Harnessing the Immune System Against Multiple Myeloma: Challenges and Opportunities

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Multiple myeloma (MM) is an incurable malignancy of plasma cells that grow within a permissive bone marrow microenvironment (BMM). The bone marrow milieu supports the malignant transformation both by promoting uncontrolled proliferation and resistance to cell death in MM cells, and by hampering the immune response against the tumor clone. Hence, it is expected that restoring host anti-MM immunity may provide therapeutic benefit for MM patients. Already several immunotherapeutic approaches have shown promising results in the clinical setting. In this review, we outline recent findings demonstrating the potential advantages of targeting the immunosuppressive bone marrow niche to restore effective anti-MM immunity. We discuss different approaches aiming to boost the effector function of T cells and/or exploit innate or adaptive immunity, and highlight novel therapeutic opportunities to increase the immunogenicity of the MM clone. We also discuss the main challenges that hamper the efficacy of immune-based approaches, including intrinsic resistance of MM cells to activated immune-effectors, as well as the protective role of the immune-suppressive and inflammatory bone marrow milieu. Targeting mechanisms to convert the immunologically "cold" to "hot" MM BMM may induce durable immune responses, which in turn may result in long-lasting clinical benefit, even in patient subgroups with high-risk features and poor survival.

Keywords: myeloma, immunotherapy, microenvironment, immune system, challanges

INTRODUCTION

Multiple myeloma (MM) is a plasma cell (PC) malignancy that accounts for approximately 1.5% of all cancers, and 10% of hematological malignancies (1). Abnormal proliferation of malignant PCs in the bone marrow (BM) in most cases leads to excessive secretion of immunoglobulin in the blood and urine, associated with organ dysfunction including hypercalcemia, renal dysfunction, anemia and/or bone disease (CRAB) (2). MM onset follows a multistep development process: tumor immune escape and accumulation of genomic aberrations in the malignant clone(s) drives the progression from precursor stages, namely monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM), to overt MM (1, 3). Current therapy consists of combination of novel agents with remarkable efficacy in MM. Specifically, combination proteasome inhibitor (PIs), immunomodulatory drugs (IMiDs), and dexamethasone used alone or integrated

into high dose melphalan and autologous stem cell transplantation (ASCT) paradigm, increased rate, extent, and duration of response (4)..

Immunotherapy has recently demonstrated remarkable activity in many human solid tumors and is also transforming MM treatment as well. Recent approval of monoclonal antibodies (moAb) for the treatment of both newly diagnosed (NDMM) and relapsed/refractory (RRMM) MM patients highlights the fundamental role of therapies targeting the immunosuppressive microenvironment. The success of these approaches underlies the potential benefit of combination of immune- and targeted-therapies to overcome inter- and intra-patient heterogeneity characteristic of MM. In this review, we will discuss the role of the immunosuppressive BM microenvironment in MM, and outline novel immunotherapeutic approaches to effectively restore anti-MM immunity.

IMMUNE DYSFUNCTION AND TUMOR IMMUNE EVASION MECHANISMS

BM-mediated immune dysfunction and tumor immune evasion represent the main challenges for immunotherapy in MM (5). However, although qualitative and/or quantitative alterations of cellular and non-cellular components of the BM *niche* in MM confer immunosuppression, they similarly represent ideal targets for novel therapeutics. Immune dysfunction not only confers MM cell growth and resistance to therapy, but also is associated with higher susceptibility to infections and impaired cellular immunity, evidenced by lack of a strong immune response to vaccinations (6–9). Alterations in accessory and immune cells in the BM including regulatory T cells, myeloid-derived suppressor cells (4, 10), Th17 cells, tumor-associated macrophages, mesenchymal stromal cells, and osteoclasts contribute to immune suppression and immune exhaustion (5, 11). Interaction of MM cells with plasmacytoid dendritic cells further promotes MM cell survival and therapy resistance, providing the rationale for targeting this interaction in novel therapeutic approaches (12, 13). Recent reports show a stepwise immune dysregulation in MM which occurs as early as in SMM stage, and the potential role of immune-based therapeutic interventions in premalignant precursor stages to delay or prevent progression to active MM in under active investigation in ongoing clinical trials (14–17).

During progression of disease, MM cells acquire the ability to evade the immune system and subvert cancer immunoediting, a dynamic process encompassing multiple aspects of tumor cell-immune system interactions (10, 18). Immunoediting, a process that is well described for solid tumors, shapes cancer cell immunogenicity in three phases: elimination, equilibrium, and escape. In the first phase, both innate and adaptive immunity recognize and eliminate early tumor cells (elimination). However, a state of dormancy next occurs in which a functional immune system maintains the survival of tumor cells under constant immune pressure (equilibrium). In this phase, resistant tumor cells acquire genetic and epigenetic alterations that eventually lead to escape the immune recognition, allowing for uncontrolled proliferation and clinical progression (escape) (19–21). A potential application of this model in MM identifies in the MGUS/SMM precursor stages a phase of immune equilibrium (22). In this context, marked heterogeneity of MM cells, along with constitutive and ongoing genomic instability, and modulations occurring in the composition of the BM *milieu* may underlie immune escape and disruption of the immune equilibrium during disease progression (22). Specifically, the strict and symbiotic interaction between MM cells and the BM microenvironment facilitate tumor immune escape *via* several mechanisms: immunosuppressive cells in the BM; disruption of antigen presentation by downregulating major histocompatibility complex and/or costimulatory molecules; loss or mutation of cancer-specific antigens; and upregulation of decoy receptors or complement inhibitory receptors (5, 23). Moreover, secretion of immunoregulatory soluble factors from both MM and BM microenvironment cells including transforming growth factor TGF-β, interleukin IL-10, IL-6, prostaglandin E2, and APRIL; as well as adhesion of MM cells to extracellular matrix proteins and accessory cells further promotes immune evasion and inhibition of apoptosis (5). Lastly, immune evasion also results from increased expression of immune checkpoints, i.e. PD-1/PD-L1, in T cells and MM cells, which has been associated with progression from precursor stages to clinically active MM, as well as with progression from NDMM to RRMM. As will be discussed later, clinically active agents blocking PD-1/PDL-1 axis have been associated with adverse events and are not approved for MM treatment; and ongoing studies are exploring the role of other potential immune checkpoint or agonist molecules including LAG 3 or TIGIT and OX40, respectively (24).

IMMUNOTHERAPY IN MM

The potential benefit of immunotherapeutic approaches in MM was first demonstrated by the curative effect achieved in some MM patients by the graft-*versus*-myeloma effect induced by allogeneic stem cell transplantation (23). Importantly, several moAbs and an immunotoxin have been FDA approved to treat MM and already improved patient outcome. Here, we review these therapies, as well as novel approaches under investigation in preclinical and clinical studies to further boost anti-MM immune response (**Figure 1**).

Direct Targeting of MM Cell Tumor Antigens
Monoclonal Antibody Therapy
Monoclonal antibody (moAb) therapy is a successful strategy for both solid tumors and hematological malignancies; and recently has also transformed MM treatment (25). A key determinant for an optimal moAb efficacy is identification of a target uniquely or selectively and highly expressed by MM cells (26). To date, the targeting of two MM surface antigens, CD-38 and SLAMF7, has led to the Food and Drug Administration (FDA) approval of
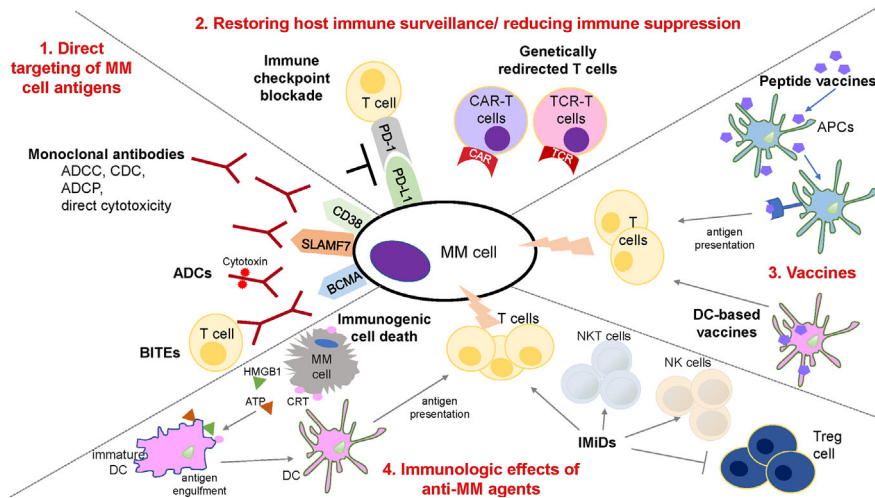
FIGURE 1 | Schematic overview of immune therapies in MM. 1. Strategies for the direct targeting of MM cell antigens includes: (a) moAbs: anti-CD38 and -SLAMF7 antibodies induce ADCC, CDC, ADCP, and direct cytotoxic effect on MM cells; (b) ADCs: conjugation of moAbs and cytotoxic compounds provides direct and selective tumor killing; (c) BiTEs: dual interaction with surface antigen of tumor cells and the TCR complex enables T cell activation and tumor lysis of MM cells. 2. Restoration of host immune surveillance and decrease of immune suppression can be achieved by the blockade of immune-checkpoint, such as PD-1/PD-L1 axis, that are responsible for inactivation and loss of proliferative capacity of T cells; or by the use of genetically redirected T cells including CAR-T and TCR-T cells. CAR-T cells mediate MHC-unrestricted tumor cell killing via recognition of tumor antigen. TCR-T cells mediate MHC-restricted tumor cell killing by recognizing the intracellular antigen fragment presented by MHC molecules. 3. Peptide- or DC-based vaccination represents an additional strategy to increase a MM specific anti-tumor immunity. Peptide vaccines binds to restricted MHC molecule in APCs and after intracellular processing, peptide/MHC complex is transported to the cell surface for antigen presentation and activation of T cells. In DC-based vaccines, DCs are generated to present tumor associated antigens to T cells. 4. Anti-MM agents such as IMiDs and PIs may affect the immune compartment composition and increase anti-MM immune response. IMiDs increase and stimulate T, NK, and NKT cells, along with a decrease of immunosuppressive Treg cells. Novel reports also show the ability of anti-MM agents, such as bortezomib to induce immunogenic cell death (ICD) and stimulate an immune response against MM cells. Specifically, dying tumor cells expose specific damage associated molecular patterns (DAMPs) that induce the functional maturation of DCs, and the efficient presentation of tumor antigens to the T cells. ADCC, Antibody-dependent cellular cytotoxicity; ADCP, Antibody-dependent cellular phagocytosis; CDC, Complement-dependent cytotoxicity; ADC, Antibody drug conjugate; BiTE, Bi-specific T cell engager; CAR, Chimeric antigen receptor; TCR, T cell receptor; APC, Antigen presenting cell; NK, Natural Killer; Treg, regulatory T cells; DC, dendritic cell; CRT, Calreticulin.

moAbs Daratumumab or Isatuximab and Elotuzumab, respectively, for MM treatment. Anti-MM immune effects of these moAbs include antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement activation, and direct effects on MM cells. Specifically, Elotuzumab is a humanized IgG1 monoclonal antibody that targets SLAMF7, which is highly expressed on PCs, natural killer (NK) cells, and activated monocytes (27). It induces ADCC while also activating NK cells and inhibiting MM cell adhesion to BMSCs (28, 29). Although no single agent activity has been reported in a phase I study (30), increased overall response (ORR) and median progression free survival (PFS) in the phase III Eloquent-2 trial provided the basis for its FDA approval in combination with lenalidomide and dexamethasone (Rd) in RRMM (31). More recently, the Eloquent-3 trial led to its approval in combination with pomalidomide and low dose dexamethasone (PomDex) in RRMM (32).

Daratumumab is an IgG1 kappa fully human moAb that targets CD38, which is highly expressed on malignant MM cells, but is also expressed on lymphoid and myeloid cells, hematopoietic progenitor cells, as well as non-hematopoietic

tissues (18, 33). Anti-MM effects of daratumumab include: Fc fragment-dependent complement-dependent cytotoxicity (CDC), where the Fc fragment binds C1q, initiates complement cascade, and induces the formation of the membrane attack complex (MAC) that leads to MM cell lysis; ADCC, where Fc fragment binds an FcR-bearing effector cells such as natural killer (NK) cells, thus stimulating MM cytotoxicity; ADCP, where Fc fragment binds an Fc-bearing macrophage, thus stimulating MM cells phagocytosis; tumor cell apoptosis upon FcγR cross-linking (34–38); and immunomodulatory effects due to killing of CD-38-positive immune suppressor cells including regulatory T and B cells (Treg and Breg) and MDSCs (35), associated with an increase in T cell number, clonality, activation, and killing capacity due to higher levels of granzyme B (35). All these effects both induce MM cytotoxicity and increase host-anti MM response, associated with durable responses (**Table 1**). In the phase I/II GEN501 study and phase II SIRIUS study, Daratumumab monotherapy induced significant responses in heavily pretreated RRMM, leading to its FDA approval as monotherapy to treat RRMM in 2015 (39, 40). Combinations of daratumumab with Rd, PomDex, Bortezomib and dexamethasone (Vd), and carfilzomib dexamethasone are all

TABLE 1 | Daratumumab.

Treatment	Clinical trials	Patient population	ORR%	PFS	OS at 12 m	Date of approval
D monotherapy	GEN501	RRMM	36*	5.6 m	77%*	Nov 16, 2015
	SIRIUS	RRMM	29.2	3.7 m	64.8%	
	POLLUX	RRMM	92.9 *vs* 76.4	12 m: 83.2 *vs* 60.1%	92.1 *vs* 86.8%	Nov 21, 2016
D-Rd vs Rd						
	MAIA	NDMM transplant-ineligible	92.9 *vs* 81.3	30 m: 70.6 *vs* 55.6%		June 27, 2019
D-Vd vs Vd	CASTOR	RRMM	82.9 *vs* 63.2	12 m: 60.7 *vs* 26.9 %		Nov 21, 2016
D plus PomDex	EQUULEUS	RRMM	60	13.1 m: 8.8 m (median)	66% (median)	June 16, 2017
D-VMP vs VMP	ALCYONE	NDMM transplant-ineligible	90.9 *vs* 73.9	18 m: 71,6 *vs* 50.2%		May 7, 2018
D-VTd vs VTd	CASSIOPEIA	NDMM transplant-eligible	92.6 *vs* 89.9	18 m: 93 *vs* 85%		Sept 26, 2019
D-RVd vs RVd	GRIFFIN	NDMM transplant-eligible	99 *vs* 91.8	24 m: 95.8 *vs* 89.9 %		

*in the cohort of patients receiving 16 mg/kg dose.
NDMM, newly diagnosed MM patients; RRMM, relapsed refractory MM patients; D, daratumumab; R, lenalidomide; Pom, pomalidomide; V, bortezomib; M, melphalan; T, thalidomide; P, prednisone; d, dexamethasone; ORR, overall response rate; PFS, progression free survival; OS, overall survival; m, months.

FDA approved to treat RRMM; moreover, recent studies led to the FDA approval of Daratumumab in combination with Rd, or bortezomib, melphalan, and prednisolone (VMP), or bortezomib, thalidomide, and dexamethasone (VTd) to treat NDMM (41–46) due increased frequency and extent of durable responses (**Table 1**). A co-formulated product of daratumumab and recombinant human hyaluronidase PH20 suitable for subcutaneous administration has recently shown non-inferiority in the COLUMBA and PLEIADES trials as compared to intravenous infusion (47); and subcutaneous Daratumumab is now FDA approved, thus reducing infusion time and rate of infusion-related reactions.

Isatuximab (SAR650984) is another humanized IgG1 chimeric moAb that targets CD38. Its mechanisms of actions include CDC, ADCC, ADCP, and direct cytotoxicity without crosslinking of the Fc receptors of the antibody (48, 49). Moreover, both Daratumumab and Isatuximab may induce the depletion of CD38+ immune suppressor cells such as Tregs and Bregs (21, 50, 51). In the phase III ICARIA-MM study, isatuximab combined with PomDex showed superiority in terms of ORR (60.4 *vs* 35.3%) and median PFS (11.5 months *vs* 6.5 months) (52). This result led the FDA to approve isatuximab as a combination therapy with PomDex to treat RRMM in March 2020.

Antibody Drug Conjugate (ADC) and Bi-Specific Antibody (BiTEs)

Monoclonal antibodies have been recently used to develop Ab drug conjugates (ADC) and bispecific T cell engagers (BiTEs). ADCs are moAbs conjugated to cytotoxic compounds (such as auristatin) *via* synthetic linkers (53, 54). This conjugation provides both selective targeting and direct tumor killing, along with immune-mediated cytotoxicity (54–58). Several ADCs are under investigation in pre-clinical and clinical settings; among them, B cell maturation antigen (BCMA)-directed ADCs are

showing promising effect due to the high and unique expression of BCMA on MM and late memory B cells, and to the oncogenic role of BCMA/APRIL pathway in the disease (56, 58, 59). Specifically, BCMA is a member of the tumor necrosis factor receptor superfamily (TNF) with high affinity for B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL). BCMA is essential for long-lived bone marrow PCs survival and regulates B cell differentiation into PCs (60, 61), thus representing an ideal target for MM therapy. Importantly, we have carried out preclinical studies of belantamab mafodotin, a BCMA-aurostatin immunotoxin, which recently received FDA approval in RRMM (58, 62). Balantamab mafodotin specifically blocks cell growth *via* G2/M arrest, induces caspase-dependent apoptosis, and ADCC (58). These multiple cytotoxic mechanisms enable potent and selective anti-MM activity.

BiTEs are bispecific antibodies which bind to specific tumor antigens on one side, and to the CD3 epsilon chain of the T-cell receptor complex on the other (63, 64). This dual interaction enables T cells engagement with tumor cells, which leads to T cell activation, cytolytic synapses, and tumor cell lysis (65, 66). In MM CD19, CD38, CD138, BCMA, GPRC5D, and Fc receptor-like 5 antigens have been tested (67–69), with early promising responses from BCMA BiTEs treatment in RRMM (66, 69). Novel bispecific antibodies are under clinical development and have shown encouraging data in preclinical studies. Specifically, AMG 701 holds an extended half-life *in vivo* and mediates T-cell dependent cellular cytotoxicity (TDCC) of BCMA positive MM cells and is currently under clinical investigation (NCT03287908). We have also shown that MM cytotoxicity can be augmented at lower effector: tumor cell ratios when low doses of AMG 701 are combined with lenalidomide or pomalidomide, suggesting a favorable therapeutic index (70). Although early results look promising and both ADC and Bites approaches have the advantage for "off the shelf" availability, longer follow-up in larger studies is needed to assess their clinical efficacy and toxicity.

Restoring Host Immune Surveillance/ Reducing Immune Suppression

Genetically Redirected T Cells

Cellular therapies represent an optimal strategy to restore host immune surveillance using either adoptive T-cell (ACT) or engineered T cell approaches (71–73). Expansion and activation of immunosuppressive T cells from the tumor microenvironment has shown best responses to date in solid tumors (72, 73). In MM, early experience showed that marrow-infiltrating lymphocytes (MILs) can be effectively used as a source of tumor specific T cells for ACT (74). Although these results are encouraging, ACT in MM has mainly utilized TCR and chimeric antigen receptor (CAR) T cell strategies, facilitated by recent progress in gene engineering technology (23). In the first approach, a TCR is cloned within patient T cells, thereby enabling specific recognition of patient's tumor antigens in an MHC-dependent manner (71). Promising results were obtained in a phase I/II trial in which MM patients received high dose melphalan, ASCT, and two days later infusion of T cells engineered to express an affinity-enhanced TCR recognizing a naturally processed peptide shared by two cancer/testis antigens NY-ESO-1 and LAGE-1 (NY-ESOc259) (75, 76). Responses were noted in 80% patients with RRMM, and severe adverse events were not observed. Long-term persistence of NY-ESOc259 targeting T cells was detected and correlated with clinical activity against antigen-expressing MM cells (75). Importantly, CAR-T cell technology overcomes potential limitations of TCR-T cells by allowing recognition of unprocessed tumor antigen in an MHC-independent manner; however TCR, but not CAR-T, cells can also recognize intracellular proteins (23, 24). CARs are chimeric proteins that couple the constant region of a TCR and the tumor-associated antigen binding domain of a variable fragment of a moAb (23, 24, 77). Second-generation CAR-T cells also include costimulatory molecules, thus enhancing T cell activation and tumor killing by mimicking a physiological T cell response (23, 24, 77, 78). Patient's T cells are engineered by means of electroporation, retroviral, or lentiviral transduction, expanded *ex vivo*, and then reinfused to the patient, leading to profound and rapid tumor killing (23, 24, 77). A major determinant of successful CAR-T therapy is the identification of the appropriate antigen, which is uniquely and highly expressed by MM cells, in order to avoid adverse events. Specifically, the main challenge of CAR-T therapy is the appropriate target selection, which is critical in the management of on-target, off-tumor toxicity to avoid excess cytokine release after target recognition on non-malignant cells (79). Similarly, the major on-target, on-tumor adverse events of CAR-T cells include cytokine release syndrome (CRS) characterized by fever, hypotension and/or renal failure, as well as neurotoxicity (80); and are mainly due to the CAR-T cell activation and expansion and uncontrolled cytokine release (79). Importantly, clinical experience has now shown that targeting interleukin-6 and use of dexamethasone can treat these toxicities (23, 24, 77, 81). Nonetheless, several strategies have been developed to overcome these toxicities and include either modifications of CAR-T cell activation kinetics to maintain activation and cytokine release under a controlled level, or approaches to restrict the recognition of normal cells by optimizing CAR-T/tumor cells

interaction (79). Among several antigens including CD19, CD138 and SLAMF7, B-cell maturation antigen (BCMA) represents the most promising to date due to its high selective expression on normal plasma and MM cells (82, 83).

Several CAR-T products have been clinically evaluated in heavily pretreated (PIs-IMiDs-CD38 mAb) RRMM and demonstrated remarkable efficacy, including high rates of CR with minimal residual disease (MRD) negativity (77, 84). In the phase 1 study of bb2121, an anti-BCMA CAR-T, 85% of heavily pretreated RRMM patients had a clinical response lasting a median of 10.9 months without additional MM treatment (84). Encouraging results from the LEGEND-2 (NCT03090659) and CARTITUDE-1 (NCT03548207) clinical trials have been recently disclosed and show high overall response rate (ORR) with deep responses by using a different CAR-T product LCAR-B38M, also called JNJ 4528, which possesses a 4-1BB costimulatory domain and two BCMA-targeting domains (*Wang et al. ASH 2019; Madduri et al. ASH 2019*). Similarly, preliminary results from a phase 1 dose-escalating trial of a dual-target BM38 CAR recognizing both CD38 and BCMA are showing high ORR with a long duration of stringent CR and elimination of extramedullary lesions in RRMM patients (*Li et al., 2019 ASH*). However, relapse of disease occurs in most patients; and ongoing studies are evaluating mechanisms of CAR-T resistance in order to achieve durable responses. These include use of combination with immune approaches, treatment earlier in the disease course, and use of gamma secretase inhibitors to upregulate BCMA expression, among others.

Immune Checkpoint Blockade

Cancer cells may escape from T cell surveillance by altering the balance of costimulatory and coinhibitory molecular interactions. Stimulatory checkpoints and their ligands (CD27/CD70, CD40/CD40L, OX40/OX40L, GITR/GITL, CD137/CD137L, CD28/CD80 and CD86, ICOS/ICOSL) support T cell activation, whereas inhibitory checkpoints and their ligands (A2AR/adenosine, CTLA-4/CD80 and CD86, KIR/MHC class I, LAG3/MHC class II, PD-1/PD-L1 and PD-L2) lead to T cell suppression and induce their apoptosis (85). The PD-1/PD-L1 axis is the most studied pathway in MM. Programmed -death 1 (PD-1) receptor is a member of B7 family of costimulatory molecules and is expressed on antigen-activated and exhausted T, B, and NK cells (60, 86). PD-L1 expressing cells may evade T cell attack *via* several mechanisms, including induction of apoptosis, anergy or exhaustion of T cells, formation of a molecular shield to protect tumor cells from lysis, increased production of immunosuppressive IL-10, and stimulation of Treg cell-mediated suppression (87). Numerous studies have shown that PD-1 is overexpressed on CD4+ and CD8+ T cells of MM patients (88, 89), and that its expression is higher in patients with RRMM and MRD positive MM (90). Likewise, MM cells express PD-L1 at varying intensity (91–93), with a progressive increase in expression with progression from MGUS/SMM to NDMM to RRMM. Its oncogenic role in MM pathophysiology is also supported by the evidence that PD-L1 expressing MGUS or

SMM show a rapid progression to symptomatic disease (94). MM cells-microenvironment interaction and secretion of proinflammatory cytokines (such as IL-6) promote PD-L1 upregulation on MM cell surface, which both inhibits T cell-mediated anti-MM immunity (94) and promotes MM cell survival by inducing reverse signaling to MM cells and activating the PI3K/AKT pathway (94). Although preclinical data have demonstrated the potential utility of PD-1/PD-L1 blockade in MM therapy, early clinical trials have been discouraging (95). Pembrolizumab immunotherapy did not show any activity in MM (96), and its combination with IMiDs, lenalidomide, or pomalidomide in RRMM patients was associated with immune-related toxicities and mortality in two phase III studies (KEYNOTE-183 and KEYNOTE-185), leading to a FDA clinical hold (24, 97). The precise mechanisms that lead to immune-related toxicities are still unknown (98); however, immune checkpoints are regulators of immunological homeostasis, and their functional disruption may unbalance immune tolerance that can lead to uncontrolled immune response (98, 99). Clinically, patients experience autoimmune-like/inflammatory reactions that can cause organ and tissue damages (98, 99). Although the mechanisms underlying the severity of such adverse events in some patients is yet to be elucidated, some reports suggest an association with underlying germline genetic factors or patient microbiota (98, 100). To date, the mechanisms underlying higher toxicity observed in MM patients as compared to other tumors are unknown. Pembrolizumab and nivolumab monotherapy in RRMM patients displayed similar safety profile as in other cancers (99); however, combination of pembrolizumab with IMiDs resulted in higher toxicity, with severe and unanticipated adverse events (99). Future analysis of combinations with other agents, patient selection, and timing of treatment initiation may allow for optimal therapeutical application of PD-1/PD-L1 axis blockade in MM. Recent studies suggest the potential role of other immune checkpoint or agonist proteins (i.e. LAG 3 or TIGIT and OX40, respectively) as MM therapeutic targets, alone and in combination with MM targeted and immune therapies (101). These novel studies, along with the identification of patients who may most benefit of immune checkpoint therapy, may allow for their future clinical use.

Vaccine Strategies

Antigen-specific anti-tumor immunity can be primed by vaccination through several strategies including tumor cell-based vaccines (autologous or allogeneic), dendritic cell (DC)-based vaccines, protein/peptide-based vaccines, and genetic vaccines (DNA vaccines, RNA vaccine, viral based-vaccines) (102, 103). Among them, tumor cell-, protein/peptide-, and DC-based vaccines have been explored, although the main challenge to their efficacy has been represented by hallmark immunosuppression in MM (104, 105). GVAX (Aduro Biotech) is a vaccine platform that uses tumor cells which are genetically engineered to produce granulocyte-macrophage colony-stimulating factor GM-CSF (106), which can recruit and activate DCs and other APCs (107). This vaccine is now being tested in combination with lenalidomide in patients with CR and near CR (NCT03376477). Several antigens that are broadly expressed in MM cells, such as MAGE-A3, WT-1, SLAMF7, CD138, and XBP-1 have been examined alone or in combination in the context of peptide/protein-based vaccines (108–110). Although the clinical efficacy seems modest, new approaches using a multipeptide-based vaccine induced an effective and durable memory multipeptide-specific cytotoxic T lymphocytes response in patients with SMM, suggesting its potential utility to delay disease progression (111). Similarly, a novel engineered heteroclitic BCMA peptide can induce BCMA-specific memory immunity, providing the rationale for its clinical evaluation (112). Additionally, previous reports have also explored the idiotype (Id) vaccination in which early-stage MM patients are immunized with autologous tumor-derived clone-specific immunoglobulin, both as a peptide vaccine and a DNA vaccine (113–115). Id specific immunological responses were reported, although clinical responses were infrequent.

DC-based vaccines are also under investigation in MM. Two approaches can be used to augment presentation of tumor antigens in DC: to chemically fuse patient DCs with autologous MM cells (MM cells/DCs fusion vaccine); or to load DCs with tumor antigens in the form of peptides, proteins, tumor lysates, and mRNAs (106, 116). In the first phase I clinical trial, 16 patients were treated with MM cell/DC fusion vaccine with GM-CSF as an adjuvant. The majority of patients (11 of 15) showed disease stabilization, associated with expansion of circulating CD4+ and CD8+ lymphocytes reactive against autologous MM cells (116). In the phase II trial, patients received vaccination post-ASCT. In this setting, vaccination induced effective anti-MM immunity and increases the depth of response, with 78% of the patients showing CR/VGPR (117). Moreover, 24% patients converted from PR to CR/near CR after vaccination at more than 3 months post-ASCT, suggesting a vaccine-mediated effect targeting residual disease (117). To confirm these results, phase II trial in the same setting (NCT02728102) is ongoing. Another DC-based vaccine approach in which Langerhans-type DCs (LCs) are electroporated with mRNAs encoding MM antigens CT7, MAGE-A3, and WT-1 is now being evaluated in the post-ASCT setting in phase I clinical trial (NCT01995708). This trial is based on preclinical data showing that LCs induce a more potent T cell response than monocyte-derived DCs, and that the electroporation of mRNA stimulates their maturation and activation (118, 119).

Of note, due to the lack of an optimal response after vaccination in MM patients to date, an ongoing trial (NCT02728102) is exploring whether combination with IMiDs may increase a clinically significant immune response.

Immunologic Effects of Anti-MM Agents

Several studies have focused on the effects of anti-MM agents on cellular and non-cellular components of the bone marrow microenvironment, including immune cells. Immunomodulatory agents (IMiDs) thalidomide and its more potent derivatives lenalidomide and pomalidomide represent the best example of drugs with both direct cytotoxic activity on MM cells and immunomodulatory effects (24). Thalidomide is approved to treat

both NDMM and RRMM in combination with bortezomib and dexamethasone (VTd), and the recent phase III CASSIOPEIA study granted its FDA approval in combination with daratumumab (D-VTd) in NDMM (46). However, occurrence of peripheral neuropathy and introduction of lenalidomide and pomalidomide in the MM armamentarium, has progressively decreased its clinical use. Lenalidomide is used in combination with bortezomib and dexamethasone (RVd) to treat transplant-eligible NDMM (120, 121); a dose modification (RVd-lite) has also shown a favorable therapeutic index in transplant-ineligible NDMM patients (121, 122). Lenalidomide is also FDA approved post-ASCT as maintenance therapy as it prolongs both PFS and OS (123); in RRMM setting, it is FDA approved in combination with daratumumab (41), elotuzumab (31), ixazomib (124), and carfilzomib (125). Pomalidomide is FDA approved to treat RRMM patients in combination with dexamethasone along with elotuzumab, bortezomib, daratumumab, and isatuximab (32, 44, 126), and its role in this setting has become more evident due to the broad use of lenalidomide in both NDMM and in maintenance and the development of lenalidomide resistance leading to relapse. Elegant mechanistic studies identified cereblon (CRBN) as a major target for IMiDs in MM cells, and showed that they induce growth arrest and caspase-8–mediated apoptosis, associated with CRBN-dependent degradation of Ikaros (IKZF1) and aiolos (IKZF3) transcription factors, followed by IRF4 downregulation (24, 127, 128). IMiDs treatment impacts the MM cell/microenvironment interaction by decreasing cell surface expression of adhesion molecules, modulating cytokine and growth factor secretion, and inhibiting angiogenesis (24). Immunomodulatory effects include activation of cytotoxic CD8+ T, NK, and NKT cells, along with a decrease of Treg (24). CRBN targeting is also responsible for the immune effects of IMiDs, as degradation of IKZF1/3 in T cells increases IL-2 secretion (129) and NK and NKT cell cytotoxicity (24). More recently, it has been shown that IMiDs can enhance NK and T cell cytotoxicity by triggering granzyme-B *via* either CRBN or ZAP-70 dependent mechanisms, thus providing the rationale for novel therapeutics to activate ZAP-70 in MM (130). Recent studies are also suggesting different mechanisms of action between pomalidomide and lenalidomide *in vivo*, consistent with clinical responses observed in patients with lenalidomide RRMM (131, 132).

Importantly, the identification of the mechanism of action of IMiDs has informed the development of a new class of drugs, CELMoD agents which are higher affinity CRBN E3-ligase modulators (24). Among them, Iberdomide and CC-92480 have shown significant preclinical activity and are currently under investigation in the RRMM clinical setting (133, 134).

Proteasome Inhibitors (PI) bortezomib, carfilzomib, and ixazomib represent the backbone of MM therapy in both NDMM and RRMM. MM cells are highly dependent on proteasome activity due to their high turnover of abnormal immunoglobulins (24, 135). Although PIs exert a primarily cytotoxic effect on MM cells, the biological outcome of proteasome inhibition also targets the MM microenvironment. PI treatment can disrupt MM cell/bone marrow cell adhesion by decreasing the expression of adhesion molecules, inhibit angiogenesis by modulating secretion of several cytokines,

and modify osteoclast activity and bone turnover (136). However, the effect of this class of agents on the immune cells is still largely unknown, with preclinical data suggesting an immunosuppressive role (137). Interestingly, a more recent elegant study has instead shown an immunogenic potential role of bortezomib in eliciting an anti-MM immune response *in vitro* (138). Moreover, our recent studies using both syngeneic *in vivo* MM model and MM patient samples show that bortezomib treatment triggers immunogenic MM cell death, which in turn primes an effective anti-MM immune response *in vivo* models and in patients (*Gulla et al., ASH 2019*). A deep understanding of the immunomodulatory role of PIs will be instrumental to inform their clinical use in combination with immune therapies.

As shown in several types of cancers, histone deacetylase (HDAC) inhibitors are powerful epigenetic regulators with a wide range of effects, including immune modulation (139). For example, recent evidence has shown that an HDAC6 specific inhibitor ACY241 exerts its anti-MM activity, at least in part, by enhancing anti-tumor response of antigen-specific central memory cytotoxic T lymphocytes against MM (140). Future studies will better inform the therapeutic use of HDAC inhibitors as immune regulators in this disease.

DISCUSSIONS

Increasing knowledge of MM pathobiology and immune microenvironment dysfunction, along with the introduction of PIs and IMiDs-based regimens, has already transformed patient outcome in MM patients. The advent of immunotherapy in MM has already shown remarkable effects in terms of extent and frequency of response. Moreover, immune-based approaches, alone and in combination, have the potential to overcome not only immune dysfunction, but also constitutive and ongoing genomic heterogeneity of MM cells, and thereby improve patient long-term control of disease. However, several challenges remain for effective translation of novel immune strategies into clinical practice, as well as for optimal clinical use of drugs including moAbs that are already incorporated in the treatment regimens (141). Clinical challenges are associated with moAbs use, including infusion reactions, infection risk and blood typing interference that causes positive indirect Coombs test occurring with Daratumumab treatment. Moreover no clear data are available that identify alternative combinations besides their incorporation in triplet regimens, or the characteristic of the patient population in which Daratumumab may be preferably used as single drug (141).

Similarly, resistance to immune approaches hamper their long-term efficacy and may develop due to the loss of target antigen or immune suppression. To address this concern, novel approaches targeting multiple antigens are under investigation (24). Along with loss of surface expression of target protein, antigen in soluble form may potentially interfere with immune-targeted strategies. For example, soluble BCMA, which is cleaved by γ-secretase, inhibits CART cell recognition of surface BCMA (142, 143). High levels of soluble BCMA are present in RRMM, and a clinical trial is testing the combination of anti-BCMA

CAR-T therapy with γ-secretase inhibitor to block BCMA cleavage from the MM cell surface (NCT03502577). Although CAR-T therapies represent a very promising strategy, several challenges intrinsic to the technology may limit their efficacy; and ongoing efforts are optimizing their design to avoid antigen-independent tonic signaling, and to increase their expansion and persistence *in vivo*, by enriching for early memory T cell phenotype and/or intensifying lymphodepletion to promote CAR-T persistence (77). Moreover, the optimal timing for immune intervention during MM the disease course remains undefined. Early immune-based intervention in high-risk SMM patients to avoid development of active MM is promising strategy, but must be balanced against adverse events and therapeutic index. Finally, correlative studies using MM patient samples will delineate mechanisms of action and resistance and thereby inform clinical application of immune therapies in combination with other anti-MM agents. Restoring host anti-MM immunity along with MRD negativity will be required for the long-term control of disease and its potential cure.

AUTHOR CONTRIBUTIONS

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