Immunotherapy in multiple myeloma

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Abstract: Therapeutic approaches in multiple myeloma (MM) are increasingly focused on restoring antitumor immunity. Immunomodulators have a variety of effects on the immune microenvironment, and are frequently incorporated into multidrug regimens. The monoclonal antibodies daratumumab and elotuzumab have been granted accelerated approval for use in the relapsed or refractory setting, and several other antibodies including immune checkpoint inhibitors are currently being evaluated for the treatment of MM. Antimyeloma vaccines have been developed, and may be useful in maintaining remission. The role of allogeneic stem cell transplantation continues to be an area of active research, as reduced intensity conditioning (RIC) regimens have significantly decreased treatment-related complications. Other immunotherapeutic approaches in development include marrow infiltrating lymphocytes, T cell receptor modified T cells (TCRts), and chimeric antigen receptor (CAR) T cells. Here we review the existing data on immunotherapy in MM, and discuss some promising areas of research which may impact the future of myeloma therapy.

Keywords: Antibodies; monoclonal; immunotherapy; multiple myeloma (MM); receptors; antigen; T-cell; stem cell transplantation

Introduction

Immune dysregulation has a powerful role in the pathogenesis of multiple myeloma (MM). A multitude of abnormalities in the immune microenvironment have been implicated, including an excess of inflammatory cytokines, imbalance of regulatory T cells and T helper cells, impaired differentiation of natural killer (NK) cells, dendritic cell dysfunction, and expansion of myeloid-derived suppressor cells (1). Novel therapies are focused on activating the immune response against myeloma cells and overcoming the tumor's immune escape mechanisms. In this review, we discuss the immunotherapies which have been recently approved for the management of MM, as well as some promising therapeutic approaches in the earlier phases of clinical development.

Immunomodulatory drugs (IMiDs)

IMiDs such as thalidomide, lenalidomide, and pomalidomide, are frequently integrated into multidrug regimens for MM. In addition to their direct antimyeloma effect, IMiDs have several proposed mechanisms, including modulation of cytokine signaling, inhibition of angiogenesis, inhibition of regulatory T cell proliferation, and augmentation of cytotoxic T lymphocyte and NK cell activity (2,3). IMiDs also interact with cereblon, resulting in cereblon-dependent destruction of Ikaros proteins, which function as B-cell transcription factors (4,5). Cereblon-binding protein levels after IMiD therapy have shown correlation with clinical outcomes (6). IMiDs significantly improve response rates when combined with other myeloma immunotherapies, and in some cases evoke response to

antibodies that have little or no single-agent activity (7,8).

Monoclonal antibodies

Antibodies targeting surface molecules

Daratumumab was the first monoclonal antibody approved by the United States Food and Drug Administration (FDA) in 2015 for relapsed or refractory multiple myeloma (RRMM). Daratumumab targets CD38, a transmembrane receptor glycoprotein highly expressed on malignant plasma cells. Several mechanisms of antimyeloma activity have been described, including promotion of complement-mediated and cell-mediated cytotoxicity, macrophage-mediated phagocytosis, direct apoptosis, and depletion of CD38 positive immune-regulatory cells (9,10).

In a phase I/II study of single agent daratumumab in a heavily pretreated population, no maximum tolerated dose was identified. Overall response rate (ORR) was 36% among patients receiving daratumumab 16 mg/kg dosed weekly for 8 doses, biweekly for the next 8 doses, then monthly for up to 24 months. The majority of responders remained progression-free at 12 months (11). Another phase II multicenter trial of single agent daratumumab in patients with a median of five prior lines of therapy showed comparable results: ORR was 29%, with 2.8% stringent complete responses, 9.4% very good partial responses, and 17% partial responses. Median time to first response was one month, progression free survival was 3.7 months, and median overall survival was 17.5 months. Infusion reactions were common (42%), although mostly grade 1 or 2, and typically occurring only during the first infusion. The most common grade 3 or 4 adverse events were anemia (24%), thrombocytopenia (19%), and neutropenia (12%), however no drug related adverse events resulted in treatment discontinuation (12).

The favorable safety and efficacy data for daratumumab have led to multiple subsequent trials investigating the drug in combination with other therapies. Daratumumab in combination with bortezomib and dexamethasone in RRMM showed an ORR of 83%, compared to 63% with bortezomib and dexamethasone alone. One-year progression free survival (PFS) was 61% in the daratumumab group, versus 27% in the control group. The addition of daratumumab was associated with slightly higher rates of thrombocytopenia and neutropenia (13).

In a phase III randomized trial of 569 patients with RRMM, the combination of daratumumab with lenalidomide and dexamethasone demonstrated an ORR of 93%, compared to 78% with lenalidomide and dexamethasone alone. CR rate was 43% in the daratumumab group, versus 19% in the control group. 22% of patients achieved remission below the threshold for minimal residual disease, compared with 4.6% of those in the control group. PFS at one year was significantly higher in the daratumumab group compared to controls (83% versus 60%). There was a slightly higher rate of neutropenia in the daratumumab group. Of note, patients who were refractory to lenalidomide were excluded from the trial (14). In November 2016, the FDA approved daratumumab for use in combination with bortezomib/dexamethasone or lenalidomide/dexamethasone for patients with MM who have received at least one prior line of therapy.

Other anti-CD38 antibodies currently being investigated include isatuximab and MOR202. Isatuximab in combination with lenalidomide and dexamethasone showed 50% ORR in a heavily pretreated population. Of note, responses were seen even among patients who were previously lenalidomide refractory (15). MOR202 is currently being studied alone or in combination with lenalidomide or pomalidomide, with promising preliminary efficacy data (16).

Elotuzumab was approved by the FDA in 2015 for use in combination with lenalidomide and dexamethasone for the treatment of patients with myeloma who have received one to three prior therapies. Elotuzumab is a monoclonal antibody targeting the signaling lymphocytic activation molecule F7 (SLAMF7), a transmembrane glycoprotein selectively expressed on plasma cell and NK cell membranes, and present on a majority of MM cells. Elotuzumab enhances NK cytotoxicity by upregulating the adaptor protein, Ewing's sarcoma associated transcript 2 (EAT-2), leading to antibody dependent cell-mediated cytotoxicity (17,18).

A phase I single agent dose escalation trial showed no objective responses to elotuzumab in RRMM; stable disease was noted in 26% (19). A phase III trial of elotuzumab with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone showed ORRs of 79% versus 66%, PFS 68% versus 57% at one year, and PFS 41% versus 27% at two years. The benefit of elotuzumab was preserved in patients with high risk features such as t(4:14), del(17p), and +1q21. The most common grade 3 or 4 adverse events were cytopenias, fatigue, and pneumonia (7). In a phase II trial, elotuzumab with bortezomib and dexamethasone showed PFS of 9.9 months compared to 6.8 months with bortezomib

and dexamethasone alone (20). Elotuzumab showed no added toxicity when combined with lenalidomide, bortezomib, and dexamethasone in a 4-drug regimen for newly diagnosed MM; efficacy data are pending (21).

Antibody-drug conjugates

CD138 functions as a growth factor receptor on malignant plasma cells, and represents one of the most specific target antigens for MM therapy. CD138 exists as a membrane-bound protein, but is also converted to soluble forms via proteinase-mediated shedding (22). The presence of soluble CD138 limits the use of free antibody against this target. Indatuximab ravtansine (BT062) is an antibody-drug conjugate comprised of an anti-CD138 antibody fused to the cytotoxic maytansinoid DM4. The drug is stable and non-toxic in circulation, but upon binding to CD138 on the cell surface, it is internalized by the cell leading to cell cycle arrest and apoptosis. Preliminary phase I/II data indicate that indatuximab ravtansine is well tolerated in combination with lenalidomide and dexamethasone, with an overall response rate of 78% in RRMM, including patients previously treated with lenalidomide and bortezomib (23).

Neural cell adhesion molecule (NCAM), also known as CD56, is expressed in NK cells, glia, skeletal muscle, and is found in approximately 75% of MM cells (24). Lorvotuzumab mertansine is a humanized monoclonal antibody to CD56, conjugated to the cytotoxic maytansinoid derivative DM1. In phase I studies, Lorvotuzumab demonstrated a 7% ORR in as a single agent in RRMM (25), and 59% ORR in combination with lenalidomide and dexamethasone (26).

B cell maturation antigen (BCMA) is universally expressed on the surface of myeloma cells. The antibody-drug conjugate J6M0-mcMMAF targeting BCMA has been shown to rapidly eliminate myeloma cells in mouse models (27). A phase I dose-escalation study is currently in progress [National Clinical Trial identifier number (NCT) 02064387] (28).

Checkpoint inhibitors

The interaction of the T cell with its target is regulated by molecular signals that help maintain self-tolerance, however these regulatory checkpoints may also interfere with immune activation against malignancy. Checkpoint inhibitors are monoclonal antibodies that bind to coinhibitory molecules, allowing T cell activation in response to antigens on malignant cells.

In a phase Ib study, the programmed cell death protein 1 (PD-1) inhibitor nivolumab as a single agent showed no objective responses in 27 patients with RRMM, however 63% of patients had stable disease at a median follow up of 66 weeks (29). Several trials using treatment combinations with nivolumab are ongoing (NCT02726581, NCT02903381, NCT01592370).

Pembrolizumab in combination with lenalidomide and dexamethasone in RRMM yielded responses in 20 of 40 patients (50%), including 11 of 29 patients (38%) with lenalidomide-refractory disease. Disease control, defined as stable disease or better, was reported in 39 of 40 patients (98%) (30). Preliminary data for pembrolizumab with pomalidomide and dexamethasone showed a 50% ORR in heavily pretreated RRMM. The most common grade 3 or 4 toxicities were neutropenia, lymphopenia, thrombocytopenia, and infection (31). A phase III randomized controlled trial of pembrolizumab with lenalidomide and dexamethasone in the frontline setting is in progress (NCT02579863) (8).

Overexpression of CTLA-4, a coinhibitory molecule expressed on regulatory T cells, has been demonstrated in the bone marrow of MM patients, making CTLA-4 an attractive target for checkpoint inhibition in these patients (32). A role for anti-CTLA-4 agents in treating MM has not yet been established, but is currently being investigated, with particular interest in combination with PD-1 blockade (NCT01592370, NCT02681302, NCT01822509).

Vaccines

Several antimyeloma vaccines are being evaluated in clinical trials. Idiotype vaccines, derived from the variable region of the patient-specific clonal immunoglobulin, were among the first to be studied in MM (33). While idiotype vaccines have been shown to induce major histocompatibility complex (MHC) restricted T cell responses and reduction in peripheral blood tumor mass, clinical benefit has been difficult to achieve (34,35). Attempts have been made to augment immunogenicity by incubating autologous dendritic cells with the idiotype protein. When patients were vaccinated with the idiotype-pulsed dendritic cell product after autologous stem cell transplant (ASCT), a significant overall survival benefit was reported (5.3 versus 3.4 years), although there was no difference in PFS (36).

A dendritic cell/tumor cell fusion vaccine has been

developed in order to generate antigen presenting cells with a patient-specific repertoire of MM antigens. The administration of the dendritic cell/tumor cell fusion vaccine in the post-ASCT period resulted in expansion of myeloma specific CD4 and CD8 T cells. Late responses were observed several months after ASCT, suggesting a durable vaccine effect (37). A multicenter randomized trial utilizing dendritic cell/tumor cell fusion vaccination is ongoing (NCT02728102).

MAGE-A3, a cancer-testis antigen expressed in MM, inhibits apoptosis of malignant cells, and has been associated with more aggressive disease. A recombinant MAGE-A3 protein has been developed for use as a vaccine. When given prior to ASCT, the MAGE-A3 vaccine has demonstrated acceptable safety and elicits a strong anti-MAGE IgG response (38). In a phase II trial, a MAGE-A3 peptide vaccine was combined with a toll-like-receptor 3 agonist before and after ASCT, followed by infusion of ex-vivo expanded costimulated autologous T cells, resulting in vaccine-specific humoral and CD4 responses in more than 3/4 of patients. Further studies are needed to determine whether MAGE-A3 antibodies have clinical benefit in myeloma (39).

The use of commercially available allogenic MM cell lines to formulate vaccines has several advantages, including the potential to create an unlimited supply of vaccine, and the possibility for use in patients from whom autologous tumor cells cannot be collected (e.g., patients with minimal residual disease). Myeloma GVAX is a granulocyte-macrophage colony stimulating factor (GM-CSF) based vaccine comprised of two allogeneic MM cell lines (H929 and U266) conjugated to a GM-CSF secreting bystander cell line (K562/GM). Among 17 patients in remission who received the myeloma GVAX in conjunction with maintenance lenalidomide, PFS was not reached at 34 months, compared to PFS 18 months among patients who continued on a lenalidomide-containing regimen without receiving the vaccine (40). This study suggests that the immune response evoked by myeloma GVAX may help prolong the duration of remission.

Adoptive T cell therapy

Allogeneic stem cell transplantation

Allogeneic stem cell transplantation as an immunotherapy approach in myeloma remains an area of active research. Myeloablative allogeneic transplantation was associated with a high treatment-related mortality, however subsequent studies using reduced intensity conditioning (RIC) have resulted in more favorable outcomes. In an Italian randomized controlled trial of tandem autologous transplant (tandem auto) versus autologous transplant followed by a RIC allogeneic transplant (auto-allo), treatment-related mortality was similar in both groups. However, disease-related mortality was much higher in the tandem auto group compared to auto-allo group (43% versus 7%, median follow-up 45 months) (41). Another phase III multicenter randomized controlled trial of tandem auto compared to auto-allo transplant with RIC demonstrated no improvement in 3-year PFS or OS with the auto-allo strategy in standard risk myeloma (42). A meta-analysis of similar trials showed a higher CR rate among patients who underwent auto-allo compared to those who underwent tandem auto transplant, however there was no significant difference in PFS or OS (43). With the reduction in transplant-related mortality using a RIC strategy as opposed to myeloablative conditioning, ongoing clinical trials are helping to better define which patients are most likely to benefit from allogeneic transplant, the appropriate timing of allogeneic transplant, and measures to further reduce graft versus host disease while maintaining the graft versus tumor effect (NCT02440464).

Marrow infiltrating lymphocytes

Expansion and reinfusion of marrow-infiltrating T lymphocytes (MILs) may confer antitumor immunity in hematologic malignancies. Since the T cells are obtained from the site of disease, they have enhanced endogenous tumor specificity in marrow-derived malignancies (44,45). Compared to peripheral blood lymphocytes (PBLs), MILs possess greater cytotoxicity and express CXCR4, which promotes trafficking to the bone marrow (45). Unlike PBLs, *ex vivo* expanded MILs do not cause significant lymphocytosis after reinfusion, and therefore do not tend to cause cytokine release syndrome (CRS) (46). In the first clinical trial using MILs in MM, the tumor specificity of the *ex vivo* expanded product correlated with clinical outcomes after MIL reinfusion. Additionally, patients whose pre-expansion MILs had a higher percentage of CD8 memory T cells and lower interferon gamma production were more likely to achieve CR (46). A randomized phase II trial of ASCT with or without MILs in high risk myeloma is currently ongoing (NCT01858558).

T cell receptor modified T cells (TCRts)

TCRts are engineered to recognize targets presented in an HLA-restricted manner. One such target is the NY-ESO-1 antigen, which is expressed in over 60% of high-risk MM (47). Twenty heavily pretreated patients receiving NY-ESO-1 TCRts showed median PFS of 19 months and OS 32 months. NY-ESO-1 TCRts were detected in the blood up to two years after infusion. Patients who relapsed were found to have developed NY-ESO-1 antigen negative clones, indicating the evolution of antigen escape variants (48).

CAR T therapy

CAR T cells are created by transducing autologous T cells, most commonly with a lentivirus, to express chimeric antigen receptors (CARs) that allow the T cells to recognize a specific tumor antigen. The CAR is typically comprised of a single chain variable fragment of a monoclonal antibody fused with a T cell intracellular signaling domain, resulting in MHC-independent tumor recognition, *in vivo* T cell expansion, and memory cell generation.

The most successful so far is the CD19 targeted CAR T, which has produced durable remissions in patients with advanced CLL and ALL (49,50). Malignant plasma cells have very low-level or absent CD19 expression, however the use of CD19 CAR T therapy in MM interestingly demonstrated a dramatic clinical response in one case despite the absence of CD19 expression in 99.95% of the patient's neoplastic plasma cells (51). MM precursors are post-germinal B cells with CD19 expression, which may play a role in the antimyeloma effect of CD19 targeted CAR T (52). This approach is currently being evaluated in a phase II trial (NCT02794246).

BCMA is strongly expressed on malignant plasma cells, and has low-level expression on normal B cells, making it an attractive target for CAR T therapy (53). Dose-dependent response to BCMA-targeted CAR T cells has been demonstrated in advanced MM, although with significant toxicities due to CRS (54). Other CAR T targets under investigation include CD38 (55), CS1 (56), CD138 (57), and kappa light chain (58).

Therapeutic efficacy of CAR T is associated with potentially life-threatening IL-6 mediated CRS, which is related to the overall tumor burden. Manifestations of CRS include fever, hypotension, and pulmonary edema. The interleukin-6 receptor antibody tocilizumab has been implemented in the management of CRS with some

success (59). CD19 targeted CAR T can result in persistent B cell aplasia and hypogammaglobulinemia due to on-target effects on nonmalignant cells. CAR T induced hypogammaglobulinemia is managed with intravenous immunoglobulin (49). Ongoing efforts directed at improving tolerability of CAR T therapy will expand the application of this approach.

Conclusions

Immunotherapy is an integral component of the management of patients with MM. Immunomodulators are currently incorporated into regimens in the frontline and beyond. Monoclonal antibodies have demonstrated remarkable efficacy in the relapsed/refractory setting, leading to accelerated approvals by the FDA for daratumumab and elotuzumab. Further studies will help better define the appropriate sequencing of these agents, including use in the frontline setting. Vaccines may be useful in maintaining remission and prolonging survival. Adoptive T-cell therapy shows very promising antimyeloma activity, however use is currently limited by toxicities. Ongoing research efforts are directed at improving the specificity of targeted agents, managing toxicities, and utilizing novel therapies in strategic combinations to optimize response. We anticipate significant improvement in the long-term outcomes for patients with MM as our treatment approach continues to evolve.

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