CAR T-Cell Therapy in the Treatment of B-Cell Malignancies

Target Audience	Oncologists, Oncology Nurses, PAs, Pathologists, Other clinicians involved in treatment
Potential Supporter(s)	**Potential Supporters**: Novartis, Kite Pharma/Gilead, Juno/Celgene **Related agents**: tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel
Preparation Date	June 7, 2018

Summary of Educational Need & Gap Analysis

Background

Immune system modulators have shown encouraging therapeutic potential in a wide variety of cancers. Chimeric antigen receptor T- (CAR T-) cell therapies have shown particular promise, and this approach was recently designated as the American Society of Clinical Oncology (ASCO) 2018 Advance of the Year. [Heymach, 2018] Within the past year, two CAR T-cell therapies have received Food and Drug Administration (FDA) approval for the treatment of a subset of non-Hodgkin's lymphoma (NHL), the most common hematologic malignancy. [FDA approval letters, 2017 & 2018]. Approximately 70,000 new NHL cases are diagnosed and 20,000 patients die of the disease each year in the US. [Siegel, 2018] NHL encompasses multiple subclasses of B-cell malignancies, including B-cell precursor acute lymphoblastic leukemia (ALL), diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma, DLBCL arising from follicular lymphoma, follicular lymphoma, mantle cell lymphoma (MCL), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), among others. [Teras, 2016]

Relapsed or refractory disease has remained a significant challenge in the treatment of these malignancies. In many cases, prior to the approval of CAR T-cell therapies, additional treatment options have not been available for disease that does not respond to first- or second-line therapy. [Brudno, 2018] However, with the recent FDA approvals, CAR T-cell therapies can now be used to treat many of these malignancies. [FDA approval letters, 2017 & 2018]

CAR T therapies employ a patient's own T cells to recognize and kill tumor cells. The recent clinical successes have utilized CD19-targeting CARs in the B-cell malignancies described above, but numerous other CARs are under development for the treatment of both hematological and solid malignancies. These agents are currently under investigation in more than 250 clinical trials worldwide. [June, 2018] In an August 2017 *Medscape* survey of oncologists, the majority of respondents (90%) believed that CAR T-cell therapies would be "important" or "very important" in hematologic malignancies, but less than half knew the names of the now-approved agents or basic information about the products. [Ault, 2017] In the January 2017 issue of the *Annual Review of Pathology*, Jonathan Esensten, MD, PhD, et al noted that "familiarity with the techniques and challenges used to develop T cell therapies is critical for scientists, pathologists, and clinicians who will be working in the development and deployment of these drugs." [Esensten, 2017] Therefore, given the rapid emergence of CAR T-cell therapies, clinicians must be familiarized with the mechanisms of action and therapeutic landscape. [Brudno, 2018]

While CAR T therapies offer promise for the treatment of hematologic malignancies, the potent activation of immune-mediated cytotoxicity using this approach has also led to severe treatment-associated adverse events, including cytokine release syndrome (CRS) and neurotoxicities. [June, 2018] Successful application of CAR T therapies moving forward will require careful monitoring and management of these toxicities. In response to the *2017 Trending Now in Cancer Care* survey, roughly one-third of providers reported feeling "very uncomfortable" with the management of immune-related adverse events and side effects. [ACCC, 2017] Therefore, clinician training is further required to improve familiarity with approaches to manage anticipated toxicities. In the initiative described below, XXX Medical Education will address the need for clinician education related to CAR T-cell therapies in B-cell malignancies.

Gap 1: Clinicians may not be familiar with the mechanisms by which CAR T-cells exert activity against B-cell malignancies and may not fully recognize the clinical potential for CAR T-cell agents.

Within the past year, the FDA has granted approval to two CAR T-cell therapies, tisagenlecleucel and axicabtagene ciloleucel, for the treatment of relapsed/refractory NHL B-cell malignancies. [FDA approval

letters, 2017 & 2018] Through exogenous expression of chimeric antigen receptors (CARs), these therapies enable a patient's own T cells to bind and kill tumor cells. [Ghobadi, 2018] Both currently approved CAR T-cell agents target CD19 expressed on tumor cells. CD19 is considered an ideal target for B-cell malignancies because tumor cells express high levels of this antigen and normal CD19 expression is restricted to B-cells. [Kuehn, 2017] This restricted expression reduces the risk of off-target effects. [Kuehn, 2017]

Knowledge of the molecular structure of CAR molecules is required to understand the mechanism by which CAR T cells exert their cytotoxic functions. CAR molecules, first described in the 1980s, were initially designed to link the single-chain variable fragment (scFv) from a monoclonal antibody to the intracellular domain from the T-cell receptor (TCR). [Gross, 1989] Expression of a CAR molecule on T cells was designed to both promote the binding of these CAR-expressing cells to the target antigen on the tumor cells and activate the effector and self-renewal functions of these T cells. [Lichtman, 2017] However, early studies of first-generation CAR molecules demonstrated limited efficacy, weak T-cell activation, and poor persistence of the CAR T cells after infusion. [Lichtman, 2017]

Given the weak performance of the early CAR-expressing cells, second-generation CAR molecules were designed to incorporate a costimulatory domain. In normal T cells, co-stimulatory molecules (such as CD28, 4-1BB, OX40, and others) expressed on the cell surface bind to cognate receptors on the surface of antigen-presenting cells. This binding is required for T cell proliferation and survival. [Lichtman, 2017] Second-generation CAR molecules include the intracellular domain from one such costimulatory molecule in tandem with the TCR intracellular domain. [June, 2018] Third-generation CAR molecules contain two costimulatory domains in tandem with the TCR intracellular domain. [June, 2018] Thus far, most clinical trials have utilized second-generation CARs containing either a CD28 or 4-1BB costimulatory domain. [Lichtman, 2017] The introduction of the costimulatory domains has led to significantly improved T cell activation and persistence. [Lichtman, 2017]

Because current CAR T therapies utilize a patient's own immune cells, the process to generate the therapy is repeated for each individual patient. Peripheral blood mononuclear cells are collected via leukapheresis, and CD3+ T cells are isolated. [Ghobadi, 2018] The T cells are then activated and expanded ex vivo using recombinant cytokines. [Lichtman, 2017] The CAR molecule is introduced into the T cells via retroviral or lentiviral vectors, and additional ex vivo expansion and quality control are performed. [Ghobadi, 2018] The patient then undergoes lymphodepleting chemotherapy, and the CAR-expressing T cells are reintroduced via a single intravenous injection. [Ghobadi, 2018] Upon recognition of the target tumor cells, the reintroduced T cells are expected to further proliferate and exert cytotoxic T cell functions through secretion of IL-6 and other cytokines. [June, 2018] Clinical responses have been observed within 3 to 4 weeks, with response rates of up to 90%. [Maude, 2018; Turtle, 2017]

Additional details regarding the design and clinical trial outcomes of the CD19-targeted CAR T therapies currently available for NHL malignancies are described below.

Tisagenlecleucel

Tisagenlecleucel is a second-generation CAR containing a CD19-targeting antibody domain coupled with the TCR endodomain in tandem with a 4-1BB activating domain. [Maude, 2018] This molecule is introduced into autologous T-cells via lentiviral transduction. [Maude, 2018] Tisagenlecleucel was approved in August 2017 for the treatment of relapsed/refractory B-cell precursor acute lymphoblastic leukemia (ALL) in pediatric patients up to 25 years of age. [FDA approval letter, 2017] In May 2018, tisagenlecleucel received additional FDA approval for the treatment of adult patients with relapsed/refractory large B-cell lymphoma. [FDA supplement approval letter, 2018]

The initial approval of tisagenlecleucel resulted from a phase 2 trial (ELIANA, NCT02435849) in pediatric ALL patients who had not responded to previous treatment. [Kuehn, 2017] Among 75 patients evaluated, the overall response rate within 3 months was 81%, including 60% of patients who achieved complete remission. [Maude, 2018] The majority (95%) of these responses occurred within 28 days after CAR T-cell infusion. [Maude, 2018] At a median follow-up of 12 months, the median duration of complete remission was not reached. [Maude, 2018] Grade 3 or 4 adverse events were reported in 73% of patients. [Maude, 2018] The tisagenlecleucel CAR T-cells could be observed in the blood for up to 4 years after infusion. [Maude, 2018]

The approval of tisagenlecleucel in adult patients with relapsed or refractory DLBCL was based on a separate phase 2 trial (JULIET, NCT02445248). Among 68 patients evaluated, the overall response rate was 50%, with 32% of patients achieving complete response. [FDA website, 2018] At a median follow-up of 9.4 months, the median duration of complete response was not reached. [FDA website, 2018] Grade 3 or higher CRS and neurotoxicity was reported in 23% and 18% of patients, respectively. [Novartis prescribing information, 2018]

Tisagenlecleucel is currently the only CAR T therapy approved for use in two distinct hematological indications, including both adult and pediatric patients with aggressive B-cell malignancies. [Novartis press release, May 2018]

Axicabtagene ciloleucel

Axicabtagene ciloleucel (axi-cel) is another second-generation CAR containing a CD19-targeting antibody domain. In contrast to tisagenlecleucel, which contains a 4-1BB activating domain, axi-cel couples the TCR endodomain to a CD28 costimulatory domain. [Neelapu, 2017] The axi-cel CAR molecule is introduced into T-cells via retroviral transduction. [Ghobadi, 2018]

Axi-cel was approved in October 2017 based on 6-month results of the ZUMA-1 (NCT02348216) phase 1 and 2 trial for the treatment of adult patients with relapsed/refractory large B-cell lymphoma. [FDA approval letter, 2017] Among 101 treated patients, the overall response rate was 82%, including 54% who experienced complete remission. [Neelapu, 2017] In addition, 40% of patients remained in complete remission at an average follow-up of 15.4 months. [Neelapu, 2017] Grade 3 or higher CRS and neurotoxicity was reported in 41% and 31% of patients, respectively. [YESCARTA package insert, 2017]

Lisocabtagene maraleucel

Lisocabtagene maraleucel (liso-cel) is an additional CD19-targeted CAR T therapy that has not yet received FDA approval. Like tisagenlecleucel, liso-cel contains a 4-1BB costimulatory domain and is transduced into autologous T-cells via lentiviral vector. [Abramson, 2018] However, unlike the therapies described above, liso-cel is formulated into a precise 1:1 ratio of CD4+ and CD8+ CAR T-cells. [Abramson, 2018] This defined composition may improve T-cell persistence and cytotoxicity and reduce treatment-associated toxicities. [Turtle, 2016]

Liso-cel is currently under evaluation in a phase 2 study (TRANSCEND-NHL-006, NCT02631044) to assess safety and efficacy in adult patients with relapsed/refractory B-cell NHL. (Clinical Trails.gov) Early reports have indicated that among 102 patients evaluated, the best overall response rate was 75% and the best complete remission rate was 55%. [Homer, 2018] The median duration of complete response was not reached. CRS was observed in 35% of patients, and neurotoxicity was observed in 19% of patients. [Abramson, 2018]

In addition to the CAR T therapies described above, CAR T agents that target distinct antigens are under investigation in hematological malignancies. These antigens include CD20, CD22, κ-light chain for B-cell

lymphomas; CD30 for Hodgkin and T-cell lymphomas; and B-cell maturation antigen (BCMA) for multiple myeloma. [Brudno, 2018]

Gap 2: Clinicians may not be aware of the toxicities that should be monitored with CAR T-cell therapy and the potential approaches to mitigate the effects of these agents.

While CAR T cells hold promising therapeutic potential, these agents also carry the risk of inappropriate immune response. [June, 2018] Indeed, treatment-associated toxicities have been observed with all CAR T therapies evaluated thus far, and severe or life-threatening adverse events occur in roughly 25% of patients. [Kuehn, 2017] As Sattva S. Neelapu, MD, noted for *HemOnc Today*, CAR T-cell therapies are "...associated with unique toxicities that are unlike side effects observed with traditional chemotherapy or radiation therapy. If the toxicities are not recognized promptly or managed appropriately, they can be fatal. Therefore, physicians and other health care providers involved in the care of these patients need to be educated on how to recognize and manage these side effects." [McDonald, 2017] CAR T-associated adverse events can include B-cell aplasia, cytokine release syndrome (CRS), and neurological toxicities. [June, 2018]

The recognition of target-expressing cells causes CAR T cells to secrete a variety of cytotoxic cytokines. [June, 2018] In addition to killing target tumor cells, normal CD19+ B cells are also targeted. [Lichtman, 2017] As a result, patients treated with CD19-targeted CAR T cells often experience profound B-cell aplasia. [June, 2018] However, replacement therapy with intravenous immunoglobulin can be delivered to manage this loss of B cells. [June, 2018]

The cytokines released by CAR T cells can also trigger a systemic inflammatory response, which can initiate CRS. [Gauthier, 2018] In patients with lymphoid malignancies, CRS is the most common and most severe CAR T-associated toxicity. [Lichtman, 2017] CRS symptoms include fever, hypotension, capillary leak, coagulopathy, and multiorgan failure. [Gauthier, 2018] These symptoms often occur within a few days of CAR T-cell infusion. [Gauthier, 2018] Risk factors for CRS include high bone marrow CD19+ tumor burden, severe thrombocytopenia, CAR T-cell generation from bulk CD8+ T-cells (rather than central memory CD8+ T-cells), lymphodepletion using cyclophosphamide and fludarabine, and high CAR T-cell dose. [Gauthier, 2018] Early and high levels of CAR T-cell expansion in the blood have been associated with severe CRS. [Gauthier, 2018]

Neurological toxicities have also been reported after CAR T-cell therapy in 7% to 63% of NHL patients. [Gauthier, 2018] Symptoms of neurotoxicity, also described as CAR T-cell related encephalopathy syndrome (CRES), include delirium, headache, decreased levels of consciousness, speech impairment, and occasionally seizures and cerebral edema. [Neelapu, 2018] Neurotoxicity usually occurs after CRS, and symptoms may begin after CRS has resolved. [Gauthier, 2018] Like CRS, the neurotoxicities are usually reversible. [Gauthier, 2018]

In September 2017, guidelines for patient monitoring and symptom grading were developed by a CAR-T-cell-therapy-associated TOXicity (CARTOX) Working Group, which was formed by investigators with experience treating patients with four different CAR T-cell therapies. [Neelapu, 2018] The guidelines indicate monitoring timeframes for specific symptoms that might suggest CRS onset as well as suggest circumstances for ICU admittance. [Neelapu, 2018] The CARTOX panel also provided recommendations for a 10-point neurological assessment to be performed at baseline and every 8 hours while the patient is hospitalized after CAR T therapy to identify patients with CRES/neurotoxicity. [Neelapu, 2018]

Approaches for managing

Given the frequency with which patients experience CRS or CRES, clinicians must be prepared with treatment strategies to manage the adverse events. Concurrent with tisagenlecleucel approval, the FDA also approved tocilizumab to treat CRS that occurs with CAR T therapy in patients 2 years of age or older. [FDA press release, 2017] Tocilizumab, an already approved arthritis drug, targets the IL-6 receptor. This molecule suppresses the immune response, leading to the reversal of CRS. [Kuehn, 2017] Responses to tocilizumab can been observed within hours after treatment [Frey, 2017], and complete resolution of the CRS symptoms is expected within 2 weeks after receiving 1 or 2 doses of tocilizumab in the majority of patients. [Kuehn, 2017]

Other approaches for managing CAR T-associated toxicities are still under ongoing investigation. For example, severe CRS is more likely to occur in patients with a high tumor load, so initiating CAR T-cell therapy earlier in the disease progression could potentially minimize this toxicity. [Kuehn, 2017] In addition, titrating the number of CAR T-cells infused into the patient could help reduce CRS cases. [Kuehn, 2017] However, a decrease in the CAR T-cell dose could also compromise the anti-tumor effect, so continued investigation of optimal dose will be important. [Gauthier, 2018]

Conclusion

The use of CAR T therapies is anticipated to continue to expand rapidly over the next few years as alternative receptor antigens are introduced to target a wide variety of both hematological and solid malignancies. [Lichtman, 2017] To continue to provide optimal patient care, clinicians must be prepared with a comprehensive understanding of the mechanisms of action and anticipated toxicities of the CAR T agents that could significantly impact clinical practice.

Learning Objectives:

1. Describe key characteristics of CAR T-cell approaches for cancer therapy, and review the CAR T-cell agents currently available to treat B-cell malignancies.
2. Discuss the safety considerations in the use of CAR T-cell therapies and evaluate potential approaches for alleviating associated toxicities.

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