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

Final Background and Scope
September 7, 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 allogeneic 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. Other aggressive B-cell lymphomas include transformed follicular lymphoma (TFL) and primary mediastinal B-cell lymphoma (PMBCL). The usual treatment for aggressive B-cell lymphoma

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 has 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 autologous 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 (Kymriah™ [CTL-019]), which was approved by the FDA on August 30, 2017.[11] 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 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.[12]

Studies of tisagenlecleucel have primarily focused on patients with relapsed/refractory B-ALL up to the age of 25 years.[13-15] In addition, Novartis has announced that it will be seeking an FDA indication for tisagenlecleucel to treat relapsed/refractory DLBCL later this year and has plans to file for other indications in 2018.[16] Studies of axicabtagene ciloleucel have focused on patients with relapsed/refractory aggressive NHL.[17-20]

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. The clinical evidence to date is limited to single-arm trials with short median follow-up time, and there are as of yet no real-world data on clinical benefits and/or harms.

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.

The final scope has been updated to reflect feedback provided in the public comments on the draft scope. We have clarified that we are performing two separate assessments with two separate models: one for pediatric B-cell ALL and one for aggressive B-cell lymphomas, which includes TFL and PMBCL in addition to DLBCL. For both indications, CAR-T therapy is used with curative intent, not as a bridge to transplant, but we will describe those who nonetheless follow CAR-T therapy with stem cell transplantation. We acknowledged the challenges of selection bias comparing the results of the single arm clinical trial results of CAR-T therapy to those of other agents used for relapsed/refractory B-cell malignancies as well as the challenges of extrapolating results from trials with short median follow-up over a lifetime horizon. Our planned modeling approach no longer has a separate "bridge" scenario and the primary outcomes will be cost per life year and cost per quality adjusted life year, not cost per responder. Finally, we clarified that drugs approved under the FDA's orphan drug designation do not always meet the requirements for use of ICER's framework for the assessment of treatments for ultra-rare conditions. In particular, tisagenlecleucel would have been appropriate for ICER's ultra-rare framework if it were only ever to be used for pediatric patients with B-ALL who are refractory to therapy or relapse following second-line therapy, but Novartis has already stated its plan to apply for additional indications in both 2017 and 2018.

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, B-cell lymphomas that could be reduced or eliminated to create additional resources 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 public comment reponses throughout this review.

Report Aim

This project will evaluate the health and economic outcomes of CAR-T therapy separately for relapsed/refractory B-ALL and for relapsed/refractory aggressive B-cell lymphomas. 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 the two CD19 CAR-T therapies to expand beyond the relapsed and/or refractory populations currently under consideration by the FDA. Some stakeholders have suggested that we use the same prevalence thresholds for "orphan" drugs as those employed by regulatory authorities. However, it is our belief that special considerations are not necessary for many of these drugs, as sufficient numbers of patients for routine clinical trial recruitment are available, and outcomes are reasonably well-standardized. Our approach is therefore limited to those therapies intended for individuals with "ultra-rare" diseases, where sample sizes and outcome measurement represent significant challenges.

Scope of the Assessment

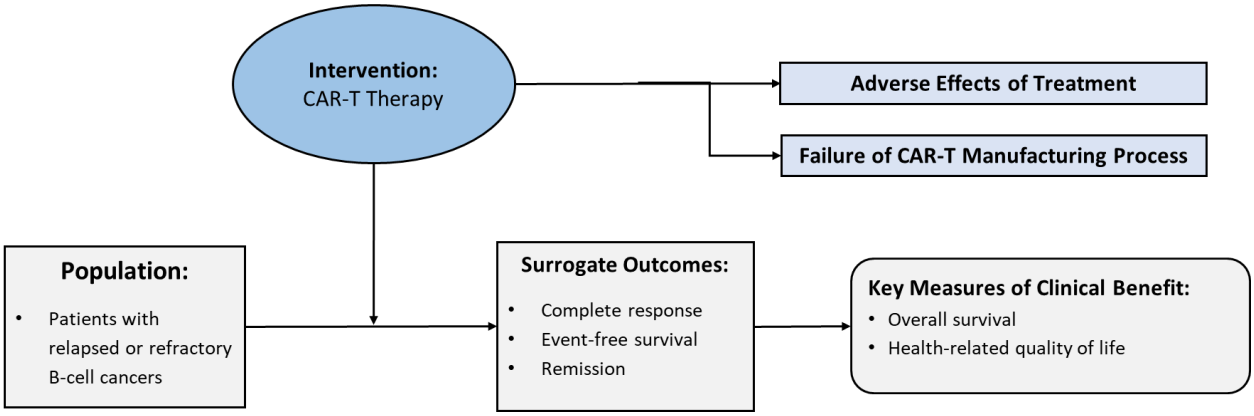
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials, high-quality comparative cohort studies, and case-series given 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 up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (B-ALL) that is refractory or in second or later relapse
2. Adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma (DLBCL, TFL, PMBCL)

Interventions

- CAR-T therapy
    - Tisagenlecleucel (Kymriah™ [CTL019], Novartis) for both B-ALL and aggressive B-cell lymphomas
    - Axicabtagene ciloleucel (axi-cel [KTE-C19], Kite Pharma) for aggressive B-cell lymphomas

Comparators

In the leukemia population, we intend to compare CAR-T therapy to palliative therapy, clofarabine-based therapy, and to blinatumomab-based therapy.[21]

In the lymphoma population, we intend to compare CAR-T therapy to salvage chemotherapy regimens such as those used in the SCHOLAR-1 study.[22]

Because there are no randomized trials comparing CAR-T therapy to salvage chemotherapy, any comparisons will be at risk for selection bias. We will carefully describe the populations in each of the trials including the number of prior chemotherapy lines that failed, prior stem cell transplants,

age, blast levels, and other important prognostic features. Similarly, we will describe all patients enrolled in the CAR-T trials, including those who did not receive CAR-T therapy due to manufacturing failures or disease progression prior to infusion.[23]

Outcomes

The primary goal of treatment is to cure the cancer. Overall survival is the primary outcome of interest. Even though CAR-T therapy can be used with curative intent, some patients treated with CAR-T therapy go on to stem cell transplant. We will describe any stem cell transplants that follow treatment with CAR-T therapy or the comparator therapies.

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.

Table 1. Key Outcomes and Harms

Outcomes	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 (for comparator treatments only)
Event-free survival	Treatment-related deaths
Duration of response	Infections
Quality of life	Secondary cancers
Stem cell transplant	Failed CAR-T therapy manufacturing process
	Disease progression that precludes CAR-T infusion

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 (tisagenlecleucel; axicabtagene ciloleucel) relative to the comparators of interest (i.e., palliative care and clofarabine-based treatment for B-ALL, salvage chemotherapy for B-cell lymphomas). The model will be evaluated from the health care system perspective (i.e., a focus on direct medical care costs only), with a scenario analysis

exploring the societal perspective, pending available evidence. There will be two separate models to reflect the two separate populations of interest, including: 1) pediatric and young adult patients with relapsed/refractory B-ALL (tisagenlecleucel), and 2) adults ages 18 years and older with relapsed/refractory aggressive B-cell lymphoma (axicabtagene ciloleucel and tisagenlecleucel [pending available data]).

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.[24] We will model CAR-T therapy as a treatment with curative intent that will include the option for stem cell transplantation for CAR-T responders, to account for the proportion of trial patients that subsequently received stem cell transplantation. The model will combine a short-term decision tree and long-term semi-Markov partitioned-survival model. The decision tree will calculate the costs and consequences from leukapheresis through assessment of response per the trial protocol. 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-infusion survival estimates. The parametric function will be selected based on best model fit using Akaike information criterion (AIC) values and visual comparison. Transition probabilities will be derived on a monthly basis using the survival function with the best model fit. 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 adjusted for excess morbidity and mortality observed among long-term survivors. 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 within a disease.

The short-term decision tree model will include costs related to infusion preparation (lymphocyte-depleting chemotherapy, bridging chemotherapy, etc.), treatment acquisition, administration and monitoring, adverse events, and other health care utilization. The semi-Markov partitioned-survival model will assess health outcomes of life years gained and quality-adjusted life years (QALYs) gained. To estimate life years, evidence on event-free survival and overall survival will be required by intervention and response, 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 from these data.

In separate analyses, 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 prices 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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