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HEALTH OUTCOMES RESEARCH

CAR-T THERAPY: CHALLENGES FOR IMPLEMENTATION

KEY MESSAGES

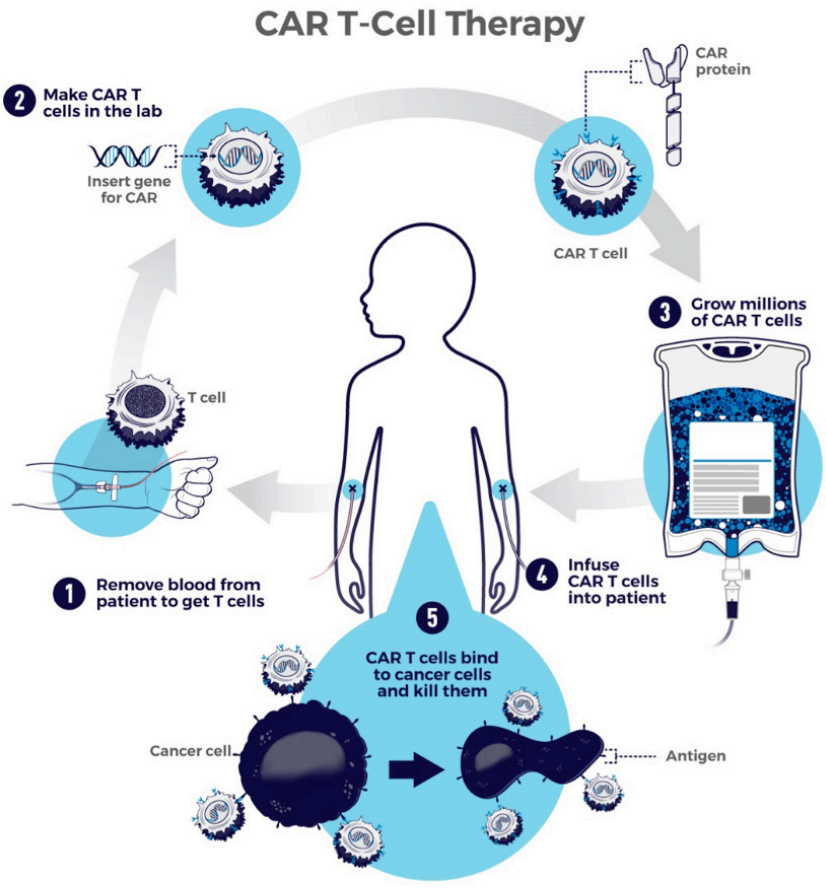
- Chimeric antigen receptor (CAR) T-cell therapy is a rapidly emerging and novel therapy which utilizes a patient's own immune cells to treat their cancer.
- CAR-T therapy has received approval from Health Canada for limited oncology indications; however, pricing and reimbursement in Canada is ongoing.
- Challenges to implementation include: administrative infrastructure (including equitable access to certified treatments centers), manufacturing challenges, standard operating procedures, and post-infusion care.
- Real-world evidence (RWE) is needed to determine the long-term prognosis and safety of CAR-T therapy and the real-world cost of treatment.

INTRODUCTION

In 2017, autologous chimeric antigen receptor (CAR) T-cell therapy, tisagenlecleucel (Kymriah®, Novartis), became the first gene therapy approved in the United States for acute lymphoblastic leukaemia in children and young adults. In 2018, regulatory approval in the UK and Canada followed suit, approving Kymriah® for some patients with relapsing/refractory (r/r) hematological malignancies. These announcements were met with both fanfare and skepticism, due to the dramatic evidence of efficacy and limited patient data, respectively. More recently CADTH has completed an Optimal Use report for Kymriah®.[1] The report confirmed clinical benefit, while acknowledging the unique administrative, regulatory, and reimbursement challenges. Here, we assess the uncertainties and challenges facing CAR-T therapy implementation in Canada.

PREPARATION AND ADMINISTRATION OF CAR-T

Administration of CAR-T therapy is a complex process involving a clinical and commercial partnership. Preparation and delivery of CAR-T therapy involves several steps. First, infection-fighting T-cells are harvested from a patient's blood. The in a laboratory environment, DNA that encodes a cancer-targeting CAR is introduced to the T-cells from the patient's blood sample via a viral vector. While the T-cells grow, the patient undergoes chemotherapy to create a receptive environment for the reintroduction of the modified T-cells. Finally, the CAR T-cells are transferred into the patient's blood stream with genetically encoded instructions to kill cancer cells.



Credit: National Cancer Institute

REGULATORY APPROVAL

For some, CAR-T therapy is a revolution in cancer care. Successful CAR-T therapy has been proven to be so powerful that a single, genetically modified T-cell returned to a patient's bloodstream has lead to complete remission.[3] The average patient response is nearly as impressive. Interim analysis of Kymriah® in a trial for r/r pediatric acute lymphoblastic leukemia (ALL) showed that 81% of patients achieved complete remission at three months.[4]

Health Canada approved Kymriah® for children and young adults (< 25 years of age) with r/r B-cell ALL and adults with r/r diffuse large B-cell lymphoma (DLBCL). Health Canada supports the use of CAR-T therapy for these restricted indications since they present life-threatening outcomes, poor prognoses and limited treatment options. Therefore, the potential efficacy of CAR-T therapy outweighs the associated uncertainties for these cancers.

While some patients have shown unprecedented responses to CAR-T therapy, as evaluated by surrogate primary endpoints, the long-term prognosis of these individuals remains uncertain. As such, CAR-T therapy is currently only indicated for patients who have exhausted all other treatment options; therefore, no standard-of-care exists with which to conduct a prospective comparison. However, these limitations did not dissuade Health Canada from approving Kymriah® for limited indications which is suggestive of the regulatory body's view of CAR-T therapy's tremendous potential. Nevertheless, potential must realistically be balanced against cost, especially when costs associated with the implementation of CAR-T therapy may lead to displacement of resources for other therapies needed for larger populations.

REIMBURSEMENT CHALLENGES

In Canada, regulatory approval does not guarantee access if the price of an emerging therapy is too high. Current pricing for a single dose of Kymriah® is $475,000 USD. Beyond the treatment itself, additional costs of administration include: for preparatory chemotherapy, leukapheresis and cell infusion, management of side-effects (occurring in nearly all tested individuals), and biologics to treat cytokine release syndrome (the most significant CAR-T toxicity occurring in about one third of patients).

While a single CAR-T infusion may enable many cancer-free years for some individuals, nearly half of CAR-T recipients require additional stem-cell transplantation during remission at an estimated cost of $200,000 USD.[7] As such, the true cost of CAR-T therapy is difficult to estimate and represents a substantial risk for payers. For instance, the editorial staff at Lancet Oncology bemoaned the payer agreement the UK National Health Service (NHS) entered into with Novartis just days after Kymriah® was approved for use in the EU.[8] Although the undisclosed price agreed by NHS was certainly less than the list price, Lancet Oncology noted that any payer agreement for an uncertain, complex treatment requiring infrastructure investment and long-term monitoring may be imprudent.[8]

In the US, the Institute for Clinical and Economic Review (ICER) released an evidence report on the effectiveness and value of CAR-T therapy modelled against a chemotherapy arm.[9] While acknowledging the limitations associated with the comparative evidence (some patients receiving CAR-T therapy had previously failed the chemotherapy comparator), the report found current pricing of CAR-T therapy to be aligned with the therapeutic and economic benefits. However, the ICER report did note in the sensitivity analyses that cost-effectiveness estimates frequently extended above commonly cited thresholds when model inputs were varied. To offset these risks, ICER recommended identifying areas of waste and low-value care in the treatment of leukemias and lymphomas. These cost savings could increase the capacity for health care budgets to incorporate CAR-T therapy in the short-term.

In January of 2019, the Canadian Agency for Drugs and Technologies in Health (CADTH) released their Optimal Use review of Kymriah®.[1] This review followed a different pathway than other therapies, reflecting the novelty of CAR-T. Review of CAR-T fell under the health technology assessment (HTA) process for medical devices and clinical interventions, diverting the review from CADTH's traditional Common Drug Review (CDR) or pan-Canadian Oncology Drug Review (pCODR). The reasons cited include feedback from the Ministries of Health and the Canadian Association of Provincial Cancer Agencies.

Broadly, CADTH's review answered the question "How should the provision of Kymriah® for pediatric and young adults with r/r B-cell ALL and adults with r/r DLBCL be structured?" Separate recommendations were issued for the two indications by the Health Technology Expert Review Panel (HTERP), informed by published reports, clinician and patient input, and CADTH reanalysis of Novartis-generated economic evaluations. Missing from the report is a clear recommendation for or against public funding. Instead, HTERP called for a reduction in price to meet the willingness-to-pay (WTP) threshold of $50,000 to $100,000 per quality-adjusted life year (QALY) gained: namely, a 10% reduction for pediatric r/r ALL and a 45-65% reduction for adult r/r DLBCL. The sizeable difference in recommended pricing reflects the indication-specific clinical efficacy and QALYs gained. The Canadian list price for Kymriah®, estimated patient population, and the costs used to calculate the budget impact submission were not reported. Price negotiations with Novartis are underway but have also taken a non-traditional route; rather than going through the pan-Canadian Pharmaceutical Alliance, Novartis is negotiating with Cancer Care Ontario who will represent all of the provinces.

While the price negotiations are underway in Canada, it will be interesting to see if a value-based agreement will be considered. In the US, Novartis offered outcomes-based pricing to designated clinical centers to cover all treated patients regardless of their insurance plan. In this scenario, Novartis only bills centers for pediatric and young adult patients who respond to CAR-T therapy at the end of the first month post-infusion. This pricing arrangement protects payers from failures in CAR-T manufacturing, occurring in 8% of patients reported in a recent trial.[10] However, the thirty day outcome may not be an appropriate time point for measuring response as 37% of the patients meeting response criteria at one-month relapse within a year.[4] Research is ongoing to improve the proliferation and persistence of CAR-T cells, enhancements that correlate with deeper and more durable responses.

IMPLEMENTATION OF CAR-T THERAPY IN CANADA

Delivering CAR-T therapy poses unique challenges, requiring new health system capacities and infrastructure. A recent review of commercial CAR-T therapy by Memorial Sloan Kettering Cancer Center identified several essential tasks that are required for successful delivery.[11] These tasks echo those outlined in CADTH's Optimal Use report.

1. ADMINISTRATIVE INFRASTRUCTURE

First, administrative infrastructure is needed to refer, screen and evaluate prospective patients. Kymriah® will only be delivered at Novartis-accredited sites by Novartis- and institution-accredited medical staff with expertise in CAR-T therapy. Therefore, administrative staff will need to know which patients to refer, and to what institutions. Once eligible patients are identified, they will undergo a consultation with doctors and staff with CAR-T expertise. CAR-T patients are required to stay within two hours of the treatment center for at least one month. Patients must have a live-in caregiver and the financial means to temporarily relocate—a requirement that may result in access inequities. To overcome potential inequities, CADTH recommends the creation of interprovincial agreements including financial and logistical support for required travel and short-term relocation.

2. MANUFACTURING

The manufacturing of CAR-T therapy involves two types of centers, a certified apheresis center and cell processing facility, both of which require extensive Novartis contracting.[1] In the US, Kymriah® is manufactured at a single facility. To scale-up production in the US, Novartis will need to certify facilities where T cells are activated, genetically modified, and expanded.

In Canada, preparation for CAR-T and other cell-based therapies in underway with the Centre for Commercialization of Regenerative Medicine (CCRM) and GE Healthcare (GE) collaborating to form the new Centre for Advanced Therapeutic Cell Technologies (CATCT). The Toronto based CATCT is funded by a $20 million grant from the Federal Economic Development Agency for Southern Ontario with matching funds from GE. The Centre brings together university and pharmaceutical scientists to optimize and scale-up CAR-T therapy production. CATCT's expertise and biomanufacturing capacity is a necessary investment given Novartis's recent struggle to produce Kymriah® in the US within dose specifications for commercial use.[12] In Canada, the manufacturing of CAR-T products will be regulated by Health Canada and the Foundation for the Accreditation of Cellular Therapy (FACT), which sets international standards for cell therapy products. Novartis will negotiate with Health Canada and FACT to establish achievable commercial standards for Kymriah® in Canada.

3. STANDARD OPERATING PROCEDURES (SOPS)

Numerous SOPs must be developed at the treatment facility for patients receiving CAR-T therapy. Since the manufacturing of Kymriah® takes two to four weeks to obtain the minimal cell dose, efforts are underway to reduce the time to infusion. Until then, patients require bridge therapy to prevent cancer progression. Several days prior to CAR-T infusion, patients undergo a lymphodepleting regimen to enhance the proliferation of CAR-T cells. Importantly, there is no current standardized conditioning regimen.

1 Procedures include plasma exchange, cytapheresis (including stem cell collections and photopheresis)

Aggressive lymphodepletion increases both T cell proliferation and toxicities. More data are needed to define bridging and lymphodepleting strategies tailored to the patient's burden of disease. Next, Kymriah® is shipped frozen to the treating facility. Protocols are needed to track, thaw, and administer the CAR-T therapy as per FACT guidelines. Additionally, pharmacy staff will need to be trained to receive and store cell products, which are designated for a specific patient. These SOPs will need to be updated in response to improvements in CAR-T technology and clinical experience.

4. POST-INFUSION CARE

Post-infusion care is complex and uncertain. While CAR-T therapy does not require hospitalization, patients are at risk for severe adverse events (AEs) and must be monitored closely. The most frequent severe AE is cytokine release syndrome, which can require intensive care and aggressive immunosuppression. Occasionally, CAR-T therapy can cause neurological toxicities including encephalopathy, seizures and death. Therefore, regulated management guidelines are needed to coordinate care across subspecialties. The rate of AEs requiring hospitalization in a real-world setting is currently unknown. Thus, treating centers must estimate patient volumes and assess capacity for inpatient admission and subspecialty care. Patients are assessed thirty days post-infusion for clinical response. Based upon clinical trial data the majority of CAR-T therapy patients will meet the criteria for remission at this time point. However, long-term monitoring is necessary to identify relapsing patients and to generate additional efficacy and safety evidence.

GENERATING ADDITIONAL EVIDENCE

1. LONG-TERM SAFETY AND EFFECTIVENESS

CAR-T therapy has only been tested in single-arm, open-label clinical trials, with small cohorts of patients. CADTH cited the current clinical evidence as insufficient, necessitating longer-term follow up studies and real-world data (RWD) generation through patient registries. FACT maintains a patient database to follow patients treated with cellular therapies. Facilities with FACT-accreditation could build upon this infrastructure to track CAR-T therapy outcomes through a pan-Canadian registry. However, not all provinces have FACT-accredited sites. Such inequities will need to be addressed to ensure access for all eligible Canadians and proper monitoring and documentation of outcomes.

2. REAL-WORLD COST OF CAR-T

The questions surrounding the real-world costs of CAR-T therapy, are currently unknown and could be address through the collection of real-world data (RWD). As commercial use of CAR-T therapy increases, healthcare utilization and associated costs could be used to determine the value of the therapy to the health systems in Canada. Using RWD to establish cost-effectiveness profiles, stratified by CAR-T therapy products and disease indications, could inform patient care and indication-based pricing.

CONCLUSION

Despite many unknowns, CAR-T therapy is poised for implementation in Canada. For patients with previously intractable malignancies, CAR-T therapy represents hope. Realizing this hope in a real-world, Canadian setting will require overcoming significant financial, regulatory, reimbursement and administrative barriers. CADTH's Optimal Use report on Kymriah® provides a road-map to building the necessary infrastructures and capacities. Provinces will need to collaborate to ensure equitable and timely access for patients across Canada.

Coordinated national-level preparation is essential for the coming deluge. CAR-T therapies in development will to target more than 40 cancers,and preclinical studies are underway for applications in infection, autoimmunity and allotransplantation. [13 & 14] Timely collection and analysis of RWD will inform best practices and refine indications to ensure cost-effectiveness and optimal outcomes.

ABOUT MEDLIOR

As an independent Canadian consultancy, Medlior offers a variety of research services, as well as access and expertise with Canadian health system data. We collaborate with experienced biostatisticians and epidemiologists from academia and the health systems to provide expertise in examining provincial and national-level datasets, surveys, and patient reported outcomes, to answer your research questions. Medlior is also experienced with both the UK and Canadian HTA processes and can support you in integrating RWE into your HTA projects. For examples of how RWE has been used in previous Canadian HTAs, see Medlior's white paper on the recent uses of RWE in CDR and pCODR submissions.

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REFERENCES

1. Tisagenlecleucel for acute lymphoblastic leukemia and diffuse large B-cell lymphoma: Recommendations. Ottawa: CADTH, 2019 Jan.
2. Maus MV, June CH. Making Better Chimeric Antigen Receptors for Adoptive T-cell Therapy. Clin Cancer Res 2016; 22(8): 1875-84.
3. Fraietta JA, Lacey SF, Orlando EJ, et al. Determinants of response and resistance to CD19 chimeric antigen receptor (CAR) T cell therapy of chronic lymphocytic leukemia. Nat Med 2018; 24(5): 563-71.
4. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med 2018; 378(5): 439-48.
5. Ruella M, Xu J, Barrett DM, et al. Induction of resistance to chimeric antigen receptor T cell therapy by transduction of a single leukemic B cell. Nat Med 2018; 24(10): 1499-503.
6. Dengler R. Cancer immunotherapy company tries to explain deaths in recent trial. Science 2017.
7. Majhail NS, Mau LW, Denzen EM, Arneson TJ. Costs of autologous and allogeneic hematopoietic cell transplantation in the United States: a study using a large national private claims database. Bone Marrow Transplant 2013; 48(2): 294-300.
8. The Lancet O. CAR T-cell therapy: perceived need versus actual evidence. Lancet Oncol 2018; 19(10): 1259.
9. Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value: Institute for Clinical and Economic Review, 2018.
10. Buechner JKMF, M; Salmon, F; Jager, U. Chimeric Antigen Receptor-T Cell Therapy: Practical Considerations for Implementation in Europe. HemaSphere 2018; 2(1).
11. Perica K, Curran KJ, Brentjens RJ, Giralt SA. Building a CAR Garage: Preparing for the Delivery of Commercial CAR T Cell Products at Memorial Sloan Kettering Cancer Center. Biol Blood Marrow Transplant 2018; 24(6): 1135-41.
12. Pagliarulo N. In CAR-T, manufacturing a hurdle Novartis has yet to clearDec. 6, 2018, 2018. https://www.biopharmadive.com/news/in-car-t-manufacturing-a-hurdle-novartis-has-yet-to-clear/543624/ (accessed January 18, 2019).
13. Kingwell K. CAR T therapies drive into new terrain. Nat Rev Drug Discov 2017; 16(5): 301-4.
14. Maldini CR, Ellis GI, Riley JL. CAR T cells for infection, autoimmunity and allotransplantation. Nat Rev Immunol 2018; 18(10): 605-16.

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