Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value

Draft Background and Scope

August 9, 2017

Background

Childhood B-Cell Acute Lymphoblastic Leukemia (B-ALL)

Pediatric acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer. There are over 3,000 new cases of ALL diagnosed in children and adolescents (ages 0-19) each year in the United States.[1] The usual treatment for childhood ALL consists of induction, consolidation, and maintenance chemotherapy. Over the past few decades, treatment has improved dramatically and the five-year survival rate, which is considered equivalent to a cure, is approximately 85%.[2-4]

Treatment options are fewer for those children with relapsed or refractory disease (i.e., patients who have relapsed within 12 months of an autologous stem cell transplant or whose disease did not respond to their last line of chemotherapy). Among the approximately 15% of patients who do not respond to initial treatment or relapse after initial treatment, the prognosis is very poor, even with stem cell transplant. Typical treatments for relapsed/refractory ALL include re-induction therapy with different chemotherapy drugs; clofarabine, which has been used as a bridge to stem cell transplant with some success; and stem cell transplant for appropriate patients who attain remission with salvage treatment. Stem cell transplant has been associated with improved survival in some children, but has been associated with an increased mortality in infants.[5,6] Better therapies are needed for those children with relapsed/refractory disease.

Aggressive B-Cell Non-Hodgkin's Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common form of adult non-Hodgkin's Lymphoma (NHL) and accounts for about 25% of newly diagnosed cases of NHL in the United States. Although DLBCL can occur in childhood, its incidence generally increases with age, and roughly half of patients are over the age of 60 at the time of diagnosis.[7]

DLBCL is an *aggressive* (i.e., fast-growing) lymphoma that can arise in lymph nodes or outside of the lymphatic system, in the gastrointestinal tract, testes, thyroid, skin, breast, bone, or brain. The usual treatment for DLBCL includes radiation and systemic chemotherapy plus rituximab. Rituximab is a monoclonal antibody that targets the CD20 antigen, which is a protein expressed in high concentration on the surface of B cells and not on the surface of other cells in the body. The addition of rituximab markedly improved survival in patients with DLBCL. Five-year survival with this regimen is approximately 95%. Options are fewer for those patients whose cancer is refractory to therapy or who relapse after initial therapy. If patients do not respond to second-line chemotherapy, then they are considered for hematopoietic stem cell transplant. However, even after stem cell transplant, five-year disease-free survival is only about 10-20%.[8-10] Thus, new treatment options are needed.

Chimeric Antigen Receptor T-Cell Therapy as a New Treatment Option

Chimeric antigen receptor T-cell (CAR-T) therapy is a novel cellular therapy that uses genetic engineering to alter a patient's own T-cells to produce unique receptors on their cell surface that recognize a specific protein. The CAR-T therapies of interest in this review target the CD19 antigen on B cells, which are the cancer cells in B-ALL and the aggressive B-cell NHLs described above.

There are two CAR-T therapies being evaluated in this review. The first, manufactured by Novartis, is tisagenlecleucel-t (CTL-019). The second, manufactured by Kite Pharma, is axicabtagene ciloleucel (Axi-Cel [KTE-C19]). Both therapies require leukapheresis, a process that allows T-cells to be removed from the patient's body. The cells are then shipped to a central facility that engineers the CAR T-cells, which are then infused back into the patient's bloodstream to fight the cancer.

As the CAR T-cells fight the cancer they release cytokines, which are chemical messengers used by cells to communicate with each other. A unique side effect of CAR-T therapy is cytokine release syndrome, in which the release of many cytokines by the CAR T-cells causes high fevers and low blood pressure requiring intensive care unit (ICU) care. This serious side effect has been observed in about one-third of patients treated with CAR-T therapy and appears to be related to the volume of cancer cells at the time of treatment.[11]

Studies of tisagenlecleucel-t have focused on patients with relapsed/refractory B-ALL ages 3-25 years.[12-14] Studies of axicabtagene ciloleucel have focused on patients with relapsed or refractory aggressive NHL who are ineligible for autologous stem cell transplant.[15-18]

While use of CAR-T therapies in patient populations with limited options has generated much clinical excitement, questions remain regarding the durability of their effects, management of adverse effects such as cytokine release syndrome, and their costs relative to other therapeutic approaches. In conversations conducted to inform this scoping document, patient advocacy organizations expressed hope that CAR-T therapy would offer improved survival and better quality of life compared to other treatments. While CAR-T therapies come with risks of their own, such as cytokine release syndrome and neurotoxicity, patients were optimistic about avoiding the toxicities of treatments like chemotherapy or stem cell transplants.

Stakeholder Input

This scoping document was developed with substantial input from several patient advocacy organizations. ICER also engaged with and received input from several specialty societies, practicing hematologists and oncologists, payers, and pharmaceutical manufacturers to inform the research direction outlined in this scope. Patients expressed hope that CAR-T therapy would be less toxic than traditional chemotherapy and stem cell transplant, resulting in improved quality of life. Clinicians urged us to focus on progression-free survival and overall survival while acknowledging the challenges in doing so given the limited numbers of patients treated and the short duration of follow-up. ICER looks forward to continued engagement with these stakeholders throughout its review of CAR-T therapies for B-cell cancers.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services used in the treatment of patients with B-ALL or NHL that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). ICER encourages all stakeholders to suggest services that could be reduced or eliminated in their responses to the draft scoping document.

Report Aim

This project will evaluate the health and economic outcomes of CAR-T therapy for B-cell cancers. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions.

While ICER has recently presented an approach to assessing value in “ultra-rare” conditions (i.e., ≤10,000 individuals affected), we will **not** be employing these adaptations for the CAR-T review, as we expect the candidate populations for CAR-T therapies to expand beyond the relapsed and/or refractory subsets currently under consideration by the FDA.

Scope of the Assessment

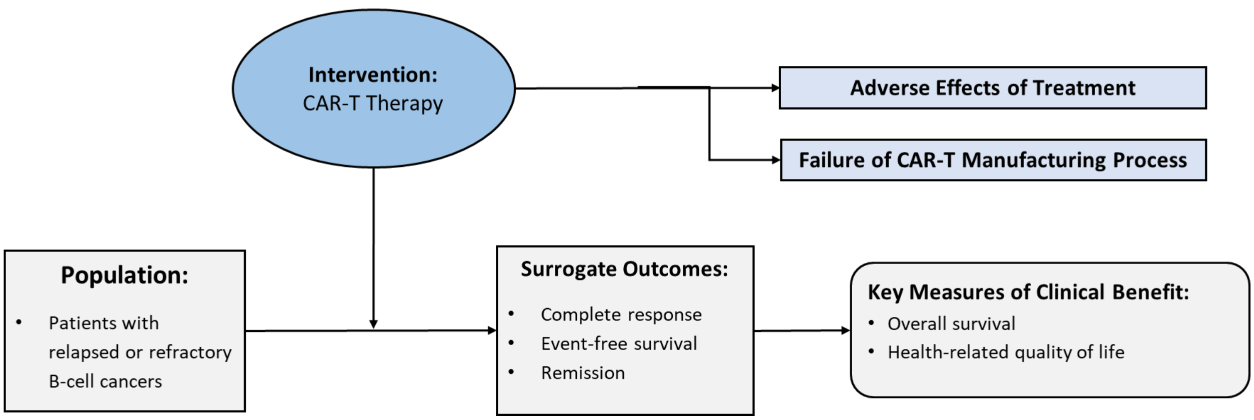
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials, high-quality comparative cohort studies, and case-series given the limited evidence base for these novel interventions. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Wherever possible, we will seek out head-to-head studies of these interventions. Recognizing the current state of the evidence base for CAR-T therapy, we will include case series and compare outcomes with historical controls.

Analytic Framework

The general analytic framework for assessment of therapies for B-cell cancers is depicted in Figure 1.

Figure 1. Analytic Framework: CAR-T Therapy for B-Cell Cancers



Populations

The two separate populations of interest for the review are:

1. Patients ages 3-25 years with relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL)
2. Adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma who are ineligible for autologous stem cell transplant.

Interventions

- CAR-T therapy
  - Tisagenlecleucel-T (CTL019, Novartis)
  - Axicabtagene ciloleucel (KTE-C19, Kite Pharma)

Comparators

In the leukemia population, we intend to compare CAR-T therapy to therapies recommended by National Comprehensive Cancer Network (NCCN) guidelines for relapsed/refractory B-ALL, such as clofarabine, tyrosine kinase inhibitor-based chemotherapy, or blinatumomab as a bridge to stem cell transplant.[19]

In the lymphoma population, we intend to compare CAR-T therapy to salvage chemotherapy regimens such as those used in the SCHOLAR-1 study[20] or second-line therapies recommended by NCCN guidelines such as gemcitabine, dexamethasone, and cisplatin (GDP) as a bridge to stem cell transplant.[21]

Outcomes

The primary goal of treatment is to cure the cancer. Overall survival is the primary outcome of interest.

Where possible, we will report the absolute risk reduction and number needed to treat in addition to the relative risk reduction for the treatment comparisons.

Outcomes	Key Harms
Overall Survival	Cytokine release syndrome
Relapse-free survival	Neurotoxicity
Complete response	Grade 3 or 4 adverse events
Overall remission rate	Discontinuations due to adverse events
Event-free survival	Treatment-related deaths
Quality of life	Infections
	Secondary cancers
	Failed CAR-T therapy manufacturing process

Timing

Evidence on intervention effectiveness and harms will be derived from studies with a median duration of at least three months.

Settings

All relevant settings will be considered including inpatient, clinic, and outpatient settings.

Models Focusing on Comparative Value

As a complement to the evidence review, we will develop a decision analytic model to assess the cost-effectiveness of the treatments of interest (CTL019, Novartis; KTE-C19, Kite Pharma) relative to the previously-mentioned comparators that have available clinical and economic evidence. The model will be evaluated from the health care system perspective (i.e., a focus on direct medical care costs only). There will be two separate populations of interest, including: 1) pediatric and young adult patients with relapsed/refractory B-ALL (CTL019, Novartis), and 2) adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma (KTE-C19, Kite Pharma). Patients are either ineligible for, or previously relapsed following, stem-cell transplantation.

The decision-analytic model structure will be informed by a mock health technology assessment for regenerative medicines and cell therapy products funded by the National Institute for Health Research.[22] Pending available evidence, we will model CAR-T therapy as two approaches: treatment with curative intent, and as a bridge to stem cell transplantation. The model will include a short-term decision tree and long-term semi-Markov partitioned-survival model. The decision tree will calculate the costs and consequences (complete response, complete response with incomplete blood count recovery, partial response, and no response) from leukapheresis through three months post-transfusion. Given available evidence, long-term survival and outcomes will be modeled through a series of semi-Markov partitioned-survival models using the direct extrapolation of event-free survival and overall survival data. The semi-Markov partitioned-survival model will include three states, including: 1) alive and event free, 2) alive with relapsed disease, and 3) dead. Patients will transition between states during predetermined cycles (e.g., one month) over a lifetime time horizon. Parametric survival modeling will inform the five-year post-transfusion survival estimates. Mortality after five years for the alive and event-free health state will be based on general population age- and sex-adjusted all-cause risks of mortality. Scenario analyses will be conducted that assume different mortality rates.

Model inputs will be informed by existing CAR-T and selected comparator clinical evidence and any published economic evaluations. Key model inputs will include the probability of response, event-free survival, overall survival, occurrence of adverse events, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ between treatments to reflect varying effectiveness between interventions; however, health state utility values will be consistent across interventions.

Each intervention will be evaluated in terms of the proportion of responders through three months post-transfusion. The short-term decision tree model will include costs related to infusion preparation (lymphocyte-depleting chemotherapy), treatment acquisition, administration and monitoring, adverse events, and other health care utilization. Results will be expressed in terms of the incremental cost per responder.

Data permitting, health outcomes of life years and quality-adjusted life years (QALYs) gained will also be evaluated. To estimate life years, evidence will be required by intervention, including health state transition probabilities and costs within each health state. To estimate QALYs, the same life-year evidence will be required as well as quality of life weights by health state, including quality of life decrements for adverse events. The incremental cost per life year gained and incremental cost per QALY gained will be calculated pending the availability of these data.

In an additional analysis, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment price and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf.

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