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Review

Current trends in immunotherapy for multiple myeloma

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ABSTRACT

Multiple myeloma is characterized by severe immune dysfunction related to the malignant plasma cells and the bone marrow microenvironment. With advances in cancer immunology, the landscape of anti-cancer treatment has been revolutionized over the last several years. Several immunotherapy-based strategies have been investigated in myeloma, some showing significant activity, while others are still being studied in earlier phases of clinical trials. Immunotherapeutic modalities being explored in myeloma can be divided into active immunotherapeutic strategies, such as tumor vaccines and checkpoint inhibitors that stimulate the endogenous immune response, and passive approaches such as monoclonal antibodies and adoptive cellular therapy, where *ex vivo*-generated antibodies or activated cells target myeloma. In this review, we will summarize various immunotherapy- based strategies being employed in multiple myeloma to date, with a special focus on treatments with proven efficacy and future promise.

KEYWORDS: multiple myeloma, immunotherapy, monoclonal antibodies, chimeric antigen receptor (CAR) T-cell therapy.

1. Introduction

Multiple myeloma (MM) is a clonal plasma cell neoplasm that starts in the bone marrow [1]. It accounts for approximately 17% of hematologic malignancies, with an estimated 30,770 new cases in the United States in 2018, and 12,770 deaths [2]. MM is a heterogeneous disease, ranging from smoldering asymptomatic disease requiring no treatment to rapidly progressive and refractory disease. The improvement in supportive care and the introduction of several novel agents have increased the median overall survival (OS) over the last two decades from less than 3 years to 7-10 years in the current era [1, 3]. Autologous stem cell transplantation (auto-SCT) remains the standard of care for eligible patients with newly diagnosed myeloma, associated with longer progression-free survival (PFS) and OS compared to conventional chemotherapy alone [4-8]. However, even with all the advances in treatment, MM remains an incurable disease and majority of patients will eventually relapse. Innovative treatment approaches to prolong responses and potentially cure MM remain an unmet need.

Immunotherapy has emerged over the last few years as a promising therapeutic modality for hematologic malignancies, and has been associated with high response rates, which were durable in selected cases [9-15]. Several immunotherapy-based strategies have been investigated in MM, some showing significant activity, while others are still being studied in earlier phases of clinical trials. Immunotherapeutic modalities being explored in MM can be divided into active immunotherapeutic strategies, such as tumor vaccines and checkpoint inhibitors that stimulate the endogenous immune response, and passive approaches such as monoclonal antibodies and adoptive cellular therapy, where

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ex vivo-generated antibodies or activated cells target myeloma. In this review, we will summarize various immunotherapy-based strategies being employed in MM to date, with a special focus on treatments with proven efficacy and future promise.

2. Immune dysfunction in multiple myeloma

MM has been long known to have "immunoparesis" characterized by severe immune dysfunction and impaired immune surveillance, thereby leading to increased susceptibility to infection, second neoplasms, disease progression, and decreased activity of existing therapeutic agents. The dysregulated immune system has been extensively studied and several mechanisms have been identified. The profound immune impairment is thought to be related to a sophisticated interplay between the myeloma cell and the bone marrow milieu [16-18]. This interaction between the tumor cell and the immune-mediated hostile bone marrow microenvironment (MM "niche") mediates the survival of MM cells and disease progression [19, 20].

The bone marrow environment components include hematopoietic and nonhematopoetic cells (e.g stromal cells, osteoclasts, T lymphocytes, dendritic cells), extracellular matrix (ECM), and soluble components (e.g cytokines, adhesion molecules, and growth factors) [21-23]. The dendritic cells (DC) are among the most important antigen presenting cells (APC) that induce tumor-specific killing by processing and presenting an array of antigens to naïve T cells [24]. However, these cells are functionally and quantitatively defective in patients with myeloma [25-27]. Likewise, regulatory T (Treg) cells in myeloma are dysfunctional and unable to regulate T-cell expansion and function [28-30]. Another key effector cells are the natural killer (NK) cells that are both quantitatively and qualitatively deficient in advanced myeloma [31, 32]. With better understanding of the role of MM niche in pathogenesis, remarkable advances in treatments have been achieved over the past several years.

3. Immunotherapy: a historical perspective

Several immune-based approaches have been utilized over the last four decades against myeloma [33]. Although they provided the proof of principle, none of these were adopted as standard of care, either due of lack of activity or due to excessive toxicity. Interferon alpha was among the first immunotherapeutic drugs tested in 1970s. It showed single agent activity with response rates up to 35% in untreated patients, either by itself or when used in combination with other agents [34, 35]. However, its development as a therapeutic agent was hampered by unacceptable toxicity, intolerability, and the emergence of newer, more active and tolerable agents [36].

Allogeneic stem cell transplantation (allo-SCT) is considered the prototype for immunotherapy in hematologic neoplasms, including myeloma. The initial concept of allo-SCT was to deliver myeloablative doses of chemotherapy or radiation to eradicate the underlying malignancy, followed by donor stem cells to rescue hematopoiesis. However, it became clearer with time that the real benefit of allo-SCT stems from graft-versus-tumor (GVT) effect mediated by donor-derived T lymphocytes that results in long-term disease control [37, 38]. Although GVT is associated with decreased relapse rates, it is difficult to separate it from the potentially harmful graft-versus-host disease (GVHD). The most powerful evidence of GVT effect is the re-induction of remission by donor lymphocyte infusion (DLI) in selected patients who relapsed after allo-SCT [37-39].

In MM, allo-SCT has been extensively studied over the last three decades, and is known to induce durable remissions and achieve potential cure for a subset of patients [40]. However, the role of allo-SCT in MM remains controversial due to high treatment-related morbidity and mortality, lack of unequivocal survival benefit compared to auto-SCT, and the availability of several novel and less toxic treatment strategies over the last decade. The GVT effect has a strong correlation with GVHD and a decrease in relapse rates [41-43]. The GVT effect is further supported by the remission induced by DLIs when used for relapsed myeloma after allo-SCT [41, 44, 45]. Despite a lower relapse rate, durable remission, and a plateau in survival curve with allo-SCT using myeloablative conditioning regimens [46-48], the unacceptably high transplant-related mortality, exceeding 50% in some studies [47], has prevented its adoption as standard of care.

To harness the benefit of GVT effect with minimal toxicity, allo-SCT with reduced intensity conditioning (RIC) regimen has been explored. Pre-transplant disease burden and treatment with multiple prior lines of therapy are known poor predictors of allo-SCT outcomes [46, 49]. A sequential approach of auto-SCT for maximum cytoreduction, followed by RIC allo-SCT showed promising results in single arm studies, with high response rates and lower transplant-related mortality [50, 51]. Subsequently, 7 prospective randomized studies were conducted comparing tandem auto-SCT with sequential auto-SCT followed by allo-SCT [43, 52-58]. There have been conflicting results from these studies with 3 studies demonstrating survival benefit with auto-allo-SCT approach [53, 57, 58]. Differences in outcomes might be explained by heterogeneity in study populations, inclusion criteria, treatment schemas, and follow up duration [57, 59]. Survival benefit in allo-SCT compared to tandem auto-SCT was more notable with a longer follow up [57, 59]. It is noteworthy that most of these studies were conducted before the advent of the novel agents in myeloma, including immunomodulatory drugs and proteasome inhibitors.

Based on these data, allo-SCT is still considered investigational, recommended in the context of a clinical trial for selected high-risk MM patients. However, the immune-based durable responses mediated by GVT provided the framework for developing modern immune and cellular-based therapies.

4. Active immunotherapy

Active immunotherapy relies on triggering an endogenous immune response, utilizing the powerful anti-tumor and memory functions of T lymphocytes [60].

4.1. Vaccines

Based on the principles of anti-microbial vaccines, cancer vaccines have been extensively studied over the last three decades as a treatment modality, albeit with little success. It is hypothesized that cancer vaccines induce endogenous B and T lymphocytes with avidity to tumor antigens to infiltrate the tumor, resulting in tumor lysis and eradication [61, 62]. In MM, these vaccine approaches can be broadly classified into peptide-based and cellular vaccines [63]. The peptide-based approach utilizes the unique peptide antigens expressed on the myeloma cell to activate T lymphocytes and harness their cytotoxicity. Several myeloma-associated antigens have been studied as potential vaccines, including the idiotype, MAGE, WT1, hTERT, NY-ESO, MUC1, XBP-1 and several others [63, 64]. The idiotype is derived from the variable region of the clonal immunoglobulin and is among the first tumor-associated antigens (TAA) to be tested as a vaccine [65]. Despite its encouraging preclinical activity, the initial clinical results were disappointing. That was attributed to both the downregulation of idiotype expression, and an inherently weak immunogenicity of the idiotype [63, 66, 67]. To improve their immunogenicity, idiotype vaccines were used with adjuvant cytokines, such as GM-CSF, or were pulsed into APCs. Using idiotype-pulsed APCs after auto-SCT, Lacy *et al*. reported significant improvement in median OS in 27 vaccinated patients (5.3 years) compared to 124 unvaccinated patients (3.4 years) [68]. Likewise, idiotype vaccines in combination with GM-CSF demonstrated improved T cell function [69]. Several other TAAs have also been explored in both preclinical and clinical studies, some of which, including cancer-testis antigens, showed promising early activity [70, 71]. Overall, the results of peptide-based vaccines have been disappointing in MM.

DC-based approaches have been tested to improve the immunogenicity of these vaccines. The DCs are the most important APCs that play a critical role in processing and presenting antigens to naïve T cells, thereby triggering an anti-tumor immune response [24]. Autologous DCs in myeloma patients are both quantitatively and qualitatively impaired, thus contributing to immunological escape [25-27]. Encouraging early results were reported with a fusion vaccine, where autologous DCs were fused with patient's own myeloma cells [64]. Based on the promising results in a phase I clinical trial, [72] the DC-myeloma fusion vaccine was tested in a phase II clinical trial in the setting of an auto-SCT, which enrolled 36 patients [73]. The DC fusion vaccine showed a robust myeloma-specific T cell (CD4 and CD8) expansion, and

an expansion in the T cells targeting the myeloma-specific antigen, MUC1 [73]. Additionally, significant clinical activity was noted with an upgrade of clinical response from partial remission to near complete/complete remission in 24% of patients [73]. Similar results were reported by Jung *et al.* in a phase I study using DCs loaded with dying myeloma cells. They reported 78% myeloma-specific immunological response in patients with relapsed/refractory myeloma, with 67% of patients achieving disease stabilization [74]. The post auto-SCT randomized phase II Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1401 clinical trial of lenalidomide maintenance with or without DC-myeloma cell fusion vaccine is still accruing, and the results are eagerly awaited (NCT02728102).

4.2. Checkpoint inhibitors

Checkpoint receptors are co-inhibitory molecules that play an essential role in regulating autoimmunity and T cell responses, and are an important component of a functioning immune system [75, 76]. These immune checkpoints are postulated to play an important role in blunting immune surveillance against cancers [75]. It was proposed that the inhibition of these checkpoint receptors, or their ligands, would unleash the immune system, specifically the T lymphocytes, against cancer. Cytotoxic T lymphocyte-associated protein 4 (CTLA-4) receptor was the first immune checkpoint to be discovered by Brunet *et al.* [77]. Ipilimumab, an anti-CTLA-4 monoclonal antibody, was the first checkpoint inhibitor tested in clinical trials with encouraging anti-tumor activity [78, 79], and was the first checkpoint inhibitor to obtain US Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma [78, 79]. The checkpoint inhibitors have since showed unprecedented activity in a variety of cancers and have revolutionized the landscape of anti-cancer therapy [75, 76]. Preliminary studies with ipilimumab as a single-agent in myeloma have not been very encouraging [80]. However, it is currently being explored in combination with other active anti-myeloma agents [81].

Programmed cell death 1 (PD-1) is a transmembrane protein that belongs to the CD28 family of receptors which is expressed on antigen-activated T cells, B cells, and NK cells [82-84]. It is the interaction between PD-1 and its ligands, PD-L1 and PD-L2, that leads to inhibition of T-cell proliferation and tumor cell apoptosis, reduced cytokine release, and an increase in Treg cells [85-87]. PD-L2 is restricted to hematopoietic cells, but PD-L1 is widely expressed on non-hematopoietic cells, including various cancer types, and has been associated with poor prognosis [88-90]. While normal plasma cells lack PD-L1 expression [91], several studies confirmed PD-L1 overexpression on clonal plasma cells, which is most pronounced in relapsed/refractory myeloma [84, 92, 93]. PD-L1 is also overexpressed in the bone marrow plasmacytoid DCs in myeloma patients [94]. Preclinical and early phase clinical trials demonstrated that the blockade of the PD-1:PD-L1 pathway enhances T cell and NK cell cytotoxic activity in myeloma and reverses tumor immune escape mechanisms [84, 94-99].

PD-1 inhibitors have shown limited single agent activity in myeloma. Nivolumab, an anti-PD-1 monoclonal antibody, was tested as a single agent in a dose-escalation phase I study in 27 patients with relapsed/refractory MM. There were no objective responses, although 63% of treated patients had stable disease for a median of 11.4 weeks [100]. To improve its efficacy, nivolumab is currently under investigation in phase I-III trials combined with other active anti-myeloma agents, including elotuzumab, pomalidomide, dexamethasone, and daratumumab. Pembrolizumab, a humanized IgG4 anti-PD-1 monoclonal antibody, has demonstrated promising activity and acceptable safety, when combined with lenalidomide and dexamethasone in a phase I study of 51 heavily pretreated myeloma patients [101]. That trial reported a 50% overall response rate (ORR) and 98% disease control rate in the 40 patients evaluable for efficacy. Responses were also noted in lenalidomide-refractory patients [101]. Pembrolizumab was combined with pomalidomide/dexamethasone in another phase II trial, which enrolled 48 heavily pretreated myeloma patients [102]. This trial reported ORR of 60%, and a median PFS of 17 months. The responses were seen in most patient subgroups, including lenalidomide-refractory patients. However, a higher-than expected rate of infection and autoimmunity was noted in the

treated patients [102]. The encouraging results of these phase II trials led to a phase III randomized clinical trial combining pomalidomide/ dexamethasone with or without pembrolizumab in relapsed/refractory myeloma (NCT02576977). However, in June 2017 an interim data review showed higher death rate in the pembrolizumab arm. This finding resulted in an immediate hold by the FDA on all clinical trials combining checkpoint inhibitors with immunomodulatory drugs, such as lenalidomide or pomalidomide, in multiple myeloma. The cause of higher death rate is still not being determined, and the data are being vigorously analyzed to understand its mechanism. The partial clinical hold was recently lifted by the FDA for 3 ongoing clinical trials that are evaluating nivolumab-based combinations in relapsed/refractory myeloma.

5. Passive immunotherapy

This approach relies on *ex vivo* generation of immunotherapeutic agents, including monoclonal antibodies and adoptive cell therapy.

5.1. Monoclonal antibodies

The development of monoclonal antibodies is considered a major scientific advancement, the culmination of decades of preclinical and clinical research in pursuit of what was described as a "magic bullet" by Paul Ehrlich in the 19th century [103]. Several monoclonal antibodies have been approved and increasingly used in both hematologic and solid malignancies. Their specificity against TAAs allows better safety and tolerability compared to conventional chemotherapy agents [84, 104]. Monoclonal antibodies are most effective when target antigens are highly expressed on tumor cells, with minimal to no expression on normal tissues, and minimal levels of soluble antigens in the circulation, which interfere with their binding to tumor antigens [104, 105]. Monoclonal antibody-induced cytotoxicity stems from several mechanisms: a) direct binding to TAAs with induction of apoptosis; b) complement-dependent cytotoxicity (CDC); c) antibody-dependent cellular cytotoxicity (ADCC), the latter two being mediated through Fc fragment of the antibody binding to either the complement or an immune effector cell, such as NK cell; and d) antibody-mediated effects on tumor microenvironment [104, 105].

Several potential TAAs have been identified in MM that may serve as targets for monoclonal antibodies. These antigens include, among others, CD20, CD38, CD40, CD56, CD74, interleukin-6 (IL-6), vascular endothelial growth factor-A (VEGF-A), epidermal growth factor receptor (EGFR), insulin-like growth factor-1 receptor (IGFR1), PD-1, B-cell activating factor (BAFF), and signaling lymphocytic activation molecule F7 (SLAMF7) [106, 107]. However, only a handful monoclonal antibodies have shown meaningful clinical activity [33, 99, 107, 108]. The first two monoclonal antibodies, elotuzumab and daratumumab, were approved by the FDA in 2015 for the treatment of relapsed or refractory MM [109, 110]. This review will highlight these two FDA-approved agents (Table 1).

5.1.1. Elotuzumab

Elotuzumab, a humanized IgG1 monoclonal antibody, targets SLAMF7, also known as CS1, a glycoprotein which is highly expressed on both normal and malignant plasma cells, on NK cells and T cells, but with minimal to no expression on other normal tissues [111-113]. Preclinical studies showed that elotuzumab inhibits MM cell adhesion to bone marrow stromal cells and induces ADCC-mediated tumor killing [111, 112]. Other potential anti-MM effects are mediated by binding of elotuzumab to CS1 expressed on NK cells [113]. Pre-clinical studies have also shown synergy between elotuzumab and other anti-myeloma agents, partly through NK cell activation [113-115]. Initial studies showed the safety and tolerability of single agent elotuzumab in relapsed/refractory myeloma, but limited efficacy [116]. In contrast, elotuzumab showed encouraging efficacy when combined with lenalidomide and dexamethasone, with an objective response rate of 82% in a phase II trial [117]. Interestingly, in the dose extension phase of this trial, elotuzumab at 10 mg/kg dose showed a higher response rate and longer PFS, compared to 20 mg/kg dose [118, 81, 119]. Subsequently, a phase III randomized trial (ELOQUENT-2) was conducted, leading to the FDA approval of elotuzumab in combination with lenalidomide and dexamethasone in November 2015 for patients with relapsed or refractory MM, who had received 1-3 previous lines of treatment. In this trial, elotuzumab/lenalidomide/

Table 1. Phase 3 randomized clinical trials for approved monoclonal antibodies in multiple myeloma.

	ELOQUENT-2 [120]	**POLLUX** [143]	**CASTOR** [144]	**ALCYONE** [147]
Combination treatment	Elotuzumab Lenalidomide Dexamethasone	Daratumumab Lenalidomide Dexamethasone	Daratumumab Bortezomib Dexamethasone	Daratumumab Bortezomib Melphalan Prednisone
Number of patients	321	286	251*	350
Median age in years	67 (37-88)	65 (34-89)	64 (30-88)	71 (40-93)
Median lines of treatment	2	1	2	Not applicable
Median follow-up in months	32.4	13.5	7.4	16.5
Response				
ORR	79%	93%	83%	91%
Median PFS in months	19.4	Not reached	Not reached	Not reached
Median OS in months	43.7	Not reached	Not reached	Not reached

Abbreviations: ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
*Evaluable for response: n = 240.

dexamethasone when compared to lenalidomide/ dexamethasone, showed a higher ORR (79% vs 66%) and a longer median PFS (19.4 months vs 14.9 months) [120]. Furthermore, these favorable outcomes for elotuzumab/lenalidomide/ dexamethasone were seen across the board, including in patients with high-risk cytogenetic abnormalities [120]. However, the majority of patients had no prior exposure to lenalidomide [120]. The updated results of ELOQUENT-2 with an extended 3-year follow up were recently published, which not only confirmed the original benefit in ORR and PFS, but also showed a trend towards improved OS in the elotuzumab group [121].

Elotuzumab has also been evaluated in combination with bortezomib in several clinical trials [122, 123]. The initial phase I study showed an ORR of 48% for elotuzumab and bortezomib combination [122]. When elotuzumab/bortezomib/dexamethasone was compared to bortezomib/dexamethasone in a phase II randomized trial, there were similar response rates (66 % vs 63 %, respectively), but a modest improvement in median PFS (9.7 months vs 6.9 months) with the 3-drug regimen with no significant added toxicity [123]. Elotuzumab is safe to use in patients with renal impairment [124], which makes elotuzumab + bortezomib-based regimen an attractive option in this high-risk population.

More recently, in a phase II randomized trial (ELOQUENT-3), elotuzumab/pomalidomide/ dexamethasone was compared to pomalidomide/ dexamethasone in patients with relapsed or refractory MM [125]. The primary endpoint was PFS. The elotuzumab-based regimen showed a significant improvement in ORR (53% vs. 26%), and a significant improvement in the median PFS (10.3 vs. 4.7 months, hazard ratio 0.54) [125], with no significant differences in toxicity between the two arms.

5.1.2. Daratumumab

Daratumumab is another first-in-class humanized IgG1κ monoclonal antibody that targets CD38 glycoprotein. The CD38 epitope is a type II transmembrane glycoprotein that is uniformly and highly expressed on myeloma cells, to a lesser extent on normal lymphoid and myeloid cells, and in some non-hematopoietic cells [126-128]. Multiple mechanisms of action have been postulated for its anti-myeloma activity. These include induction of

apoptosis, ADCC, CDC, and antibody-dependent cellular phagocytosis (ADCP), among others [129-132]. It is to be noted as well that daratumumab may interfere with ectoenzymes which lead to activation of a subset of regulatory CD38-positive cells (Tregs) and cause cell-mediated tumor lysis [133-135].

Daratumumab was the first monoclonal antibody to show significant single-agent activity in heavily pretreated, relapsed/refractory myeloma in the phase II SIRIUS trial [136]. With an ORR of 29%, median duration of response of 7.4 months, and adequate safety, it was granted FDA approval for relapsed/refractory myeloma patients who had received 3 or more prior lines of treatment [136]. Preclinical and early phase clinical studies showed excellent synergy between daratumumab and other anti-myeloma agents, including dexamethasone, lenalidomide, bortezomib, and pomalidomide [137-142]. This paved the way for several clinical trials using daratumumab-based combination regimens. In the MMY3003 study (POLLUX), daratumumab/lenalidomide/ dexamethasone was compared to lenalidomide/ dexamethasone in a randomized phase III trial. In this trial, daratumumab-based combination showed an ORR of 93% compared to 76% in the control group, with a 63% reduction in the risk of progression [143]. Somewhat similar results were noted in the MMY3004 study (CASTOR) trial, where daratumumab/bortezomib/dexamethasone was compared to bortezomib/dexamethasone. In this trial, daratumumab-based combination showed an ORR of 83% versus 63% in the control group, and a 61% reduction in the risk of progression [144]. In the EQUULEUS, MMY1001 trial, dartumumab was combined with pomalidomide/ dexamethasone for patients with relapsed/refractory myeloma who had received at least 2 prior lines of therapy, including a proteasome inhibitor and lenalidomide [145]. The study showed an ORR of 60% and a median PFS of 8.8 months with the daratumumab triplet [145]. Except for an increased risk of infusion reactions and cytopenias, safety profile was overall comparable to control arms in these studies. [146] In the first major trial in the frontline setting, daratumumab combined with bortezomib/melphalan/prednisone was compared to bortezomib/melphalan/prednisone in transplant-ineligible patients. In this phase III ALCYONE trial, daratumumab-based regimen showed an ORR of 91% compared to 74% in the control group, with higher complete response rates (43% vs 24%) and 18-month PFS estimates (72% vs 50%) [147]. Although serious adverse effects, mainly infections and infusion reactions, were more common in the daratumumab group, the rate of discontinuation of the assigned treatment due to adverse effects was lower in the daratumumab group [147].

In addition to daratumumab, two other anti-CD38 monoclonal antibodies (MOR202 and isatuximab) have shown promising activity in early phase clinical trials [148, 149]. However, more data are awaited before they become a part of standard therapeutic strategy against MM.

5.2. Adoptive cellular therapies

5.2.1. Chimeric antigen receptor (CAR) T-cell

CAR T-cells are genetically engineered T lymphocytes with antigen-binding domain derived from a B lymphocyte, and signaling and co-stimulatory domains from the T lymphocytes, hence chimeric. The antigen-recognition domain is a single-chain variable fragment (scFCv) derived from monoclonal antibodies [150]. CD3Zeta molecule is the most commonly used T-cell signaling domain, and CD28 and 4-1BB are the commonly used co-stimulatory domains [150]. Binding to a tumor antigen activates the T lymphocyte, which kills tumor cells by direct cytotoxicity as well as by the release of cytokines. This is a rapidly evolving area with three generations of CAR T-cells being tested in preclinical and clinical studies. The first-generation CAR T-cells did not use co-stimulatory molecules, which resulted in a limited clinical activity. The incorporation of co-stimulatory molecules, such as CD28 and 4-1BB, in the construct improved the expansion and persistence of CAR T-cells *in vivo*, which translated into a robust clinical activity [38, 151-153]. Most of the current clinical trials, including for MM, are using second-generation CAR T-cells [38, 81]. These engineered T-cells are designed to target selective tumor-associated surface antigens with high affinity and specificity. For effective and safe CAR T-cell therapy, it is critical that the target antigens are mainly expressed on tumor cells, with minimal to no expression on normal tissues [38, 150].

Table 2. Myeloma CAR T-cell clinical trials with published outcomes.

	Anti-CD19 CAR T-cell	**Anti-CD138 CAR T-cell**	**Anti-Kappa CAR T-cell**	**Anti-BCMA CAR T-cell**				
Study reference	[158]	[159]	[160]	[161]	[162]	[163]	[164]	[165]
Number of patients	10	5	8	12	21**	21[#]	19	16†
Median age in years	61 (48-68)	57 (48-68)	57 (43-69)	Not published	58 (37-74)	57 (44-73)	Not published	Not published
Median lines of treatment	6	8	4	7	7	7	Not published	9.5
Intracellular domain	4-1BB; ICD-CD3zeta	CD28; ICD-CD3zeta	CD28; ICD-CD3zeta	CD28; ICD-CD3zeta	4-1BB; ICD-CD3zeta	4-1BB; ICD-CD3zeta	Not published	CD28; ICD-CD3zeta
Conditioning (Yes/No)	Yes	Yes	Yes	Yes	Yes	Yes[$]	Not published	Yes
Response	ORR 8/10 (80%); 6 VGPR; 2 PR; 2 PD	4 SD; 1 PD	5 SD; 3 NR	ORR 4/12 (33%); 1 sCR; 2 VGPR; 1 PR; 8 SD	ORR 16/18 (89%); 5 PR; 4 sCR/CR; 7 VGPR; 1 SD; 1 PD	ORR 13/20 (65%); 2 sCR/CR; 2 VGPR; 5 PR; 4 MR	ORR 19/19 (100%); 14 sCR; 4 VGPR; 1 PR	ORR 13/16 (65%); 2 sCR/CR; 8 VGPR; 3 PR
Cytokine release syndrome	Only 1 patient (10%) with grade 1	Not reported*	None	Total 6/12 (50%); 3 (25%) G1-2 and 3 (25%) G3-4	Total 15/21 (71%); 13 (62%) G1-2 and 2 (10%) G3-4	Total 17/21 (81%); 11 (52%) G1-2 and 6 (29%) G3-4	Total 14/19 (74%); 12 (63%) G1-2 and 2 (11%) G3-4	Total 15/16 (94%); 9 (56%) G1-2 and 6 (38%) G3-4
Neurotoxicity	None	None	None	G3-4 in 1 patient with delirium; G1-2 in 1 patient with delirium; G1-2 in 1 patient with headache	G1-2 not reported; No G3-4 toxicities	G1-2 in 1 patient with confusion/ aphasia; G3-4 in 2 patients with encephalopathy	Not published	G1-2 not reported; G3-4 in 3 patients with delirium/ confusion‡

Table 2 continued..

Abbreviations: CR, complete response; G, grade; MR, minimal response; PD, progressive disease; PR, partial response; ORR, overall response rate; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

*However, authors reported 4 patients with grade 3 fever.

**Eighteen patients were evaluable for response.

[#]Twenty patients were evaluable for response.

[$]The first 9 patients enrolled in first cohort didn't receive conditioning chemotherapy.

†Two of the 16 patients were also included in the study by Ali *et al*.

‡One patient of which had encephalopathy with polyneuropathy/polymyopathy.

After the demonstration of unprecedented clinical activity of anti-CD19 CAR T-cells in acute lymphoblastic leukemia and B-cell lymphoma [154-156], there is great interest in developing effective CAR T-cells for myeloma and other malignancies. A number of myeloma-associated antigens, such as CD19, CD38, CD56, CD138, immunoglobulin kappa light chains, and BCMA, have been identified [150]. Table 2 summarizes key efficacy and toxicity data from published CAR T-cell clinical trials in myeloma. With the hypothesis that CD19 might be expressed in precursor myeloma stem cells, anti-CD19 CAR T-cells were among the first to be tested in MM. Despite encouraging initial activity, limited efficacy was seen after treating a larger number of patients and a longer follow up [157, 158]. Similarly, modest clinical activity was noted with anti-CD138 and anti-kappa light chain CAR T-cells [159, 160]. The anti-BCMA CAR T-cell therapy has been the most promising so far. The key outcome measures from recent clinical trials with anti-BCMA CAR T-cells are summarized in Table 2. These trials have reported an ORR ranging from 33% to 100% in heavily pretreated patients, with a significant correlation between the infused CAR T-cell dose and the depth of response [161-165]. Cytokine release syndrome was common across anti-BCMA CAR T-cell studies [161-165], but the incidence of neurotoxicity was lower compared to anti-CD19 CAR T-cell studies [165]. Several clinical trials with anti-myeloma CAR T-cells are ongoing, which will define their role in the treatment of MM [166].

6. Conclusions

MM is characterized by severe immune dysfunction related to the malignant plasma cells and the bone marrow microenvironment. With advances in cancer immunology, the landscape of anti-cancer treatment has been revolutionized over the last several years with the availability of several immunotherapeutic agents. In myeloma, monoclonal antibody-based regimens using daratumumab and elotuzumab have become standard of care for relapsed/refractory patients, and are moving to the frontline line setting. DC vaccines and checkpoint inhibitors showed significant activity in early phase clinical trials, but results from large randomized studies are awaited to better define their role. More recently, CAR T-cell has emerged as one of the most promising immunotherapeutic modalities in myeloma, associated with high response rates in heavily pretreated patients. Overall, these immune-based approaches are expected to transform the treatment of multiple myeloma in the coming years.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing financial interests.

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