New Frontiers: The Role of CAR T-Cell Therapy in 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

Multiple myeloma remains the second most common hematologic malignancy, and relapse rates are high, with refractory disease common with each relapse. Chimeric antigen receptor (CAR)–modified T cells are a promising new treatment, and at JADPRO Live Virtual 2021, presenters compared pivotal trials in CAR T-cell therapy for multiple myeloma, discussed how to recognize and manage common toxicities after CAR T-cell infusion, and reviewed pre-CAR-T consultation and post-CAR-T management.

The second most common hematologic malignancy, multiple myeloma remains incurable, with high rates of relapse. Recent advances in combination therapies and new treatment options, however, continue to improve prognosis and survival.

During JADPRO Live Virtual 2021, Alli McClanahan, APRN, and Megan Spychalla, PA-C, of the Mayo Clinic Rochester, in Minnesota, discussed the increasing role of chimeric antigen receptor (CAR) T-cell therapy to treat multiple myeloma and how to manage common toxicities post-CAR T-cell infusion.

"CAR T-cell therapy is producing unprecedented response rates for patients with relapsed/refractory multiple myeloma," said Ms. McClanahan. "However, CAR T-cell therapy has a unique toxicity profile, and advanced practitioners need to recognize and manage these toxicities early to mitigate adverse events in CAR T-cell infusion.

"CAR T-cell therapy education for patients and their caregivers, pre- and post-CAR T-cell therapy, is necessary to ensure supportive care needs are met," she added.

CELLULAR THERAPY IN MULTIPLE MYELOMA

As Ms. Spychalla explained, B-cell maturation antigen (BCMA), which regulates B-cell proliferation and differentiation into plasma cells, is a great target for multiple myeloma because it is largely overexpressed on malignant plasma cells but not expressed on other hematopoietic cells or other areas of the body, therefore reducing off-target effects. Targeting BCMA has led to the success of two CAR T-cell products.

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Idecabtagene Vicleucel (Ide-Cel)

Idecabtagene vicleucel (Abecma), or ide-cel, the first CAR T-cell therapy approved for multiple myeloma, is composed of a single BCMA extracellular domain binding to a BCMA antigen on a malignant plasma cell. Approval for ide-cel was based on results of the pivotal phase II KarMMa trial, which consisted of heavily pretreated relapsed/refractory multiple myeloma patients with high-risk cytogenetics and presence of extramedullary disease (Munshi et al., 2021).

The overall response rate was 73%, with an 81% response rate at the highest dosing level (450×10^6). Median duration of response was 10.7 months, and progression-free survival was 8.8 months. The overall survival of all treatment groups was 19.4 months.

Findings also showed that a patient's best response correlated to a longer disease-free duration.

"If a patient's best response was a partial response, they could expect a median duration of response to be 4.5 months, and if a best response was a very good partial response, they could expect a median duration of 10.4 months," said Ms. Spychalla. "However, if a patient's best response was complete response or stringent complete response, then a median duration of response increased to 19 months."

Of note, the highest dosing level showed increased progression-free survival at 12.1 months, which improved further in patients with complete response or stringent complete response to 20.2 months. The median duration of response also increased from 10.7 months to 11.3 months in patients receiving the highest dose.

Ide-cel was approved by the U.S. Food and Drug Administration (FDA) in March 2021.

Ciltacabtagene Autoleucel (Cilta-Cel)

Ciltacabtagene autoleucel (Carvykti), or cilta-cel, is a BCMA CAR T-cell therapy composed of a dual BCMA-targeting domain, which is thought to confer enhanced binding affinity. The pivotal phase Ib/II CARTITUDE-1 trial studied cilta-cel in patients with relapsed/refractory multiple myeloma who had received three lines of prior therapy (Berdeja et al., 2021).

With a median follow-up of 12.4 months (as of September 2020), overall response rate was 97%, and 67% of patients achieved a stringent complete response. Of the 35 patients who evaluated for minimal residual disease (MRD) status, 33 were found to be negative for MRD (94%).

Overall, 12-month progression-free survival was 77%, and for those who achieved a complete response or better, progression-free survival at 12 months improved to 85%. The overall survival rate was 89% at 12 months, and mediation duration of response was not reached at the 12.4-month follow-up.

An update at 18 months presented at ASCO 2021 showed a 97.9% response rate, including 80.4% of patients with a stringent complete response, and an overall survival of 81% (Usmani et al., 2021).

"The median duration of response of 21.8 months and progression-free survival of 22.8 months continues to show that responses are deepening over time," said Ms. Spychalla.

Cilta-cel was approved by the FDA in February 2022.

CAR T-CELL THERAPY HORIZON

Currently, there is no true head-to-head comparison of ide-cel and cilta-cel. Although these CAR T-cell therapy products have similar lymphodepletive chemotherapy and bridging restrictions, triple-class exposed patients, and measurable disease prior to CAR T-cell infusion, there is varied dosing, and the products are constructed differently. The disease characteristics of the patient cohorts were also different, which could account for the higher toxicity profile of cilta-cel, said Ms. Spychalla.

Investigators are already exploring giving CAR T-cell therapy at earlier time points in the disease course. In both the ide-cel and cilta-cel trials, patients had up to six prior lines of therapy, but these agents could eventually move to earlier settings, said Ms. Spychalla.

"Ultimately, the question many of us continue to ask is, 'Where is CAR T-cell therapy with respect to transplant?'" she said. "Does it come before or after transplant, and at what point in time can we have a comparison for further guidance on decision-making?"

INDICATIONS FOR CAR T-CELL THERAPY

As Ms. McClanahan explained, relapsed/refractory disease status with at least four lines of pre-

vious therapy is currently required to receive idecel for multiple myeloma. Prior treatment must also include an immunomodulatory drug (e.g., lenalidomide or pomalidomide), a protease inhibitor (e.g., bortezomib, carfilzomib, or ixazomib), and an anti-CD38 antibody (e.g., daratumumab or isatuximab).

CAR T-cell therapy is not indicated for patients with plasma cell leukemia, active central nervous system involvement, concurrent POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin abnormalities) or concurrent systemic amyloidosis. Other inclusion criteria include adequate organ functions, ECOG performance status of 0 to 1, no active infections, and no history of stroke, seizure, intracranial bleeding, or memory loss.

"Patients undergo a thorough workup, including an echocardiogram, iothalamate creatinine clearance to monitor kidney function, pulmonary function tests, and oxygen saturations, to ensure that organs can handle both chemotherapy and the potential toxicities that are noted after CAR T-cell therapy," said Ms. McClanahan. "However, even if you have concerns that a patient may not meet these inclusion/exclusion criteria, it's still important to refer them to a CAR T-cell therapy center, as they may qualify for studies that use CAR T-cell therapy in multiple myeloma."

FROM REFERRAL TO INFUSION

Like autologous stem cell transplant, patients undergoing CAR-T therapy require a 24/7 caregiver during treatment to help manage their medications, observe them closely for toxicities, and help them get to appointments. Patients receiving CAR-T therapy are also required to remain close to the center for at least 30 days.

"It's important to discuss the different set of toxicities that patients experience following CAR-T from transplant, including cytokine release syndrome (CRS) and neurotoxicity," said Ms. McClanahan, who noted that there is no driving for at least 8 weeks following therapy due to the risk for seizures and neurotoxicity after therapy.

Because the time from referral to CAR T-cell infusion can take up to 4 to 6 weeks or more, it's also important to monitor these heavily pretreated patients for disease progression prior to infusion.

Day 0 is the day of the infusion, which most patients tolerate quite well. Starting after the infusion, however, patients are watched closely for CRS and neurotoxicity, which can manifest within days or hours of the infusion. Some centers require inpatient monitoring, while other centers can monitor in the outpatient setting through day +7.

"Patients receiving outpatient monitoring require 24/7 access to emergent care for providers that understand the toxicities following CAR T-cell therapy," said Ms. McClanahan. "These patients are provided a wallet card that explains the product that they received, side effects that may happen, and medications that should be avoided post-CAR T-cell therapy."

Patients experiencing any symptoms related to CRS, neurotoxicity, or any symptoms not being controlled in the outpatient setting, are admitted to the hospital.

TOXICITIES POST-CAR-T

According to Ms. McClanahan, many patients who have undergone both autologous stem cell transplant and CAR T-cell therapy share that CAR T-cell therapy is harder to endure because of its unique toxicities. These toxicities include CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS) or MAS-like, pancytopenia, or hypogammaglobulinemia.

Cytokine Release Syndrome

Cytokine release syndrome involves fevers, hypoxia, hypotension, fatigue, and often organ dysfunction. Because these symptoms often overlap with other complications that can occur following CAR T-cell therapy, it's important to work patients up for neutropenic fevers, including blood cultures, chest x-rays, and other concerning infectious symptoms.

"Patients can have fevers related to pulmonary embolism or deep vein thrombosis, which can be common in multiple myeloma patients, so it's important to not just assume that any new fever is related to CRS," said Ms. McClanahan, who noted that CRS severity is determined using the American Society of Transplantation and Cellular Therapy consensus grading system.

Cytokine release syndrome is typically managed with tocilizumab or an anti-cytokine release medi-

cation, in addition to steroids, with frequency and dosing dependent on the improvement of symptoms. It occurred in 84% of patients who received ide-cel, with a median duration of 5 days (Table 1).

Immune Effector Cell-Associated Neurotoxicity (ICANS)

ICANS includes altered mental status, tremor, dysphasia, perseveration (uncontrollable repetition of a word phrase or gesture), somnolence, and seizures and can progress to cerebral edema. ICANS can occur concurrently with CRS, after CRS has resolved, or in the absence of CRS altogether.

ICANS is graded using the immune effector cell-associated encephalopathy (ICE) scoring system, which includes orientation (to year, month, city, hospital), naming of objects, following commands, handwriting ability, and attention (e.g., the ability to count backwards from 100 by 9).

According to Ms. McClanahan, most CAR T-cell therapy protocols utilize similar ICANS management strategies, starting with anti-seizure medications and progressing on different steroid dosing per symptoms. If there are concerns for cerebral edema, the recommendation is for hyperventilation, hyperosmolar therapy, increasing methylprednisolone, and potentially cyclophosphamide to help shut down the CAR-T inflammation.

"Start interventions early if you have concerns for CRS or neurotoxicity," said Ms. McClanahan. "Studies show that using tocilizumab and steroids for treatment of CRS and ICANS does not negatively affect CAR T-cell therapy outcomes."

Finally, Ms. McClanahan underscored the importance of managing provider and caregiver expectations. Patients who have undergone significant ICANS may have persistent symptoms of delayed responses or "not being quite themselves." Depending on their hospitalization course, patients may also continue to have some weakness and need for continued therapy.

"Patients often ask when they'll start to feel normal," said Ms. McClanahan. "It can often take weeks or even months to recover from CAR T-cell therapy."

Table 1. Cytokine Release Syndrome Management for Idecabtagene Vicleucel

Grade	Tocilizumab	Corticosteroids
Grade 1	Onset < 72 hours after infusion, consider tocilizumab (8 mg/kg) Onset > 72 hours after infusion, treat symptomatically	Consider dexamethasone (dex) 10 mg IV every 24 hours
Grade 2	Administer tocilizumab; repeat every 8 hours as needed. (Do not exceed 3 doses of tocilizumab in 24 hours; maximum total of 4 doses.)	Consider dex 10 mg IV every 12–24 hours
Grade 2	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexe (20 mg every 6 to 12 hours) If no improvement within 24 hours or continued progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day After 2 doses of tocilizumab, consider alternative anticytokine agents	
Grade 3	Per grade 2	Administer dex 10 mg every 12 hours
Grade 3	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dex (20 mg every 6 to 12 hours) If no improvement within 24 hours or continued progression, switch to methylprednisolone 2 mg/kg followed by 2 mg/kg divided 4 times per day After 2 doses of tocilizumab, consider alternative anticytokine agents	
Grade 4	Administer dexamethasone 20 mg IV every 6 hours After 2 doses of tocilizumab, consider alternative anticytokine agents If no improvement within 24 hours, consider methylprednisolone (1–2 g, repeat after 24 hours as needed and taper as indicated)	

Note. Information from Bristol Myers Squibb (2021).

Disclosure

The presenters had no conflicts of interest to disclose.

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