PI or have received ≥3 prior lines of therapy: 4 dose cohorts	5-6	96	9-29	8-13	NA	NA
Isatuximab + Pom	Phase 1/2	≥2 prior anti-MM therapies, including Len and a PI	4 (3-11)	26	65	27	9	NA
MOR202	Phase 1	At least 2 prior lines of therapy	5	18	28	11	NA	4.7
MOR202 + Len	Phase 1	At least 1 prior line	3	17	71	18	NA	NR
MOR202 + Pom	Phase 1	At least 2 prior lines of therapy	4	13	46	8	NA	17.5
Nivolumab[36]	Phase 2	Relapsed refractory	4 (2-6)	27	0	0	NA	NA
GSK2857916	Phase 1	Relapsed refractory	>4 (70%)	30	27	10	NA	NA
Marizomib	Phase 1 weekly	Relapsed, at least 2 prior regimens	4 (1-11)	32	3	0	NA	NA
	Phase 1 twice weekly		6 (2-19)	36	11	0	NA	NA
Melflufen	Phase 2		4 (2-9)	31	33	3	NA	7.6

Btz, bortezomib; Cfz, carfilzomib; DOR, duration of response; IMiD, immunomodulatory drug; Len, lenalidomide; MM, multiple myeloma; NA, not applicable; NR, not reached; ORR, overall response rate; PFS, progression-free survival; PI, proteasome inhibitor; Pom, pomalidomide; TTP, time to progression; VGPR, very-good partial response.

and implicated in MM cell survival.[10] Venetoclax is a potent, selective, orally bioavailable inhibitor of BCL-2. In vitro data showed a high sensitivity to venetoclax in human MM cell lines and primary MM samples, with those positive for the (11;14) translocation being more sensitive.[11] t(11;14) is seen in 15% to 20% of patients with MM and is correlated with higher ratios of *BCL2* to *MCL1* expression making these cells particularly susceptible to BCL2 inhibition.[12]

In a phase 1 study, patients with relapsed/refractory MM were treated with venetoclax at escalating doses of venetoclax as a single agent, with dexamethasone (Dex) added for disease progression.[13] Sixty-six patients with relapsed MM, with a median of 5 prior therapies, were enrolled, including 30 patients with t(11;14). Venetoclax was generally well tolerated, with the most common adverse events (AEs) including mild gastrointestinal symptoms and cytopenias. The overall response rate (ORR) was 21% including 15% with a very-good partial response (VGPR) or better. The responses were seen mostly among the t(11;14) patients, with a response rate of 40%, and highly correlated with increased ratios of *BCL2:BCL2L1* and *BCL2:MCL1* messenger RNA expression.

In a parallel phase 1b study, patients with relapsed/refractory MM were treated with a combination of venetoclax with bortezomib and Dex.[14] The ORR among the 66 patients with a median of 3 prior therapies (range, 1-13) was 68% with 40% very VGPR or better. The best responses were seen in patients who were nonrefractory to bortezomib and had 1 to 3 prior therapies, with all patients who were bortezomib naive and who had 1 to 3 prior lines of therapy responding to the combination. An ongoing phase 3 trial (BELLINI) is comparing bortezomib and Dex with or without venetoclax in patients with relapsed MM. Additional trials are examining venetoclax alone as well as in combinations with monoclonal antibodies, immunomodulatory drugs (IMiDs), and newer proteasome inhibitors in all patients with MM and specifically in patients with t(11;14) abnormality.

KPT (Selinexor)

Regulation of nucleocytoplasmic transport plays a major role in maintaining cellular homeostasis and requires transport receptors belonging to the karyopherin (Kap) family, which includes importins, exportins, and bidirectional Kaps.[15] Among the exportins, XPO1 is responsible for transporting most of the tumor suppressors and growth regulators including p53, p21, FOXO, phosphatidylinositol 3-kinase/AKT, Wnt/β-catenin, etc. Selinexor is an oral selective XPO1 inhibitor that has shown preclinical efficacy against a wide variety of tumor types, including MM.[16] In a phase 1/2 study, 79 MM patients with disease refractory to bortezomib, carfilzomib (Cfz), lenalidomide (Len), and pomalidomide (Pom), including some refractory to daratumumab, were treated twice weekly with oral selinexor 80 mg for 6 or 8 doses per 28-day cycle and Dex 20 mg twice weekly.[17] Among the evaluable patients, the ORR was 21%, including 5% with a VGPR. Common AEs included hematologic (thrombocytopenia, neutropenia, and anemia) and gastrointestinal (nausea, anorexia, vomiting, diarrhea) toxicity. Toxicities were substantially reduced when the drug was used in combination with Dex. The median overall survival (OS) was 9.3 months for all patients; for the responders it was over 11 months.

In another phase 1b/2 study, 22 patients with refractory MM were treated with selinexor in combination with bortezomib and Dex.[18] Selinexor was dose escalated in once-weekly (starting at 80 mg) or twice-weekly (starting at 60 mg) regimens. The maximum tolerated dose (MTD) was not reached. Overall, the response rate was 77% with a VGPR or better rate of 27%. In patients with PI-refractory MM, the ORR was 58%. Selinexor has been combined

with Cfz as well, with the combination being quite effective with manageable toxicity.[19]

Phase 3 trials with selinexor are ongoing. A phase 3 trial (BOSTON) is examining bortezomib and Dex with or without selinexor. A large phase 2 trial of selinexor as a single agent in patients who are refractory to currently available drug classes is also under way.

Marizomib

Marizomib is a β-lactone-γ-lactam proteasome inhibitor derived from the marine actinomycete *Salinispora tropica*. Irreversible binding translates to sustained inhibition of proteasome activity, the duration of which is dependent upon cell/tissue type, and correlates with greater in vitro efficacy. In a phase 1 study (NPI-0052-101 part 1), marizomib was administered IV on 2 different schedules: schedule A (0.025-0.7 mg/m^2 once weekly on days 1, 8, and 15 of 4-week cycles) and schedule B (0.15-0.6 mg/m^2 twice weekly on days 1, 4, 8, and 11 of 3-week cycles); concomitant Dex was allowed with schedule B.[20] The trial enrolled relapsed or refractory MM patients with 5 to 7 prior treatment regimens: 32 patients in schedule A and 36 patients in schedule B. The recommended phase 2 dose was established as 0.7 mg/m^2 infused over 10 minutes in schedule A and 0.5 mg/m^2 infused over 2 hours in schedule B. The most common AEs were fatigue, headache, nausea, diarrhea, dizziness, and vomiting. Six patients had a minimal response (MR) or better, including 5 partial responses (PRs). Another report highlighted the effect in patients with central nervous system myeloma, underscoring the high degree of central nervous system penetration of this drug, and may result in a unique property from a therapeutic standpoint.[21]

Signaling pathway inhibitors

Several intracellular signaling pathways are upregulated in the MM cells, usually a reflection of the complex interaction with the tumor microenvironment. These pathways can also be upregulated because of the common mutations seen in MM, such as the MEK/extracellular signal-regulated kinase pathway in the setting of RAS mutations. Signal transduction inhibitors have been a favorite therapeutic target in MM with several small molecules having been examined in the laboratory with a few making it to clinical trials.

Afuresertib

Afuresertib, an oral AKT inhibitor, was initially examined in a phase 1 study to evaluate the MTD in patients with advanced hematologic malignancies. Seventy-three patients were treated at doses ranging from 25 to 150 mg per day, including 34 patients with MM.[22] Three MM patients attained PRs; an additional 3 attained MRs. The most frequent AEs were nausea, diarrhea, and dyspepsia. In another phase 1 study, afuresertib was given orally, continuously, once daily until progression or unacceptable toxicity, in combination with bortezomib and oral Dex given on days 1, 4, 8, and 11 every 21 days for a maximum of 8 cycles. Confirmed ORR during dose escalation was 41% (1 complete response [CR], 3 VGPR, 10 PR), and 3 additional patients had MR.[23] The most common (>20%) AEs were diarrhea, fatigue, thrombocytopenia, nausea, dyspepsia, constipation, hyperglycemia, vomiting, and anemia. The future plans for development of this drug remain unclear at this time.

LGH447

The provirus integration site for Moloney leukemia (PIM) kinase gene family encodes 3 serine/threonine protein kinases that play a role in cell cycle progression and survival. Elevated levels of Pim1 and Pim2 are seen in hematologic malignancies, with MM showing high expression of Pim2. LGH447 is a novel, specific pan-Pim kinase inhibitor, which has shown inhibition of MM cells in preclinical studies. In a phase 1 dose-escalation study, 54 patients with relapsed MM were treated with increasing doses, and MTD was determined to be 500 mg once daily.[24] Patients were heavily pretreated with a median of 4 prior lines of therapy treatment. Responses included 1 VGPR and 4 PRs noted at doses above 150 mg. Most common grade 3/4 AEs were thrombocytopenia, anemia, neutropenia, and fatigue. The future plans for development of this drug remain unclear at this time, though other Pim kinase inhibitors continue to be explored in early-phase clinical trials.

Trametinib

In a biomarker-driven trial by Trudel et al, patients were recruited into biomarker-positive (K/NRAS or BRAF mutated) or biomarker-negative (K/NRAS, BRAF wild-type) groups and treated with trametinib 2 mg per day on a 28-day cycle.[25] Patients who had progression or less than a PR after 4 cycles had GSK2141795 (pan-AKT inhibitor) added to the treatment. Of the 25 patients enrolled (12 mutated and 13 wild-type Ras), 1 patient in the mutated group had a PR.

Vemurafenib

Vemurafenib has been studied in a subgroup of patients with relapsed refractory BRAF V600m-positive MM.[26] Median duration of treatment was 3.3 months (range, 1-5) with 1 PR and 4 patients with stable disease at the end of 2 cycles.

Immune therapies

Monoclonal antibodies

Monoclonal antibodies represent an exciting advance in MM, given the promising data seen with this approach in other hematological malignancies. Daratumumab targeting CD38 and elotuzumab targeting SLAMF7 have been approved and available for use in the clinic.[27] Several other monoclonal antibodies targeting other plasma cell antigens are currently under investigation (Table 2).

Isatuximab

Isatuximab (SAR650984) is a humanized immunoglobulin G1 monoclonal antibody that binds selectively to a unique epitope on human CD38 with high expression on plasma cells, similar to daratumumab. Multiple mechanisms of action have been proposed for the observed anti-MM effect including antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, complement-dependent cytotoxicity, direct cytotoxicity without crosslinking, and inhibition of CD38 enzymatic activity.[28,29]

In a phase 2 study, 24 patients each with relapsed refractory MM were treated at 3 mg/kg every 2 weeks, 10 mg/kg every 2 weeks, or 10 mg/kg every 2 weeks for 4 doses followed by every 4 weeks, or 20 mg/kg every week for 4 doses followed by every 2 weeks.[30] The median number of prior lines of therapy was 5 (2-14) with 100%, 99%, and 98% having prior exposure to PIs, IMiDs, and alkylator-containing therapy, respectively. Overall, 78% of patients had previously received Pom and/or Cfz; 55% had been exposed to both agents. A PR was seen in 9%, 20%, 29%, and 24% of patients in the 4 groups, respectively. The most common drug-related AEs were nausea, chills, dyspnea, chest discomfort, flushing, headache, and cough. Infusion reactions occurred in 50% of patients, predominantly grade 1/2 and mostly limited to cycle 1.

Table 2. Immune approaches in myeloma and plasma cell targets

Target	Antibody	Current status
Cell surface targets		
CD38	Daratumumab	Effective as single agent, in combination with IMiDs and PIs, approved for clinical use
	Isatuximab	In clinical trials, effective as single agent, in combination with IMiDs
	MOR202	In clinical trials
SLAMF7	Elotuzumab	Effective in combination with IMiDs and PIs, approved for clinical use
CD138	Indatuximab ravtansine (BT062)	In clinical trials for myeloma, as single agent overall response was 4%, in combination with Len ORR was 78%
CD56	Lorvotuzumab	Response rate of 7% single agent and 56% with Len-Dex, in clinical trials for myeloma
CD40	Dacetuzumab (SGN40) and lucatumumab	In clinical trials for myeloma, no responses with single agents
CD74	Milatuzumab (hLL1)	In phase 1 trial, no objective responses. Combination trials ongoing
Cytokine/growth factor targeted		
IL-6	Siltuximab	No clinical efficacy in MM, approved for treatment of Castleman disease
VEGF	Avastin	No clinical efficacy in MM
BAFF	Tabalumab (LY2127399)	In a phase 1 study in relapsed MM, combination with Bort-Dex had an ORR of 46%
DKK1	BHQ880	Bone beneficial effects seen in early trials
CXCR4	Ulocuplumab	ORR was 55% in combination with Len-Dex and 40% with Btz-Dex
T-cell approaches		
CD19	CART	In early-phase trials, CRs noted
BCMA	CART	In early-phase clinical trials, CRs noted
BCMA	BiTE	Entering clinical trials

BAFF, B-cell activating factor; BiTE, bispecific T-cell engager; Bort, bortezomib; IL-6, interleukin 6; VEGF, vascular endothelial growth factor.

In another phase 1 study, patients with ≥2 prior therapies were treated at 10 or 20 mg/kg (weekly × 4 doses, then every 2 weeks) plus Len and Dex in 28-day cycles.[31] The ORR was 50% in both dose cohorts (10 mg/kg [n = 12]: VGPR, 25%; PR, 25%. 20 mg/kg [n = 10]: VGPR, 20%; PR, 30%). Most frequent AEs were fatigue (46%), pyrexia (35%), and diarrhea (31%). Infusion reactions were seen in most patients, mostly grade 2 or less, primarily during the first infusion. Isatuximab has a shorter infusion time compared with daratumumab.

MOR202

MOR202 is a fully human monoclonal HuCAL antibody directed against CD38 on MM cells. As with the other monoclonal antibodies, the main modes of action for MOR202-induced lysis of MM cells are antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis. In a phase 1/2 study, MOR202 has been studied in combination with Dex with or without an IMiD (Len or Pom). Eighty-three patients have been treated with MOR202, including 48 patients treated in combination with Dex only or an IMiD plus Dex. Among this group of patients with a median of 3 to 5 prior lines of therapy, the ORR was 28% for Dex combination, 71% for the Len combination, and 46% for the Pom combination, including CRs. Clinical trials of IMiD combinations are ongoing.

GSK2857916

GSK2857916 is a humanized, afucosylated immunoglobulin G1 anti–B-cell maturation antigen (BCMA) antibody conjugated to microtubule-disrupting agent monomethyl auristatin F via a stable, protease-resistant maleimidocaproyl linker. Preclinical studies demonstrate its selective and potent activity in MM. In a first-in-human dose-escalation study, 30 patients with relapsed MM were enrolled, with 70% of patients having received 5 or more prior lines of therapy. AEs included ocular toxicity, cytopenias, and hepatotoxicity. It was well tolerated with no dose-limiting toxicities up to 4.6 mg/kg every 3 weeks; MTD was not reached. ORR was 27% including 1 patient with a CR and 3 with a VGPR.

Checkpoint inhibitors

The programmed death 1 (PD1)/programmed death ligand 1 (PDL1) pathway is a negative costimulatory pathway that leads to a T-cell exhaustion phenotype preventing appropriate T-cell response to antigens. In vitro studies in MM have pointed toward an important role for the PD1/PDL1 axis in the immune defects observed in MM and thus a potential role for PD1/PDL1 inhibitors in its treatment.[32-35] The plasmacytoid dendritic cells and marrow stromal cells in MM express PDL1 along with the tumor cells likely contributing to the T-cell exhaustion phenotype observed in MM. Natural killer cells from MM patients also express PD1, and engagement by PDL1 on primary MM cells can downmodulate the natural killer cell–mediated anti-MM effect.

Nivolumab. In a phase 1, open-label, dose-escalation, cohort-expansion study, 81 patients with relapsed or refractory B-cell lymphoma, T-cell lymphoma, and MM were treated with nivolumab, including 27 patients with MM.[36] No objective responses were seen among the MM patients.

Pembrolizumab. Pembrolizumab was studied in combination with Len or Pom in patients with relapsed and refractory MM. When used in combination with a standard dose of Len and Dex in patients with

relapsed refractory disease, the ORR was 50% including 38% responses in Len-refractory patients.[37] Responses were durable with a median duration of response of 11.3 months. The toxicity profile was similar to that observed with other diseases states, and immune-mediated reactions were relatively uncommon. In another phase 2 trial, pembrolizumab was combined with Pom in patients with relapsed MM, including 70% of patients who were double refractory to an IMiD and a proteasome inhibitor.[38] The overall response was 60% including a 55% response rate for the double-refractory population. Based on this promising data, 2 phase 3 trials were initiated to evaluate the combination of Len (NCT02579863) and Pom (NCT02576977) with pembrolizumab in newly diagnosed and relapsed MM, respectively. Recently, both trials were terminated early due to unanticipated deaths on the arms containing pembrolizumab, though the exact cause of the deaths remain unclear. Combinations of checkpoint inhibitors with monoclonal antibodies such as daratumumab and elotuzumab are all being explored.

Chimeric antigen receptor T cells

Chimeric antigen receptors are chimeric proteins that bring together the signaling components of the T-cell receptor complex and variable domains of an antibody targeted to an antigen of interest. T cells from a given patient are modified to express the chimeric protein, expanded ex vivo, and reinfused into the patient. Chimeric antigen receptor T cells (CARTs) can then recognize the tumor antigen in a major histocompatibility complex–independent manner, leading to T-cell activation and tumor cell cytotoxicity. Current CARTs also have costimulatory molecules such as CD28 and 4-1BB to enhance T-cell proliferation and survival, thus producing a persistent antitumor effect. Several antigen targets have been studied including BCMA, SLAMF7, CD138, NKG2DA ligands, κ light chain, and CD19. The first clinically reported success with the CART approach in MM was in a patient with refractory MM who had previously received Len, bortezomib, Car, Pom, vorinostat, clarithromycin, and elotuzumab as well as a prior autologous stem cell transplantation.[39] The patient received an autologous stem cell transplantation followed by infusion of autologous T cells transduced with an anti-CD19 chimeric antigen receptor, leading to a CR that was sustained for about 12 months. Cohen et al reported on 6 IMiD/PI-refractory patients with a median of 9 lines of therapy all of whom expressed BCMA on MM cells and were treated with a minimum dose of 1×10^8 CART-BCMA cells.[40] Cytokine release syndrome occurred in 5 patients: 2 grade 3 requiring tocilizumab, 1 grade 2, and 2 grade 1. Predominant grade 3/4 toxicities included hypophosphatemia, hypocalcemia, anemia, neutropenia, lymphopenia, thrombocytopenia, hypofibrinogenemia, fatigue, and pneumonia. One patient developed posterior reversible encephalopathy syndrome. CART-BCMA cells were detected in blood and marrow by chimeric antigen receptor–specific polymerase chain reaction (PCR) in all 6 patients, with stringent CR and VGPR seen in 1 patient each. Lin et al[41] reported on 18 patients treated on a dose-escalation study with bb2121, a BCMA-targeted CART. Twenty-one patients with a median of 7 (3-14) prior lines of therapy were enrolled. No dose-limiting toxicity was observed, and the cytokine release syndrome was readily manageable. ORR was 89% with all patients receiving $>50 \times 10^6$ chimeric antigen receptor–positive cells responding. MRD-negative status was seen in all MRD-evaluable patient samples (N = 4) with no disease progression in patients treated with doses $>50 \times 10^6$ thus far, with 1 patient past 1 year and 8 patients past 6 months.

Vaccination approaches

Several antigens, such as the cancer testis antigens like NY-ESO, WT-1, RHAMM, HSP96, MUC1, MAGE, DKK1, and HM1.24, have been the target of vaccination strategies. To overcome the lack of necessary costimulatory molecules, dendritic cell–based vaccination approaches, which rely on leading the cells with the antigen of interest, have been evaluated. One study did demonstrate an improved[42] OS compared with historical controls, but with no effect on progression-free survival (PFS), suggesting that the vaccination may help reset the immune system.[43] Preclinical studies have shown benefit to adding immunomodulatory drugs such as Len to the vaccination approaches.[44] In a phase 1/2 study, ImMucin (a 21-mer cancer vaccine encoding the signal peptide domain of the MUC1 tumor-associated antigen) was coadministered with granulocyte-macrophage colony-stimulating factor to 15 MUC1-positive MM patients following autologous stem cell transplantation, resulting in enhancement of antigen-specific cellular and antibody response along with stable disease or improvement.[45] Several ongoing clinical trials are evaluating the role of different vaccination approaches at various disease stages.

Epigenetic therapies

Epigenetic alterations have been well described in MM and appear to play a key role in disease progression and development of drug resistance.[46] Preclinical studies demonstrated synergy when it was combined with bortezomib, leading to a phase 3 trial of vorinostat in combination with bortezomib, which demonstrated improvement in PFS compared with bortezomib alone.

Panobinostat

Panobinostat was studied in combination with bortezomib in a randomized, phase 3 trial that included 768 patients with relapsed and refractory MM.[47] They received 21-day cycles of placebo or panobinostat (20 mg; on days 1, 3, 5, 8, 10, 12, orally), both in combination with bortezomib and Dex. Median PFS was significantly longer in the panobinostat group than in the placebo group (12 vs 8 months) with no significant OS difference. The proportion of patients with a CR or near CR was significantly higher in the panobinostat group than in the placebo group. Common grade 3-4 AEs included thrombocytopenia, lymphopenia, diarrhea, fatigue, and peripheral neuropathy. The results were more striking among those who had been exposed to bortezomib and Len, and led to its approval for these patients. The toxicities with the current schedule remain the main impediment to its routine use. Ongoing clinical trials are exploring alternate dosing schedules with the goal of reducing toxicities.

Ricolinostat

Ricolinostat (ACY-1215) is a selective HDAC6 inhibitor that has shown activity in a preclinical setting. In a multicenter phase 1b trial, 38 patients with relapsed or refractory MM were treated with escalating doses of oral ricolinostat in combination with Len and Dex.[48] Ricolinostat 160 mg once daily on days 1 to 21 of a 28-day cycle was chosen for phase 2 studies in combination with Len 25 mg and Dex 40 mg. A confirmed response was seen in 21 patients (55%). The most common AEs were fatigue and diarrhea.

Other new drugs

Melflufen

Given the activity of alkylating agents in MM, there has been significant interest in improving the selectivity and toxicity profile of this class of drugs. Melphalan flufenamide is a highly lipophilic alkylator, allowing for rapid cellular uptake, followed by its hydrolysis via intracellular peptidases and the release of active metabolite melphalan. Melphalan being hydrophilic remains trapped in

the cell, leading to high intracellular concentrations. Aminopeptidase N, which hydrolyses melflufen into melphalan, is elevated in MM cells leading to tumor cell selectivity and differential toxicity to the myeloma cells. As a result of these properties, melflufen allows for a more rapid and higher intracellular accumulation of melphalan in the tumor cells than is achievable by direct exposure to equimolar doses of melphalan. In vitro studies suggest that melflufen is a more potent anti-MM agent than melphalan, overcomes melphalan resistance, and induces synergistic anti-MM activity in combination with bortezomib, Len, or Dex.[49]

Melflufen was evaluated in combination with Dex 40 mg weekly in a phase 1/2a study involving relapsed MM. The MTD of melflufen was 40 mg every 3 weeks in combination with low-dose Dex. Among the 23 evaluable patients treated at the MTD, 1 patient achieved a VGPR and 10 patients achieved a PR; ORR was 48%. The median number of prior therapies was 4 (2-9), with 97% of patients exposed to IMiDs and 90% to PIs; 71% had prior autologous stem cell transplant. Responses were rapid and the median PFS was 7.6 months. The most frequent AEs were thrombocytopenia, anemia, neutropenia, asthenia, fatigue, and nausea. This drug is moving forward in a phase 3 clinical trial (OCEAN) comparing melflufen and Dex with Pom and Dex.

Aplidin

Aplidin (plitidepsin) is a chemical compound extracted from the marine invertebrate *Aplidium albicans*, which is currently undergoing clinical trial testing in myeloma. It is a member of the class of compounds known as didemnins. By binding to the eEF1A2 protein, which is involved in protein synthesis, Aplidin inhibits protein synthesis in tumors, leading to cell death. In various preclinical models of myeloma, Aplidin has been shown to induce potent cytotoxicity.[50] A phase 3 trial (ADMYRE) of Aplidin and Dex compared with Dex alone in relapsed patients had led to a 35% decrease in death or disease progression and may lead to its approval in the near future. Clinical trials combining this drug with bortezomib are ongoing.

Conclusion

The past decade saw the introduction of 3 important classes of drugs that have become the backbone of the current treatment of newly diagnosed and relapsed MM: the IMiDs, proteasome inhibitors, and monoclonal antibodies. In addition, different drugs within each of these drug classes with unique characteristics have been introduced, leading to continued improvements in the treatment choices. Development of effective drug combinations incorporating 1 or more of these drug classes has resulted in deeper and longer remissions for newly diagnosed and relapsed patients. However, relapses remain inevitable and novel treatments addressing the biological heterogeneity of the disease need to be developed with the goal of eradicating the tumor clones. The emerging therapies are increasingly being focused on specific targets or specific aspects of disease biology and have the potential to be combined with the current drugs to develop highly effective therapies. Immune therapies in particular appear to hold great promise and are likely to take center stage in the near future. The challenge going forward is to identify the right patient for the right drug or drug combinations. Current standard of care calls for a combination of a proteasome inhibitor and an IMiD for the newly diagnosed patient with transplant integrated into that initial set of therapies where applicable. Subsequent therapies for relapsed disease should increasingly rely on combinations of at least 2 drugs with nonoverlapping mechanisms of action reflecting a class change from prior therapy. In addition, continued therapy to achieve deep responses remains a common goal.

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