Promise of Immune Therapies in Multiple Myeloma

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ASSOCIATED CONTENT

See accompanying article on page 403

There has been major progress in the treatment of multiple myeloma (MM) in the past 15 years with the bench-to-bedside translation of novel agents targeting the tumor in its microenvironment, including the proteasome inhibitors bortezomib, ixazomib, and carfilzomib; the immunomodulatory drugs thalidomide, lenalidomide, and pomalidomide; the histone deacetylase inhibitor panobinostat; and the monoclonal antibodies daratumumab and elotuzumab.[1,2] As a direct result, overall survival in MM has been extended at least three- to four-fold. The most promising strategies for additional progress include personalized medicine and immune therapies.

Precision medicine has been challenging in MM because of its complex genetic profile, with ongoing genomic evolution underlying relapse of disease.[3] The most commonly mutated pathway is RAS-Raf-MAPK signaling, and attempts to block this cascade with single or targeted agents have achieved only transient responses.[4] Importantly, venetoclax targeting Bcl-2 together with bortezomib achieves responses in the majority of patients with t(11;14) translocation and likely represents the first personalized medicine in MM.[5] Both basket and umbrella trials will further evaluate targeted therapies, alone and in combination, in MM.

After decades of preclinical studies and clinical trials, immune therapies have come of age in MM, as reviewed by Baljevic and Holstein in this issue of the *Journal of Oncology Practice*.[6] Immune-based strategies have the potential to overcome the intrinsic and ongoing evolving genetic complexity in MM. The anti-CD38 monoclonal antibody daratumumab, alone or in combination with lenalidomide/dexamethasone, bortezomib, or pomalidomide/dexamethasone, has been approved by the U.S. Food and Drug Administration (FDA) to treat relapsed MM and can achieve minimal residual disease negativity, even in advanced disease.[7-9] Although daratumumab has an acceptable therapeutic index, CD38 is broadly expressed in endothelial cells, activated blood and immune cells, and hematopoietic progenitor cells, and lowering of blood counts and of normal immunoglobulins can be observed with long-term use. In phase III trials in relapsed MM, daratumumab/lenalidomide/dexamethasone and daratumumab/bortezomib/dexamethasone were superior to lenalidomide/dexamethasone and bortezomib/dexamethasone, respectively. However, in North America, lenalidomide/bortezomib/dexamethasone is commonly used as initial therapy,[10] and relapsed MM is therefore refractory to both lenalidomide and bortezomib. Because the activity of daratumumab/lenalidomide/dexamethasone or daratumumab/bortezomib/dexamethasone in lenalidomide/dexamethasone–refractory MM is unknown, daratumumab/pomalidomide/dexamethasone is recommended to treat relapsed disease. Recently, daratumumab plus bortezomib/melphalan/prednisone (VMP) was superior to VMP in nontransplantation candidates with newly diagnosed MM,[11] providing the basis for FDA approval of daratumumab as initial therapy. However, in North America, VMP is rarely used, and ongoing trials are comparing

DOI: https://doi.org/10.1200/JOP.18.00311

lenalidomide/bortezomib/dexamethasone or lenalidomide/dexamethasone with or without daratumumab in newly diagnosed MM, which may provide the basis for quadruple induction treatments more broadly in the future. Isotuximab, a CD38 monoclonal antibody that triggers lysosomal MM cell death in addition to its immune activity, has shown promising results in late-stage clinical trials.[12] Finally, elotuzumab targeting SLAMF7 on MM cells has minimal single-agent activity, but is FDA approved in relapsed MM because of high response rates when combined with lenalidomide/dexamethasone.[13] Importantly, elotuzumab/lenalidomide/dexamethasone has achieved an overall survival advantage compared with lenalidomide/dexamethasone at 4 years. As with daratumumab/pomalidomide/dexamethasone, promising early responses have been observed with elotuzumab/pomalidomide/dexamethasone in relapsed MM. Monoclonal antibodies therefore seem to have an increasing role in treating relapsed MM and at earlier stages of disease.

Perhaps the most promising target for immune therapies is B-cell maturation antigen (BCMA), because of its restricted expression in normal and malignant plasma cells. Ongoing studies are now evaluating monoclonal antibodies targeting BCMA, BCMA monoclonal antibody bound to auristatin,[14] and BCMA bispecific T-cell engagers designed to recruit CD3-positive T cells locally to the tumor microenvironment.[15] APRIL, the most prevalent ligand for BCMA in the bone marrow plasma of patients with MM, binds to BCMA and triggers growth, survival, and drug resistance signaling, and upregulates programmed death ligand-1 expression in MM cells; conversely, anti-APRIL monoclonal antibody blocks this binding and checkpoint expression,[16] and is entering clinical trials soon. Finally, nuclear factor-kappa ligand is present in MM bone marrow plasma and activates osteoclasts and bone resorption in MM. In phase III trials, monoclonal antibody to nuclear factor-kappa ligand (denosumab) has shown non-inferiority to zoledronic acid in abrogating skeletal-related events in MM, with similar rates of attendant osteonecrosis of the jaw.[17] Importantly, its major use should be reserved for patients with renal compromise, in whom it can be given safely to reduce skeletal-related complications.

As in solid tumors, programmed death ligand-1 is expressed in MM and programmed death-1 (PD-1) on T and natural killer cells in MM[18]; however, minimal single-agent activity of anti–PD-1 monoclonal antibodies has been noted. Combination phase II clinical trials of either lenalidomide or pomalidomide with pembrolizumab, but not with nivolumab, showed excess toxicity, and checkpoint inhibitor trials have therefore been suspended by the FDA. However, preclinical studies suggest the promise in MM of targeting inhibitors of checkpoints, such as Lag 3, and/or immune activators, such as OX 40. Judicious use of such combinations may be clinically useful, particularly in the setting of MM with high mutational burden, analogous to solid tumors with high microsatellite instability, where efficacy of PD-1 inhibition has led to its FDA approval.

Vaccines are being evaluated in MM, alone and in combination. For example, ongoing trials are evaluating cocktails of CD138, CS-1, and XBP-1 peptides in smoldering MM to delay progression to active disease.[19] Already, memory MM–specific cytolytic T-cell responses have been observed, which are amplified by lenalidomide, and combination vaccine trials with checkpoint inhibitors and histone deacetylase inhibitors are directed to trigger sustained autologous anti–MM memory T-cell responses. In addition, vaccination with fusions of MM cells to autologous dendritic cells can induce MM selective cytolytic T-cell responses,[20] and randomized trials are currently evaluating lenalidomide with or without this vaccine to treat minimal residual disease post-transplantation.

A most exciting and promising development in MM is the development of CAR T-cell therapy incorporating various costimulatory molecules (CD28, 41BB) and target antigens on MM (BCMA, CD19, CD138, kappa).[21] Minimal residual disease-negative responses to CAR T-cell therapy have been observed, even in far advanced MM. Ongoing research will define the optimal targets and stimulatory molecules, as well as optimal CD8 and CD4 composition, to ensure sustained memory antitumor response. Parallel efforts will define methods to reduce cytokine release syndrome and improve the therapeutic index. As safety is improved, it is likely that CAR T cells will be used earlier in the disease course after response to induction treatment, just as autologous stem cell transplantation is performed today. Excitingly, in the future, it may be possible to use CRISPR editing technology to abrogate alloreactivity of normal allogeneic donor T cells, which are also engineered to target BCMA, thereby providing for off-the-shelf CAR T-cell therapy.

In the future, combination targeted and immune therapies defined in preclinical studies will be used to treat subsets of patients, defined by profiling and informed by biomarkers. Collaborative effort of academia, industry, the National Institutes of Health/National Cancer Institute, FDA, and patient advocacy groups will facilitate continued rapid advances. Most

importantly, long-term disease-free survival and potential cure of MM will require not only achieving minimal residual disease negativity, but also restoration of host anti-MM immunity. JOP

Acknowledgment

Supported by National Institutes of Health (P50 100707, RO1 CA207237, RO-1 CA 050947, RO1 CA178264, and PO1 155258). K.C.A. is an American Cancer Society Clinical Research Professor.

Author's Disclosures of Potential Conflicts of Interest

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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