OCULAR EFFECTS OF CAR-T CELL THERAPY

Know the risks and potential therapeutic benefits associated with this treatment modality.

BY LARS H. ANDERSEN, MD; JASKIRAT S. TAKHAR, MD; AND JOSE J. ECHEGARAY, MD

The advent of chimeric antigen receptor-T (CAR-T) cell therapy in the late 2010s heralded a new era in the treatment of hematologic malignancies and provided new hope in refractory cases. To date, the FDA has approved CAR-T cell class therapies for B-cell acute lymphoblastic leukemia (B-ALL), B-cell non-Hodgkin lymphoma, mantle cell lymphoma, and multiple myeloma.[1-5]

Leukemia can affect nearly any structure of the eye either due to direct tissue infiltration or, more commonly, secondary to anemia, thrombocytopenia, blood hyperviscosity, or immunosuppression.[6,7] Treatment options for ocular disease in the setting of systemic leukemia include systemic chemotherapy, intrathecal chemotherapy, radiotherapy, and bone marrow transplantation.[7] In cases of isolated ocular disease, intravitreal methotrexate and adjunct intrathecal chemotherapy are alternative management options.[8]

ABOUT CAR-T CELLS

CAR-T cells are manufactured from autologous T-cells that have been isolated and genetically modified to express cancer-specific antigen recognition domains on their cell surface.[9,10] This is typically achieved via DNA transfection or transduction via a viral vector into an isolated T-cell population to express CAR-T molecules.[10] These consist of an extracellular domain, an attached transmembrane domain, and an intracellular domain.[10] An effector cellular response can be activated by these CAR-T cells in response to malignant cells expressing specific antigens independent of major histocompatibility complexes, which may be downregulated by malignant cells.[11] The process of manufacturing CAR-T cells takes 2 to 5 weeks, and patients are lymphodepleted prior to the readministration.[12,13]

The effects of CAR-T cell agents on the eye, both therapeutic and deleterious, have been increasingly described in the literature since the initial approval of tisagenlecleucel (Kymriah, Novartis) in 2017. Herein, we present a review of the ocular therapeutic benefits and adverse effects related to CAR-T cell therapies.

THERAPEUTIC POTENTIAL

While the systemic benefits of CAR-T cell therapy are promising, comparatively little is known about the efficacy of CAR-T cell therapy in cases of ocular involvement of hematologic malignancy or in primary malignancies arising in the eye. Prospective studies remain limited due to the infrequency of primary ocular malignancy compared with systemic malignancy.

Preclinical investigations have determined a possible role for CAR-T cell therapy in the treatment of retinoblastoma; in one study, use of chimeric receptors against *CD171* and *GD2* resulted in destruction of nearly all retinoblastoma lines in vitro.[14] In addition, in vitro assays and mouse models of uveal melanoma have shown promising responses to CAR-T cell agents targeted to *HER2*.[15]

A key determinant in the efficacy of CAR-T cell therapy for ocular disease is its ability to penetrate the blood-aqueous and blood-retina barriers. There is single-case evidence demonstrating cytology-proven anterior chamber CAR-T infiltration in a 2-year-old patient treated for combined central nervous system relapse of B-ALL.[16] In addition, promising clinical results have been reported with use of tisagenlecleucel in conjunction with radiotherapy for isolated ocular relapse of B-ALL in a 21-year-old patient.[17]

Another case involved a 61-year-old patient with intravascular lymphoma presenting with a primary vitreoretinal lymphomatous-like lesion. This patient experienced mild

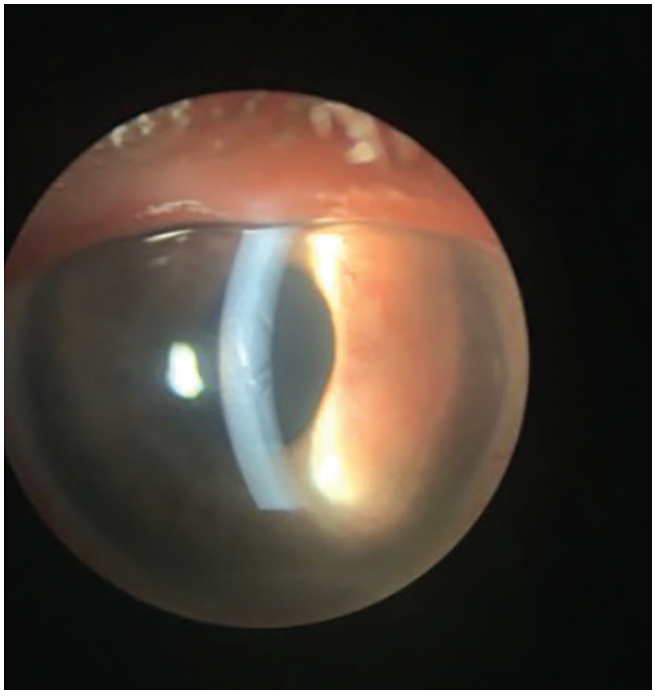

Figure 1. Ocular recurrence of acute lymphoblastic leukemia with pseudohypopyon, iris neovascularization, and nodularity. Uveal infiltration was confirmed via biopsy.

Figure 2. Resolution of iris neovascularization and nodularity with smooth-appearing iris contour.

benefit from local intravitreal methotrexate, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, and systemic high-dose methotrexate therapy, but, thereafter, responded more robustly to CAR-T cell therapy with resolution of the retinal lesion.[18] A recent patient of ours with relapsing ALL (Figure 1) also responded to *CD19*-targeted CAR-T cell therapy with complete resolution (Figure 2).

Conversely, there was a report of ocular recurrence of vitreoretinal lymphoma despite good systemic response to CAR-T cell therapy, as well as presumed recurrence or possible persistent malignancy in the eye despite systemic disease control in a pediatric patient treated with tisagenlecleucel.[19,20] Bilateral orbital plasmacytoma causing ptosis and proptosis as the first sign of plasma cell leukemia recurrence after CAR-T cell therapy has also been reported.[21]

The ability of CAR-T cells to be introduced intravenously and treat diseases in the central nervous system, eyes, and testes begs the question: Which factors determine the success or failure of this treatment in the eyes, as well as other immune-privileged structures?[22] CAR-T cell therapy is a welcome addition to the armamentarium for the treatment of ocular malignancy in the setting of multicentric or systemic disease, but further investigation is warranted.

ADVERSE EVENTS

Serious but medically treatable systemic adverse events associated with CAR-T cell therapy are relatively common, including myelosuppression, cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome. The lymphodepletive course required for most patients prior to CAR-T therapy can result in neutropenia, anemia, thrombocytopenia, B- and T-cell aplasia, and resultant opportunistic infections.[11,12]

CRS represents the most common adverse effect directly attributable to CAR-T cell therapy and has been documented in up to 90% of treatment cases.[10] CRS is characterized by varying degrees of fever, hypotension, and hypoxia and can typically be treated with supportive care in a hospital setting but may progress to circulatory collapse and death. Therefore, in rare cases, it requires more aggressive treatment in the form of corticosteroids or intravenous tocilizumab (Actemra, Genentech/Roche).[23] In our own experience with CRS after a single CAR-T cell infusion, subsequent infusion was deferred. However, the patient did well regarding local and systemic control of disease with the single CAR-T cell infusion, without relapse for 15 months.

Neurotoxicity is another common complication of CAR-T cell therapy, occurring in 60% of patients in the ZUMA-3 trial, with severity ranging from mild (depressed level of consciousness) to severe (comatose).[10] Coagulopathy and encephalopathy syndromes have also been reported with use of CAR-T cell agents.[24,25]

Several ophthalmic adverse effects of CAR-T cell therapy have also been reported, including a variety of new visual, ophthalmic, or periorbital complaints, such as ocular graft-versus-host disease, herpes zoster ophthalmicus, and suspected acute retinal necrosis.[26] Exudative retinal detachment (RD) has been reported secondary to systemic

A KEY DETERMINANT IN THE EFFICACY OF CART-T CELL THERAPY FOR OCULAR DISEASE IS ITS ABILITY TO PENETRATE THE BLOOD-AQUEOUS AND BLOOD-RETINA BARRIERS.

inflammatory syndrome associated with CAR-T cell therapy.[27] Bilateral RD and leukemic infiltration into the retina and optic nerve have also been associated with CAR-T cell use.[28] Cytomegalovirus retinitis confirmed by DNA analysis of a vitreous sample and resultant RD have been reported with CAR-T cell therapy targeted toward multiple myeloma.[29,30] In addition, papilledema has been reported in a patient affected by CAR-T cell therapy-associated encephalopathy.[31]

Overall, ocular adverse events are rare compared with systemic side effects. Many occur secondary to systemic immunosuppression or cytokine release and inflammation secondary to the mechanism of action of CAR-T cell therapy.

FURTHER APPLICATIONS

CAR-T cell therapy has already demonstrated its promise as a treatment for refractory systemic hematologic malignancies, which has garnered interest in expanding its clinical uses. From an ophthalmic standpoint, there has been success with its use in vitro and in animal models for the treatment of retinoblastoma and uveal melanoma, and case reports have shown adequate short-term local control. Further studies of the treatment of primary ocular malignancies and secondary infiltration of ocular and periorbital structures by systemic malignancies with CAR-T cell therapy are warranted to further confirm their potential for ophthalmic care. ■

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LARS H. ANDERSEN, MD
- Ophthalmology Resident, University Hospitals, Case Western Reserve University, Cleveland
- Financial disclosure: None

JOSE J. ECHEGARAY, MD
- President and Owner, Retina Consultants of Orlando, Altamonte Springs, Florida
- Adjunct Professor, Department of Ophthalmology, University Hospitals, Case Western Reserve University, Cleveland
- jjechegaray@retinaconsultantsorlando.com
- X/Twitter @jjeche; Instagram @retina_consultants_orlando
- Financial disclosure: None

JASKIRAT S. TAKHAR, MD
- Ophthalmology Resident, University Hospitals, Case Western Reserve University, Cleveland
- Financial disclosure: None