RESEARCH PAPER

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, MSc
Graduate Student
School of Pharmacy
University of Waterloo
Waterloo, ON

KELLY GRINDROD, PharmD
Associate Professor
School of Pharmacy
University of Waterloo
Waterloo, ON

STEPHEN TULLY, PhD
Postdoctoral Fellow
School of Pharmacy
University of Waterloo
Waterloo, ON

TOM MCFARLANE, PharmD
Clinical Lecturer
School of Pharmacy
University of Waterloo
Waterloo, ON
Clinical Oncology Pharmacist
Sunnybrook Odette Cancer Centre
Toronto, ON

KELVIN K.W. CHAN, MD, PhD
Medical Oncologist
Sunnybrook Odette Cancer Centre
Toronto, ON

WILLIAM W.L. WONG, PhD
Assistant Professor
School of Pharmacy
University of Waterloo
Waterloo, ON

Abstract

In Canada, chimeric antigen receptor (CAR) T-cell therapy was recommended for funding for the treatment of select hematological cancers. Canadian hospitals have limited experience and capacity in administrating this therapy. We conducted a qualitative interview-based study with stakeholders in Canada. Questions were asked related to the development, administration, implementation and logistical planning of CAR T-cell therapy. Results were summarized into four main themes: (i) novel; (ii) patient characteristics and the delivery of care; (iii) processes from "bench-to-bedside"; and (iv) the future state, including both

challenges and recommendations to ensure sustainability. Valuable perspectives from stakeholders highlight some of the unique challenges to implementing a highly personalized and expensive-to-deliver therapy.

Résumé

Au Canada, on a recommandé le financement de la thérapie par lymphocytes T à récepteur antigénique chimérique (thérapie CAR-T) pour le traitement de certains cancers hématologiques. L'expérience et la capacité des hôpitaux canadiens pour l'administration de ce type de thérapie demeurent limitées. Nous avons mené une étude qualitative à l'aide d'entrevues auprès des intervenants au Canada. Nous les avons questionnés au sujet du développement, de l'administration, de la mise en œuvre et de la planification logistique de la thérapie CAR-T. Les résultats ont été résumés en quatre thèmes principaux : (i) nouveauté; (ii) caractéristiques des patients et prestation de soins; (iii) processus « du laboratoire au chevet du patient »; et (iv) la situation à venir, notamment les défis et recommandations pour assurer la durabilité. Le point de vue précieux des intervenants révèle certains des défis uniques liés à la mise en œuvre d'une thérapie hautement personnalisée et dont l'administration est coûteuse.

Introduction

In 2019, it was estimated that there would be 10,000 new cases of non-Hodgkin lymphoma in Canada, including 2,700 deaths. Of these, 30% to 40% were estimated to have diffuse large B-cell lymphoma (DLBCL) (Levine et al. 2017). For patients with DLBCL, approximately 60% can be successfully treated with first-line chemo-immunotherapy, whereas the remaining 40% are likely to experience a relapse and require second-line therapy – usually a second chemo-immunotherapy (Gisselbrecht and Van Den Neste 2018; Sehn and Gascoyne 2015; Staton et al. 2015). If DLBCL patients respond effectively to chemo-immunotherapy but their cancer recurs, they may go on to receive high-dose chemotherapy followed by an autologous stem cell transplant (SCT; Chaganti et al. 2016; Jain et al. 2018; NCCN 2018). Those who do not respond effectively to these treatments, who experience resistance to chemotherapy or who relapse again following an SCT have a poor prognosis, as there are few treatment options left (Jain et al. 2018). For this reason, there has been considerable interest in the recent development of a novel gene therapy called chimeric antigen receptor (CAR) T-cell therapy, as it offers potentially life-saving treatment for relapsed and refractory patients with DLBCL (Neelapu et al. 2017; Schuster et al. 2019).

The response rate with CAR T-cell therapy in patients with relapse/refractory DLBCL is as high as 71%, and is dramatically greater than the 20% seen in the historical control of patients treated with traditional salvage/palliative regimens (CADTH 2019c). This improved response rate translates to an overall survival rate of 49.0% at 12 months. To date, two different CAR T-cell therapies for refractory large B-cell lymphomas in adults have been approved by Health Canada, including axicabtagene ciloleucel and tisagenlecleucel (Health Canada 2019). The dramatic improvement in the overall survival rate seen in patients with DLBCL

treated with CAR T-cell therapy led the Canadian Agency for Drugs and Technologies in Health (CADTH) to conclude that there was a clinical benefit associated with the medications axicabtagene ciloleucel and tisagenlecleucel for patients with relapse/refractory DLBCL (CADTH 2019c, 2019d). There are, however, numerous adverse events associated with the treatments. During the first 28 days, common adverse events included cytokine release syndrome (CRS), neurologic events (CAR T-cell associated neurotoxicity), cytopenias, infections and febrile neutropenia (Maude et al. 2018; Neelapu et al. 2017; Schuster et al. 2019). CRS is seen in up to 93% of patients with DLBCL and is characterized by symptoms ranging from mild hypotension and fever to severe capillary leak syndrome, disseminated intravascular coagulation, coagulopathy and multiple organ failure. Up to 22% of patients with DLBCL experienced grade 3 and higher CRS (Schuster et al. 2019). Neurotoxicity is seen in up to 64% of patients and is characterized by mild cognitive impairment and delirium in mild cases and hallucination, global encephalopathy, aphasia, seizure and cerebral edema in the most severe cases. Grade 3 and higher neurotoxicity is reported in up to 28% of patients (Neelapu et al. 2017). Grade 3 or higher CRS or neurologic events commonly required intensive care unit (ICU) admission (Levine et al. 2017). Thus, patients must be closely monitored for severe side effects such as CRS and neurotoxicity over the next few days to a few weeks after infusion.

CAR T-cell therapy is unique because it is highly personalized and can lead to long-term remission, but it comes at a very high cost. These costs are believed to reflect the complexity of the product as well as the original investment of the companies that did the pivotal studies (Pharmaceutical Technology 2018). With a number of CAR T-cell therapies recently evaluated by regulators and health technology agencies in Canada and recommended for funding, the anticipated impact on the capacity of the current healthcare system is great, as the CAR T-cell therapies require hospitals and healthcare professionals with specialized skills for development and effective delivery. In this way, CAR T-cell therapy would disrupt existing markets by displacing previous technologies. This therapy is proving to be one of the first disruptive interventions to undergo the regulatory approval process in Canada, leading to many questions, concerns and hope. The cost of axicabtagene ciloleucel and tisagenlecleucel are US$373,000 and US$475,000, respectively (IBM Micromedex RED BOOK n.d.). Converting the USD list price to CAD using purchasing power parity would be Can$464,385 and Can$591,375, respectively (OECD 2017). However, in both cases, the products are patient-specific, and the processes for manufacturing them and administering them to Canadian patients are not well-described. Although CADTH has identified some ethical and implementation challenges of CAR T-cell therapies (CADTH 2019c, 2019d), barriers to the adoption of CAR T-cell therapy in the healthcare system have not been well-documented or described in a Canadian context (Lam et al. 2019; Tong et al. 2007). Our aim is to use a qualitative approach to describe stakeholder perspectives on the state of CAR T-cell therapy in patients with large B-cell lymphomas within the context of the Canadian healthcare system.

Method

A qualitative interview-based study was conducted with CAR T-cell therapy stakeholders including scientists, clinicians, manufacturer representatives and policy makers in Canada. This study was approved by a University of Waterloo research ethics committee. The Consolidated Criteria for Conducting Qualitative Research checklist was used for reporting results (Tong et al. 2007). Questions were designed for the three different target participant groups including: scientists involved in CAR T manufacturing; clinicians who treat pediatric or adult hematological cancers; and reimbursement specialists that include manufacturers' representatives who work in pharmaceutical market access and reimbursement in Canada and policy makers who are members of agencies that are involved in the reimbursement decision and/or the implementation process in Canada. Semi-structured interview questions (Table A1, available online at longwoods.com/content/26430) were developed by the authors to address the purpose of the study and to learn about the specific processes in Canada for developing CAR T-cell therapy and administering it to the patients; the patient experience; and the processes of drug review for reimbursement approval. Open-ended questions were also developed to understand the views of participants on the challenges to implementing CAR T-cell therapy in Canada. Participants were asked semi-structured questions most relevant to their role as a scientist, a clinician, a manufacturers' representative or a policy maker.

Participants

Participants were recruited using a combination of purposive and snowball sampling and were identified because of their known role in CAR T-cell–related projects based on publicly available information that include funding announcements and new releases from national and provincial agencies. The sample of participants included three scientists/researchers, five clinicians in hematology and five reimbursement specialists that included four policy makers and one manufacturers' representative who works in the drug review and reimbursement space. All participants were based in Canada. A total of 13 interviews were conducted between March and July 2019. The detailed recruitment and interview processes are described in Appendix 1 and Figure A1, available online at longwoods.com/content/26430.

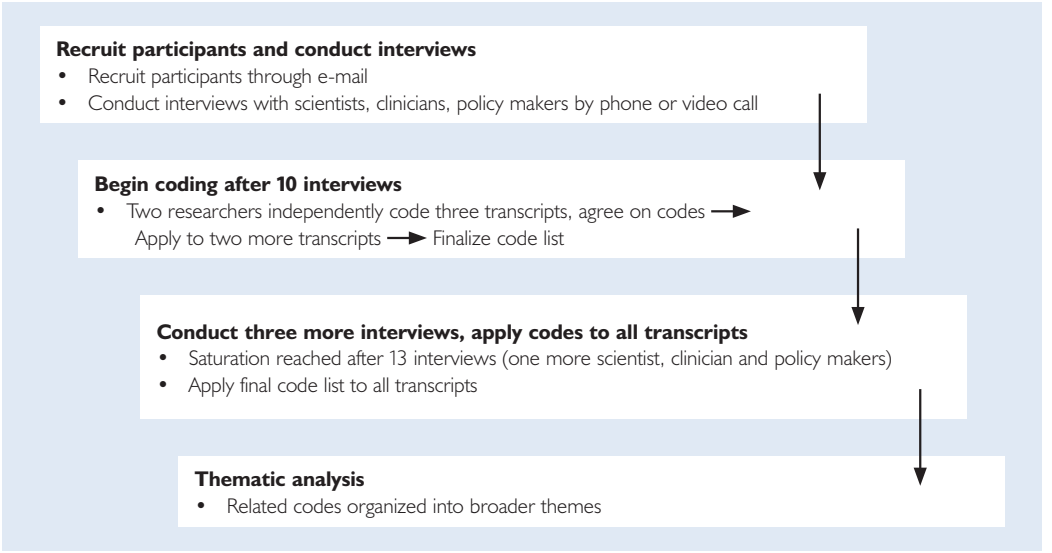
Analysis

After the interview process, each interview was transcribed and de-identified using a transcription service, and each participant was given a unique identifier using a number and their role in the study. Data analysis was completed in four stages:

(1) Independent coding by two researchers (Kristina Ellis and Stephen Tully) to reduce bias: The interviewer and another researcher independently coded three transcripts of three different types of participants and met to refine codes. Another researcher (Kelly Grindrod) was consulted to resolve differences in coding schemes.

(2) Agreement on codes and applying to new transcripts: Ellis and Tully agreed on a set of common codes and then applied these codes to two more transcripts of the three different participant groups.
(3) Finalization of codes and application to all transcripts: Ellis and Tully finalized the list of codes and reviewed them with other members of the research team (Table A2 available online at longwoods.com/content/26430). This set of codes was then applied to all the transcripts using the NVivo 12 (QSR International) qualitative data analysis software.
(4) Thematic analysis: Related codes were organized into broader themes. Saturation was determined through the repetition of ideas and themes in the developed code categories (Saunders et al. 2018; Vasileiou et al. 2018). Three additional interviews were conducted after saturation to fill any gaps identified by the primary researcher and to confirm saturation had been reached (Figure 1). A complete description of the study methodology, interview questions and coding list can be found in Appendix 1, available online at longwoods.com/content/26430.

FIGURE 1. Interview and analysis process



Results

Four key themes were identified through qualitative analysis:

- *Novel:* CAR T-cell therapy is novel in many ways: it has a unique mechanism of action as a gene therapy; it is highly personalized; it has a high per-patient upfront cost; it can lead to long-term survival and remission in patients; and it requires significant hospital and health system resources. These characteristics make CAR T-cell therapy difficult to classify as a typical drug.

- *Patient characteristics and the delivery of care*: This theme includes characteristics of patients who are eligible to receive CAR T-cell therapy based on Health Canada–approved indications; the impact of CAR T-cell therapy on patients; the current unmet need of patients who have not been successfully treated with previous lines of therapy; and why equitable access to CAR T-cell therapy for patients across Canada needs to be considered.
- *Processes from "bench-to-bedside"*: There are specific processes and requirements to deliver CAR T-cell therapy: each CAR T product must be effectively manufactured for each individual patient; the patient must undergo leukapheresis and be medically stable to receive treatment; the product must be transported from the manufacturer to the treating facility; and the product must be administered to the patient in an accredited institution.
- *Future state of CAR T-cell therapy in Canada*: Planning for CAR T-cell therapy needs to consider the current barriers and challenges to the implementation of CAR T-cell therapy in the healthcare system; the long-term sustainability of CAR T-cell therapy implementation in Canada; ways to enhance and improve the ability to deliver CAR T-cell therapy; addressing current barriers such as education and training; and planning the logistics of implementation of CAR T-cell therapy across Canada.

Novel

When asked to describe CAR T-cell therapy in their own words or talk about why it is unique, participants often described CAR T-cell therapy as difficult to classify because it is more than just a drug – it is an extremely expensive and a highly personalized therapy. One participant said:

> Well, it's unique because it's really a game changer, that's one thing. Second of all, it's completely different in terms of it's not a drug, at least not as we see it presently. It's a cellular therapy, it's got its whole set of complications and it's got a significant cost. It needs special expertise in terms of manufacturing. (Clinician, C3)

In addition, participants stated that CAR T-cell therapy offers patients a potentially curative and life-saving treatment option when they would have otherwise received salvage chemotherapy or palliative care. As one clinician stated,

> It's the only chance at cure, or at complete responses. So, I think it has the ability to prolong life, which is what the current regimens for relapsed or refractory disease (DLBCL) don't have. (Clinician, C1)

CAR T-cell therapy was also described by participants as novel in terms of the infrastructure and resources required to effectively deliver it, and that poses a unique challenge to

ensuring equitable access across Canada. On equity, a participant stated,

> There have been a lot of discussions around equity, the fact that there really isn't [any]. Even if the drug was available and cheap, the access is a different issue because of the fact that ... because of how it's supposed to be delivered, because of expertise required, because of the infrastructure that's required. (Reimbursement specialist, P2)

Although many participants commented on CAR T-cell therapy being novel in some way, participants also recognized that the complexity of delivering CAR T-cell therapy is similar to that of an SCT, which has set a precedent for CAR T-cell therapy. As one participant pointed out,

> It's more similar to administering stem cell therapy where it's kind of a stem cell transfer versus administering chemo. (Reimbursement specialist, P2)

Patient characteristics and the delivery of care

Participants indicated that DLBCL patients who would be eligible for CAR T-cell therapy do not have other treatment options and a poor prognosis. One clinician stated,

> … it actually causes disease remission … for refractory lymphoma ... That's kind of a big, important thing. It meets an unmet need. (Clinician, C2)

Clinicians described eligible patients as being very sick but also physically well enough to survive until the CAR T-cell manufacturing process of a few weeks is completed for the patients to receive the therapy. One participant said,

> The challenge is to just give them just enough chemotherapy to keep them well, but not enough that you make them sick and land them in the hospital … and result in an infection, because that all delays getting to the CAR T-cells. (Clinician, C4)

After being infused with CAR T-cell therapy, which was described as a straightforward in-patient procedure, patients are monitored for side effects. Clinicians discussed two common side effects that can be life-threatening and require immediate treatment, namely, CRS and neurotoxicity that occurred in most of the patients in the pivotal clinical trials for the two Health Canada–approved CAR T-cell products. When summarizing these adverse events, one clinician said,

> ... It all depends on what it is. If we're talking about, let's say, cytokine release syndrome. I said 80% [of patients] develop it. Then it depends what kind of degree you

> have ... If they have higher degrees of CRS, then they may need ICU care, they may need (vaso)pressors, they may need to be on the ventilator, they may need dialysis. Neurotoxicity, same thing… (Clinician, C5)

Clinicians indicated that patients would be heavily monitored during the first week after the infusion as an in-patient and treated for side effects if they occur. The patients return home after the first week of heavy monitoring, and clinicians are then likely to see them as outpatients every week for a few weeks, and then monthly for a few months. One clinician stated,

> Well, if the risk-period for CRS and neurotoxicity is over, so if they haven't developed that, then I'd say [in] 10 days they'd probably go home. Their ongoing follow-up would be once or twice a week in clinic, blood count checks, like that, for the rest of the month, and then less frequently if they're doing well. (Clinician, C2)

Processes from "bench-to-bedside"

Participants described the process of leukapheresis, which is the collection and isolation of white blood cells from a blood sample to be used to create the CAR T product (Figure 2). This can be done at a hospital facility in Canada. The cell sample is then transported to the manufacturing facility, where the cells are re-engineered by combining the cell sample and the lentivirus/retrovirus and growing them in large numbers to produce the final product. Participants highlighted how the manufacturing sites of the two commercial products that have been approved by Health Canada are located in the US (Health Canada 2019). As with similar commercial products, the final CAR T-cell product needed to be frozen and sent back to the treating hospital. Researchers developing products in Canada noted that the manufacturing turnaround time may be reduced to around two weeks if manufacturing facility set-up is in Canada. Participants with experience in manufacturing were also asked to discuss errors that could occur in manufacturing that would lead to a failure. They noted that although errors can still occur, the cause of such errors has changed over time, with one participant stating,

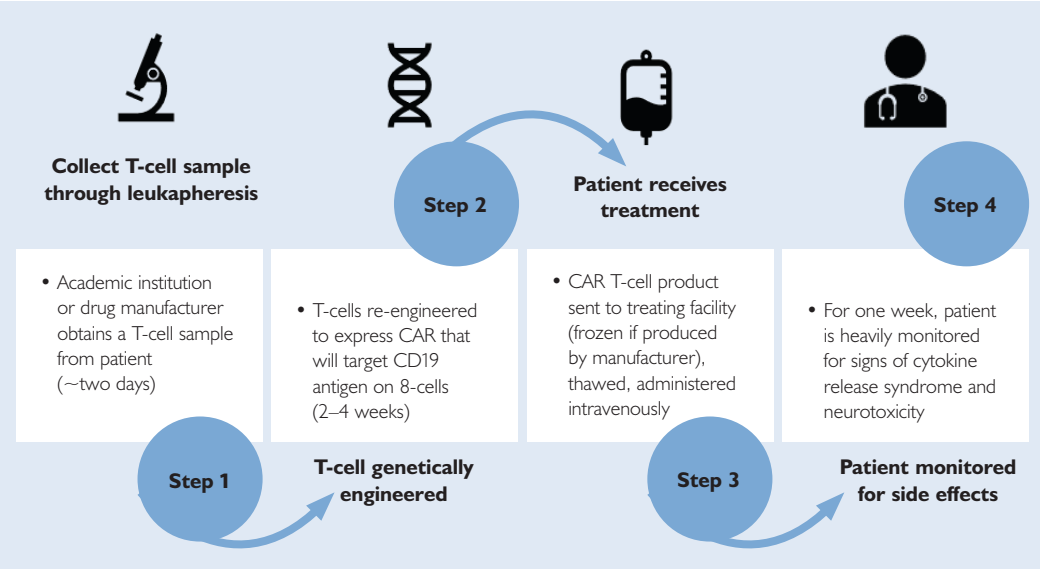
> So, you know, the 7% manufacturing failure that we saw with Novartis when the studies were published, that was because (they) couldn't expand enough cells to make it a viable CAR T product. Nowadays, the manufacturing failures are often related to the functionality of the product. (Clinician, C1)

Future state of CAR T-cell therapy in Canada: The challenges

Participants were asked about current challenges to effective implementation of CAR T-cell therapy in Canada and for recommendations to ensure long-term sustainability. Some key challenges identified were as follows:

- the high cost of CAR T-cell therapy to the healthcare system and maintaining funding;
- limited capacity of manufacturers and hospitals to develop and deliver CAR T-cell therapy; and
- government and regulatory agencies working with short-term efficacy data and having to make decisions for the future with limited evidence.

FIGURE 2. Processes from "bench-to-bedside"



CHALLENGE 1: HIGH COST TO THE HEALTHCARE SYSTEM

Participants noted that CAR T-cell therapy products are already very expensive, but there are many additional hospital costs to consider as well. The cost for the approved CAR T-cell products ranges from US$373,000 to US$475,000 (IBM Micromedex RED BOOK n.d.), or Can$464,385 to Can$591,375 (OECD 2017). Because administering CAR T-cell products to patients is new to Canadian hospitals, clinicians noted that patients would likely be admitted as an in-patient in the days leading up to the therapy and may stay in the hospital for one to two weeks. Some patients who experience serious adverse events may need to be transferred to the ICU, which also increases costs. Summarizing this theme, one participant stated,

> Well, the biggest challenge is clearly the costs associated with it, right? The commercial products that are coming out of the US companies have costs of hundreds of thousand[s] on top of the actual clinical treatment costs. (Scientist, S3)

CHALLENGE 2: LIMITED CAPACITY

Across all areas of expertise, participants felt that one of the largest barriers to implementation is capacity. Participants spoke about capacity in the context of the current healthcare system not being able to meet the demand for CAR T-cell therapy. Participants agreed that even if CAR T-cell therapy was affordable, hospitals are currently at capacity with other procedures such as bone marrow transplants, which clinicians noted are similar to CAR T-cell therapy in terms of the hospital resources required. Participants were concerned about the number of patients who would be eligible for CAR T-cell therapy, which may exceed the capacity of the limited hospital resources – specifically regular ward beds and ICU beds. One participant stated,

> Everything you need to treat these complicated patients is what we're short of. And we've been working to improve that, so we're just sort of catching up on the transplant side and then these guys came along. (Clinician, C4)

Another noted, "at this point, we don't have enough bed space in the province to meet the need for the number of patients who would be eligible for CAR-T in [Ontario]" (reimbursement specialist, P4).

CHALLENGE 3: LIMITED EVIDENCE

Based on interview responses, "limited evidence" refers to the lack of long-term efficacy data for the approved CAR T-cell therapy products. Participants described how decisions are being made at the government level about the funding and implementation of CAR T-cell therapy based on data from single-arm clinical trials that ranged from 14 to 27 months of follow-up (Neelapu et al. 2017; Schuster et al. 2019). The following quote shows the challenge of working with short-term data to make long-term decisions about healthcare.

> ... we also don't have long-term data on the products that are currently marketed. And so, when you try to do planning at a system level, it becomes very difficult because you're not planning for today or even the year after, you're trying to plan five to 10 years down the road. So, trying to estimate the number of patients that would require this therapy, and then the proper resources as far as health human resources, capital infrastructure … is quite difficult. So, the costs of not just purchase of the CAR T-cell but the cost of the actual care and management of these patients, there is limited information to go on. Even the clinical trials that have occurred have fairly small numbers when you compare them to clinical trials in other therapeutic areas … That's a big challenge for us in the planning phase. (Reimbursement specialist, P1)

Future state of CAR T-cell therapy in Canada: Planning at the system level

The recommendations to support the sustainability of CAR T-cell therapy and other cell and gene therapies fell under four main categories:

- coordinating among stakeholders;
- implementing infrastructure, training and education;
- considering reimbursement strategies and cost-effectiveness; and
- adapting to emerging evidence.

RECOMMENDATION ONE: COORDINATE AMONG STAKEHOLDERS

Participants discussed the need for CAR T-cell therapy stakeholders to be aligned to ensure that patients can get timely access to CAR T-cell therapy. Key stakeholders included government and regulatory agencies, manufacturers, clinicians, hospitals and patients.

> I think the manufacturer working with the provinces to achieve a price that's equitable, sustainable for the success of CAR T. The first step. I think that's one. In terms of other steps to maintain or improve the success, or sustainability of the treatments, I think we need to continue with research, which we're doing. It can't stop with these three indications, or two indications that exist in the market. If the technology is going to be sustainable, you need the evidence to support funding it. (Reimbursement specialist, P3)

Another participant stated,

> I have to say that my perception is that there's a lot of people on the various levels that are involved being in politics, being in health administration, being at the hospitals, that there's a lot of good will, enthusiasm to make this happen. (Clinician, C5)

Participants felt that CAR T-cell therapy stakeholders were willing to achieve effective and efficient implementation.

RECOMMENDATION TWO: IMPLEMENT INFRASTRUCTURE, TRAINING AND EDUCATION

Participants recognized that infrastructure is an important consideration regarding which hospitals would be best suited to deliver CAR T-cell therapy and the resources that would be required. Participants reported that establishing centres of excellence that are accredited through the Foundation of Accreditation for Cellular Therapy (FACT) will be required to effectively deliver CAR T-cell therapy (http://www.factwebsite.org/). To summarize these points, a participant stated,

> In terms of treating patients, a lot of the infrastructure already exists, so if sites administer, for example, allogeneic stem cell transplant, a lot of these procedures already exist to accommodate CAR T therapies. It's one of the main reasons why some of the first centres that we approach are the FACT-certified centres. They have the infrastructure, for the most part, to accommodate these therapies. (Reimbursement specialist, P3)

Along with infrastructure comes training and education within manufacturing facilities and hospitals. Participants agreed that safely and effectively delivering CAR T-cell therapy in the hospital requires specific training, as illustrated by one participant stating,

> I think in Canada what we need to do is get the infrastructure in place, which we're beginning to do now, get the training … It'd take a lot of training to get people up to speed, so the technicians who run the machines, the doc[tor]s who give the treatment, they have to become familiar with what to expect and how to treat it and so on, and all that has to be built. (Scientist, S1)

RECOMMENDATION THREE: CONSIDER REIMBURSEMENT STRATEGIES AND COST-EFFECTIVENESS

Another key area for system-level planning was reimbursement. While funding was mentioned as one of the most prominent challenges, it was noted that provinces will have to make decisions about which budget the funding for these therapies will come from for reimbursement. A participant stated,

> So, in essence, all of that is the same for CAR T except who is actually funding it. It's a bit different depending on the jurisdiction. So, it may come out of the hospital or whether it may come out of the cancer agency or whether it may come out of something else. That's a bit of a challenge, and a bit of a uniqueness to this particular product. And I'm not really sure entirely whether every single province and territory have sorted out exactly where the money or the funding is going to come from. (Reimbursement specialist, P2)

Some participants also discussed the importance of establishing value for money for CAR T-cell therapy. One participant said,

> In terms of sustainability, I think again, we have to do everything we can to negotiate the prices down as far as we can to make sure that, because we do have limited healthcare dollars, and we're in a socialized medicine environment, we do need to make sure that we're using our money wisely. And so, if we can negotiate the prices down, and maybe even come up with novel ways of administering the therapy. So,

> like, maybe moving it to the outpatient setting in the hospitals, could result in less cost to the tax payer. (Reimbursement specialist, P4)

RECOMMENDATION FOUR: ADAPT TO EMERGING EVIDENCE

Participants discussed that while there are two Health Canada–approved indications for CAR T-cell therapies at present, there are many more being developed and tested, which should be accounted for in long-term planning. A quote illustrating this is as follows:

> I think we have to change our mindset and say we have to deliver these drugs, or these therapies, in a different way. We have to approach it differently because they're [going to] continue to evolve. This is not the end. This is the very … I'm [going to] sound very Churchill-like. This is the end of the beginning. We really are beginning to see these expand and if you keep going at it in a one-at-a-time in the sort of side-level approach of pharma, it'll take 50 years. (Scientist, S1)

Thinking ahead, participants recognized that, in its current state, the healthcare system is not fully prepared to implement CAR T-cell therapy for the approved products for the anticipated number of patients. A participant shared,

> … if in fact the indications stand and grow and CAR T becomes more commonplace, then we do have to look at how it would be more broadly available. We can't rely on just a handful of sites in the province, or in the country to do this. So, where should we be planning and how should we be training these individuals for this therapy? (Reimbursement specialist, P4)

On the topic of developing CAR T-cell products in Canada and the evolution of CAR T-cells, one scientist stated,

> There is a push to allow centres that have bone marrow expertise but are not necessarily set up for GMP [good manufacturing practice] labs, to have a manufacturing facility to actually make these CAR T-cells on machines that you can just put in your lab as we normally do for cell sorting during the transplant process, and in a way like that, produce CAR T-cells that meet all the criteria to be given to a patient. (Clinician, C5)

Discussion

The results of this study highlight the challenges policy makers face with the implementation of CAR T-cell therapy in the Canadian healthcare system. The qualitative interviews led to the development of four key themes: CAR T-cell therapy is novel; patient characteristics and the delivery of care; processes from "bench-to-bedside"; and the future of CAR T-cell

therapy in Canada, including challenges to implementation and recommendations for long-term sustainability. Participants consistently described CAR T-cell therapy as novel in terms of its therapeutic benefit and the way it is developed and administered to patients. In addition, participants focused on the patient experience living with large B-cell lymphoma and their experiences with CAR T-cell therapy, emphasizing on the two common but serious adverse events CRS and neurotoxicity. In the experiences of both scientists and clinicians, the processes range from collecting cells and manufacturing CAR T-cell therapy in a lab to administering the therapy in the hospital and monitoring patients after therapy. Lastly, participants in all the fields outlined key barriers to implementation, including high drug and hospital costs and many hospitals' current lack of capacity to effectively deliver an additional resource-intensive therapy. Participants commented on the future of CAR T-cell therapy in Canada, giving recommendations for planning at the system level and looking ahead to what is next in the cell therapy space. To facilitate implementation of CAR T-cell therapy, participants noted that alignment and coordination with stakeholders, tailored training and education at hospitals and establishing cost-effectiveness and negotiating a fair price are all important.

The results presented in this study align with other reports on challenges with implementing CAR T-cell therapy in the healthcare system, although they have not been described qualitatively through interviews in a Canadian context. In the Optimal Use reports published by CADTH for approved CAR T-cell therapy products, ethical, legal and implementation issues were highlighted as part of a comprehensive review (CADTH 2019a, 2019b). CADTH highlighted views from stakeholders about how to roll out the delivery of CAR T-cell therapy (CADTH 2019c, 2019d).

High cost of the therapy remains one of the reimbursement challenges when adopting CAR T-cell therapy into the healthcare system in Canada and other developed countries. The centralized manufacturing model was associated with high per-unit manufacturing costs, which may allow a limited room for potential price negotiation (Harrison et al. 2019). Other countries are looking into innovative ways to potentially lower the price and improve access. For example, an alternative mode of regulation pathway instead of a traditional "drug" pathway was suggested (Chalasani et al. 2020). Countries such as Germany, Italy and Spain have come up with innovative reimbursement models that linked the reimbursement-staged payment/rebates to individual patient outcomes (Jørgensen et al. 2020).

Limitations

This study had several limitations. Although saturation was reached, there was a small sample size of 13 participants (three scientists/researchers, five clinicians and five reimbursement specialists that included policy makers and manufacturers' representatives). In addition, this study did not include patients, who are at the centre of discussions about CAR T-cell therapy. Future research would benefit from patients' perspectives on their own experiences with CAR T-cell therapy and their views on challenges to implementation. Another limitation is that the majority of participants (12) were from Ontario, with only one participant from

British Columbia. The perspectives are limited to the experiences of participants in these areas and may not be generalizable to the perspectives across all of Canada. This was the case due to certain national drug regulatory agencies located in Ontario, the leadership demonstrated by Ontario and British Columbia with developing CAR T-cell therapy products and the location of currently specialized hospital centres in delivering cell and gene therapies.

Conclusion

Our study highlighted some of the unique challenges to implementing CAR T-cell therapy in Canada and considerations for the future of novel cell and gene therapies entering the Canadian healthcare system. There has been tremendous growth in the number of clinical trials in the field of advanced therapy medical products (ATMPs)/cell and gene therapies. At the end of 2016, there were 220 documented CAR T-cell clinical trials, and this number continues to grow (Hartmann et al. 2017). The findings from this study can be used to inform policy makers in Canada and other countries and the public about logistical and feasibility concerns with implementing CAR T-cell therapy and other ATMPs/cell and gene therapies. Canada-specific views on barriers to implementation and recommendations for planning at the system level had not been well-documented prior to this study. Future research would benefit from the perspectives of Canadian patients and their experiences with accessing CAR T-cell therapy before and following funding approval.

Acknowledgements

The authors would like to thank all the participants for their valuable time and for the suggestions and insights they provided during the conduct of this study.

Funding

This study has been funded by an unrestricted grant from the Biotherapeutics for Cancer Treatment Networks of Centres of Excellence program. The funding organization did not have any role in the design of the study, management, analysis or interpretation of the data, or the preparation, review or approval of the manuscript. The researchers have no conflict of interest to report.

Correspondence may be directed to: Dr. William W.L. Wong, University of Waterloo, School of Pharmacy, 10A Victoria St. S., Kitchener, ON N2G 1C5. He can be reached by phone at 519-888-4567 x21323 and by e-mail at wwlwong@uwaterloo.ca.

References

Canadian Agency for Drugs and Technologies in Health (CADTH). 2019a, January. *CADTH Optimal Use Report – Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma: Ethics and Implementation Report*. Retrieved October 1, 2019. <https://cadth.ca/sites/default/files/pdf/car-t/op0538-tisagenlecleucel-ethics-and-implementation-jan2019.pdf>.

Canadian Agency for Drugs and Technologies in Health (CADTH). 2019b, August. *CADTH Optimal Use Report – Axicabtagene Ciloleucel for Large B-Cell Lymphoma: Ethics and Implementation Report*. Retrieved October 1, 2019. <https://www.cadth.ca/sites/default/files/pdf/car-t/ct0002-ipe-report.pdf>.

Canadian Agency for Drugs and Technologies in Health (CADTH). 2019c, August. Axicabtagene Ciloleucel for Large B-Cell Lymphoma: Recommendations. Retrieved October 1, 2019. <https://www.cadth.ca/axicabtagene-ciloleucel-large-b-cell-lymphoma-recommendations>.

Canadian Agency for Drugs and Technologies in Health (CADTH). 2019d, January. *Tisagenlecleucel for Diffuse Large B-Cell Lymphoma: Economic Review Report*. Retrieved October 1, 2019. <https://www.cadth.ca/sites/default/files/pdf/car-t/ct0002-ipe-report.pdf>.

Chaganti, S., T. Illidge, S. Barrington, P. Mckay, K. Linton, K. Cwynarski et al. 2016. Guidelines for the Management of Diffuse Large B-Cell Lymphoma. *British Journal of Haematology* 174(1): 43–56. doi:10.1111/bjh.14136.

Chalasani, R., T.B. Hershey and W.F. Gellad. 2020. Cost and Access Implications of Defining CAR-T Therapy as a Drug. *JAMA Health Forum*. Published online July 22, 2020. doi:10.1001/jamahealthforum.2020.0868.

Gisselbrecht, C. and E. Van Den Neste. 2018. How I Manage Patients with Relapsed/Refractory Diffuse Large B Cell Lymphoma. *British Journal of Haematology* 182(5): 633–43. doi:10.1111/bjh.15412.

Harrison, R.P., E. Zylberberg, S. Ellison and B.L. Levine. 2019. Chimeric Antigen Receptor–T cell Therapy Manufacturing: Modelling the Effect of Offshore Production on Aggregate Cost of Goods. *Cytotherapy* 21(2): 224–33. doi:10.1016/j.jcyt.2019.01.003.

Hartmann, J., M. Schüßler-Lenz, A. Bondanza and C.J. Buchholz. 2017. Clinical Development of CAR T Cells – Challenges and Opportunities in Translating Innovative Treatment Concepts. *EMBO Molecular Medicine* 9(9): 1183–97. doi:10.15252/emmm.201607485.

Health Canada. 2019. Regulatory Decision Summary – Kymriah – Health Canada. Retrieved October 1, 2019. <https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?lang=en&linkID=RDS00423>.

IBM Microdex RED BOOK. n.d. Retrieved October 1, 2019 <https://www.ibm.com/ca-en/products/micromedex-red-book>.

Jain, M.D., C.A. Bachmeier, V.H. Phuoc and J.C. Chavez. 2018. Axicabtagene Ciloleucel (KTE-C19), an Anti-CD19 CAR T Therapy for the Treatment of Relapsed/Refractory Aggressive B-Cell Non-Hodgkin's Lymphoma. In G. Walsh ed. *Therapeutics and Clinical Risk Management* 14: 1007–17. doi:10.2147/TCRM.S145039.

Jørgensen, J., E. Hanna and P. Kefalas. 2020. Outcomes-Based Reimbursement for Gene Therapies in Practice: The Experience of Recently Launched CAR T-cell Therapies in Major European Countries. *Journal of Market Access & Health Policy* 8(1): 1715536. doi:10.1080/20016689.2020.1715536.

Lam, C., E. Meinert, C.L. Halioua-Haubold, A. Carter, A. Yang, D. Brindley et al. 2019. Systematic Review Protocol: An Assessment of the Post-Approval Challenges of Autologous CAR-T Therapy Delivery. *BMJ Open* 9(7): e026172. doi:10.1136/bmjopen-2018-026172.

Levine, B.L., J. Miskin, K. Wonnacott and C. Keir. 2017. Global Manufacturing of CAR T Cell Therapy. *Molecular Therapy – Methods and Clinical Development* 4: 92–101. doi:10.1016/j.omtm.2016.12.006.

Maude, S.L., T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt et al. 2018. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *New England Journal of Medicine* 378(5): 439–48. doi:10.1056/NEJMoa1709866.

National Comprehensive Cancer Network (NCCN). 2018. NCCN Guidelines for Patients: Diffuse Large B-Cell Lymphoma. Retrieved October 1, 2019. <https://www.nccn.org/patients/guidelines/content/PDF/nhl-diffuse-patient.pdf>.

Neelapu, S.S., F.L. Locke, N.L. Bartlett, L.J. Lekakis, D.B. Miklos, C.A. Jacobsonet al. 2017. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *New England Journal of Medicine* 377(26): 2531–44. doi:10.1056/NEJMoa1707447.

Organisation for Economic Co-operation and Development (OECD). 2017. Prices and Purchasing Power Parities (PPP). Retrieved October 1, 2019. <https://www.oecd.org/sdd/prices-ppp/>.

Pharmaceutical Technology. 2018, November 1. Selling Cells: The Economics of CAR-T Therapy. Retrieved October 1, 2019. <https://www.pharmaceutical-technology.com/features/selling-cells-car-t-therapy/>.

Saunders, B., J. Sim, T. Kingstone, S. Baker, J. Waterfield, B. Bartlam et al. 2018. Saturation in Qualitative Research: Exploring Its Conceptualization and Operationalization. *Quality and Quantity* 52(4): 1893–1907. doi:10.1007/s11135-017-0574-8.

Schuster, S.J., M.R. Bishop, C.S. Tam, E.K. Waller, P. Borchmann, J.P. McGuirk et al. 2019. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *New England Journal of Medicine* 380(1): 45–56. doi:10.1056/NEJMoa1804980.

Sehn, L.H. and R.D. Gascoyne. 2015. Diffuse Large B-Cell Lymphoma: Optimizing Outcome in the Context of Clinical and Biologic Heterogeneity. *Blood* 125(1): 22–32. doi:10.1182/blood-2014-05-577189.

Staton, A.D., J.L. Koff, Q. Chen, T. Ayer and C.R. Flowers. 2015. Next-Generation Prognostic Assessment for Diffuse Large B-Cell Lymphoma. *Future Oncology* 11(17): 2443–57. doi:10.2217/fon.15.144.

Tong, A., P. Sainsbury and J. Craig. 2007. Consolidated Criteria for Reporting Qualitative Research (COREQ): A 32-Item Checklist for Interviews and Focus Groups. *International Journal for Quality in Health Care* 19(6): 349–57. doi:10.1093/intqhc/mzm042.

Vasileiou, K., J. Barnett, S. Thorpe and T. Young. 2018. Characterising and Justifying Sample Size Sufficiency in Interview-Based Studies: Systematic Analysis of Qualitative Health Research over a 15-Year Period. *BMC Medical Research Methodology* 18(1): 148. doi:10.1186/s12874-018-0594-7.