Immune Therapy in Multiple Myeloma

Katarina Luptakova, MD, and David Avigan, MD

Dr Luptakova is a hematologist-oncologist affiliated with Beth Israel Deaconess Medical Center in Boston, Massachusetts. Dr Avigan is the chief of the Section of Hematological Malignancies and Bone Marrow Transplantation at Beth Israel Deaconess Medical Center and a professor of medicine at Harvard Medical School in Boston, Massachusetts.

Corresponding author:
David Avigan, MD
Chief, Section of Hematological Malignancies and Bone Marrow Transplantation
Beth Israel Deaconess Medical Center
KS121
Boston, MA 02215
Tel: (617) 667-9932
davigan@bidmc.harvard.edu

Abstract: Although the advent of biologic therapies has resulted in improved outcomes for patients with multiple myeloma (MM), patients ultimately develop progressively resistant disease. As such, novel approaches are needed. There has been a renewed focus on the development of therapies that would allow redirection of patients' own immune systems to target malignant myeloma cells. Compared with healthy individuals, patients with MM exhibit immune dysregulation and an impaired capacity to develop antitumor immunity. Tumor cells induce tolerance by exploiting native immune pathways responsible for preventing autoimmunity and maintaining immunologic equilibrium. In this review, we will discuss the development of potent humoral and cellular agents directed against myeloma antigens, including novel monoclonal antibodies, myeloma vaccines, and T-cell therapies. We will also discuss the development of immune checkpoint inhibitors and immunomodulatory agents that allow manipulation of the immunologic milieu and support a more robust native immune response. There is a growing interest in combining these 2 approaches—such as pairing antimyeloma vaccines with immune checkpoint blockade—to achieve maximum efficacy of immunotherapy.

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy, with an estimated 26,850 cases to be diagnosed in 2015 in the United States.[1] The disease is characterized by clonal expansion of malignant plasma cells, and associated clinical sequelae that may include skeletal lesions, renal failure, anemia, and hypercalcemia. MM is associated with progressive immune dysregulation, resulting in a tumor microenvironment that promotes disease tolerance and progression. B-cell dysfunction is characterized by immunoparesis—hypogammaglobulinemia of the uninvolved immunoglobulins—

and increased susceptibility to infections due to viruses and encapsulated bacteria. Disease evolution is associated with defects in T-cell immunity,[2] natural killer (NK) cell function,[3] and the antigen-presenting capacity of dendritic cells (DCs).[4,5] The T-cell repertoire is characterized by the selective loss of myeloma-specific lymphocytes. A concomitant rise in suppressor cells, including regulatory T cells[2] and myeloid-derived suppressor cells, is observed in the peripheral blood and within the bone marrow microenvironment.[6] Immune checkpoint pathways that help maintain immune equilibrium in health are upregulated in the presence of malignant plasma cells, fostering a state of immune tolerance.[7,8] The upregulation of negative costimulatory signals induces a state of T-cell exhaustion. This blunts T-cell activation and expansion, and blocks T-cell–mediated killing of myeloma targets. In addition, myeloid and plasmacytoid DCs have been shown to accumulate in the bone marrow of MM patients, where they can paradoxically protect myeloma tumor cells from cytotoxic CD8+ T lymphocytes,[9] thus playing a dual role in cellular antimyeloma immunity.

The notion that MM can regress in response to immune manipulation has been long supported by the potency of the graft-vs-myeloma effect seen with allogeneic stem cell transplantation (allo-SCT). Indeed, in patients with relapsed MM after allo-SCT, donor lymphocyte infusion can lead to clinical responses.[10] The development of chronic graft-vs-host disease after allo-SCT in MM is associated with improved disease control and survival,[11] which further underscores the immune graft-vs-myeloma effect. Unfortunately, allo-SCT is also associated with a high risk of early nonrelapse mortality, driven in large part by nonspecific immune attack of the donor lymphocytes and manifested as acute graft-vs-host disease. As such, the role of allo-SCT in MM remains a topic of ongoing controversy.[12,13]

To harness the potency of cellular immunity while minimizing toxicity due to off-target effects, investigators have explored strategies to generate myeloma-specific immunity using: (1) passive immunotherapy with monoclonal antibodies that target myeloma-associated antigens; (2) active immunization with cancer vaccines; (3) adoptive T-cell therapy, including bioengineered T cells; and (4) reversal of critical aspects of the immunosuppressive milieu of the bone marrow microenvironment via immunomodulatory agents or by blockade of the negative immune checkpoints.

It is becoming evident that successful deployment of antimyeloma immune therapy will require a combined approach, in which specific targeting of myeloma cells is paired with tactics reversing the immunosuppressive milieu. In this review, we will describe the current state and future directions of development of myeloma immunotherapy.

Passive Immunotherapy With Monoclonal Antibodies

It is thought that monoclonal antibodies (mAbs) promote antibody-dependent cell-mediated cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC) upon tumor antigen recognition by the mAb.[14] The development of effective antibody therapy depends on the identification of antigens that differentiate myeloma cells from normal tissue, that are present throughout disease evolution, and for which binding results in cell death. Candidate antigens include CD138, CD38, CS1, CD56, CD74, and CD40.[15] Malignant plasma cells also express the receptor for interleukin 6 (IL-6), a key growth factor supporting plasma cell proliferation and conferring myeloma drug resistance.[16]

However, until recently the development of mAbs for MM was met with only limited success. Several anti-CD40 antibodies (dacetuzumab and lucatumumab) and an anti-CD74 antibody (milatuzumab) showed minimal clinical activity in phase 1 studies.[17-19] Siltuximab (Sylvant, Janssen), the IL-6 antibody, yielded a partial response (PR) rate of 17% when used in combination with dexamethasone in a small phase 2 study.[20] Subsequent randomized studies, however, failed to confirm an improvement in overall or progression-free survival (PFS) when siltuximab was combined with bortezomib (Velcade, Millennium Pharmaceuticals), melphalan, and prednisone,[21] or with bortezomib.[22] However, very promising clinical data were seen with mAb targeting of CS1 (elotuzumab) and CD38 (daratumumab). Both of these mAbs likely provide additional mechanisms of action beyond simple recognition of a plasma cell antigen leading to ADCC or CDC, as discussed below.

Elotuzumab

Elotuzumab (HuLuc63/BMS-901608) is a humanized monoclonal immunoglobulin G1 antibody against human CS1 (CD2 subset-1, also known as CRACC and SLAMF7), a cell surface glycoprotein.[23] High CS1 expression was seen in plasma cells obtained from normal healthy donors and from patients with monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, and active MM, in both newly diagnosed and relapsed disease.[24] Expression of CS1 also was confirmed on the cell surface of NK cells, NK-like T cells, activated monocytes, CD8+ T cells, and tissue plasma cells, although at lower levels than seen on malignant plasma cells. Importantly, CS1 is not expressed on hematopoietic CD34+ stem cells.[24] Interestingly, it is thought that CS1 expressed on NK cells acts as an activating receptor, and recent preclinical work suggests that elotuzumab may paradoxically enhance NK cell function directly and confer anti-MM efficacy by means beyond ADCC alone.[25]

Phase 1 trials of elotuzumab showed that it was safe and well tolerated, with the most common side effects being infusion related.[26] When administered as a single agent, minimal clinical activity was noted.[26] However, studies in combination with either lenalidomide (Revlimid, Celgene) and dexamethasone[27] or bortezomib and dexamethasone[28] showed overall response rates (ORRs) of 82% and 48%, respectively, with responses seen even in patients who were refractory to the approved drugs. In the recently reported ELOQUENT-2 study (Phase III Study of Lenalidomide and Dexamethasone With or Without Elotuzumab to Treat Relapsed or Refractory Multiple Myeloma), more than 600 patients with relapsed or refractory (R/R) MM were randomly assigned to receive lenalidomide and dexamethasone with or without elotuzumab. Median PFS was 19.4 months in the elotuzumab group vs 14.9 months in the control group (P<.001). The ORR was 79% in the elotuzumab group vs 66% in the control group (P<.001).[29] It is important to note that although there was a median of 2 prior lines of therapies in this trial, only 6% of patients were previously exposed to lenalidomide. Elotuzumab is now being evaluated in combination with lenalidomide and dexamethasone in a phase 3 trial for newly diagnosed MM in patients who are not candidates for autologous stem cell transplant (ASCT) (NCT01335399, ELOQUENT-1).

Daratumumab

CD38 has emerged as another promising target for mAbs in MM. CD38 is a transmembrane molecule that is widely expressed in multiple cell types of the immune system. It is present at high levels on bone marrow precursors, downregulated in resting B cells, and strongly expressed by terminally differentiated plasma cells.[30] Preclinical studies showed that daratumumab induced target-cell killing of CD38-expressing tumor cells by means of multiple mechanisms beyond ADCC and CDC, including antibody-dependent cellular phagocytosis, apoptosis, and inhibition of the enzymatic activity of CD38.[31-33]

Three mAbs against CD38 (SAR650984, MOR03087, and daratumumab) are currently being investigated in clinical trials. Daratumumab, which is in the most advanced stage of development, was the first mAb to show single-agent activity in R/R MM. In a phase 1/2 study with a total of 104 patients who had a median of 4 prior lines of therapy, daratumumab was well tolerated and no maximum tolerated dose was found. Among the 72 patients enrolled in the dose-expansion phase, the ORR was 36% (2 patients had a complete response [CR], 2 had a very good partial response [VGPR] and 11 patients had a PR) in the cohort receiving 16 mg/kg, and 10% in the cohort receiving 8 mg/kg.[34] Another phase 2 study of single-agent daratumumab was reported at the 2015 annual meeting of the American Society of Clinical Oncology (ASCO), in which 106

heavily pretreated patients with R/R disease and at least 3 lines of prior therapy achieved an encouraging ORR of 29%. A total of 3 patients achieved a stringent complete response (sCR), and 7 patients achieved a VGPR.[35]

Anti-CD38 mAbs are currently being studied in a variety of phase 2 trials, including in combination with standard agents (NCT02136134, NCT02195479, NCT01421186, and NCT01084252) and in the newly diagnosed and asymptomatic disease settings (NCT01998971, NCT02252172, and NCT02316106). An ongoing phase 1/2 study of daratumumab given in combination with lenalidomide and dexamethasone to R/R patients was recently presented. The combination treatment was well tolerated and the available preliminary efficacy data from 20 patients demonstrated marked decrease in M-protein in all patients; 15 patients achieved PR or better, including 3 patients with a CR and 6 patients with a VGPR. The ORR was 75%.[36] Daratumumab received breakthrough drug designation from the US Food and Drug Administration in 2013.[37]

It is of clinical interest that panreactivity on red blood cell (RBC) panel testing was noted in patients treated with daratumumab, potentially due to daratumumab binding to CD38 on reagent RBCs. It is recommended that reagent RBCs be treated with dithiothreitol to negate the daratumumab interference. Because dithiothreitol denatures Kell antigens, Kell-negative blood is provided to these patients.[38] Patients are also advised to have red blood cell antigen phenotyping before treatment with daratumumab is initiated.

Antibody-Drug Conjugates

To circumvent the need to rely only on ADCC and CDC as mechanisms for cell death, there has been an interest in developing antibody-drug conjugates that would allow the delivery of a cytotoxic compound to the malignant cell. The furthest in development is the anti-CD138 conjugate indatuximab ravtansine (BT062). The single-agent phase 1 study of indatuximab ravtansine in R/R myeloma showed an ORR of 11%.[39] In a phase 1/2a trial of indatuximab ravtansine in combination with lenalidomide and dexamethasone in 36 evaluable patients, the ORR was 78%. This included 1 sCR, 2 CRs, 10 VGPRs, and 15 PRs. Of note, the ORR was 70% among the 23 patients with prior exposure to lenalidomide and bortezomib, and among 10 patients refractory to prior treatment with lenalidomide.[40]

Myeloma Vaccines

Although antibody therapy has demonstrated efficacy in targeting MM, the lack of a cellular memory response to provide ongoing immune surveillance after antibody clearance will likely limit the durability of the responses. Alternatively, tumor vaccines are being explored to

reeducate host immunity to recognize myeloma cells as foreign, expand tumor specific lymphocytes, and create long-term memory to prevent recurrence. The design of an effective tumor vaccine is dependent on presenting tumor antigen in the context of effective costimulation, and modulation of the immune environment to promote activation and limit the effects of tumor-mediated immune suppression.

The identification of myeloma-associated target antigens is a necessary first step in the effort to develop vaccines to induce tumor-specific immunity. The cancer-testis antigens (CTAs) represent a large family of tumor-associated antigens, such as New York-esophageal squamous cell carcinoma (NY-ESO-1), melanoma antigen family A, 3 (MAGE-A3), MAGE-C1, and receptor for hyaluronan-mediated motility receptor (RHAMM). These antigens are notable for strong immunogenicity, and are expressed in various human tumors,[41] including MM,[42,43] but not in normal tissues except for testis and placenta. Of note, expression of CTAs is increased with disease evolution from monoclonal gammopathy to more advanced MM.[44] Other MM-associated antigens include Wilms protein 1 (WT1), mucin 1 (MUC1), sex determining region Y-box 2 (SOX2), CS1, HM1.24, and idiotype protein, which is selectively expressed by the malignant clone.[45] Humoral and cellular immune responses directed against these tumor-associated antigens have been detected in the peripheral blood and bone marrow of myeloma patients[46,47]; however, these responses wane in more advanced disease.[48] Clinical trials with peptide-based vaccination, including vaccines against idiotype protein,[49] idiotypic DNA vaccination,[50] heat shock protein 96 (HSP96),[51] MUC1,[52,53] RHAMM,[54] and MAGE,[55] were able to demonstrate generation of immune responses against respective myeloma antigens; however, no objective clinical responses were seen. Antigenic escape, the ability of tumor to evade immune recognition by downregulation of the target antigen, is likely one of the reasons for the ineffectiveness of the single-antigen vaccines. One approach to circumvent this problem is to use simultaneously a cocktail of peptides such as heteroclitic X-box–binding protein 1 (XBP1) $US_{184-192}$, heteroclitic XBP1 $SP_{367-375}$, native $CD138_{260-268}$, and native $CS1_{239-247}$, which was shown to generate strong cytotoxic T-lymphocyte response in vitro,[56] and hold promise for further clinical development.[57]

Dendritic Cell–Based Vaccines

In order to assure effective immune responses, antigens need to be presented in the context of costimulatory molecules. However, antigen presenting cells (APCs), including DCs, that are isolated from patients with MM are reduced in number and have functional limitations.[58,59] DCs constitutively express costimulatory molecules and are uniquely capable of presenting an array of antigens

to naive T-cell populations, promoting tumor-specific killing.[60] As such, major strategies to enhance antigen presentation have focused on DC-based vaccines.[61] Approaches for generation of DC-based vaccines include DCs pulsed by peptides,[62,63] tumor-derived RNA and DNA loading,[64] or the use of autologous tumor as the source of myeloma antigens, either in the form of tumor lysate[65,66] or as intact tumor cells. The latter approach—in which a fusion vaccine is created from the patient's own tumor and autologous DCs, which will be discussed in detail later—seems to hold the most hope as an effective personalized cell-based vaccine.

The authors have developed a personalized vaccine strategy in which patient-derived myeloma cells are fused ex vivo with autologous DCs such that a broad array of tumor antigens are presented in the context of DC-mediated costimulation. Fusion cells elicit both CD4- and CD8-mediated responses, with potent efficacy in preclinical models.[67] In a murine model, vaccination with DC/tumor fusions was protective from an otherwise lethal dose of tumor cells, and induced disease regression in animals with established metastatic disease.[68] In a phase 1 study, 17 patients with active MM, with a mean of 4 prior treatment regimens, underwent serial vaccination with autologous DC/MM tumor fusions and granulocyte-macrophage colony-stimulating factor (GM-CSF). Vaccination was well tolerated, with toxicity limited to injection site reactions. Vaccination resulted in expansion of autologous myeloma-specific T cells in 11 out of 15 patients, as evidenced by the percentage of CD8+ T cells expressing interferon γ (IFN-γ) following ex vivo exposure to autologous tumor lysate. Approximately 66% of patients, all with advanced malignancy, demonstrated disease stabilization after vaccination, ranging from 2 months to longer than 2 years.[69]

In order to improve responses to vaccination, our group had subsequently conducted a phase 2 trial in which 36 patients with MM were administered the DC/tumor vaccine in the period following ASCT, in the setting of significant tumor cytoreduction. Post-transplant lymphopoietic reconstitution is further characterized by transient reversal of tumor-mediated tolerance, regulatory T-cell depletion, and expansion of myeloma-reactive T cells.[70] Expansions of CD4 and CD8 cells were observed following vaccination after transplantation. Complete responses were observed in 47% of patients, with a 78% combined VGPR and CR rate. More than half of observed CRs were achieved only after completing vaccination with DC/MM fusions, suggesting an independent effect of immunotherapy.[71] Based on these encouraging results, a phase 2 randomized multicenter study is being launched through the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Clinical Trials Network, in which MM patients

undergoing ASCT will be randomly assigned to receive either post-transplant DC/MM fusion vaccination with lenalidomide maintenance, or lenalidomide maintenance alone. The treatment arms will be compared with respect to clinical response, PFS, and an integrated assessment of cellular and humoral immune response.

Adoptive T-Cell Strategies

Adoptive T-cell therapy refers to isolation and ex vivo expansion of tumor-specific T cells, which are then infused as effector cells. Approaches to adoptive T-cell therapy include isolation and culture of tumor-infiltrating lymphocytes (TILs), isolating and expanding one particular T cell or clone, and T-cell bioengineering, which includes generation of chimeric antigen receptor (CAR) T cells.

One strategy for adoptive transfer of TILs involves the harvesting and activation of bone marrow–infiltrating cells (MILs). In the microenvironment of the bone marrow, T cells are primed to tumor-specific antigens, maturing into memory T cells with enhanced recognition of a malignant clone. MILs expanded ex vivo demonstrate greater antitumor specificity than similarly manipulated peripheral blood–derived lymphocytes.[72] The first clinical trial using MILs in treatment of MM was recently reported: 25 patients who were candidates for an upcoming ASCT, but did not achieve CR to their last treatment, had their MILs harvested from bone marrow containing active disease. MILs were activated and expanded with anti-CD3/CD28 beads and interleukin 2 (IL-2), and reinfused on the third day after ASCT. Clinical responses included a CR rate of 27%, a PR rate of 27%, a stable disease (SD) rate of 23%, and a progressive disease rate of 14%.[73]

Ex vivo manipulation of T cells often includes stimulation by the tumor antigen, nonspecific stimulation by anti-CD3/CD28, and/or exposure to cytokines. Two phase 1/2 trials sought to accelerate immune reconstitution after ASCT in advanced MM by injecting ex vivo anti-CD3/CD28 costimulated autologous T cells along with post-transplant vaccinations with the pneumococcal vaccine,[74] or with the addition of a tumor vaccine made from human telomerase reverse transcription and survivin.[75] The transfer of costimulated T cells was well tolerated, with side effects limited mainly to rash, and patients demonstrated a robust immune response. More recently, anti-CD3/CD28 ex vivo expanded autologous T cells primed in vivo using a MAGE-A3 multipeptide vaccine combined with adjuvant immunostimulants were given to 27 patients with active and/or high-risk myeloma. Patients received autografts accompanied by MAGE-A3 peptide immunizations before T-cell collection and 5 times after ASCT. Immune responses were documented in the majority of patients.[76]

Bioengineered T Cells: Chimeric Antigen Receptor T Cells and T-Cell Receptor–Modified T Cells

The use of CAR T cells is a promising immunotherapeutic strategy in which antibody-mediated tumor antigen binding is incorporated into a constitutively activated T cell with the capacity for ongoing in vivo expansion. CAR T cells are synthetically engineered using a retroviral (either a oncoretroviral or lentiviral) vector to transduce a specific antibody into the zeta chain of the CD3 complex of the T-cell receptor (TCR) apparatus in conjunction with a costimulatory molecule such as CD28 or 41BB. Engagement of the antibody receptor induces T cell–mediated cytotoxicity.[77] Importantly, the extracellular binding motif is a single-chain antibody and, unlike with other adoptive T-cell therapies, the target killing by CAR T cells is independent of major histocompatibility complex (MHC) restrictions.

Anti-CD19 CAR T cells have demonstrated remarkable potency in such diseases as chronic lymphocytic leukemia[78] and acute lymphoblastic leukemia.[79] Notable toxicities seen in clinical trials with CAR T cells include the cytokine release syndrome, which also correlates with treatment efficacy.[80] Of interest, anti-CD19 CAR T cells may also be effective in myeloma, targeting the "premyeloma" CD19-positive B cells. Preliminary results from a pilot study were presented at the 2015 ASCO annual meeting, where patients relapsing within 1 year of ASCT were treated with a second ASCT followed by an infusion of second-generation anti-CD19 CAR T cells. Three out of 5 evaluable patients remained in CR with follow-up ranging from 74 to 339 days.[81]

Other emerging targets for bioengineered adoptive T-cell therapy in MM include B-cell maturation antigen (BCAM),[82] kappa light chain (NCT00881920), and CD138 (NCT01886976). In addition, there is an interest in developing CS1-specific CAR-engineered NK cells.[83] Perhaps the most mature clinical results in MM were described with the administration of TCR-engineered T cells recognizing CTAs in the post-ASCT setting. In a phase 1/2 trial, 20 HLA-A*0201–positive patients with active MM expressing antigens NY-ESO-1 or LAGE-1 underwent apheresis. Collected peripheral blood mononuclear cells were transduced with lentiviral vector encoding the affinity-enhanced NY-ESO^{c259} TCR, and expanded using anti-CD3/CD28 beads. Patients subsequently underwent standard ASCT. Two days after the procedure, they received an infusion of autologous engineered T cells, which were documented to expand and traffic to the bone marrow. Encouraging clinical responses among patients with active and high-risk disease included 14 patients with a near CR, 2 patients with a VGPR, 2 patients with PRs, and 1 patient with SD. The ORR was 90%. Adverse events included skin rash with lymphocytosis and a diarrheal

syndrome. Interestingly, disease progression was associated with loss of T-cell persistence or antigen escape.[84]

Antigenic escape is indeed one of the major limitations of CAR T-cells directed against a single antigen on the tumor cells. Preclinical work aiming to overcome this problem has been conducted in which MM patients' T cells were transduced with lenti-CAR vectors targeting several known MM surface antigens: CS1, CD317 (HM1.24), CD138, and BCAM. Interestingly, CS1 and CD317 were also expressed on T cells and led to self-killing of the CAR T cells themselves, likely limiting the use of these antigens in further development of antimyeloma CAR T cells. On the contrary, targeting 2 antigens by dual CD138/BCAM CAR T cells showed significantly more effective and consistent killing of MM cells.[85] Such an approach may overcome the issue of antigen escape seen in single CAR strategy.

Reversal of the Immunosuppressive Milieu

Immunomodulatory Agents

Immunomodulatory agents (IMIDs), such as thalidomide (Thalomid, Celgene), lenalidomide, or pomalidomide (Pomalyst, Celgene), exhibit potent antimyeloma activity through a variety of mechanisms, including effects on the immunologic milieu. In a recent study, both thalidomide and lenalidomide were found to bind to cereblon,[86] and there is evidence pomalidomide works through the same mechanism.[87] Cereblon forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1, cullin 4A, and regulator of cullin 1, resulting in ubiquitination and proteolysis of target proteins such as Ikaros family zinc finger protein 1 (IKZF1) and IKZF3, which are important transcription factors for B-cell differentiation.[88] Cereblon-based degradation of IKZF1 and IKZF3 in myeloma cells induce direct myeloma cell cytotoxicity by downregulation of interferon regulatory factor 4 (IRF4) and MYC.

Thalidomide and lenalidomide are potent costimulators of primary human T cells, synergizing with stimulation via the T-cell receptor complex to increase IL-2–mediated T-cell proliferation and IFN-γ production.[89] Secretion of IL-2 and IFN-γ increases the number of NK cells, improves their function, and mediates lysis of MM cells by the increase of activator protein 1 transcriptional activity.[90] These data support the notion that IMIDs may mediate their anti-MM effect, at least in part, by modulating NK cell number and function. Furthermore, recent observations suggest that pomalidomide and lenalidomide enhance tumor antigen uptake by DCs with an increased efficacy of antigen presentation.[91]

The authors have demonstrated that exposure to lenalidomide in the context of T-cell expansion with direct ligation of CD3/CD28 complex results in polarization toward a Th1 phenotype characterized by increased IFN-γ, but not IL-10 expression. In vitro exposure to lenalidomide resulted in decreased levels of regulatory T cells and a decrease in T-cell expression of the inhibitory marker, programmed death 1 (PD-1). Lenalidomide also enhanced T-cell proliferative responses to allogeneic DCs.[92] As such, there is an ongoing interest in combining other immunotherapeutic strategies with IMIDs.

Immune Checkpoint Blockade

The presentation of an antigen to the T cell can lead to either T-cell stimulation with resulting inflammatory response or, alternatively, T-cell anergy. The response depends on the concurrent engagement of the costimulatory molecules, or conversely, negative costimulatory factors, such as cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), PD-1, lymphocyte activation gene 3 (LAG-3), and T-cell immunoglobulin and mucin protein 3 (TIM-3). Binding to the negative costimulatory molecules, also termed immune checkpoints, induces T-cell anergy and blunted immune response. As a result, antibody blockade of negative costimulatory molecules such as CTLA-4 and PD-1/programmed death ligand 1 (PD-L1) are being explored in the clinical setting, with promising results. Dramatic disease regression and durable responses have been noted with mAbs directed against PD-1 in subsets of patients with solid tumors and hematologic malignancies including melanoma, renal cell carcinoma, non–small cell lung cancer and Hodgkin disease.[93-95] Similarly, mAbs against PD-L1 have shown activity in solid tumors.[96] The PD-1/PD-L1 pathway is upregulated in MM.[7,97] PD-L1 expression in MM is increased in the setting of advanced disease, therapy resistance, and the presence of stromal elements.[98] Increased PD-1 expression has been noted in circulating T cells of patients with advanced disease, and patients with residual disease.[98] PD-L1 is also found in immunoregulatory cells such as plasmacytoid DCs in bone marrow derived from myeloma patients.[99] Early-phase clinical trials are investigating checkpoint inhibitors in hematologic malignancies including MM, in some cases in combination with standard agents or combinations of CTLA-4 and PD-1/PD-L1 targeting agents. Preliminary findings reported in MM have shown stable disease without significant disease regression.[100]

The efficacy in PD-1 blockade in tumors characterized by tumor infiltrating lymphocytes supports pairing this strategy with vaccine or adoptive T-cell approaches in MM. In this vein, we have been examining the potential synergy of the DC/myeloma fusion vaccine and PD-1 blockade.[97] Our preclinical findings supported an ongoing clinical trial in which patients with MM will receive 3

doses of DC/tumor vaccine in conjunction with the PD-1 antibody pidilizumab following ASCT (NCT01067287).

Although preclinical studies have demonstrated increased expression of several other checkpoint inhibitors during myeloma progression, including LAG-3, TIM-3, and CD48,[8] antibodies against these checkpoint inhibitors are in early stages of clinical development and have not been tested yet in MM.

Conclusions and Future Directions

Appreciation has been increasing of the complex interactions between the immune system and cancer and their role in promoting immune escape and disease growth. This understanding has led to a revolution in the development of effective immune-based treatments, which have fundamentally changed the horizon for cancer therapeutics. Critical components of tumor-mediated immune suppression in MM include loss of the T-cell repertoire, antigen presentation in the context of increased negative costimulation, and the presence of accessory cells in the tumor microenvironment that foster tolerance. The identification of myeloma-associated antigens and strategies to reverse tumor-mediated immune suppression holds great promise for the development of effective immunotherapy in this setting. Antibody therapy alone or in combination with other anti-MM agents appears to be highly effective for inducing disease regression. Vaccine therapy targeting individual antigens or whole-tumor cells demonstrates potent expansion of MM-specific lymphocytes and the possibility of greater disease control. Adoptive T-cell strategies, including the use of MILs and CAR T cells, are under active exploration. Checkpoint blockade is viewed as a promising area of cancer therapeutics, where its efficacy in MM may be dependent on combination therapy. The immune system has emerged as a highly potent tool to target cancer cells, capturing tumor heterogeneity and providing memory to prevent recurrence. The development of cell therapeutics in combination with immune modulatory therapy will likely significantly improve the long-term outlook for patients with MM.

Disclosures
Dr Luptakova became an employee of Takeda Oncology after the writing of this manuscript. Dr Avigan has no disclosures to report.

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