Novel Treatments for Patients With Relapsed/Refractory Multiple Myeloma

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Therapeutic options for patients with multiple myeloma have multiplied in the past decade. However, multiple myeloma remains an incurable disease, and relapsed/refractory myeloma is characterized by genetic and cytogenetic alterations that drive resistance and result in progressively shorter durations of remission to each subsequent therapy. At JADPRO Live 2022, presenters discussed the multifactorial process for choosing the right therapy for a particular patient and strategies to manage unique treatment complications associated with novel treatment modalities used for patients with relapsed/refractory multiple myeloma.

The field of myeloma therapeutics is entering a new age with unprecedented outcomes in overall response rate and progression-free survival. During JADPRO Live 2022, Cesar Rodriguez, MD, and Donna Catamero, ANP-BC, OCN®, CCRC, of Mount Sinai School of Medicine, explained mechanisms of action of agents used in relapsed/refractory multiple myeloma, discussed strategies to manage unique treatment complications associated with novel treatment modalities, and interpreted current clinical trial data.

APPROVED TREATMENT OPTIONS

As Dr. Rodriguez reported, more than half of all multiple myeloma drugs have been approved by the US Food and Drug Administration (FDA) in the past 10 years, which has significantly changed both the treatment paradigm and survival outcomes for patients with this disease. Despite increased therapeutic options, however, Dr. Rodriguez noted that the attrition rate remains high, and at first relapse, only 60% of patients can receive therapy (Yong et al., 2016).

"At the second relapse, less than half of the patients can receive therapy, and when they do, each relapse has a shorter duration of time and shorter efficacy in terms of how well we control the disease," said Dr. Rodriguez, who underscored the importance of using the best therapies up front. "The first punches are the best ones at controlling the disease."

While combination therapy with FDA-approved drugs in myeloma

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are highly effective, Dr. Rodriguez also noted that there are approximately 40 different combinations that can be used to treat this disease.

"It is impossible to do a head-to-head comparison to see which is the next best therapy for a particular patient," he noted.

CHOOSING THE RIGHT THERAPY

As Ms. Catamero explained, there are many factors to consider when determining the next best therapy in relapsed/refractory multiple myeloma, including prior therapies, comorbid conditions, and whether the patient has a caregiver, as that impacts eligibility for CAR T-cell therapy. Most importantly, said Ms. Catamero, providers should consider performance status and whether it is being affected by disease burden or comorbidities.

"Age should not be a factor in choosing therapy," said Ms. Catamero, who added that geriatric assessments should be done to classify patients as fit or frail. "Research shows that patients, regardless of age, who are fit have better survival and outcomes and tolerate therapy better."

Dr. Rodriguez noted that even if a patient is refractory to a certain class of drugs, there are still multiple options available.

"When patients start to have more relapses, and they've developed resistance to the three big ones, such as proteasome inhibitors, immunomodulators, and monoclonal antibodies, there are still new therapies that have been FDA approved," he explained. "It's important to consider re-challenging previous therapies, second transplant, stem cell boost, and clinical trials for these patients."

NEW TARGETED IMMUNOTHERAPIES

Targeted immunotherapies have recently been approved in multiple myeloma. Belantamab mafodotin (Blenrep) was approved in August 2020 and is a monoclonal antibody that binds to the surface protein B-cell maturation antigen (BCMA) on myeloma cells and delivers a toxin, causing direct toxicity and enhancement of antibody-derived cell toxicity.

Results from the DREAMM-2 study showed a 30% response rate in heavily pretreated, refractory patients and a median duration of response of 11 months (Trudel et al., 2021).

"Despite a median 6 to 7 lines of therapy, we saw nearly one third of patients respond to belantamab, which, at that time, was amazing," said Dr. Rodriguez. "Moreover, this response was sustained for an average of 11 months."

Combining belantamab mafodotin with other class drugs such as proteasome inhibitors, immune modulators, or monoclonal antibodies to improve response is currently being studied.

Ms. Catamero noted new toxicities that need to be considered with this agent. The most common adverse event in the DREAMM-2 study was ocular disorders, with over 70% of patients experiencing some degree of keratopathy, over 50% experiencing a decrease in visual acuity, and almost 25% experiencing blurred vision.

"A REMS program is in place for belantamab mafodotin, which advises patients to use preservative-free lubricating eye drops and to have an eye exam prior to each dose of belantamab mafodotin to monitor for changes in visual acuity and in the epithelial cells of the cornea," said Ms. Catamero.

After JADPRO Live, GSK (2022) withdrew belantamab mafodotin from the market based on outcomes of the DREAMM-3 phase III confirmatory trial, which did not meet the requirements of the FDA Accelerated Approval regulations.

CAR T-CELL THERAPY

As Dr. Rodriguez reported, T-cell redirecting therapies, such as chimeric antigen receptor (CAR) T-cell therapy, are a new and exciting development in the treatment of relapsed/refractory multiple myeloma. These therapies are designed to redirect T-cells in patients to identify and destroy myeloma cells more effectively (Figure 1).

"CAR T-cell therapy works by taking T cells from the patient with active myeloma and myeloma cells, expanding them in the laboratory, and infusing them back to the patient," said Dr. Rodriguez. "The goal is to create T cells that are smart enough to identify myeloma cells for that patient, attack them, and destroy them."

The process of taking the cells and reinfusing them can take between 3 to 6 weeks, but in some cases, it may take up to 10 weeks due to delays.

There are two CAR T-cell therapies that have been FDA approved for myeloma: idecabtagene vicleucel (ide-cel; Abecma) and ciltacabtagene autoleucel (cilta-cel; Carvykti). The CRB-401 study showed response rates of 73% in heavily pretreated

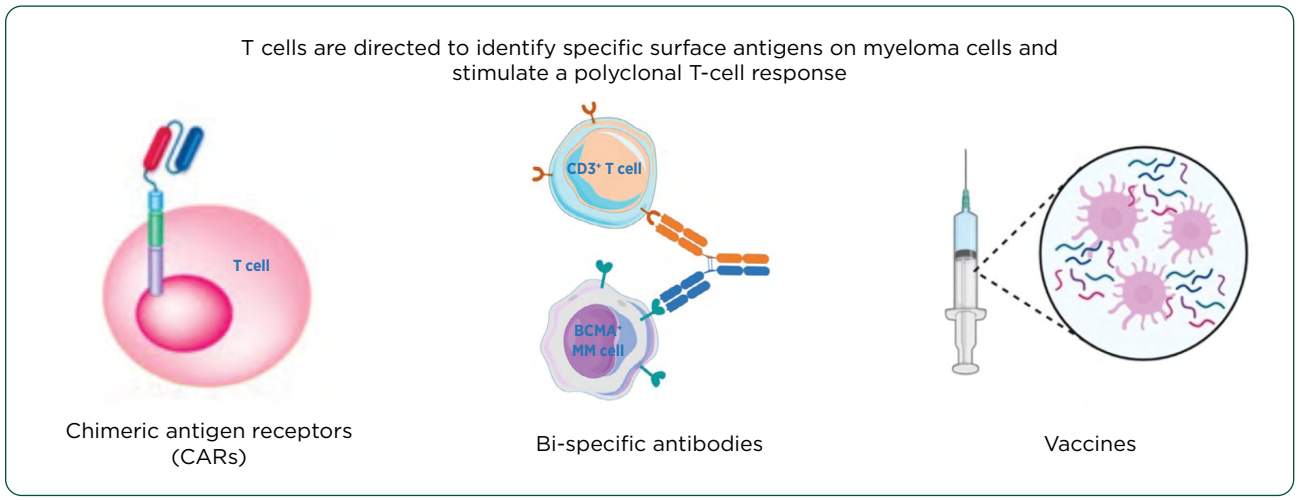

Figure 1. T-cell redirecting therapies.

patients, with 33% complete remission for ide-cel (Anderson et al., 2021). The CARTITUDE-1 study showed response rates of 98% in triple class refractory patients for cilta-cel (Usmani et al., 2021).

"Almost every patient responded to this therapy, even in cases where we normally were not expecting significant responses," said Dr. Rodriguez. "Importantly, 80% of the patients also achieved remission, which is incredible."

However, these therapies may come with certain side effects, such as gastrointestinal toxicities, cytopenias, and ocular disorders. Therefore, it's important to carefully weigh the potential benefits and risks of these therapies before deciding to use them, said Dr. Rodriguez, who added that more research is needed to fully understand their potential and long-term effects.

Cytokine Release Syndrome

As Ms. Catamero explained, cytokine release syndrome (CRS) is a side effect of CAR T-cell therapy that can occur due to overactivation of the immune system in response to the infused CAR T cells. It can vary in terms of timing and symptoms depending on the CAR T-cell product used. The most common symptoms of CRS are fever, cardiovascular symptoms, hypotension, tachycardia, respiratory distress, hypoxia, and organ toxicity.

"CRS is typically monitored for in an inpatient setting, but some institutions are now doing this on an outpatient basis," said Ms. Catamero, who noted that the management of CRS varies from supportive care to tocilizumab, corticosteroids, and a combination of both depending on the severity of the CRS (Table 1).

Neurotoxicity

Neurotoxicity is another side effect that can occur with CAR T-cell therapy in relapsed/refractory multiple myeloma patients, separate from CRS. The exact mechanism of neurotoxicity is not yet known, said Ms. Catamero, but it's suspected to be due to capillary leak of CAR T cells or activated immune cells into the central nervous system. The onset of neurotoxicity can occur between day 1 and 3 to 4 weeks after the CAR T-cell infusion. These toxicities tend to be self-limited and reversible, and can be managed.

BISPECIFIC ANTIBODY THERAPY

An alternative to CAR T-cell therapy is the use of bispecific antibody therapy. Bispecifics are recombinant proteins that have two arms: one that binds to the myeloma cell and one that binds to the T cell. According to Dr. Rodriguez, this is a more efficient form of immunotherapy compared with traditional monoclonal antibodies, which can only bind to one antigen on the myeloma cell.

Several drug companies are studying bispecific antibody therapy, with most focusing on BCMA, a protein found on the surface of multiple myeloma cells. These bispecifics are in different stages of clinical trials and are designed differently, said Dr. Rodriguez, which can affect how long they last in the body, how potent they are, and which side effects are associated with them. Some of these drugs

Table 1. Grading for Cytokine Release Syndrome

CRS grade	Presenting symptoms	Tocilizumab	Corticosteroids
Grade 1	• Temperature ≥ 38°C	• May be considered	• N/A
Grade 2	• Temperature ≥ 38°C • Hypotension responsive to fluids • O_2 low flow nasal canula	• Toci q8h at 8mg/kg • Limit to a max 3 doses/24 hr • Max 4 doses	• Manage per guidance below if no improvement within 24 hr of starting toci.
Grade 3	• Temperature ≥ 38°C • Hypotension requiring one vasopressor • O_2 requirement of high flow nasal canula, facemask, non-rebreather mask, or Venturi mask	• Toci q8h at 8 mg/kg • Limit to a max 3 doses/24 hr • Max 4 doses	• Administer methylprednisolone 1 mg/kg q12h or dexamethasone 10 mg q6h. • Continue steroid until the event is grade 1 or less, then taper over 3 days.
Grade 4	• Temperature ≥ 38°C • Hypotension requiring multiple vasopressor • O_2 requirement of positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Toci q8h at 8 mg/kg • Limit to a max 3 doses/24 hr • Max 4 doses	• Administer methylprednisolone 1 mg/kg q12h, or dexamethasone 10 mg q6h. • If no improvement, consider alternate immunosuppressants.

must be given on a weekly basis, while others can be given every other week or even every 3 weeks.

"The results from the clinical trials of bispecifics targeting BCMA have been promising," said Dr. Rodriguez. "The overall response rate for a single agent is 60% or higher, even in patients who have had multiple rounds of treatment, which is similar to the response rates seen with CAR T-cell therapy and is unprecedented as a single agent."

Common side effects of bispecific therapies for multiple myeloma include low-grade CRS, which is managed in the same way as it is for CAR T-cell therapy, and high risk of infection, including viral and bacterial infections, particularly airway infections.

Bispecifics can also cause hypogammaglobulinemia and cytopenias, noted Ms. Catamero, which are managed with intravenous immunoglobulin and growth factor support. Subcutaneous administration of bispecifics can also cause injection site reactions, which are limited to the first cycle of treatment and can be managed with oral antihistamines and topical steroids. A generalized body rash can also occur and can be managed with topical steroids, oral antihistamines, and in some cases, oral steroid taper, said Ms. Catamero.

TALQUETAMAB

Talquetamab, an alternative bispecific antibody therapy that targets GPRC5D, a surface protein on the myeloma cell, has also demonstrated excellent responses in patients, with overall responses ranging between 63% and 70% in the MonumenTAL-1 study, which compared two different doses (405 µg/kg and 800 µg/kg; Minnema et al., 2022).

"Talquetamab demonstrated deep responses, with more than 56% of patients having a very good partial response or better, and a durable response, with a median duration of response of 13 months," said Dr. Rodriguez.

Talquetamab can cause skin and nail toxicities, oral toxicities such as altered taste, dry mouth, difficulty swallowing and weight loss. These side effects can be managed with cuticle oil, vitamin E, nail strengthener polish, ammonia lactate lotion, saliva substitutes, and steroid swish and spit with nystatin. Dose holds and adjustments can help mitigate these toxicities.

CEVOSTAMAB

Finally, cevostamab is a bispecific antibody therapy that targets FcRH5 in the myeloma cell and uses the CD3 receptor for the T cell. Results of a phase I study showed good responses in heavily pretreated patients, with overall response rates of 56% and a median duration of response of approximately 11.5 months (Trudel et al., 2021). According to Dr. Rodriquez, side effects are similar to those seen with bispecifics targeting BCMA, but with less frequent infections.

Despite the advances made with these therapies, however, none have cured myeloma, and

when patients relapse, alternative options are being explored. Another approach being studied is genetic profiling.

"Every time a patient relapses, bone marrow biopsies and restaging are performed to look for targetable mutations in available therapies," said Dr. Rodriguez. "This information is then used to create a more personalized therapy, often in combination with conventional chemotherapy. The results of this research will be presented in the coming years." ●

Disclosure

Dr. Rodriguez has served as a consultant and speaker for Amgen, Janssen, GSK, BMS, Artiva, Karyopharm, and Sanofi. Ms. Catamero has served as a consultant for BMS, Amgen, Janssen/Johnson & Johnson, Legend Biotech, and Sanofi, and a speaker for GSK.

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