

# Adoptive Cell Therapies: Keeping Pace With New and Emerging Advances

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

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## Abstract

At JADPRO Live 2019, Patricia Mangan, RN, MSN, CRNP, and Edward Stadtmauer, MD, discussed the emerging world of chimeric antigen receptor (CAR) T-cell therapy, including the CAR T-cell process, approved indications and studies in hematologic malignancies, strategies for monitoring and managing emerging toxicities, and future directions in the use of this novel therapy.

While chemotherapy is an effective front-line treatment for numerous hematologic cancers, including acute lymphocytic leukemia (ALL), non-Hodgkin lymphoma (NHL), and multiple myeloma, it doesn't cure all patients of their disease. For those in the relapsed or refractory setting, chimeric antigen receptor (CAR) T-cell therapy has become an effective intervention, and its use in these and other malignancies is on the rise. It's also a multi-step process that requires a great deal of coordination of care. At JADPRO Live 2019, Patricia Mangan, RN, MSN, CRNP, and Edward Stadtmauer, MD, both of Abramson Cancer Center, University of Pennsylvania, reviewed the appropriate indications for CAR T-cell therapy, shared strategies for monitoring and managing associated toxicities, and outlined future directions for the use of these therapies.

As Dr. Stadtmauer explained, CAR T-cell therapy has overcome some of the limitations of chemotherapy by combining the advantages of antibody therapy, which confers novel antigen specificity, cellular therapy, which enables an amplified response, and vaccine therapy, which involves memory activity and promotes persistence (Milone et al., 2009; Figure 1).

## CD19-TARGETED CARs

CD19 is an ideal tumor target, said Dr. Stadtmauer, because it is expressed on the surface of most B-cell malignancies, but its expression is restricted to B cells and their precursors. Furthermore, CD19 is not expressed on pluripotent bone marrow stem cells.

The first FDA-approved gene therapy was for tisagenlecleucel for CD19-positive B-cell precursor ALL that is refractory or in second or later relapse in the treatment of patients up to 25 years of age. Approval was based on

data from the ELIANA study that showed a 6-month overall survival of 78% and a 2-year overall survival of approximately 70% (Maude et al., 2018). In fact, said Dr. Stadtmauer, median duration of remission and median overall survival remain unreached.

Based on this success, adoptive cell therapy was then tested in NHL. As Dr. Stadtmauer reported, between 70% and 80% of patients responded in the original studies, and approximately half of these patients were long-term responders. ZUMA-1 was the pivotal study that led to the approval of axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (Neelapu et al., 2017).

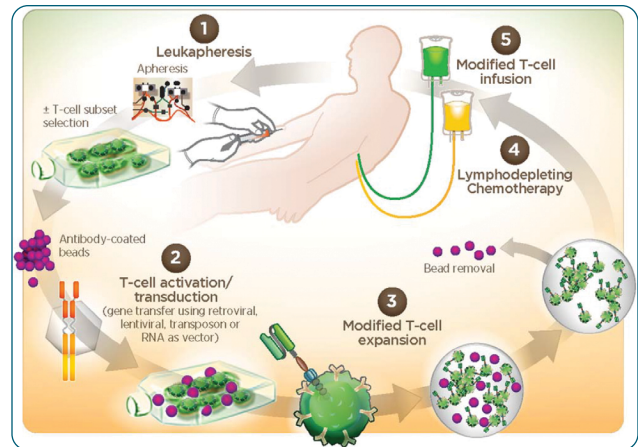
“Although only 50% of patients with NHL go into remission on CAR T-cell therapy vs. 80% response rates in ALL, those who are in remission by 6 months seem to stay there and are doing well in the long term,” said Dr. Stadtmauer. “In ALL, CAR T-cell therapy has also been used as a successful bridge to allotransplant for curative therapy, although many patients have prolonged remissions just from the CD19-directed CAR T cells.”

“These CAR T cells are truly living drugs,” Dr. Stadtmauer continued. “They stay in the patient’s system for a long time, and we think that’s part of the reason they can be so effective.”

## DESIGNING A MYELOMA CAR

As Dr. Stadtmauer reported, B-cell maturation antigen (BCMA) is a candidate antigen target for myeloma because it’s expressed on all plasma cells, highly expressed on myeloma cells, and seems to promote myeloma growth. Initial studies in myeloma using BCMA-directed CAR T cells in heavily-treated patients (seven or more prior lines of therapy, on average) led to responses in 63% to 86% of patients across four studies with very small doses (D’Agostino & Raje, 2019).

According to Dr. Stadtmauer, however, the difference between myeloma CAR T cells and NHL or ALL CAR T cells is that it doesn’t seem to be curative in relapsed and/or refractory patients. Because of this, researchers have explored the



**Figure 1.** Manufacturing overview of CTL019 (a CD19 CAR T-cell product). Courtesy of Dr. Noelle Frey.

idea of using a PI3-kinase inhibitor to enrich the T cells.

“If you can infect and proliferate the T cells that are going to live the longest, then that might improve the outcomes, and early studies with this approach have shown a high response rate (83%) and reduced toxicity,” said Dr. Stadtmauer.

Another approach is to have a dual-binding CAR for improved latching to BCMA. Initial studies with this CD3/4-1BB co-stimulation have yielded very high response rates (88%) and complete responses (68%), said Dr. Stadtmauer, but also high toxicity and diminished progression-free survival (Zhao et al., 2018).

## CANCER TESTIS ANTIGENS

As Dr. Stadtmauer reported, there are a number of other targets being explored with CAR T-cell technology across multiple cancer types, including CD38 and CS1 (SLAMF7), but one promising approach involves cancer testis antigens, which are expressed in a wide variety of cancers, including multiple myeloma (Rapoport et al., 2015). These are good immunotherapy targets due to limited expression on normal somatic tissue, he explained, which decreases the likelihood of ‘on-target off-tumor’ effects. Moreover, the frequency of cancer testis antigen expression tends to increase with cancer stage and recurrence. NY-ESO-1 and LAGE-1a have been detected at higher levels in advanced multiple myeloma.

In the setting of autologous stem cell transplant, said Dr. Stadtmauer, NY-ESO-1c259T-cell

therapy has promising efficacy and acceptable safety, and long-term survival was shown in a refractory population (Stadtmauer et al., 2019).

“It is possible to achieve negative minimal residual disease with this therapy,” said Dr. Stadtmauer. “However, the data have been inconclusive so far. We have yet to see long-term progression-free survival.”

## TOXICITIES ASSOCIATED WITH CAR T-CELL THERAPY

### Cytokine Release Syndrome

Impressive response rates notwithstanding, CAR T-cell therapy carries side effects, and the major off-target toxicity is cytokine release syndrome (CRS).

“The clinical picture of CRS looks very similar to septic shock, with sudden change in status with high fevers, low blood pressure, and hypoxia with supplement oxygen requirement,” said Ms. Mangan, who noted that CRS tends to occur quickly after the infusion of CAR T cells and is thought to be associated with robust cell expansion (Bonifant, Jackson, Brentjens, & Curran, 2016).

As Ms. Mangan reported, lab tests can be monitored to signal CRS with ferritin, which is a marker of acute inflammation, and C-reactive protein, which is a surrogate marker of interleukin 6 (IL-6). Both of these levels increase with active CRS and normalize with the resolution of CRS, she explained. According to Ms. Mangan, CRS can be self-limiting and not require an intervention, but if it progresses, anti-IL-6 therapy with tocilizumab is recommended.

“The onset of CRS varies, but usually occurs within the first 2 weeks of infusion and can last between 7 to 10 days or longer,” said Ms. Mangan. “The first symptom that we tend to see is a very high fever, as high as 104°F or 105°F, followed by malaise, fatigue, and anorexia. As the syndrome progresses, it can become much more systemic, causing loss of blood pressure, hypotension, and hypoxia requiring intensive support. There can also be altered mental status, encephalopathy, and even seizures.”

Because it can rapidly reverse CRS in most patients, said Ms. Mangan, it is mandated to have two doses of tocilizumab on hand prior to the infusion of the CAR T cells (Le et al., 2018). If CRS continues to

worsen after its administration, repeating the dose of tocilizumab and administration of steroids may be warranted. Because CRS is thought to be associated with robust cell expansion, patients with very active disease are sometimes administered CAR T cells over multiple infusions along with careful observation, she added (Figure 2).

### Neurotoxicity

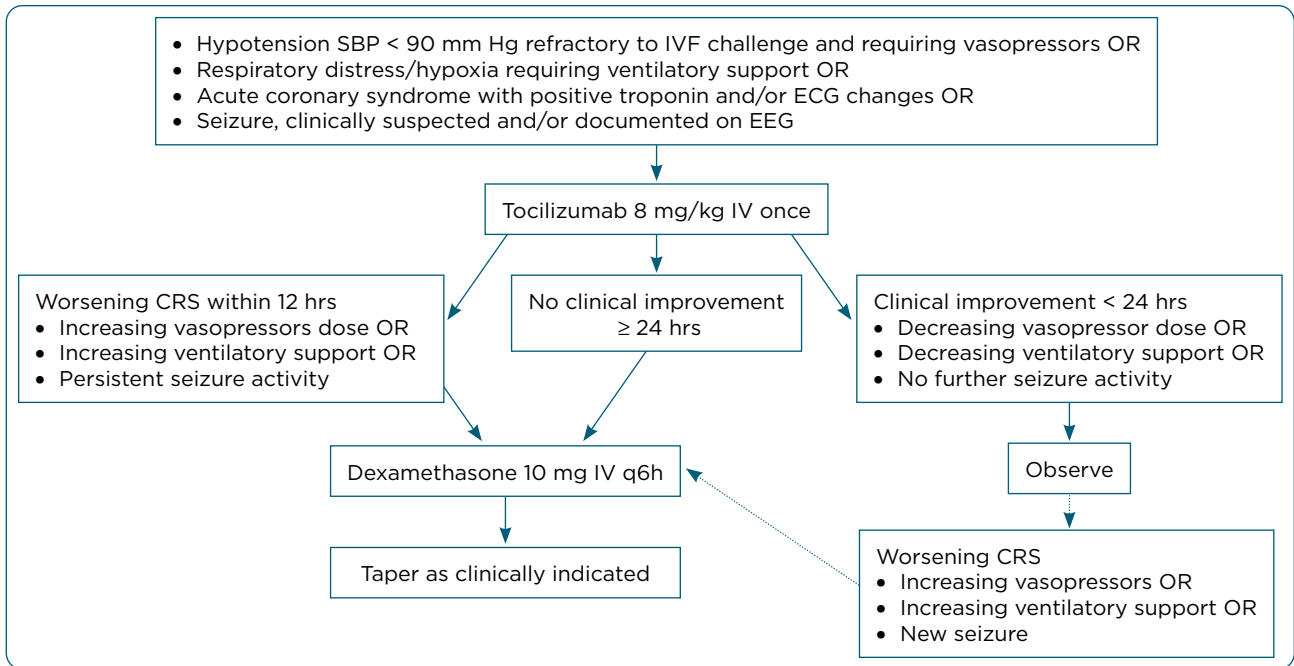
Neurotoxicity is the second most common toxicity associated with CAR T-cell therapy and involves a range of symptoms: diminished attention, language disturbance, confusion, disorientation, agitation, aphasia, tremors, seizures, and encephalopathy.

“Although the pathophysiology is unclear, it is thought to be related to CRS and the expansion of CAR T cells within the central nervous system (CNS),” said Ms. Mangan, who noted that predictors of neurotoxicity include high disease burden and high IL-6 levels on day 1.

Neurotoxicity and CRS follow a different course of onset and resolution. The onset for neurotoxicity varies and can be biphasic. In the early phase, symptoms occur concurrently with CRS symptoms (within the first 5 days). In the later phase, neurotoxicity symptoms begin after CRS symptoms have resolved. According to Ms. Mangan, most neurotoxicity events (88%–98%) occur within 8 weeks after cell infusion (Lee et al., 2018).

Regarding management of symptoms, Ms. Mangan noted that tocilizumab might reverse neurotoxicity during the first phase but not the second phase, and corticosteroids may be used if tocilizumab is not effective. Prophylaxis for seizures is also recommended. Finally, CAR-related encephalopathy syndrome (CRES) requires vigilant supportive care, a neurological consult with diagnostic imaging, and daily electroencephalogram (EEG). Tocilizumab should be considered even for grade 1 CRES, said Ms. Mangan (Table 1).

Additional toxicities associated with CAR T cells include tumor lysis syndrome, B-cell aplasia, and hypogammaglobulinemia. B-cell aplasia and hypogammaglobulinemia correlate with CAR-T persistence, said Ms. Mangan, who noted that these side effects can be successfully managed with intravenous immunoglobulin replacement.



**Figure 2.** Management of cytokine release syndrome. SBP = systolic blood pressure; IVF = intravenous fluid; ECG = electrocardiogram; EEG = electroencephalogram; CRS = cytokine release syndrome; EEG = electroencephalography. Adapted from Park et al. (2016).

To avoid tumor lysis syndrome, uric acid–lowering medications are utilized with high burden of disease. In addition, prophylaxis for opportunistic infections is recommended, including antifungal and fluoroquinolone during the neutropenic period.

**CAR T-CELL THERAPY: A MULTIDISCIPLINARY EFFORT**

Finally, Ms. Mangan emphasized that it takes a village to provide CAR T-cell therapy. It is a labor of many multidisciplinary teams, requiring train-

**Table 1. Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)**

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7–9	3–6	0–2	0 (patient is unarousable and unable to perform ICE)
Depressed LOC attributed to no other cause	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing’s triad

Note. LOC = locus of control; ICP = increased intracranial pressure; EEG = electroencephalogram. Information from Lee et al. (2018).

ing and education about the toxicities, including the patients and their families.

“We couldn’t administer this therapy without a coordinated effort,” she concluded. “As Dr. Stadtmauer mentioned earlier, patient selection is a very important part of success—getting people who need this in as quickly as possible and through the system safely.” ●

### Disclosure

Ms. Mangan and Dr. Stadtmauer have no conflicts of interest to disclose.

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