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INBRIEF | Summarizing the Evidence

Axicabtagene Ciloleucel for Large B-Cell Lymphoma

Key Messages

- The Health Technology Expert Review Panel recommends the provision of axicabtagene ciloleucel in Canada, with conditions, including a reduced price.
- Though patient outcomes following the use of axicabtagene ciloleucel appear promising, there are many uncertainties, including limited long-term data regarding safety and effectiveness.
- There are challenges and opportunities for providing axicabtagene ciloleucel in Canada, which relate to managing adverse events, collecting long-term data, determining appropriate oversight of treatment sites, providing access to treatment sites, possible patient and caregiver travel, and the need for clear and transparent patient eligibility criteria.

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. These therapies involve manipulating immune cells outside of the body and transferring them back into the patient.

Large B-cell lymphomas are aggressive cancers of the blood, and some of the most common types of non-Hodgkin lymphoma (NHL). NHL accounts for 83% of all cases of lymphoma in Canada, and there are several subtypes, some of which may be treated in a similar manner. Treatments for large B-cell lymphomas include chemotherapy, immunotherapy, radiation therapy, and stem cell transplant. These therapies work for some patients; however, in the most common subtype of NHL, an estimated 10% of patients do no respond to these treatments, and an estimated 30% to 50% of patients relapse after treatment. For patients who experience relapse, or have hard-to-treat disease (i.e., refractory disease), there are limited treatment options and a short life expectancy. Patients with relapsed or refractory large B-cell lymphomas have typically exhausted all 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. Axicabtagene ciloleucel is a CAR T-cell therapy for the treatment of adults with certain types of large B-cell lymphoma. In February of 2019, Health Canada approved the use of axicabtagene ciloleucel for adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and diffuse large B-cell lymphoma arising from follicular lymphoma.

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 axicabtagene ciloleucel into the health system. Given that CAR T-cell therapies are so new — the first therapy (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 greater than US$1 million. This makes decisions about funding additionally complex and could create a barrier for the provision of these therapies. Finally, patients who undergo CAR T-cell therapies may experience serious adverse effects (i.e., a negative side effect of using the therapy), 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 the need to monitor and treat potential adverse events, there may be special requirements for manufacturing facilities, treatment sites, 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, implementation and ethical considerations, and patient and caregiver experiences related to providing and accessing axicabtagene ciloleucel. The reviews were additionally informed by patient group and

clinician input submissions. The Health Technology Expert Review Panel developed recommendations on the provision of axicabtagene ciloleucel based on the evidence presented in the CADTH reports and the Health Technology Expert Review Panel deliberative framework.

Results

Clinical Findings

Treatment with axicabtagene ciloleucel appears promising, but there are many uncertainties. A large percentage of patients who were treated in the pivotal trial achieved either complete or partial response within six months (71%) or 24 months (74%) after infusion with axicabtagene ciloleucel. The overall survival at 24 months was 50.5% of patients. All patients experienced at least one adverse event, and 56% of patients experienced a serious adverse event. However, there was uncertainty regarding the evidence — specifically, how well axicabtagene ciloleucel works in the long term, any long-term side effects, and how well the therapy performs in the real world.

Economics Findings

Researchers evaluated the manufacturer's submitted economic evaluation and budget impact analysis. The results should be interpreted with caution because the uncertainty in the clinical evidence could not be fully accounted for in the reanalyses conducted by CADTH. Axicabtagene ciloleucel compared with best supportive care was associated with an incremental cost of $226,131 per quality-adjusted life-year (QALY; a measure of the quantity and quality of life for a patient). Axicabtagene ciloleucel was not likely to be cost-effective if the willingness-to-pay threshold was $50,000 or $100,000 per QALY (both of which are often used as standard thresholds in Canada). The cost-effectiveness of axicabtagene ciloleucel compared with other CAR T-cell therapies is unknown. It was estimated from the budget impact analysis that, from the perspective of the public health care payer, the three-year additional cost of reimbursing axicabtagene ciloleucel nationally is $98.8 million if tisagenlecleucel (the other CAR T-cell therapy currently available for this indication) is also reimbursed.

Ethics Findings

The ethics review involved a review of published literature and analysis on ethical issues relating to the provision of axicabtagene ciloleucel. The ethics review considered the uncertainty of the clinical and economic evidence; because this is such a new therapy, a key ethical consideration involves balancing the protection of patients with the possible benefits received from the treatment. Additionally, there may be barriers to accessing the therapy (such as living far from a treatment facility or limited availability of CAR T cells due to manufacturing constraints) that may need to be considered and may require the development of clear and transparent eligibility criteria. The high cost of the treatment, from both the patient and societal perspectives, must also be considered. Issues such as informed choice and patient consent remain relevant. 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 axicabtagene ciloleucel, and a synthesis of qualitative literature on patients' and caregivers' perspectives. The implementation review highlighted the challenges of how to best provide axicabtagene ciloleucel in Canadian jurisdictions. There is a need to adequately manage potential toxicities and adverse events and collect data to address uncertainties in long-term safety and effectiveness. The proposed model for offering axicabtagene ciloleucel is in manufacturer trained and qualified hematopoietic stem cell treatment sites. As more CAR T-cell products enter the Canadian market, the manufacturers' role in the oversight of treatment facilities may mean additional complexity for treatment sites that deliver CAR T-cell therapies. Additionally, decision-makers may face challenges in supporting patients and their caregivers who need to travel for treatment. There exists a need to develop eligibility criteria for real-world patient selection that anticipates potential clinician and patient challenges that may arise.

Read more about CADTH and this topic at:
cadth.info/31wa1Jw

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