

Understanding the Feasibility of Implementing CAR T-Cell Therapies from a Canadian Perspective

Comprendre la faisabilité d'une mise en œuvre des thérapies CAR-T au Canada

KRISTINA ELLIS, KELLY GRINDROD, STEPHEN TULLY, TOM MCFARLANE,
KELVIN K.W. CHAN AND WILLIAM W.L. WONG

Appendix 1

Recruitment

Participants were recruited using a combination of purposive sampling and snowball sampling and were initially recruited because of their known role in CAR T-cell related projects. During interviews, the participants were asked if they could refer suitable interview candidates, and in some cases, these individuals were contacted by the researcher. An initial invitation e-mail was sent out in February 2019 to 10 individuals with four interview confirmations. A reminder e-mail was sent in March 2019 to the other six people, and two more interviews were confirmed. A second round of invitation e-mails were sent in April 2019 to eight more individuals, resulting in four confirmed participants. E-mails were sent out three more times in May, June and July, based on referrals and other known CAR T stakeholders who were not contacted initially. Three more interviews were conducted in this time (Appendix Figure 1). After participants confirmed interest in participating, an interview consent form was sent out to be signed and returned prior to the set interview date. The interview questions were sent out ahead of time so that participants had enough time to prepare answers, as some questions required technical responses (Appendix Table 1). A total of 13 interviews were conducted between March and July 2019.

Interviews

One-on-one semi-structured interviews were conducted by video call using Zoom or by phone with audio only. Interviews were scheduled for one hour and were between 30 minutes and one hour in length. Participants were informed that they would not be personally identified and only their perspectives would be shared. Interviews were recorded using Zoom when this platform was used or with a recording device if by phone. Participants were asked a set of questions most relevant to their field: scientists, clinicians and reimbursement specialists that included manufacturers' representatives and policy makers. Probing and follow-up

questions were asked by the interviewer to encourage more detailed responses. After role-specific questions were asked, participants were asked open-ended questions about perceived challenges to the adoption of CAR T-cell therapy, potential changes in the healthcare system and, broadly, why CAR T-cell therapy is unique. Interviews were coded throughout the interview process to determine when the saturation of ideas and themes was reached. Interviews were stopped after saturation was reached. This occurred after 13 interviews.

Analysis

Each interview was transcribed using a transcription service, and each participant was given a unique identifier using a number and their role in the study as a scientist, clinician, or reimbursement specialist (manufacturers' representative or policy maker). Data analysis was completed in four stages as described in the main paper.

Deductive coding was used when participants were directly asked questions about certain processes and therefore organized in this manner (e.g., the manufacturing process). Inductive coding was used to understand responses to open-ended questions and to allow unanticipated themes to emerge. After codes were applied to all transcripts, the codes were organized into a matrix and a set of themes was generated. Themes were created with sub-categories aligning with the codes that were applied.

After 10 interviews were conducted, the researchers began qualitative analysis and found that saturation was reached through the reiteration of ideas in interviews. Saturation was determined through the repetition of ideas and themes in the developed code categories (Saunders et al. 2018; Vasileiou et al. 2018). When no new codes or themes were developed after conducting 10 interviews, it was determined that saturation was reached. Three more interviews were conducted after this to fill any gaps identified by the primary researcher and to confirm saturation had been reached. Adding additional participants did not result in new themes but did help to clarify processes and timelines described for developing CAR T-cell therapy and administering it to patients, and it showed that there was consistency in answers about challenges to implementation and suggestions for ensuring long-term sustainability of CAR T-cell therapy across the three different participant groups.

FIGURE A1. Interview participant recruitment



TABLE A1. Qualitative interview questions

Interviewee	Questions
Scientist	<p>1. Describe the process of obtaining a T-cell sample from a patient who will undergo therapy.</p> <p><i>Follow-up questions:</i></p> <ul style="list-style-type: none"> • Describe the resources and health professionals that are required for this process. • How long does it take to obtain a sample? <p>2. Is your lab/facility able to manufacture CAR T-cell therapy?</p> <p>3. Based on your knowledge, how many facilities/labs in Canada can produce CAR T-cell therapy (other than the manufacturer)?</p> <ul style="list-style-type: none"> • What is the capacity of these centres? (The number of patients they can accommodate?) • How many hospitals in Canada/Ontario can administer the therapy? <p>4. Based on my understanding, CAR T-cells are generated from a patient's blood sample, which is then genetically engineered to express a certain antigen.</p> <p>Describe the process of generating CAR T-cells at your facility/centre. Probe, if needed: If/when sent to the manufacturer, what steps must be completed first, and which steps does the manufacturer complete?</p> <p><i>Follow-up questions:</i></p> <ul style="list-style-type: none"> • What resources and health professionals are required for this process? • Where is the therapy manufactured? • What is the typical turnaround time from leukapheresis to infusion? <p>5. Can errors occur during the manufacturing process?</p> <ul style="list-style-type: none"> • Can you estimate the percentage or number of patients who undergo leukapheresis but do not receive a CAR T infusion? • What are the reasons why a patient may not receive an infusion after initiating the process to receive treatment? • Can you estimate the manufacturing failure rate? <p>6. What do you estimate the average time (or wait time) is for the following?</p> <ul style="list-style-type: none"> • Leukapheresis • Manufacturing of cells (time from cells sent to centre for manufacturing and sent back to treatment facility) • Transport from facility with cell sample to manufacturing facility, then from manufacturing facility to treatment centre • Infusion once the therapy is transported to the treatment centre <p>7. What are the challenges with developing the therapy for use?</p>

Interviewee	Questions
Clinician	<p>1. Describe the standard(s) of care of treatment that would be used if a patient was not able to receive CAR T-cell therapy. (Probe: What combination of chemotherapy drugs is required?)</p> <p><i>Follow-up questions:</i></p> <ul style="list-style-type: none"> • What are the most important benefits of CAR T-cell therapy compared to standard therapy? (How many rounds of treatment are required for CAR T?) • What are the differences? Or disadvantages? (Probe: Cost?) <p>2. Where does CAR T-cell therapy fit into the current clinical treatment pathway? (When would it be used?)</p> <p>3. What are the most common and serious side effects and how are they managed?</p> <p>4. Describe the types of patients who are eligible to receive CAR T-cell therapy. (Probe: Patient and disease characteristics, age, sex, stage, type of cancer, previous treatments.)</p> <p><i>Follow-up questions:</i></p> <ul style="list-style-type: none"> • Is there a specific subgroup? What percentage of patients do you estimate are eligible of the patients with aggressive DLBCL or ALL? (Or do you know where I could find this information?) • Which patient group should be prioritized to receive this therapy? • How many patients are there with DLBCL/ALL in Canada? (Or do you know where I could find this information?) • What is the typical prognosis for a patient with aggressive DLBCL/ALL (at initial diagnosis, and following the trajectory to be eligible for CAR T)? <p>5. My understanding is that a patient may receive chemotherapy while waiting to get CAR T, and they may need to remain close to the treatment centre. Can you describe what happens during the period of time while a patient is waiting to receive CAR T (treatment, travel, how long they will have to wait)?</p> <p>6. Describe the process of administering the treatment to the patient.</p> <p><i>Follow-up questions:</i></p> <ul style="list-style-type: none"> • Where is it done? (e.g., a hospital) • Who administers the therapy? • How long does the treatment take? • How long is the patient monitored during administration? • Which healthcare providers are involved? • What resources are required? • What errors have you seen occur with administering CAR T-cell therapy? <p>7. What does follow-up look like during treatment (after infusion) and in the following weeks (in-patient versus outpatient care, when they leave the hospital)?</p> <p><i>Follow-up questions:</i></p> <ul style="list-style-type: none"> • How many days are required in the hospital? How many days in the ICU? • Are there any adverse events that significantly impact length of stay in the hospital? • After the patients leave the hospital, how are they monitored? How many office visits are required? • Are patients required to be close to a treatment centre after they leave the hospital? And for how long? • Can you compare monitoring and follow-up of patients who have received CAR T-cell therapy to those who will receive the standard care? • If a patient progresses after treatment, how is this handled? <p>8. Which processes (developing therapy, delivering it, monitoring side effects, administration) use the most resources? How does this differ from the standard of care?</p> <p>9. Can you estimate the number of hospitals/centres in Canada or Ontario that can administer CAR T-cell therapy (number of patients/beds)?</p> <p>If a clinician is familiar with all the processes:</p> <p>10. Can you describe the process of (1) obtaining T-cells from the patients, (2) genetically engineering the cells, and (3) administering the therapy to the patient?</p>

Interviewee	Questions
Reimbursement specialists	<ol style="list-style-type: none"> 1. Describe your understanding of CAR T-cell therapy from a system-level perspective (economic, reimbursement, policy, healthcare). 2. Describe the role that you have for CAR T-cell therapy in the Canadian healthcare system. 3. What are the challenges to providing CAR T-cell therapy in Canada? (Probe: Policy angle, clinical angle.) 4. Based on your knowledge of cancer drug reimbursement, how would CAR T-cell therapy fit within the current budget for cancer therapies in Canada? (Probe: Is it much different than other cancer drugs? Do you anticipate it to be a high priority? Will it displace other drugs?) 5. Compare CAR T-cell therapy to other novel treatments such as other cancer drugs. What is unique about CAR T in the context of drug reimbursements, the approval process and pricing? How will this be assessed and managed for CAR T? What path is CAR T likely to follow for coverage? <ul style="list-style-type: none"> • Are there any treatments that have been approved that are similar to CAR T-cell therapy in terms of its novelty, cost and potential for long-term survival? 6. Can you estimate the average time for reimbursement approval by CCO following a patient's/clinician's request for a patient to receive CAR T?
General questions	<p>Thinking about CAR T from a system level:</p> <ol style="list-style-type: none"> 1. What do you expect the biggest challenges to be with adopting this new therapy? (Or with each area of the process?) 2. What do you think may need to be changed for this therapy to be adopted in Canada? (Or do you think there is anything?) 3. How does therapy differ from what is currently done? (How is it unique?) 4. From your perspective, to implement CAR T in Canada effectively, what do you think Canada needs to prioritize to facilitate access? 5. What do you think needs to be implemented for the sustainability of patient access to high-cost cancer therapies?

ALL: acute lymphocytic leukemia; CAR T-cell = chimeric antigen receptor T-cell; CCO = Cancer Care Ontario; DLBCL = diffuse large B-cell lymphoma; ICU = intensive care unit.

TABLE A2. Code list for qualitative analysis

Category/theme	Code	Definition
Novel	Novel, personalized therapy, not a drug	It is difficult to classify CAR T-cell therapy. It is not a drug. It is personalized. It does not fit into typical classifications.
Novel	Novel development, evolving, cell and gene therapies require innovation in healthcare system	CAR T-cell therapies and others are evolving, but the current government and hospitals systems are inflexible, which makes it a challenge.
Novel	Long-term survival – curative	Novel in its ability to cure.

Category/theme	Code	Definition
Novel	Access, healthcare policy, infrastructure	Novel in the additional resources required.
Unmet need	Unmet need	Patients have no other treatment options at the stage they need CAR T-cell therapy.
Equity	Ensuring equitable access	Will be difficult to provide equal access across the country (e.g., Toronto vs. Prince Edward Island [PEI]). Need to have systems to plan for people who are not located near a CAR T-cell site. CAR T won't be offered in all provinces, only specific centres.
Future state	Sustainability	If the indications grow, how will it be made more broadly available? It will likely replace some current standards of therapy, but how can provinces afford multiple new breakthrough drugs?
Manufacturing	Manufacturing model	Can be manufactured industrially or in an academic setting.
Manufacturing	Manufacturing process – lentivirus	How the lentivirus is created.
Manufacturing	Manufacturing process – patients	Obtaining cell samples from patients.
Capacity	General	Does not fit into one category, there are problems with demand.
Capacity	Government and regulatory	Governments and regulatory agencies need to be able to review and make decisions about these emerging cell and gene therapies.
Capacity	Hospital resources	Need beds (i.e., infusion, ICU). Can be expanded/built in centres that already have capacity for stem cell and bone marrow transplant. Challenge in provinces that won't be able to have this capacity (e.g., PEI).
Capacity	Health human resources	Personnel are required to deliver CAR T.
Capacity	Manufacturing facilities	Need enough facilities that can abide by GMP to satisfy demand.
Capacity	Manufacturing human resources	What is needed to manufacture CAR T?
Problems	Error in manufacturing/ quality control	It can happen when making the lentivirus (but quality control catches this); contamination of batches.
Problems	Patient health status and cell sample	When patients cannot provide a good sample of T-cells.
Problems	Infusion/ administration of CAR T-cell	Very unlikely to have a problem or error during infusion. Cannot be infused as an outpatient visit and doesn't require in-patient admission as side effects happen within a few days.

Category/theme	Code	Definition
System-level planning	Funding	At the moment, there is no funding in Canada, which means patients are going to the US to access treatment. Who pays? It's out of scope of the provincial drug program budgets. A budget must be established.
System-level planning	Infrastructure – hospital	Ensuring manufacturers/hospitals have sufficient tools to manufacture a product on site. Needs to have redundancy. Includes FACT accreditation and specialized centres – bone marrow transplant.
System-level planning	Training	Ensuring technicians are trained to run machines, clinicians who give treatment are trained, GMP employees have proper training.
System-level planning	Hospital care	Ensuring hospitals have capacity to care for patients after infusion. Can rely on past programs that are large and stable – will need to use the same policies. ICU beds.
System-level planning	Leadership	Who leads implementation in Canada? Includes CCO, pCPA, and mentioned as having experience with these types of therapies and other organizations involved in system-level planning.
System-level planning	Planning – data management (infrastructure needed)	Data need to be collected, sorted, analyzed and used to make decisions about future steps and to assess the current systems of reimbursement, cost of treatment delivery, measuring quality and measuring outcomes.
System-level planning	Regulatory	Planning through CCO, pCPA, approval process, reviewing cases and relationships between drug companies and the government and hospitals.
System-level planning	Coordination	Logistics, institutions working together (manufacturers, governments, hospitals) in collaboration.
Time	Bedside-to-bench-to-bedside	Time for leukapheresis, shipping, manufacturing CAR T in Prodigy machine, shipping, prepping patient, administering to patient and aftercare.
Time	Manufacturing	Two to three weeks in manufacturing. Need to move to point-of-care model where manufacturing happens on site, not industrially.
Time	Patient waiting	Patients know that when they are waiting for CAR T to reach the stage of infusion from manufacturing, they need to remain stable.
Time	Reimbursement approval time and price negotiation time	Regulatory – time for assessment if drug will be reimbursed – either for each individual patient or generally by CADTH.
Time	In hospital during treatment/monitoring	Talked about the time involved in infusion in the hospital and adverse events.
Cost	To system	Talked about broadly, cannot be categorized.
Cost	CAR T-cell products	Current CAR T-cell therapy is unaffordable. Very expensive; cost will limit use.
Cost	Hospital	Need to account for hospital and healthcare provider costs.

Category/theme	Code	Definition
Cost	Pricing, cost-effectiveness and value	Needs to be negotiated with the manufacturer to bring cost down to be affordable for the healthcare system, and cost-effectiveness needs to be established before implementation and re-evaluation because of uncertainty in data.
Evidence	Limited evidence	Efficacy, effectiveness (mostly these two but also limited knowledge about the hospital resources required, etc.). There is uncertainty about the effectiveness of CAR T-cell therapy, which makes it difficult to make decisions regarding this therapy (i.e., policy, clinical, etc.). Many clinical trials are happening now, which may point to new indications. Lacking long-term data.
Evidence	Emerging evidence	Priority regarding who will receive the therapy next, new indications for CAR T, new drugs other than CAR T for cancer. Includes: How does the system act on new evidence? Will it be a last resort or the standard of care? Specifically mentions emerging evidence but doesn't use novel.
Patient eligibility	Patient eligibility/ patient population criteria – current (general characteristics)	Currently, it is for adult and pediatric ALL and DLBCL patients, when patients have failed BMT or cannot receive a BMT, and usually the only other treatment option is palliative. No age limit but patient needs to be physically well enough to tolerate it (i.e., no organ failure) and have T-cells that can be harvested.
Patient eligibility	Patient eligibility – exclusion	Who actually gets treatment? You may not get treatment if you are too old (80 to 90 years of age), the cancer is too aggressive and if you don't have T-cells.
Patient eligibility	Patient eligibility – access, healthcare policy	Who determines who has access to and coverage for CAR T-cell therapy, and the timing of when that decision occurs after the request? - Evaluating case by case - Describing the number of cases and impact on system - Access in Canada vs. the US
Patient eligibility	Specific indication for therapy	Who is eligible for the therapy?
Patient experiences	Current burden of treatment process on patient	There is more burden on the patient to access CAR T-cell therapy.
Patient experiences	Patient complications/ adverse events (collapsed with process adverse events)	Cytokine release syndrome, infection, central nervous system toxicity (ranges from minor to fatal), late cytopenias. More manageable (less fatal) as time goes on compared to clinical trials.
Patient experiences	Patient trajectory/ prognosis	What is the patient's disease course (dismal at this point)? How will the treatment alter the disease course? Describing treatments patients will get and in what order.
Process	Storing, shipping, transport	Cell product storage and how/when it is shipped and how it is transported.

Category/theme	Code	Definition
Process	Preparing the patient	Patients need to have chemotherapy beforehand. Challenge is in keeping the patient well enough from leukapheresis to CAR T-cell infusion.
Process	Infusion	Describing how this process works.
Process	Monitoring	How is the patient infused with CAR T-cells, monitored for side effects as an in-patient and outpatient?
Similarity to transplant	Transplant	Comparing to a transplant process in any way.

ALL = acute lymphocytic leukemia; BMT = bone marrow transplant; CAR T-cell = chimeric antigen receptor T-cell; CCO = Cancer Care Ontario; DLBCL = diffuse large B-cell lymphoma; FACT = Foundation of Accreditation for Cellular Therapy; GMP = good manufacturing practices; ICU = intensive care unit; pCPA = pan-Canadian Pharmaceutical Alliance; PEI = Prince Edward Island.