INBRIEF | Summarizing the Evidence

Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma

Key Messages

- Tisagenlecleucel is the first chimeric antigen receptor T-cell therapy to be approved for use in Canada. It is approved for use in children and young adults with relapsed and refractory acute lymphoblastic leukemia and for adults with diffuse large B-cell lymphoma.
- Though patient outcomes following the use of tisagenlecleucel appear promising, there are many uncertainties, including limited long-term data regarding safety and effectiveness.
- The Health Technology Expert Review Panel recommended the provision of tisagenlecleucel in Canada, with conditions, including a reduction in price.

Context

An area of recent research and medical development has been therapies for cancers that do not respond, or do not respond well, to conventional treatment (e.g., chemotherapies and radiation). Chimeric antigen receptor (CAR) T-cell therapies to treat cancers of the blood and lymphatic system show promise as some of these therapies involve manipulating immune cells outside of the body and transferring them back to the patient.

Acute lymphoblastic leukemia (ALL) is a cancer of the blood that is common in childhood, and accounts for 80% of leukemia cases in children. In Canada, it is estimated that 240 children per year will be diagnosed with ALL. With conventional therapies, the cure rate is fairly high (80% to 85%); however, about one in four patients will relapse — meaning their cancer comes back.

Diffuse large B-cell lymphoma (DLBCL) is an aggressive cancer of the blood, and the most common type of non-Hodgkin lymphoma. Although DLBCL can occur at any age, it is more common in adults. It is estimated that each year, one in 10,000 adults will be diagnosed with DLBCL. Approximately 30% to 50% of these patients experience relapse and 10% have refractory disease, meaning their disease does not respond well to treatment. If left untreated, the life expectancy of patients with relapsed or refractory (r/r) DLBCL is three to four months.

Patients with r/r ALL or r/r DLBCL have typically exhausted all curative therapies and are managed with end-of-life care.

Technology

CAR T-cell therapy is a type of therapy that modifies a patient's own cells. CAR T cells are engineered by removing T cells (immune cells) from the blood, modifying them in a laboratory to recognize antigens (protein labels) commonly expressed on cancer cells, and reinjecting them into the patient, where they multiply and attack diseased cells. Tisagenlecleucel is a CAR T-cell therapy for the treatment of adults with r/r DLBCL and children and young adults with r/r ALL.

Issue

While there is a lot of excitement about CAR T-cell therapy, it is a new and complex therapy, and there are some considerations for the implementation of tisagenlecleucel into the health system. Given that CAR T-cell therapies are so new — tisagenlecleucel was approved for use in Canada in September 2018 — they may reach the market with limited evidence on long-term safety and effectiveness. Additionally, these novel therapies tend to be quite expensive, with listed costs ranging from US$65,000 to more than US$1 million. This makes decisions about funding additionally complex and could create a barrier for the provision of these therapies. Lastly, patients who undergo CAR T-cell

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therapies may experience serious side effects, such as cytokine release syndrome, a reaction that can cause various symptoms, including fever, headache, rash, low blood pressure, and trouble breathing. Because of the complexities of CAR T-cell therapy treatment and monitoring, and the need to monitor and treat potential adverse events, there may be special requirements for manufacturing facilities, care facilities, clinician training, and follow-up care for patients.

Methods

CADTH undertook a review of manufacturer-submitted materials and published literature to assess the clinical effectiveness, cost-effectiveness, and implementation and ethical considerations relating to providing and accessing tisagenlecleucel, as well as patient and caregiver perspectives and experiences. The reviews were additionally informed by patient group and clinician input submissions. The Health Technology Expert Review Panel (HTERP) developed recommendations on the provision of tisagenlecleucel based on the evidence presented in the CADTH reports and the HTERP deliberative framework.

Results

Clinical Findings

Treatment with tisagenlecleucel appears promising, but there are many uncertainties. For r/r ALL, a large percentage of patients who remained in the pivotal and supporting trials achieved overall remission within three months (82%) or six months (69%) of infusion. For r/r DLBCL, approximately half (52%) of patients experienced remission within three months of infusion; at 12 months, the chance of survival was estimated at 49%. All patients — for both indications — experienced adverse events, or harms related to the therapy, but it was reported that these were generally manageable with supportive care. However, an important area of uncertainty is the large number of patients who discontinued the studies before and after tisagenlecleucel infusion. Another important area of uncertainty is the lack of long-term data on both how well tisagenlecleucel works and any harms related to the therapy. There is also no evidence on how well tisagenlecleucel works compared directly with other CAR T-cell therapies or other interventions (e.g., stem cell transplant).

Economics Findings

Researchers evaluated the manufacturer's economic evaluations and budget impact analyses. Results should be interpreted with caution because the uncertainty in the clinical evidence could not be fully accounted for in reanalyses conducted by the researchers.

For r/r ALL, tisagenlecleucel, compared with end-of-life chemotherapy, was associated with an incremental cost per quality-adjusted life-year (QALY — a measure of the quantity and quality of life for a patient, as well as value for money for medical interventions) of $53,269. Tisagenlecleucel is likely to be cost-effective for r/r ALL if the willingness-to-pay threshold is $100,000 per QALY. It was estimated from the budget impact analysis that the three-year additional cost of reimbursing tisagenlecleucel, from the perspective of the public health care payer, is $25.6 million.

For r/r DLBCL, tisagenlecleucel, compared with palliative chemotherapy, was associated with an incremental cost per QALY of $211,870. Tisagenlecleucel is not likely to be cost-effective if the willingness-to-pay threshold is $100,000 per QALY. It was estimated from the BIA that the three-year cost of reimbursing tisagenlecleucel is $387.4 million from the perspective of the public health care payer.

Ethics Findings

The Ethics Review conducted a review of published literature and analysis on ethical issues relating to the provision of tisagenlecleucel. Because tisagenlecleucel is such a new therapy, this meant that some of the key ethical considerations needed to balance the hope and possible benefit from the treatment, with uncertainty and lack of clinical evidence. Additionally, there may be barriers to accessing the therapy (such as patient criteria or being far from a treatment facility) that need to be considered. The cost of the treatment, from both the patient and societal perspectives, must also be taken into account. There may also be legal questions about who owns genetically modified T cells.

Implementation Findings

The Implementation Review considered input from patient groups and clinicians, published literature relating the implementation of tisagenlecleucel, and a synthesis of qualitative literature on patients' and caregivers' perspectives. The Implementation Review highlighted the challenges surrounding how to provide access to tisagenlecleucel and the challenges decision-makers might face. Issues such as access to treatment sites, supporting patients and their caregivers who need to travel for treatment, and concerns about unequal access are challenges decision-makers may face. There exists a need to develop eligibility criteria for patient selection that anticipates potential clinician and patient challenges that may arise when applied. The review also highlighted the limited and uncertain clinical evidence, and the need for monitoring long-term safety and effectiveness.

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