The immunotherapy era of myeloma: monoclonal antibodies, vaccines, and adoptive T-cell therapies

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The treatment of multiple myeloma has evolved significantly over the last decades from primarily alkylator-based chemotherapeutic agents with minimal efficacy to the introduction of more effective agents including immune modulators and proteasome inhibitors, which have changed the landscape of therapy for this disease. We are now entering a new era that will increasingly integrate immunotherapy into standard treatment. This review discusses the current immune-based strategies currently approved, as well as various immune approaches being actively investigated including monoclonal antibodies, checkpoint inhibitors, vaccines, and adoptive T-cell therapies.

Introduction

The treatment of multiple myeloma (MM) has evolved significantly over the last decades from alkylating agents and steroids to an increasing compendium of agents that have improved the 5-year overall survival (OS) of patients from 29.7% in 1990% to 45.1% in 2007.1 Some of the hurdles to long-term remissions/cures are a result of the inherent resistance of malignant plasma cells to conventional cancer treatments, as well as the genomic instability2 and immune-deficient state3 that characterize myeloma. The addition of the newer treatment options including proteasome inhibitors (PIs) and immune modulators (IMIDs) such as thalidomide and lenalidomide has improved OS, but again failed to provide a cure for the majority of patients, with >90% still dying of their disease.

Immunotherapy is rapidly establishing itself within the armamentarium of many diseases, from the first monoclocal antibody (mAb), such as rituximab, that revolutionized the treatment of lymphomas to the introduction of checkpoint inhibitors that have imparted impressive clinical results in diseases including melanoma, lung cancer, and Hodgkins lymphoma4,5 and gene-modified T cells targeting CD19 in ALL showing durable responses in multiply relapsed patients.6 Taken together, these results have ushered in a new era of treatment and led to significant interest and excitement in developing immunotherapeutic options for various malignancies, including MM, where it offers the benefit of a therapy that is non-cross-reactive with standard cytotoxic chemotherapy and capable of inducing long-term remissions with a potentially more tolerable toxicity profile.

This review highlights the immune based therapeutic options available and in development and attempts to place these within the context of current treatment paradigms.

Immunosuppressive mechanisms in myeloma

Myeloma is associated with profound immune dysfunction affecting both the innate and adaptive immune system.7 Although this review does not aim to focus on these mechanisms, it is important to understand general concepts of immune suppression in MM to effectively develop strategies to overcome them.

Although many lymphoid malignancies, including MM, express HLA class II and may thus be capable of direct presentation, cross-presentation remains the dominant mechanism of tumor antigen priming8; a mechanism that can be augmented by the use of tumor targeting monoclonal antibodies.9 As such, the functional status of antigen presenting cells (APCs) becomes critical. Dendritic cells (DCs) isolated from patients with MM are functionally impaired and express/produce lower levels of crucial molecules that initiate an immune response including interleukin 12 (IL-12), HLA-DR, CD40, CD86, and CD80.10,11 This phenotype is likely due to exposure to cytokines produced by the cancer cells and its surrounding microenvironment including transforming growth factor β (TGFβ), IL-6, and IL-10.

Regulatory T cells have multiple mechanisms of immunosuppression including the production of the anti-inflammatory cytokines, IL-10 and TGFβ, and depletion of IL-2 from the bone marrow (BM).12,13 Several groups have correlated the amount of regulatory T cells in MM (CD4+CD25+FoxP3+) with disease stage and treatment response, although the exact role they play in disease progression remains unclear.14,15

Myeloid derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that accumulate in the BM and peripheral blood of patients with MM and whose numbers correlate with a poor prognosis.16 They inhibit T cells by producing arginase-1, reactive oxygen species, and nitric oxide.17,18 Therapies targeting MDSCs are appealing as standard antimyeloma treatments have minimal effects on this population. However, some evidence suggests a role of lenalidomide.19 Our group has previously reported the use of phosphodiesterase-5 inhibitors to reduce MDSC function and shown some activity in MM.20

Macrophages are the main source of the immunosuppressive cytokines IL-10, IL-1β, and tumor necrosis factor α within the tumor microenvironment. They also produce angiogenic factors, leading to tumor growth and invasion, such as vascular endothelial growth factor, IL-8, fibroblast growth factor-2, metalloproteinases, cyclooxygenase-2, and colony-stimulating factor-1, and can also increase myeloma drug resistance through a direct cell–cell interaction.16,21

Myeloma cells also play an important role in maintaining immunosuppression. Their production of TGFβ and expression of
PDL-1 leads to significant T cells inhibition. Malignant plasma cells also shed the major histocompatibility complex (MHC) class I chain-related protein A (MICA), resulting in downregulation of NKG2D and impaired cytotoxicity. The IL-17 pathway has also been involved in favoring MM cell growth, as well as mediating osteoclast activation and lytic bone disease. Taken together, these pathways all provide putative targets for immune-mediated targeted therapies.

**Current immune approaches**

MM immunotherapy can be divided into several categories (Figure 1): (1) monoclonal antibodies targeting surface molecules present on the myeloma cells; (2) monoclonal antibodies targeting checkpoint inhibitors on immune cells; (3) pharmacologic immunomodulation; (4) cancer vaccines; and (5) adoptive cellular therapy (ACT). Immune-based strategies in MM will undoubtedly require an integration of these various modalities. An understanding of their benefits and limitations is critical in developing effective therapies.

**Monoclonal antibodies**

Monoclonal antibodies have significantly altered the treatment landscape in cancer due to their high specificity and minimal side effect profile. The major obstacle to defining their efficacy includes finding the appropriate target molecule. In MM, several surface molecules have been explored as potential targets of monoclonal antibodies including SLAMF7 (CS1), CD38, CD138, CD56, CD54, IL-6, PD1, CD74, CD162, β2-macroglobulin, and GM-2. Here we will discuss monoclonal antibodies that are furthest along in their clinical development and that have the potential for significant clinical impact in the treatment of MM. Table 1 summarizes the clinical trials with these MM-targeting monoclonal antibodies.

**SLAMF7 (CS1).** SLAMF7 is a cell surface glycoprotein receptor highly expressed on MM cells mediating adhesion to BM stromal cells. It is selectively expressed on plasma and natural killer (NK) cells and lacks expression on other tissues. Elotuzumab is an anti-SLAMF7 monoclonal antibody. Interestingly, SLAMF7 engagement induces both direct cell killing of MM cells and enhances NK cytotoxicity through upregulation of EAT-2 (adaptor protein present on NK cells). A phase 1 dose escalation trial of 34 heavily pretreated patients demonstrated a safe toxicity profile limited...
mostly to infusion-related reactions. There were no objective responses, and stable disease (SD) was reported in 26% of patients. However, in a phase 3 trial comparing elotuzumab, lenalidomide, and dexamethasone vs lenalidomide and dexamethasone (Rd), elotuzumab, lenalidomide, and dexamethasone showed an overall response rate (ORR) of 79% vs 66% and progression-free survival (PFS) of 41% vs 27%, respectively.

In patients with relapsed/refractory MM (RRMM), elotuzumab + bortezomib/dexamethasone (Evd) was studied compared with Vd alone in a phase 2 randomized trial of 152 patients. Results showed minimal incremental toxicity and a median PFS of 9.9 months (EVd) vs 6.8 months (Vd). The role of elotuzumab alone in a phase 2 randomized trial of 152 patients. Results showed 83%, with DVd of 63% with an associated improvement in PFS. The most benefit was seen in patients who had received 1 prior line of treatment, indicating that earlier treatment might provide the most benefit for patients with RRMM.

Two additional anti-CD38 antibodies, isatuximab (SAR650984) and MOR03087, are currently being investigated in clinical trials. Isatuximab + Rd in heavily pretreated RRMM patients (median 4-6 lines of therapy and 85% IMID refractory) showed a 57% ORR including 38% of patients achieving a VGPR or better.

CD38. CD38 is a transmembrane receptor protein highly expressed on malignant plasma cells and on normal B cells during different stages of their maturation. The intracellular presence of this molecule has been reported in normal tissues including brain, smooth muscle, and osteoclasts. CD38−/− mice exhibited marked deficiencies in antibody responses to T cell–dependent antigens, suggesting its role in regulating humoral immunity. Its expression on activated T cells is associated to drug infusion and few serious AEs that mainly consisted of nausea, anemia, diarrhea, and fatigue as the most common AE(s). Only 1 patient had a PR (4%). SD was noted in 50% of patients. As with the other monoclonal antibodies mentioned, combination with Rd improved the ORR in RRMM patients (median 3 prior therapies) to 78%.

IL-6. IL-6 is a cytokine that has been implicated in the proliferation and survival of MM cells. Preclinical studies suggested that the combination of siltuximab (an anti–IL-6 monoclonal antibody) and bortezomib might have synergistic effects. However, the results of a randomized control trial in combination with bortezomib failed to report statistically significant differences in response rate, PFS, or OS, whereas it did increase the frequency of adverse events including cytopenias. Currently it is being tested in patients with high-risk smoldering myeloma.

CD56. Lorvotuzumab mertansine is a humanized anti-CD56 monoclonal antibody conjugated to DM1 (cytotoxic maytansinoid derivative). CD56 is expressed on MM cells and functions as a growth factor receptor. A conjugated anti-CD138 monoclonal antibody with cytotoxic maytansinoid derivatives (DM4) was developed: BT062. A dose-escalating phase 1 trial of 29 patients with RRMM (failed IMID and PI treatment) reported a favorable safety profile, with nausea, anemia, diarrhea, and fatigue as the most common AE(s). Only 1 patient had a PR (4%). SD was noted in 50% of patients. As with the other monoclonal antibodies mentioned, combination with Rd improved the ORR in RRMM patients (median 3 prior therapies) to 78%.

Checkpoint inhibitors

T cells are major contributors of the antitumor immune response. A major determinant of their ability to generate clinically meaningful responses is dictated by the effective engagement of the T cell with

Table 1. Monoclonal antibodies in clinical development

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Trials phase</th>
<th>Side effects</th>
<th>Monotherapy</th>
<th>Combination therapy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elotuzumab</td>
<td>CS1 (SLAMF7)</td>
<td>3</td>
<td>Infusion reactions, lymphopenia, fatigue, pneumonia</td>
<td>No objective responses</td>
<td>With Rd: ORR 84% with Vd: ORR 65% with PFS of 9.9 vs 6.8 months</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>CD38</td>
<td>3</td>
<td>Infusion reactions, cytopenias</td>
<td>ORR 35% at 16 mg/kg 10% CR</td>
<td>With Rd: ORR 93% with Pd: ORR 58% with Vd: ORR 83%</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Isatuximab</td>
<td>CD38</td>
<td>1/2</td>
<td>Fatigue, nausea, cytopenias, hyperglycemia, fever</td>
<td>ORR: At ≥10 mg/kg: 24%</td>
<td>With Rd: ORR 57%</td>
<td></td>
</tr>
<tr>
<td>BT062 (indatuximab ravtansine)</td>
<td>CD138</td>
<td>1/2a</td>
<td>Nausea, fatigue, diarrhea, hypokalemia</td>
<td>Disease control (PR + SD) in 50% patients</td>
<td>With Rd: ORR 70-83% depending on dose and prior therapies</td>
<td>Conjugated with DM4</td>
</tr>
<tr>
<td>Lorvotuzumab</td>
<td>CD56</td>
<td>1</td>
<td>Cytopenias, peripheral neuropathy, fatigue, GI symptoms</td>
<td>Clinical benefit (stable disease): 41% including PR and 4 mR</td>
<td>With Rd: ORR 56.4% including 3% stringent complete remission, 28% VGPR and 26% PR</td>
<td>Conjugated with DM1</td>
</tr>
<tr>
<td>Siltuximab (CNTO 328)</td>
<td>IL-6</td>
<td>1, 2</td>
<td>Cytopenias, liver toxicity</td>
<td>No response</td>
<td>No advantage of combining with bortezomib</td>
<td></td>
</tr>
<tr>
<td>Pembrizumab</td>
<td>PD-1</td>
<td>1, 2</td>
<td>Cytopenias, diarrhea</td>
<td>With Rd: ORR 50% with Pomalidomide:ORR 50%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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its target. This interaction is regulated by a complex balance of costimulatory and coinhibitory molecular interactions (Figure 2) whose physiologic role is the maintenance of self-tolerance and prevention of autoimmunity.

The checkpoint inhibitors anti–CTLA-4 and anti–PD-1 have shown impressive results as measured by both depth and durability of the response that has led to their FDA approval in a broad range of malignancies. Although single agent anti–CTLA-4 has not been significantly examined in MM, single agent PD-1 blockade has been disappointing, with 0 of 27 MM patients achieving sustainable responses. More recently, the anti–PD-1, pembrolizumab, in combination with Rd (PRd), showed activity in 20 of 40 patients (50%) tested, with a 38% response rate (11 of 29) in lenalidomide-refractory patients with an acceptable toxicity profile. A phase 1/2 study combining pembrolizumab with pomalidomide in 24 patients had a median number of prior therapies of 3 (1-6). Seventy-five percent of patients were double refractory to IMIDs and PIs. The overall response rate was 50% (11 of 22). This has prompted a front-line PRd of patients who were double refractory to IMIDs and PIs. The overall setting in the presence of disease burden; and (3) many of these vaccine approaches attempt to target few antigens. To date, several vaccination approaches have been used for myeloma (Table 2).

**Idiotype vaccines.** The initial vaccines used to treat MM took advantage of the unique expression of a specific immunoglobulin by malignant plasma cells. These monoclonal immunoglobulins have somatically mutated variable regions and represent a unique antigen known as the idiotype (Id). These antigens can be expressed and presented in an HLA-restricted manner on the surface of malignant plasma cells, which enables them to serve as patient-specific tumor associated antigens. Furthermore, their HLA presentation enables plasma cells to serve as both a target and APCs for Id-specific T cells. However, vaccines using only the Id were found to be weakly immunogenic and failed to elicit a response with a measurable clinical benefit even when combined with strong adjuvants such as granulocyte–monocyte colony-stimulating factor (GM-CSF), IL-12, and alum or keyhole limpet hemocyanin.

**DC-based vaccines.** A major mechanism of vaccine-mediated priming is through cross-presentation. The antigens within the vaccine are taken up by resident APCs, traffic to draining lymph nodes, process and present antigen to T cells, and generate systemic immunity. DCs are the most efficient APCs, and as such have also been used in vaccine formulations. One such approach was Myelovence, in which DCs were pulsed with the patient’s Id and vaccinated following an autologous stem cell transplantation (ASCT). The clinical responses were compared retrospectively to contemporaneous controls and they found an OS advantage of 5.3 vs 3.4 years with no differences in PFS. This approach has not been further developed.

An alternative approach is fusion of DCs with patient-derived tumor cells. The rationale is to optimize antigen presentation and immune priming against the entire antigenic repertoire of each unique patients’ tumor. A phase 1 trial administering this vaccine following ASCT showed evidence of tumor-specific immunity and long-term disease stabilization in 3 of 17 patients. These results have led to the development of an ongoing randomized trial.

**Cancer testis antigens.** Cancer testis antigens (CTAs) are normally expressed in male germ cells and are pathologically upregulated in a variety of tumors, including MM. In MM, CTAs fulfill several parameters, making them ideal antigens to target including their low expression on normal tissues and the association of their expression with more aggressive disease, as well as advanced stage disease. Vaccines using CTAs to generate tumor immunity have been tested. DCs pulsed with a CTA NY-ESO-1 peptide generated tumor-specific responses in vitro.

A phase 2 trial in MM patients after ASCT was conducted with a MAGE-A3 peptide vaccine (compound GL-0817) combined with TLR-3 agonist (Hiltonol), GM-CSF, and ex vivo anti-CD3/CD28 costimulated autologous T cells. They found an 88% dextramer positive frequency of CTAs in MM and underscore the need for immunomodulation by IMIDs to achieve this response. Checkpoint inhibition will likely play a key role in the treatment paradigm of myeloma in light of the results observed in these early studies.

**Vaccines**

Vaccines aim to increase the precursor frequency of antigen-specific T cells or antibodies through in vivo priming. Infectious vaccines are mostly administered to healthy individuals with relatively intact immune systems with the purpose of generating a humoral and/or cellular immune response in a disease-free setting. These vaccines are typically comprised of a multitude of antigens from live attenuated or killed organisms. Tumor vaccines, as currently used, face significant hurdles that account for their limited efficacy. These primarily include the following: (1) the intrinsic immune dysfunction associated with cancer-bearing hosts; (2) the approach is used in a therapeutic setting in the presence of disease burden; and (3) many of these vaccine

Figure 2. Signaling between T cells and APCs. This figure illustrates the different possible costimulatory and coinhibitory molecular interactions between T cells and APCs (or myeloma cell). The upper half (red) shows the inhibitory signals and the lower half (green) depicts the activating interactions.
Table 2. Potential vaccine approaches

<table>
<thead>
<tr>
<th>Type of vaccines</th>
<th>Vaccine antigens tested in clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idotype (Id) vaccines + adjuvants</td>
<td>hTERT peptides: IS40, R572Y, D988Y</td>
</tr>
<tr>
<td>Dendritic cells + Id</td>
<td>Survivin peptide: Suro1M2, SVN53-67/M67, KLH-Id</td>
</tr>
<tr>
<td>Dendritic cell tumor fusion vaccine</td>
<td>WT1 peptides: A1, 427, 331, 122A1</td>
</tr>
<tr>
<td>Dendritic cells + cancer testis antigen</td>
<td>MAGE-A3: GL-0817, 168-176</td>
</tr>
<tr>
<td>Dendritic cells electroporated with mRNA of target antigens</td>
<td>NY-ESO-1: 1156-1253, SP(367-375)</td>
</tr>
<tr>
<td>Peptide vaccine + adjuvant</td>
<td>XIAP: (280-288)</td>
</tr>
<tr>
<td>Allogeneic myeloma cell lines with GM-CSF bystander line</td>
<td>CS1: (239-247)</td>
</tr>
</tbody>
</table>

Settings where vaccines are tested in clinical trials

- Sustained near complete remission (nCR) for 4 months
- Post auto-SCT
- Post allo-SCT
- Undergoing auto-SCT
- Newly diagnosed on maintenance lenalidomide
- Symptomatic MM
- Off treatment with stable disease
- Smoldering myeloma

ACTs

ACTs aim to enhance T-cell antitumor activity through ex vivo manipulations. This can be achieved through nonspecific stimulation of CD3, resulting in activation and expansion, specific stimulation by exposure to tumor antigens, or genetic engineering to express synthetic receptors that redirect T-cell specificity toward surface proteins (chimeric antigen receptors) or defined tumor-specific T-cell receptors (T-cell receptor transgenic T cells; Tables 3 and 4).

Role of IMIDs

The agents described thus far target myeloma in an immune-specific manner. However, the global immune suppression present in cancer-bearing hosts limits many immune-based approaches. Lenalidomide (Len) was developed as a thalidomide analog with more immune-modulatory properties. Using the pneumococcal 7-valent conjugate vaccine (Prevnar; Pfizer, New York, NY), vaccine-specific humoral and cellular responses were augmented with Len in MM patients that provided evidence of in vivo immune modulation to vaccines in myeloma patients.67

Further evidence of these immunomodulatory properties has been discussed above in reference to the emerging combination with tumor targeting monoclonal antibodies, elotuzumab and daratumumab, where Len significantly provided or added antitymoma activity, respectively, as well as PD-1 blockade that went from no activity to a 50% response rate.31,69

The overall explanation for Len-based enhanced immunogenicity is likely multifactorial and includes T-cell activation through increased tyrosine kinase activity of the CD28 receptor, downregulation of CD45RA on T cells, and downregulation of SOCS1 on the stromal elements of the tumor microenvironment.19

Table 3. ACT approaches

<table>
<thead>
<tr>
<th>ACTs</th>
<th>Advantages</th>
<th>Challenges</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCR</td>
<td>Broader array of possible targets</td>
<td>Find target antigens that are tumor specific</td>
<td>Tumor escape, MHC restricted, Risk of cross-reactivity, Require vectors, Possible mispairing with endogenous TCR</td>
</tr>
<tr>
<td>CAR</td>
<td>Highly tumor specific, HLA independent</td>
<td>Find target antigens that are tumor specific</td>
<td>Tumor escape, Cytokine storm, Limited to extracellular antigens, Require vectors</td>
</tr>
<tr>
<td>MILs</td>
<td>No vectors involved in production, Polyclonal (multiple targets)</td>
<td>Identify antigens being recognized, Increase tumor specificity</td>
<td>Heterogeneous product, Lower efficiency</td>
</tr>
</tbody>
</table>
modality as a foundation to build more effective tumor-targeted immune-based approaches.

Marrow infiltrating lymphocytes

Most ACTs used to date have used peripheral blood lymphocytes (PBLs). Although access to these cells is easy, a major limitation is their endogenous lack of tumor specificity. Our group has developed the use of marrow infiltrating lymphocytes (MILs). In addition to being the site of disease, the BM also possesses a unique immune environment that enables us to obtain a lymphocyte product enriched for both tumor-specific and central memory T cells: 2 factors essential for effective ACT. In contrast to PBLs, MILs possess greater cytotoxicity and express CXCR4, which increases their likelihood of trafficking to the BM on reinfusion. In the first clinical trial of 25 patients with active disease, MILs were expanded and administered after autologous SCT. Ex vivo tumor specificity of the expanded MILs product and tumor specificity of T cells obtained from the BM after transplant directly correlated with clinical outcomes. Furthermore, the cells were administered with minimal, self-limiting toxicity. A randomized multicenter clinical trial is currently under way in patients with high-risk myeloma of ASCT ± MILs.

Chimeric antigen receptor T cells

Chimeric antigen receptor T cells (CARs) are engineered molecules that fuse the specificity of a monoclonal antibody with the activation of the T-cell receptor signaling domain. CARs usually recognize their target via a single-chain variable fragment (scFv) derived from a monoclonal antibody and possess a very high affinity for their target with a T-cell intracellular signaling domain consisting of CD3ζ alone or coupled to costimulatory domains such as CD28 or 4-1BB. The largest success with this approach has been observed with CD19-directed CAR in chronic lymphocytic leukemia and ALL showing sustained remission in patients with advanced disease. However, therapeutic efficacy has also been associated with a potentially life-threatening, IL-6–mediated, cytokine release syndrome (CRS), which appears to be related to the overall tumor burden and responds to the anti–IL-6 antibody tocilizumab.

A CD19 CAR approach in MM was reported in a patient with an immunoglobulin A myeloma, which interestingly had a very low level of CD19 expression as detectable by flow cytometry, and yet experienced a rapid and dramatic response to treatment. Clinical studies are currently ongoing with this approach. Although our group has shown that the MM precursors represents a postgerminal B cell with CD19 expression, the rapid decrease in the malignant plasma cell population would argue against having primarily targeted a precursor population.

B-cell maturation antigen is expressed on plasma cells and >70% of malignant MM cells with limited expression on normal B cells. As such, it represents an attractive target. A B-cell maturation antigen CAR trial at the National Cancer Institute has shown early evidence of dose-dependent activity in patients with advanced MM that was associated with a CRS. Other targets being examined for CAR therapy include CS-1, CD138, and CD38. Although demonstrating powerful antitumor activity, the significant toxicity associated with the CRS thus far limits its use outside of the multiply-relapsed setting.

T-cell receptor-modified T cells

Unlike CARs, T-cell receptor-modified T cells (TCRs) are HLA restricted. The TCRs typically recognize peptides presented by HLA-A2 molecules as to maximize its use in the majority of patients. The first TCR used in MM recognizes the complex of HLA-A*0201 with a peptide shared by NY-ESO-1 and LAGE1. Of note, NY-ESO-1 expression is found in ~60% of advanced MM cases. The first 20 patients receiving NY-ESO-1 TCR-specific T cells (NY-ESO(c259)) experienced only grade 3 or lower AEs and no CRS. Persistence of NY-ESO(c259) in the blood was observed up to 2 years after infusion. Ex vivo tumor specificity of the expanded MILs product and tumor specificity of T cells obtained from the BM after transplant directly correlated with clinical outcomes. Furthermore, the cells were administered with minimal, self-limiting toxicity. A randomized multicenter clinical trial is currently under way in patients with high-risk myeloma of ASCT ± MILs.

Conclusion

Our increased understanding of the immune system and the availability of targeted reagents has now enabled immunotherapy to impart clinically meaningful responses. Immunotherapy is quickly establishing itself as a critical component of MM therapy. The current availability of various immune-based agents offers the possibility of numerous combinations to maximize their efficacy. Monoclonal antibodies will be incorporated into upfront cytoreductive regimens to deepen the initial response to therapy. Vaccines, in combination with immunomodulatory agents, may serve to achieve and/or maintain minimal residual disease with the hope of potentially prolonging PFS (and possibly OS). Finally, ACT therapy approaches could be integrated into 2 aspects of the treatment paradigm of MM: (1) in combination with high-dose therapy to further consolidate high-risk disease potentially using MILs or TCR ACT approaches where the overall toxicity is minimal or (2) in the setting of fulminant relapsed disease using CARs when there is a need for a rapid reduction in disease burden that would justify the associated toxicity. Whatever the final combination or actual reagents used, it is fair to say that we have now entered into a new era. Immunotherapy will increasingly play a role in MM treatment.

Table 4. Currently active ACTs

<table>
<thead>
<tr>
<th>Type of ACT</th>
<th>Setting in which tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated MILs</td>
<td>After ASCT</td>
</tr>
<tr>
<td>CAR T cells anti–B-cell maturation antigen</td>
<td>RRMM</td>
</tr>
<tr>
<td>CAR T cells anti-NKG2D ligands</td>
<td>RRMM</td>
</tr>
<tr>
<td>CAR T cells anti-CD138</td>
<td>RRMM</td>
</tr>
<tr>
<td>CAR T cells anti–κ light chain</td>
<td>RRMM</td>
</tr>
<tr>
<td>NY-ESO-1– and LAGE-specific TCR-modified T cells</td>
<td>RRMM</td>
</tr>
<tr>
<td>T cells selected for NY-ESO-1, MAGEA4, PRAME, Survivin, and SSX specificity</td>
<td>Active myeloma after first line</td>
</tr>
<tr>
<td>Expanded haploidentical NK cells</td>
<td>After ASCT</td>
</tr>
<tr>
<td>NK cells from donor</td>
<td>After allo-SCT</td>
</tr>
</tbody>
</table>

Authorship

Contribution: V.H. and I.B. wrote and edited the manuscript.

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References


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