Chimeric antigen receptor T-cells in New Zealand: challenges and opportunities

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ABSTRACT

Chimeric antigen receptor (CAR) T-cells are a personalised cell and gene therapy for cancer that are becoming an international standard of care for some refractory B-cell leukaemias, non-Hodgkin lymphomas and myeloma. A single CAR T-cell administration can result in durable complete response for some recipients. Domestic CAR T-cell manufacturing capability was established for Aotearoa New Zealand's first CAR T-cell trial (ENABLE, ClinicalTrials.gov NCT04049513). This article outlines CAR T-cell manufacturing and logistical considerations, with a focus on New Zealand's environment for this personalised cell and gene therapy. We discuss Māori engagement in CAR T-cell trial and clinical service design, and propose enhancing Māori guardianship (kaitiakitanga) over cells and genetic material through on-shore manufacture. Strategies to safely deliver CAR T-cells within New Zealand's healthcare system are outlined. Finally, we discuss challenges to, and opportunities for, widening CAR T-cell availability and assuring equity of access. Based on our experience, we consider Aotearoa New Zealand to be in an excellent position to develop and implement investigational and commercial CAR T-cell therapies in the future.

Chimeric antigen receptor (CAR) T-cells are an emerging modality of cancer therapy. CAR T-cells are patient lymphocytes that have been engineered to express a synthetic receptor, which enables them to target tumour cells.[1] Internationally, CAR T-cell therapies are becoming a standard of care. They are a potentially curative treatment for certain relapsed and refractory (r/r) B-cell malignancies. In adult patients with r/r B-cell lymphomas and leukaemias, overall response rates of 73–83 % and complete response rates of 51–83 % have been reported following CAR T-cell therapy.[2–4] These responses can be durable, with 75% of patients with agressive B-cell lymphoma who respond at three months reporting being progression free at 24 months following CAR T-cell therapy.[3] Promising results have also been reported for other malignancies, notably myeloma.[5] CAR T-cell therapies involve a single cell administration, offer curative potential and can often be delivered in a near-hospital outpatient setting.

As a personalised cell and gene therapy, CAR T-cells present unique regulatory requirements. The logistics of CAR T-cell production and delivery, and the potential for specific adverse events, demand preparation by treatment sites. The nature of CAR T-cell therapies may raise ethical and equity issues that need to be addressed to ensure equity of access and outcomes.

We recently established local Good Manufacturing Practice (GMP) manufacture of lentiviral vectors and CAR T-cells and commenced enrolment to New Zealand's first CAR T-cell trial, ENABLE (ClinicalTrials.gov reference NCT04049513).[6] This involved close liaison with regulators and stakeholders and multidisciplinary input for safe clinical delivery of CAR T-cell therapies. Here we build on this experience by outlining the regulatory landscape for CAR T-cell therapies in New Zealand, summarising the preparation of sites and discussing the opportunities to broaden access to this new cancer treatment modality in New Zealand.

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CAR T-cell manufacturing and logistics

Leukocyte harvest and leukapheresis

Figure 1 illustrates a typical CAR T-cell manufacturing process. In brief, white blood cells are collected using an automated apheresis machine or by venesection of whole blood. Following initial processing and purification of T-cells, a new gene (the "transgene") encoding the CAR is introduced, typically using a lentiviral or retroviral vector.[7] CAR T-cells are expanded and then either administered fresh or cryopreserved following quality control testing.[8]

Commercially licensed autologous CAR T-cell products, such as tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel), require a leukapheresis procedure.[7] The New Zealand Blood Service (NZBS) is a national service that routinely performs leukapheresis for haematopoietic stem cell harvest across New Zealand. The NZBS is licensed by Medsafe to collect and manufacture therapeutic cells by apheresis and has conducted leukapheresis procedures for cellular therapy trials, including our own ENABLE CAR T-cell trial.[9,6,10] Leukapheresis product testing for blood-borne viruses is routinely performed at the Medsafe-licensed NZBS Donation Accreditation Laboratory. For the ENABLE trial, the leukapheresis procedure and leukapheresis product testing is funded from the trial research budget. Manufacturers of commercial and investigational CAR T-cell products are likely to have specific requirements for patient identification, infectious agent testing, leukapheresis performance and product labelling and shipping—and in our opinion, the NZBS network is likely to be well placed to conduct leukapheresis or venesection procedures for CAR T-cell manufacture in New Zealand in the future.

Current commercial CAR T-cell therapies are manufactured in a limited number of centres globally, none of which are in New Zealand. This offers advantages of scale, standardisation and cost, but the need for bidirectional international shipping of cells can present a logistical challenge, especially if travel is disrupted by pandemic or natural disaster. Māori regard tissue and genetic material as a taonga (precious item), and international manufacture limits opportunities for Māori engagement and kaitiakitanga (guardianship) over the cells and the genetic material they contain[11]—the destination(s) and use of the cells must be made clear during consent processes. In our view, future CAR T-cell manufacture within Aotearoa, either of locally developed products or through distributed manufacture of commercial products,[12] would improve opportunities for Māori engagement in the governance of tissue use and disposal.[11]

Manufacture and release of CAR T-cells

Although not viable except under specialised laboratory culture conditions or within the intended recipient (ie, the patient who underwent white blood cell collection used for the manufacture of that specific CAR T-cell product), CAR T-cells are defined as genetically-modified organisms (GMOs) by New Zealand legislation. Therefore, CAR T-cell manufacture is regulated by the Environmental Protection Authority (EPA) under the Hazardous Substances and New Organisms (HSNO) Act 1996 (Table 1).

Before granting approval to manufacture CAR T-cells for the ENABLE trial, the EPA sought assurance that the cells could not escape into the environment. To meet these containment requirements, we modified our GMP manufacturing facility and its operating procedures. The facility is inspected and audited by the Ministry for Primary Industries (MPI) and Medsafe.

CAR T-cells are manufactured according to validated protocols and must meet the requirements of the Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme (PICS) Guide to Good Manufacturing Practice (Table 1). Once a CAR T-cell product has been manufactured and met pre-specified "release criteria," the CAR T-cells are retrieved from storage and prepared for delivery to the hospital.

Shipping, product traceability, cell storage and disposal

Release of CAR T-cell products to the hospital site for administration to patients also required EPA approval. Measures to

Figure 1: Outline of CAR T-cell manufacture. Manufacture of CAR T-cells involves white blood cell harvest, typically by leukapheresis (1), followed by purification of T-cells, and transduction of the T-cells (2), typically using a lentiviral or retroviral vector. Transduced cells express a CAR directed against a tumour antigen (3), and are expanded *in vitro* in the presence of cytokines (4). Once CAR T-cell product release testing is complete, the patient received lymphodepleting (conditioning) chemotherapy (5), followed by intravenous administration of CAR T-cells (6). The recipient is then monitored for toxicities.

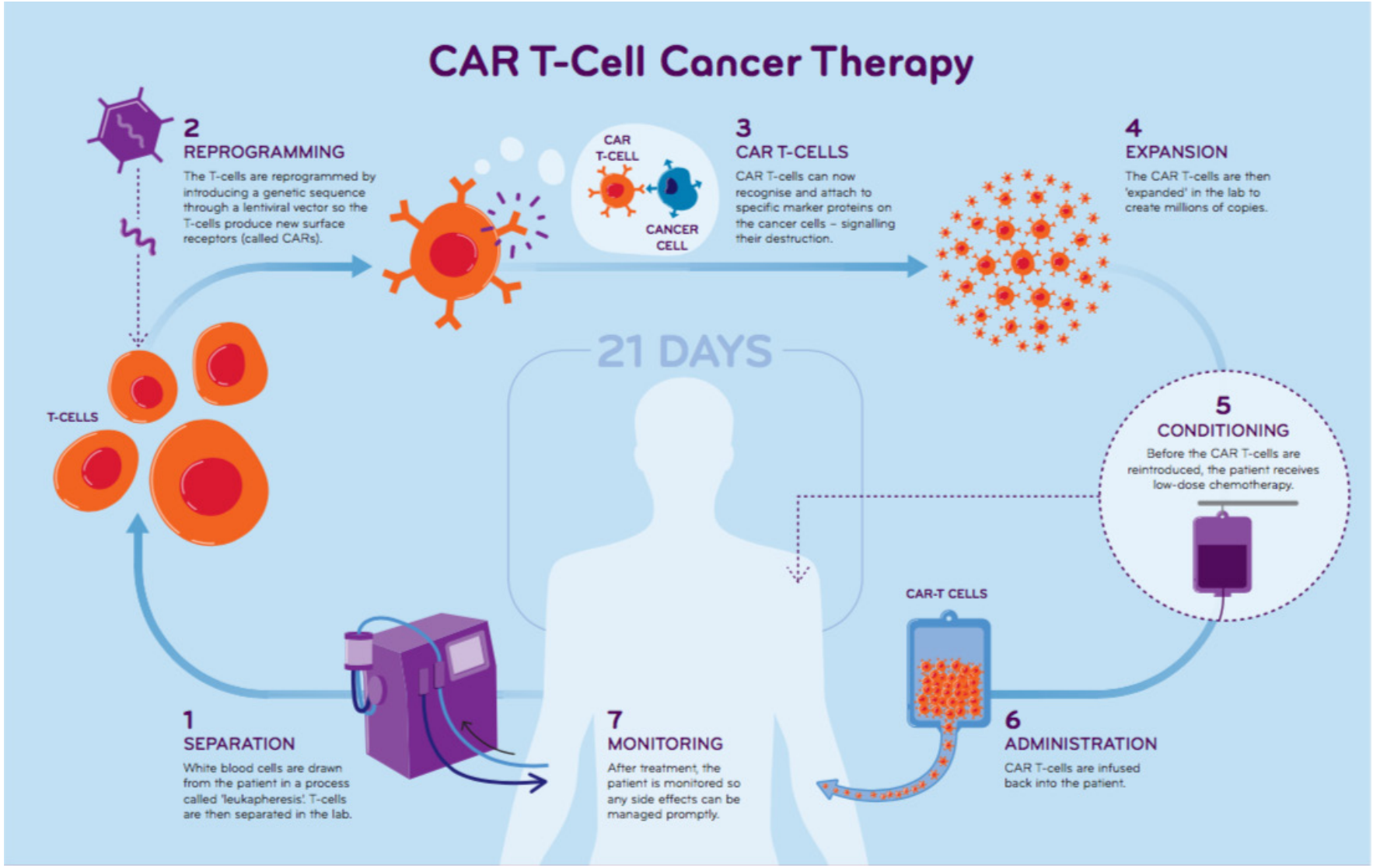

Table 1: Regulatory requirements for manufacture, release and delivery of CAR T-cell therapy in New Zealand.

Regulatory body	Application to CAR T-cell therapy	New Zealand legislation or guidance	Standards to be met
Health and Disability Ethics Committee (HDEC)	Approval required before conducting CAR T-cell clinical trials.	Medicines Act 1981, the Guideline on the Regulation of Therapeutic Products in New Zealand* Standard Operating Procedures for Health and Disability Ethics Committees, v 2.0, August 2014	Conduct according to CHMP† guidance document EMA/CHMP/IHC/135/95 Guideline for Good Clinical Practice E6(R2) to meet International Conference on Harmonisation Good Clinical Practice (IHC GCP) criteria.
Gene Technology Advisory Committee (GTAC) ‡	As a cell therapy comprising gene-modified cells, CAR T-cells require GTAC approval.	Section 30 of the Medicines Act 1981	Demonstration of: • clinical benefit (or scientific rationale for potential benefit, if investigational) • acceptable safety and toxicity data • risk assessments and risk mitigation procedures in place • if investigational, qualifications and experience of investigators suitable.
Māori consultation	Consent and equity of access. Māori consultation is an ethical and legislative requirement for research carried out within New Zealand's district health boards .	Te Ara Tika Guidelines for Māori research ethics, Health Research Council New Zealand Ministry of Health document- Equity of Healthcare for Māori: A framework The Treaty of Waitangi Guidance about consent with respect to the Human Tissue Act	Equity of access to therapy, including for those living distant from treatment centres. Consent to treatment, including consent to cell shipment and storage, and future use of tissue. Māori consultation processes for research vary regionally.

Table 1: Regulatory requirements for manufacture, release and delivery of CAR T-cell therapy in New Zealand (continued).

Regulatory body	Application to CAR T-cell therapy	New Zealand legislation or guidance	Standards to be met
Environmental Protection Authority (EPA)	Approval required to: • manufacture CAR T-cells, classified as GMOs (genetically modified organisms) in containment • release CAR T-cells from containment to treatment delivery site and to clinical laboratory for safety testing.	Hazardous Substances and New Organisms (HZNO) Act 1996, Section 40	• Demonstrate satisfactory containment level in place to prevent escape of the GMOs into the environment. • Demonstrate negligible risk of GMO forming a self-sustaining population outside of containment when released. • Ensure necessary controls to mitigate potential risk are in place to release GMO from containment.
Medsafe	License to manufacture cell therapy product (pack, label and sell by wholesale). Licenses the New Zealand Blood Service to collect and manufacture therapeutic cells by apheresis.	PIC/S§ Guide for Good Manufacturing Practice for Medicinal Products, annexes 13 and 14	Ensuring the manufacturing facility and manufacturing procedures (including batch manufacturing records and product release criteria) meet Good Manufacturing Practice (GMP) standards. Leukapheresis service audited against the code of GMP.

*Under this legislation all clinical trials in New Zealand must receive HDEC approval.

†CHMP (The Committee for Medicinal Products for Human Use) is the European Medicines Agency's (EMA) committee responsible for human medicines.

‡ A committee maintained by the Health Research Council (HRC) of New Zealand to consider applications for trials involving gene or other biotechnology therapies.

§ PIC/S Pharmaceutical Inspection Convention Pharmaceutical Inspection Co-operation Scheme.

assure safe release within the ENABLE trial included rigorous product labelling, shipping and traceability measures. The International Society of Blood Transfusion (ISBT) standards recommend standardised bar codes to allow blood products to be shipped internationally with clear, unambiguous labelling and help to overcome language barriers.[13] Furthermore, there are stringent procedures for packaging, transport, administration and disposal.

Rigorous identity checks using independent patient and product identifiers are performed and recorded on designated forms, to ensure the "chain of custody" is maintained and that the right patient receives the right product. Unused CAR T-cell vial(s) are returned to the manufacturing facility for safe disposal.

The number and expansion of T-cells varies widely between patients, so the manufacturing facility often has an excess of lymphocytes and/or CAR T-cells following product manufacture. Some cells must be retained for quality control purposes, and unless made available for future research (which requires proper consent), the remaining cells are typically destroyed. For our own CAR T-cell trial (ENABLE), we seek consent to store unused cells within an Immune Tissue Bank. This tissue bank was formed with input from Māori researchers, and its governance group includes Māori representation. At present, unused CAR T-cells cannot be returned to their recipient or to the recipient's whānau due to the cell's legal status as a GMO, although it is our opinion that this might be possible in a domestic CAR T-cell manufacturing facility in future, with appropriate risk assessment and controls.

Table 1 summarises the agencies involved in regulating CAR T-cell manufature, release and delivery in New Zealand.

CAR-T cell therapies and equity for Māori

In Aotearoa New Zealand, Māori are afforded the right to equitable health outcomes under Te Tiriti o Waitangi and ethical obligations under the United Nations Declaration on the Rights of Indigenous Peoples. Clinicians in New Zealand have an obligation to consider the degree to which they can contribute to improving Māori health outcomes, and Māori consultation is an ethical and legislative requirement[16,17] for research carried out within district health boards. Yet significant health inequities exist. Māori are approximately 20% more likely to develop cancer than non-Māori and are twice as likely to die from cancer,[14] including from non-Hodgkin lymphoma.[15] These inequities are driven by delays in diagnosis and treatment, worse access to the wider determinants of health and inequities embedded in health system design.

Cancer research has the opportunity to contribute to Māori health advancement. The Health Research Council (HRC) of New Zealand has implemented the Māori Health Advancement Guidelines, which require meaningful collaboration, consultation and partnership with Māori at the research design stage.[16] Māori expertise within the research team is recommended to ensure the research results in Māori health advancement and that tikanga Māori (Māori processes and protocol) is valued in the research design and the sharing of results. This framework provides an excellent resource for all health research conducted in Aotearoa New Zealand.

If access were equitable, investigational CAR-T cell therapies within Aotearoa New Zealand would provide an opportunity for Māori to benefit from treatments that are not publicly funded and that would otherwise be cost prohibitive. Māori, who regard genetic material as tapu (sacred/restricted), may be concerned with the application of genetic engineering. However, where there are direct health benefits for Māori, and provided that these benefits are well communicated, many will be supportive of this application.[11,17] A Māori consultation process is essential for CAR T-cell research and standard of care delivery, and this should include development of educational materials for Māori, their whānau and their clinicians.

For our own trial (ENABLE), Māori consultation was sought at an early stage during protocol development. In order to address issues relating to Māori involvement and recruitment and contribute to Māori health development, our CAR T-cell researchers met with Research Advisory Group Māori (RAG-M) at Capital and Coast District Health Board (CCDHB) and Te Urungi Māori, the

Māori steering group at the Malaghan Institute. Following consultation, a brief patient-focussed summary, in both English and te reo Māori, and a visual representation of the CAR T-cell treatment process (Figure 1) were incorporated into the participant information and consent form. ENABLE participants are able to donate tissue to an Immune Tissue Bank, and we have consulted with our (Māori) Tissue Bank Manager at the Malaghan Institute regarding tissue retention and karakia arrangements. We collaborated with a Māori clinician and researcher familiar with managing patients with haematological malignancies. To reduce the risk that distance from the treatment centre impedes study access, an agreement was reached with a national cancer charity to support the travel costs for study participants and a family member, if they were not eligible for the National Travel Assistance Scheme.

Clinical delivery of CAR T-cell therapy

CAR T-cell toxicity working group

CAR T-cell therapies can cause specific toxicities, particularly cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS; neurotoxicity).[18] The consensus guidelines for the diagnosis and grading of CRS and ICANS published by the American Society for Transplantation and Cellular Therapy (ASTCT) can be readily applied in New Zealand hospitals.[19] Consensus recommendations for the management of CRS and ICANS are also available.[18,20]

For the ENABLE trial, we convened a CAR T-cell toxicity (CARTOX) working group, which included representatives from haematology, neurology, intensive care, immunology and nursing. The CARTOX group developed and reviewed CRS and ICANS recognition and management pathways, based on consensus recommendations[18] and advice from experts in the field (Neelapu and Turtle, personal communications). These management pathways have been posted on the hospital intranet at the CAR T-cell treating site, with clear paper-based management algorithms being available for easy reference on the haematology ward where patients are treated.

The CARTOX group was also consulted regarding CAR T-cell toxicity education and training material for clinical staff. Since commencing the ENABLE trial, the CARTOX group have met at least every six months in order to review CAR T-cell-related toxicities reported in the ENABLE trial and to evaluate up-to-date published guidance on CAR T-cell toxicity management. This has led to modifications of both CRS and ICANS management pathways as well the production of a working document reviewing the evidence for second-line management of severe CAR T-cell-related toxicities. Given our early experience and feedback from international CAR T-cell treating clinicians and , we recommend implementation of a CARTOX group (or similar) for other centres administering CAR T-cell therapies.

CAR T-cell toxicity education

To safely deliver CAR T-cell therapy, clinical teams must be trained in the recognition and management of CAR T-cell-related toxicities. For commercial products, specific risk evaluation and mitigation strategies (REMS) may be required by the manufacturer, which are likely to involve product-specific training and knowledge assessments for specific clinical staff.[21] Training typically encompasses areas such as prescribing, dispensing and administering CAR T-cells and monitoring for, recognising and treating CAR T-cell related toxicities.[21] For the ENABLE Trial, we developed an educational tool and competency assessment for clinical staff in our inpatient and day-ward areas and for members of the Patient at Risk and intensive care teams. Regular educational updates are held. One-page CRS and ICANS "quicksheets" were produced, and are displayed prominently in the clinical area in which a CAR T-cell recipient is being treated.

Availability of anti-cytokine therapy

The hallmark of CRS is fever caused by high levels of interleukin-6 (IL-6) during CAR T-cell recognition of, and activation by, tumour cells. Tocilizumab, a monoclonal antibody against the IL-6 receptor, is highly effective for management of CRS and can be useful for ICANS.[20] Although tocilizumab is not licensed by Medsafe in New Zealand for the treatment CAR T-cell therapy toxicities, it is registered by the US Food and Drugs Administration (FDA) for this indication[22]

and is universally recommended in international guidelines for CRS and ICANS.[18,20] The REMS strategy for axicabtagene ciloleucel requires that at least two doses of tocilizumab are available on site for each patient when they are treated.[21] Tocilizumab was alraedy approved for treating paediatric Acute Lymphoblastic Leukaemia (ALL) trial participants, so a clinician-led application to PHARMAC was made in order to extend this existing approval to include ENABLE trial participants. This application was successful, and PHARMAC will now fund up to three doses of tocilizumab to treat CRS and/or ICANS in ENABLE trial participants.[23] In our opinion, emergency availability of anti-IL-6 therapies will need to be assured for future investigational or commercial CAR T-cell therapies in New Zealand. High-dose corticosteroids are used for severe CRS and ICANS; there are no restrictions on the use of these in New Zealand.

Expert opinion, preclinical data and case reports have recommended anakinra, siltuximab and dasatanib as second-line treatments for severe CRS or ICANS.[24–26] Although there are no definitive recommendations on which second-line agent to use first, many sites use anakinra (a human intereukin-1 receptor antagonist) in this setting because pre-clinical studies have suggested that IL-1 plays a crucial role in the pathogenesis of CRS and neurotoxicity, and because of anakinra's clinical efficacy in similar settings, such as for macrophage activation syndrome (MAS), which can have features that overlap with severe CRS.[26,27] In conjunction with the CARTOX group, we developed contingency plans for second-line treatment of severe CRS or ICANS, which included the study sponsor purchasing a supply of anakinra to be stored at the treatment site.

Patient education

Patients and their whānau need to receive education about the potential adverse effects of CAR T-cell therapy. As CRS and ICANS are typically early toxicities, it is often recommended that patients remain close to the CAR T-cell treating centre, alongside a support person, for at least 21 days after CAR T-cell therapy.[28] We provide in-person and written education on CAR T-cell toxicities for recipients and their support person, as well as 24/7 contact details for the CAR T-cell treatment centre. After 3–4 weeks, most CAR T-cell recipients will be able to return to a home further afield. Recipient education is key. Because their primary and secondary care clinicians may lack CAR T-cell experience, recipients should also receive clear and accurate information to pass on to other healthcare professionals they may meet.[28] For the ENABLE Trial, CAR T-cell recipients are given a wallet emergency card and a discharge summary sheet (Supplementary Materials).

Cellular therapy registries

As CAR T-cells are a relatively new treatment modality, there is a possibility that low incidence or late onset toxicities will emerge, such as second malignancies or adverse pregnancy outcomes. Cellular therapy registries provide an important framework for long-term follow-up and detection of such risks.[29] The Center for International Blood and Marrow Transplant Research (CIBMTR), to which New Zealand stem cell transplant centres already report safety and efficacy data following stem cell transplantation, opened its Cellular Therapies Registry in June 2016, which aims to standardise CAR T-cell toxicity reporting and data collection.[29] Participation in the CIBMTR Cellular Therapies Registry is open to CAR T-cell treatment centres worldwide, provided ethical approval for data collection and sharing is in place. Within Australasia, the Australian Bone Marrow Transplant Recipient Registry (ABMTRR) has recorded outcomes of haematopoietic stem cell transplantation since 1992 and has expanded its remit to collect data from CAR T-cell recipients.[30]

Challenges and opportunities

In many respects, New Zealand's healthcare system is well-suited to the delivery of CAR T-cell therapies for haematological malignancies. Although our regulatory processes are unique, they have been successfully tested for CAR T-cells through the ENABLE trial. The New Zealand Blood Service (NZBS) runs a national network of blood collection and leukapheresis centres, and NZBS electronic systems and National Health Index (NHI) numbers facilitate vein-to-vein traceability

of transfused products, follow-up and the recording of national healthcare alerts. Clinical haematology services benefit from a national network of bone marrow transplantation centres, with established referral pathways, and with comprehensive on-site services, including intensive care, neurology, immunology, infectious diseases, oncology pharmacy and specialist laboratory services. Although commercial CAR T-cells are manufactured in large global hubs at present, the capability to manufacture CAR T-cells within New Zealand will facilitate Māori engagement and guardianship and could offer logistical advantages for CAR T-cell delivery.[31] Furthermore, future developments, such as outpatient management following CAR T-cell treatment and the use of automated CAR T-cell product manufacturing systems, may be means of lowering the cost of delivering treatment in New Zealand.[32]

Equity of access is a key consideration for all new therapies. Some mechanisms needed to address this are in place, and some require strengthening. A network of sites offering CAR T-cell therapies across Aotearoa New Zealand will reduce travel requirements for patients, but the nature of CAR T-cell therapy means that most recipients will have to spend time away from home; travel and accommodation support will be essential. The need to travel is offset by the one-off nature of CAR T-cell delivery and the fact that its principal toxicities occur early after administration.

Cost is a barrier to commercial CAR T-cell therapies at present, and list prices for the licensed autologous CAR T-cell products axicabtagene ciloleucel and tisagenlecleucel are high, at US$373,000 and US$475,000, respectively.[33] However, increasing competition between manufacturers, negotiations including schemes that link payment to clinical response and the likely future availability of tocilizumab and anakinra biosimilars are expected to lower total treatment costs in future. Pending funding

Table 2: Opportunities and challenges for CAR T-cell therapies in New Zealand.

Challenges	Opportunities
Unique regulatory environment	Medsafe regulations are harmonised with EMA*; ENABLE trial provides regulatory experience
Logistics of cell harvest and manufacturing	National leukapheresis & blood collection network (NZBS†); national patient identifiers (NHI‡); domestic CAR T-cell and lentiviral vector manufacturing capability (MIMR§; small-scale)
Equity of access	Involve Māori in service planning; leverage national stem cell transplant network; one-off CAR T-cell therapy possibly preferable to ongoing treatments; inter-district funding and national travel assistance schemes
High cost of commercial CAR T-cell therapies	CAR T-cells are a "one-off" rather than ongoing cost; declining costs due to competition; clinical trial access pending commercial delivery; outpatient administration can lower costs
Limited clinician experience of CAR T-cell delivery	National network of stem cell transplant centres; clinical trial experience of CAR T-cell delivery (ENABLE)
Restrictions on medicines used to treat CAR T-cell toxicities	Tocilizumab and anakinra biosimilars are in development; PHARMAC provides a national funding mechanism ("Special Authority")

* European Medicines Agency (EMA).

†New Zealand Blood Service (NZBS).

‡ National Health Index (NHI).

§ Malaghan Institute of Medical Research (MIMR

of CAR T-cell therapies, clinical trials can help bridge the gap in availability, at least for some patients, and prepare our regulatory and clinical systems for routine CAR T-cell delivery. Table 2 summarises key challenges and opportunities for CAR T-cell therapies in New Zealand.

Conclusions

CAR T-cell therapy is shifting the treatment paradigm of relapsed and/or refractory B-cell malignancies internationally. In this viewpoint, we have outlined the regulatory processes and clinical preparations involved in establishing the first CAR T-cell therapy programme in New Zealand, with particular consideration to Māori engagement and access to treatment. Having reviewed the challenges and opportunities, we believe Aotearoa New Zealand is in an excellent position to develop and implement both investigational and commercial CAR T-cell therapies in the future.

Supplementary material

- Supplementary Materia 1: CAR T-cell Wallet Emergency Card
- Supplementary Material 2: ENABLE Trial Discharge Summary Sheet

Competing interests:
RW, PG, TH and GG are employees of the Malaghan Institute of Medical Research, which sponsors the ENABLE trial. The authors do not have proprietary or financial interests in the WZTL-002 CAR T-cell product.

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