Accelerating the Journey from Idea to Utilization

CAR-T: A Next Gen Immunotherapy

About I2U

Idea to Utilization (I2U) is an initiative committed to identifying and addressing the barriers impeding the uptake of breakthrough medicines across Canada. With foundational funding from Novartis, this collaborative mechanism is being led by Santis Health and guided by an independent panel of advisory board experts. **To learn more, visit www.i2u.ca**

ABSTRACT

CAR-T Therapy showcases advances in personalized medicine by re-engineering the human body's immune cells to treat otherwise incurable cancers. This report focuses on the implementation challenges associated with delivering CAR-T therapy in Canada. Through the analysis, four key barriers are identified: the additional need for administrative infrastructure (i.e., specialized healthcare personnel), limited manufacturing capabilities, the need for cold chain management infrastructure and constrained capacity for post-infusion care. These lessons are designed to support the current and future scope of CAR-T therapies, especially as it expands to address broader treatment areas with new applications coming down the pipeline.

CAR-T Therapy: A Breakthrough Therapeutic

Around the globe, an estimated 1.28 million blood cancer cases occur annually, accounting for approximately 7% of all cancer cases.[i] The conventional treatments for blood cancers, including Leukemia, Lymphoma and Multiple Myeloma, has been chemotherapy and stem cell transplants.[ii] Unfortunately, some patients will still experience refractory cancer, or relapse after receiving treatment. Immunotherapy, in the form of CAR-T cell therapy, has created significant elation amongst researchers and oncologists because it has demonstrated the ability to eliminate advanced blood cancers and maintain patient remission.[iii] CAR-T Therapy has generated a new personalized, targeted treatment option for patients facing an otherwise debilitating prognosis. It showcases the advances in immunology and drug development as a personalized therapeutic borne out of a patients' own T-cells, re-engineered to fight cancer. Currently, there are six commercial CAR-T cell therapies approved by Health

Canada[iv], of which five have been recommended for reimbursement by the Canadian Agency for Drugs and Health Technology[v] (CADTH).

Mechanism and Delivery

CAR-T Therapy involves the manufacturing and infusion of CAR-T cells. Specifically, a patient's T-cells (i.e., a type of immune cell) are harvested from their blood, re-engineered in a laboratory environment with cancer-targeting DNA (forming CAR-T cells), and then transferred back into the patient's blood stream for treatment. While CAR-T cells are being prepared, the patient must also undergo lymphodepleting chemotherapy to enhance the efficacy of CAR-T therapy.

Overall, the treatment protocol can be broken down into 6 steps [vi]:

1. **Screening**: to determine eligibility for CAR-T therapy.
2. **Leukapheresis**: to extract T-cells.
3. **T-Cell Engineering**: where T-cells are shipped to a designated lab to create CAR-T cells (process takes 2 - 4 weeks).
4. **Patient Pre-Treatments**: lymphodepleting chemotherapy must be done 2 - 14 days before infusion.
5. **CAR-T Infusion**: must be done at a treatment centre.
6. **Observation**: patients are advised to stay near their treatment centre for ~1 month for regular monitoring to see if the CAR-T therapy is effective and to address any side effects.

Given the highly personalized nature of CAR-T therapy, there is significant infrastructure and expertise required for safe and successful delivery of treatment.

Access in Canada

There are four commercial CAR-T therapies offered by Novartis, Gilead Life Sciences and most recently, Bristol Myers Squibb, that have been approved by Health Canada and have received a positive recommendation from CADTH. Since then, only 4 provinces - Ontario, Quebec, Alberta, and most recently, Nova Scotia - have implemented funding

and treatment sites. In provinces/territories where it is not available, patients may receive access to CAR-T through out-of-province or out-of-country programs where they are eligible for treatment based on physician referral. However, travel for treatment can be especially difficult for immunocompromised patients. [vii]

Implementation Challenges in Canada

Each step in CAR-T therapy's treatment protocol brings a unique set of challenges for its implementation in Canada:

1. **Additional Need for Administrative Infrastructure**

   There is a need for improved administrative infrastructure for referral, screening and evaluation of patients. Accredited sites with institution-accredited staff who have expertise in CAR-T therapy are required to deliver this therapeutic. Pharmacy staff must also be trained to receive and store CAR-T cells. There is a further added challenge of ready access to these certified treatment centres, both in-terms of provinces that have approved commercially available CAR-T therapy for reimbursement, as well as from an urban and rural standpoint. For Ontario, Quebec, Alberta and Nova Scotia, there are a limited number of treatment centres that are based out of larger metropolitan cities, including the GTA and Ottawa, Montreal and Laval, Calgary, and Halifax, respectively. This creates a magnified barrier for vulnerable populations such as Indigenous, low income, and other marginalized groups who may need to travel and be displaced for extended periods of time to be near a treatment centre.

2. **Manufacturing Capabilities of CAR-T Cells**

   To manufacture CAR-T cells, two types of facilities are required: an apheresis center and a cell processing facility. This essential step is completed by the parent pharmaceutical companies of branded CAR-T therapies and requires shipping T-cells to and from the US.

   There are efforts in Canada for in-house CAR-T manufacturing, such as the Canadian-Led Immunotherapies in Cancer-01 (CLIC-01) trial[viii] which began in The Ottawa Hospital's Biotherapeutics Manufacturing Centre and BC Cancer's Conconi Family Immunotherapy Lab. This initiative has shown encouraging results, and is currently being expanded to other Canadian cities such as Toronto and Winnipeg to create CAR-T development infrastructure for more patient trials.[ix] Alberta Health Services has also developed an in-house solution in collaboration

with the University of Alberta, that began its first trials in March 2021 and is showing promising results.[x] However, these are both in early stages and will need further development before patients have widespread access across Canada.

3. **Need for Cold Chain Management Infrastructure**

   CAR-T cells must be cryopreserved and stored in a temperature monitored system at or below -120˚C (up to -150 ˚C, depending on the manufacturer) and must remain frozen until the patient is ready to receive treatment. For commercially available CAR-T therapies that are manufactured outside of Canada, it is even more essential to have these systems in place starting from manufacturing facilities, during transport and at treatment centres to ensure safe delivery of this gene therapy.

4. **Capacity for Post-Infusion Care**

   Although hospitalization is not required, patients must be monitored closely after receiving treatment due to the risk of severe adverse events that can require intensive care. The rates of such events are not well documented, and therefore, treatment centres must estimate patient volumes, and have capacity for potential in-patient admission. Given the ongoing health human resources crisis across Canada, there are added challenges around hospital capacity.

Future Scope

The current recommended, commercially available CAR-T therapies in Canada are only designed to treat certain types of Leukemia and Lymphoma. However, Johnson & Johnson's Carvykti developed for treating Multiple Myeloma is currently under review by CADTH.

One budding research direction for CAR-T Therapy is the development of allogeneic CAR-T Therapies, that use donor cells and essentially removes the need to extract T-cells from patients. Although they would still require a matching process, allogeneic therapies, developed through genomic-editing technologies such as CRISPR-Cas9, have fewer production and manufacturing steps, and are closer to emulating an "off-the-shelf" product. Unfortunately, existing allogeneic cell therapies in clinical development are still far from commercialization as their efficacy is well below that of autologous (i.e., personalized) CAR-T therapies. A major challenge comes from graft versus host disease, where the body launches an immune response against donated cells, leading to serious

adverse events. Further research is required to determine how to "hide" donor CAR-T cells from patients' immune systems.[xi]

Another motivating direction for CAR-T therapy is expanding its application to solid tumours so that it can be used to treat other cancers. There have been several promising studies for treating brain cancer, skin cancer and metastatic pancreatic, gastric and prostate cancers.[xii] This broader scope of application for the future makes it even more essential for Canada to be better prepared for system-wide implementation of this breakthrough therapeutic.

Conclusion

CAR-T Therapies represent a breakthrough therapeutic indication with significant scope to change the face of cancer treatment using personalized medicine. Canada currently faces two layers of challenges for effective and equitable implementation of this class of therapeutics in the health system.

First, given that highly specialized treatments like these can only be located in large urban centres with the necessary infrastructure and human resources, it is important to ensure equitable access for Canadians who live in smaller jurisdictions and in rural and remote areas. Second, the existing system infrastructure – including few administrative resources (for referral, screening and evaluation of patients), inadequate in-house manufacturing capacity and constrained post-infusion care capacity significantly hinders Canada's ability to maximize the value of this breakthrough therapeutic.

Given both the current and future scope of CAR-T Therapies, Canada has a real opportunity to reflect on these lessons learned to ensure better system preparedness for this class of breakthrough drugs.

References

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[iv] Kymriah®, Yescarta®, Tecartus®, Breyanzi®, Abecma® & Carvykti®

[v] Kymriah®, Yescarta®, Tecartus® & Breyanzi®

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