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Review Article

Chimeric Antigen Receptor-T (CAR-T) Cells as "*Living Drugs*": A Clinical Pharmacist Perspective

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Background. Chimeric antigen receptor (CAR) T cell therapy, a "living drug" immunotherapy, harnesses the power of T-cells from a patient (autologous) or healthy donor (allogeneic) to target and kill cancer cells and has shown unprecedented outcomes in patients with relapsed and refractory malignancies. Treatment with CAR-T cells requires the application of unique skillsets in recognised specialist centres for successful outcomes and requires management by the multidisciplinary team incorporating the specialist pharmacist. *Method*. A multimodal research strategy was employed for this literature review whereby PubMed, Google Scholar, Embase, Stella Library Search, EMA website, and EBMT website were sources of information. The search was limited from 2020 onwards with key terms referring to CAR-T cell therapy. *Results and Discussion*. There are six CAR-T cell products currently approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) which target haematological malignancies with abundant clinical trials underway exploring new and improved CAR designs and antigen targets. As CAR-T cell therapy is an advanced therapy medicinal product (ATMP), there is need for an extensive regulatory framework underpinning its safety and efficacy. The clinical pharmacist plays an integral role in the provision of safe and effective CAR-T cell therapy including governance, operational and clinical aspects of treatment. Pharmacists may also be involved through provision of "Qualified Person" (QP) expertise in clinical trials and for release within hospitals under certain circumstances. There is a need for harmonised and accessible guidance on the clinical delivery of ATMPs such as CAR-T cells, with fully delineated responsibilities of pharmacists involving the oversight and supervision of CAR-T cell treatment. *Conclusion*. There is an unmet need to provide suitable and applicable literature for clinical pharmacists who are involved in the delivery of CAR-T cells. We have provided an overview of T-cell biology and an explanation of CAR-T cell design and the biomanufacturing process. We reviewed the complex and multifaceted treatment cycle requiring considerable logistics, and described the involvement of the clinical pharmacist in each part of this cycle from patient selection to postinfusion care. Finally, we look to the challenges and future opportunities that will require the involvement of the clinical pharmacist.

1. Introduction

According to the World Health Organization (WHO), cancer is one of the leading causes of death globally accounting for approximately 10 million deaths in 2020 [1]. Conventional cancer treatment regimens include surgery, chemotherapy, and radiation therapy [2], which are variably effective and widely used. Nonetheless, severe adverse effects, recurrence, resistance, and metastasis remain commonplace [3, 4]. In a bid to revolutionise cancer treatments and bring about lasting remission, immunotherapy has brought about treatment alternatives which can better target tumour cells, thus transforming the treatment landscape for many malignancies [5].

Cancer immunotherapy can be classified as active (i.e., actively boosting the immune system) or passive (i.e., through the transfer of cells to target the cancer) and provides an alternative treatment strategy to treat more advanced and/or recalcitrant diseases [6]. Adoptive cell therapy (ACT) is a form of passive immunotherapy whereby cells of the immune system (either tumour resident or peripheral blood modified immune cells) are infused into cancer patients to mediate anticancer effects [7]. A proven ACT strategy is chimeric antigen receptor-T (CAR-T) cells, where T cells are genetically reprogrammed to possess properties to target, bind, and kill specific tumour cells. CAR-T cells and CAR-T cell therapy are considered an active area of research with 9,098 papers published on CAR-T cells (accessed from Scopus on May 18, 2023), 3,008 of which have been published since 2022. According to the https://ClinicalTrials.gov database under "CAR-T Cells" (accessed on May 18, 2023), there are 1,395 interventional clinical trials of which 1,091 are in phase I and 688 are actively recruiting participants. Despite the success of CAR-T cell treatment for B-cell malignancies in bringing about complete remission (CR) in patients with relapsed and refractory conditions, this novel therapy is not without its drawbacks [8].

Six CAR-T cell products are currently approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA), yet there remain many unknowns regarding persistence, short- and long-term toxicity and side effects, and applications beyond haematological malignancies [9]. CAR-T cell therapy can potentiate life-threatening immune-mediated conditions such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and potentially graft versus host disease (GvHD) in the allogeneic setting [10]. Furthermore, the persistence of CAR-T cells *in vivo* and the lengthy production times of CAR-T cell products are significant challenges that can impact the efficacy and availability of CAR-T cell therapy [11]. Due to the complexity of care associated with such innovative therapies, the safe provision of CAR-T cell therapy demands a multidisciplinary team (MDT) approach [12]. ATMP pharmacists have a key role in the management of CAR-T cell therapies within the MDT such as selection, coordination, ordering, procurement, preparation, and dispensing of the CAR-T cell product, providing education to staff and patients, and supporting toxicity management [13]. The duties and specific training for pharmacists are defined by the European Society of Blood and Marrow Transplant and the European Haematology Association (EBMT-EHA) [14], yet these therapies are evolving at such rapid pace with widening indications that a more flexible approach is required with consideration of earlier training modules in the area of "Living Drugs" for clinical pharmacists.

In this review, we focus on the role of T cells in cancer immunotherapy, how CAR-T cell therapy is shifting oncotherapeutic paradigms, and the intrinsic role of the pharmacist for the safe provision of CAR-T cell therapy.

2. The Role of Normal T Cells in Immune Responses and Immunometabolism

2.1. T Cells in the Immune Response. T cells are a population of white blood cells which play a fundamental role in protecting the body against pathogens and tumours, as well as in mediating tolerance. They are distinguished from other immune cells mainly by the presence of a T cell receptor (TCR), which confers specificity in binding to a target. T cells have multiple functions such as cytotoxicity, recruitment, and regulation [15] (Figure 1). The functionalities of T cells vary according to their phenotypic profile (which can also be related to cell trafficking through tissues and homing), gene expression, and secreted proteins and enzymes [16]. Prior to antigen exposure, T cells are quiescent or naïve (T_n) and require activation to differentiate into the many effector phenotypes. In adults, T cells for the most part express either CD4 or CD8 as coreceptors, which determine the mechanism by which they can detect antigens and their effector functions (Figure 1). Via the TCR, $CD4^+$ T cells (or T-helper cells) detect peptide antigens presented on major histocompatibility complex (MHC) class II of antigen-presenting cells. In response, they elicit an adaptive immune response by producing cytokines which can enhance or suppress the Type 2 immune responses [17]. These cytokines activate and recruit $CD8^+$ T cells [18]. $CD8^+$ T cells are activated upon the detection of an antigen on MHC class I, followed by proliferation to generate a "cytotoxic effector T cell pool" [19, 20]. This population of T cells can recognise cells expressing tumour-specific antigens and induce apoptosis of tumour cells via perforin, granzyme B, and other cytotoxic cytokines. A subpopulation of $CD4^+$ T cells includes regulatory T-cells (T_{regs}), which mediate immune suppression by downregulating effector T cells and maintaining tolerance to self-antigens [21]. T_{regs} are exploited by tumour cells to mediate immune suppression of effector cells in the tumour microenvironment (TME) resulting in exhausted T cell phenotypes and anergy [20]. The different lineages of T cell subsets differentiate in the peripheral nodal tissues to execute specialised effector functions.

Activation of T-cells is mediated by antigen presentation on the MHC of an antigen presenting cell (e.g., dendritic cell) with an accompanying costimulatory signal [22]. Upon activation, T cells secrete proliferative/survival cytokines such as IL-2, IL-4, and IL-7, which in turn enable the proliferation of effector T cells (T_{EFF}) to carry out their respective functions [15]. The microenvironment, coupled with the cytokines secreted, determines the phenotype in which they differentiate into: terminally differentiated effector T cells (T_{EMRA}), which ultimately exhaust and experience cell death, stem central memory T cells (T_{SCM}), central memory T cells (T_{CM}), or effector memory T cells (T_{EM}) (smaller proportion) facilitated by IL-7 and IL-15 (Figure 1) [15]. The different subtypes of T cells and their level of differentiation are regulated by different metabolic profiles, which can impact longevity, persistence, and antitumour cytotoxicity [16, 17, 20].

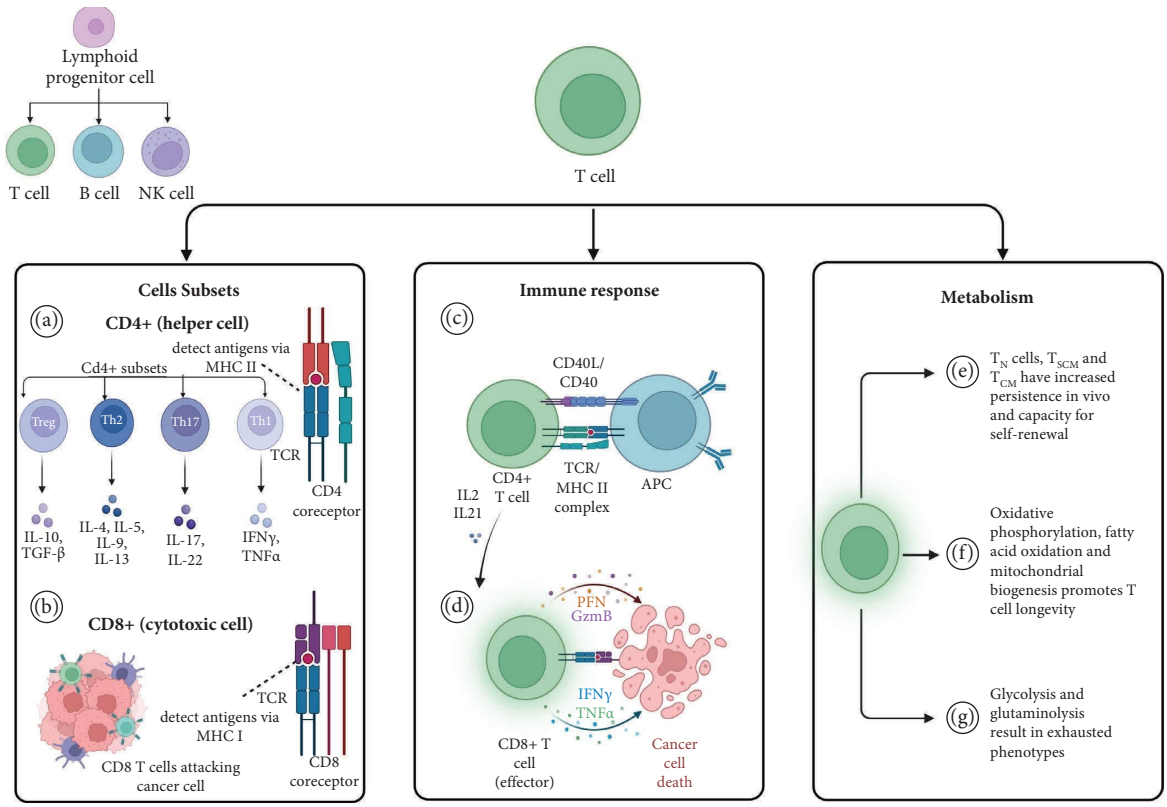

Figure 1: Key features of T-cells. The T-cell populations can be divided into two broad effector classes with their differing immune and metabolic profiles. T cells are naïve until primed with two signals: (i) antigen presentation and (ii) costimulation. Once primed, the T cells are activated and become effector T cells and express CD40L on their surface. (a) $CD4^+$ T-cells are helper T cells which have a variety of functions such as recognition of antigen peptides on dendritic cells via MHC class II and secrete cytokines dependent on the subtype of $CD4^+$ T cell, for instance, Th1, Th2, Th7, and T_{reg} release different cytokines which bring about various responses. (b) $CD8^+$ T cells are cytotoxic cells which bind via MHC class I. (c) T cells secrete cytokines in response to activation via their cognate antigen/MHC and coligation with various cell surface molecules, such as CD40/CD40L. (d) $CD8^+$ T cells bring about cancer cell death through the secretion of perforin (PFN) and granzyme B (GzmB) and cytokines such as IFN-γ and TNF-α. T cell metabolism differs greatly between the different subtypes; (e) naïve T cells, memory T cells, and stem cell memory T cells depend on (f) oxidative phosphorylation and mitochondrial biogenesis to satiate their energetic demands and effector T cells, whereas effector memory T cells depend on (g) glycolysis and amino acid metabolism for sustenance. These metabolic profiles explain why effector $CD8^+$ T cells exhaust and differentiate into terminally differentiated effector phenotypes and experience cell death. Key: MHC = major histocompatibility complex, IL-10 = interleukin 10, TGF-β = transforming growth factor beta, IL-4 = interleukin 4, IL-15 = interleukin 15, IL-9 = interleukin 9, IL-13 = interleukin 13, IL-17 = interleukin 17, IL-22 = interleukin 22, IFNγ = interferon Γ, TNF-α = tumour necrosis factor alpha, TCR = T-cell receptor, Th2 = T helper cell 2, Th17 = T helper cell 17, Th1 = T helper cell 1, T_{reg} = regulatory T cells, PFN = perforin, GzmB = granzyme B, T_n = naïve T cells, T_{scm} = stem cell memory T cell, and T_{cm} = central memory T cell.

2.2. T Cell Immunometabolism. The ability of T cells to adapt to their environment and sustain energy intensive processes involved in activation, proliferation, differentiation, and survival is dictated by T cell immunometabolism [20]. Immuno-metabolic regulation is mediated by the complex interplay between extracellular and intracellular signalling pathways and metabolic enzymes [20–23]. The main metabolic pathways that sustain T cell function include glycolysis and oxidative phosphorylation (Figure 1) [20, 22]. The glycolytic pathway is characterised by the breakdown of glucose to pyruvate, which is affected positively or negatively based on transcriptional, posttranslational, and metabolic regulators. Glycolysis rapidly generates two molecules of ATP per molecule of glucose (low yield) and provides other metabolic substrates such as lactate which can be transported into the mitochondria to be used in the tricarboxylic acid cycle [22, 23]. Glycolysis is required to maintain the maximum metabolic rate. Oxidative phosphorylation slowly generates 36 ATPs per molecule of glucose (high yield) by coupling the tricarboxylic acid cycle and the mitochondrial electron transport chain. The fatty acid oxidation (FAO) pathway also plays a role in T cell metabolism by providing substrates to the tricarboxylic acid cycle and mitochondrial electron transport chain and thus is an essential player in oxidative phosphorylation [22, 23]. Oxidative phosphorylation is at play in lower energetic demands and higher energetic demands (coupled with anaerobic glycolysis). The dynamic switch from one metabolic pathway to another depends on the T cell's energetic demands as well as its level of differentiation and phenotype [22, 23].

$CD8^+$ T_n cells rely on oxidative phosphorylation and FAO to sustain their homeostatic proliferation and survival [20]. Upon activation, $CD8^+$ T_n cells require both glycolysis and oxidative phosphorylation for their metabolic reprogramming and cell growth [20]. When fully differentiated into their effector phenotype, $CD8^+$ T_{EFF} cells have comparatively high energetic demands relying on glycolysis and glutamine metabolism to proliferate and secrete cytotoxic cytokines [24]; this increased energy is required to clear the inciting antigen and ultimately differentiate into the senescent T_{EMRA}. T_m cells have an efficient metabolic profile by utilising oxidative phosphorylation, FAO, and mitochondrial biogenesis (via cytokines inducing mitochondrial morphological modifications) to enable this phenotype to remain for years until they encounter the same inciting antigen again [25]. Activation of T_{EM} cells occurs upon a secondary encounter with the inciting antigen; glycolysis and amino acid reuptake are required to sustain this energetic demand [26]. $CD4^+$ T cells have a differing metabolic profile due to their differentiation into diverse subtypes [16–18].

$CD4^+$ T_n cells have low energetic demands that are satisfied by oxidative phosphorylation and the action of the homeostatic cytokine, interleukin-17 (IL-17), which initiates the PI3K/AKT/mTOR signalling cascade, promoting glucose uptake and facilitating the FAO pathway in the mitochondria [16]. Activated $CD4^+$ T cells undergo subset differentiation which have various functions such as proinflammatory and anti-inflammatory effects. Proinflammatory subsets include Th1, Th2, and Th17 which are energetically sustained by the combination of oxidative phosphorylation and glycolysis with high levels of glucose uptake [17]. Anti-inflammatory T_{regs} are sustained mostly by oxidative phosphorylation coupled with FAO and have Foxp3-blunted glycolysis [16].

There are various metabolic barriers that compromise T cell fitness within the TME. The tumour microenvironment suppresses T cells due to the accumulation of toxic metabolites such as reactive oxygen species [22]. The acidic and hypoxic conditions due to rampant glycolysis accumulating lactate and protons also contribute to suppression of T cells [27]. In addition, nutrient depletion of glucose and arginine by the TME further suppresses T cell function [22]. Tumour cells express immune checkpoint molecules such as programmed cell death protein 1(PD1) and cytotoxic T-lymphocyte association protein 4 (CTLA4) and T cell inhibitors such as myeloid-derived suppressor cells, tumour-associated macrophages, and T_{regs} [22]. These factors act synergistically to exhaust T cells, thereby dampening their bioenergetics [17]. The less differentiated T cell phenotypes such as T_n cells, T_{SCM}, and T_{CM} have increased persistence in vivo and capacity for self-renewal which are conducive to enhanced and sustained antitumour activity [17]. Targeting the bioenergetics of T cells provides a potential strategy to enhance the efficacy of cancer immunotherapy [17, 28].

3. Harnessing T Cells in Cancer Immunotherapy

Cancer immunotherapy is a therapeutic modality where the immune response is enhanced to eradicate tumour cells with the goal of extending progression-free survival (PFS) and overall survival (OS) [5–7]. When harnessed appropriately, cellular immunotherapy is intrinsically superior to conventional drugs, as cells are dynamic living agents with a multitude of dynamic capacities such as signalling cascades, secretion of cytokines, formation of immunological memory, and persistence in the body for months, or even years [29–31]. In contrast, conventional pharmaceuticals, which generally target specific molecules or pathways, are excreted on average within hours of administration [4]. Conventional therapies also lack the ability to differentiate between tumour and nontumour cells and indiscriminately target rapidly growing cells (cancerous or otherwise) [4]. Cancer immunotherapy can specifically recognise unique mutations and protein expression of tumour cells and optimise the immune response to overcome standard evasive defence mechanisms of treatment resistance [29, 30]. This capacity can be attributed to antigen-directed cytotoxicity, the ability to provoke a signalling cascade resulting in clearance of tumour cells and the durability, longevity, and functionality of the response [29]. There are three main categories of cancer immunotherapy which harness T cells: immune checkpoint blockade, cancer vaccines, and ACT such as CAR-T cells whereby T cells are redirected towards tumour-associated antigens for cytotoxic effect [29, 30].

4. CAR-T Cells as "Living Drugs"

CAR-T cell therapy is a form of personalised cancer treatment in which T cells from a cancer patient (autologous) or a healthy donor (allogeneic) are harvested and reprogrammed *ex vivo* to express a genetically engineered receptor that targets and kills cells expressing tumour-specific antigens [2]. Due to these properties, CAR-T cells are termed as "living drugs" [31]. In contrast to endogenous TCRs, CARs execute the effector function and memory specificity of the T cell in a non-MHC-restricted manner [32]. These genetically enhanced CAR-T cells are infused into the patient to target recalcitrant and resistant malignancies with remarkable success in B-cell haematological malignancies [33], such as leukaemias, lymphomas, and plasma cell dyscrasias. Unfortunately, there is a significant challenge in translating CAR-T cell therapies to non-B cell malignancies such as T cell malignancies, myeloid neoplasms, and solid tumours [33, 34]. These challenges are in part due to shared antigen expression between malignant and normal cells resulting in life-threatening complications such as aplasia and other on-target toxicities. Continued advancements in technology, unique target identification, and combination therapies hold promise for expanding the application of CAR-T cell therapy beyond B-cell tumours [34, 35].

4.1. CAR Architecture. The CAR is a hybrid receptor composed of four domains which combines differing functional components to form a synthetic receptor which targets specific antigens and stimulates the T cell to exact its cytotoxicity effects (Figure 2). The domains are classified as the extracellular, transmembrane, hinge, and intracellular signalling domains, which can be optimised to enhance

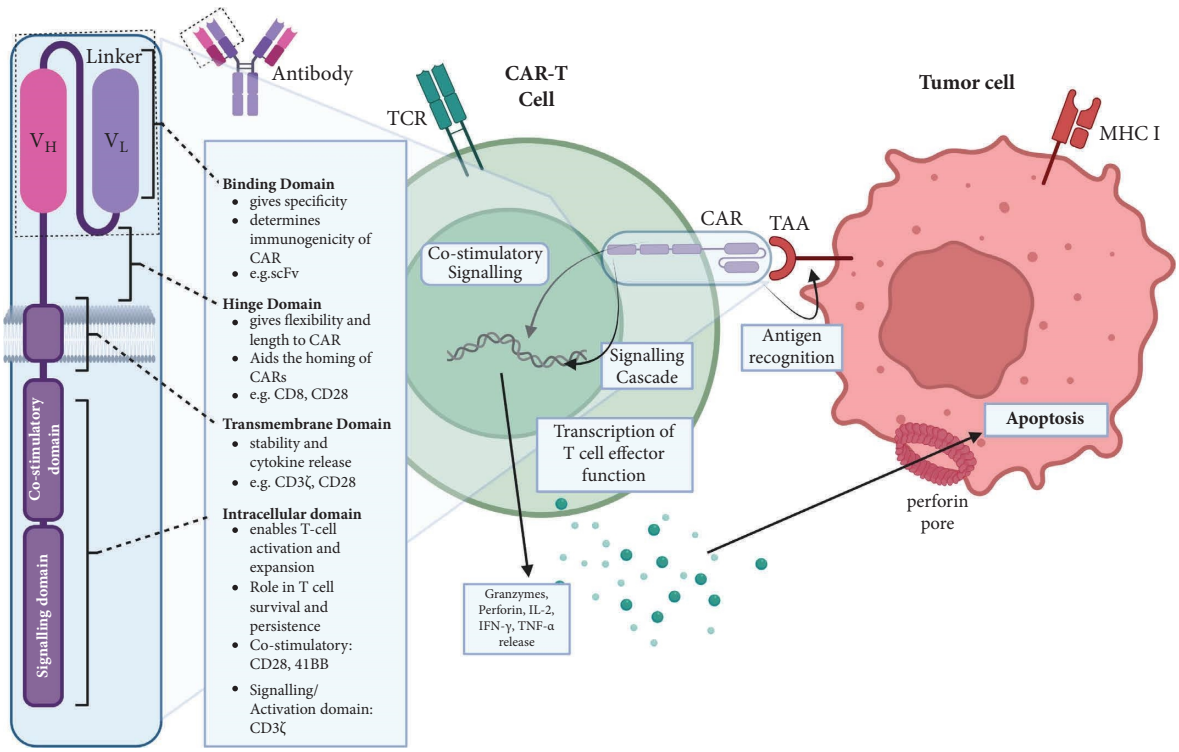

Figure 2: CAR-T cell architecture. The CAR construct is composed of four domains which support its functionality. The single chain variable fragment (scFv) domain is the extracellular domain which is involved in recognition and binding. It also can induce immunogenicity if obtained from murine sources. The hinge domain gives flexibility to the CAR enhancing binding and homing. The transmembrane domain provides stability and cytokine release and enables incorporation into exogenous TCR. The intracellular domain has two regions, the costimulation and activation regions, which together initiate a signalling cascade to induce proliferation and activation of T-effector functionality. These domains function synergistically to reprogram the T cell to specifically bind tumour-associated antigens (TAAs) and execute their cytotoxic functions. Key: VH = variable heavy chain, VL = variable light chain, IL-2 = interleukin 2, IFNy = interferon gamma, TNF-α = tumour necrosis factor alpha, TCR = T cell receptor, MHC = major histocompatability complex, TAA = tumour-associated antigen, and CAR = chimeric antigen receptor.

efficacy and safety [36]. The extracellular domain of the CAR is responsible for antigen recognition and binding. This can be attributed to the heavy and light single-chain variable fragment of a monoclonal antibody (murine- or human-derived), which is interconnected with a peptide linker (Gly4Ser) forming a single-chain variable fragment (scFv) [37]. The relative position of the heavy and light chain variable regions can affect the affinity and specificity of the CAR to the target antigen and is therefore carefully considered to avoid excessive affinity resulting in activation-induced cell death (AICD) of the CAR-T cell or T-cell terminal exhaustion [38]. Other antigen-binding domains are being explored to improve function in CAR-T cell-related approaches, including nanobodies, cytokines, and peptides [39]. The hinge and transmembrane domains connect the extracellular and intracellular domains to provide flexibility, which is correlated with binding and signalling [40]. CD28 and CD3ζ are commonly used in the transmembrane domain to improve stability and CAR dimerization/incorporation into endogenous TCRs, respectively. The intracellular signalling domain is composed of two sections: the activation domain and the costimulatory domain. The activation domain, which is composed of CD3ζ-derived immunoreceptor tyrosine-based activation motif, is not sufficient to activate the CAR-T cell, and thus the costimulatory domain is necessary. CD28 and 41BB are the most used costimulatory domains, yet they have different functional and metabolic profiles [39].

The blueprint of CAR constructs is an active area of research to improve the functionality and safety of the CAR-T cell product. To date, five generations of CARs have been developed; the second generation CAR is most widely used and clinically advanced [39]. Engineering modifications of the CAR can potentially maximise the therapeutic window, reduce CAR-related toxicity, enhance the efficacy of CAR-T cells including their persistence *in vivo* and within solid tumours, and fortify the CAR by armouring it with other capabilities, e.g., immunomodulatory molecules [39, 41–43]. The emerging engineering strategies are paving the way for a generation of optimised and personalised CAR-T cell therapies.

4.2. CAR-T Cell "Vein-to-Vein" Treatment Process. The CAR-T cell treatment process is lengthy and complex posing many potential treatment barriers for patients (Figure 3). The production, bio-manufacturing, and shipment logistics of CAR T cells can take up to five weeks, representing a major

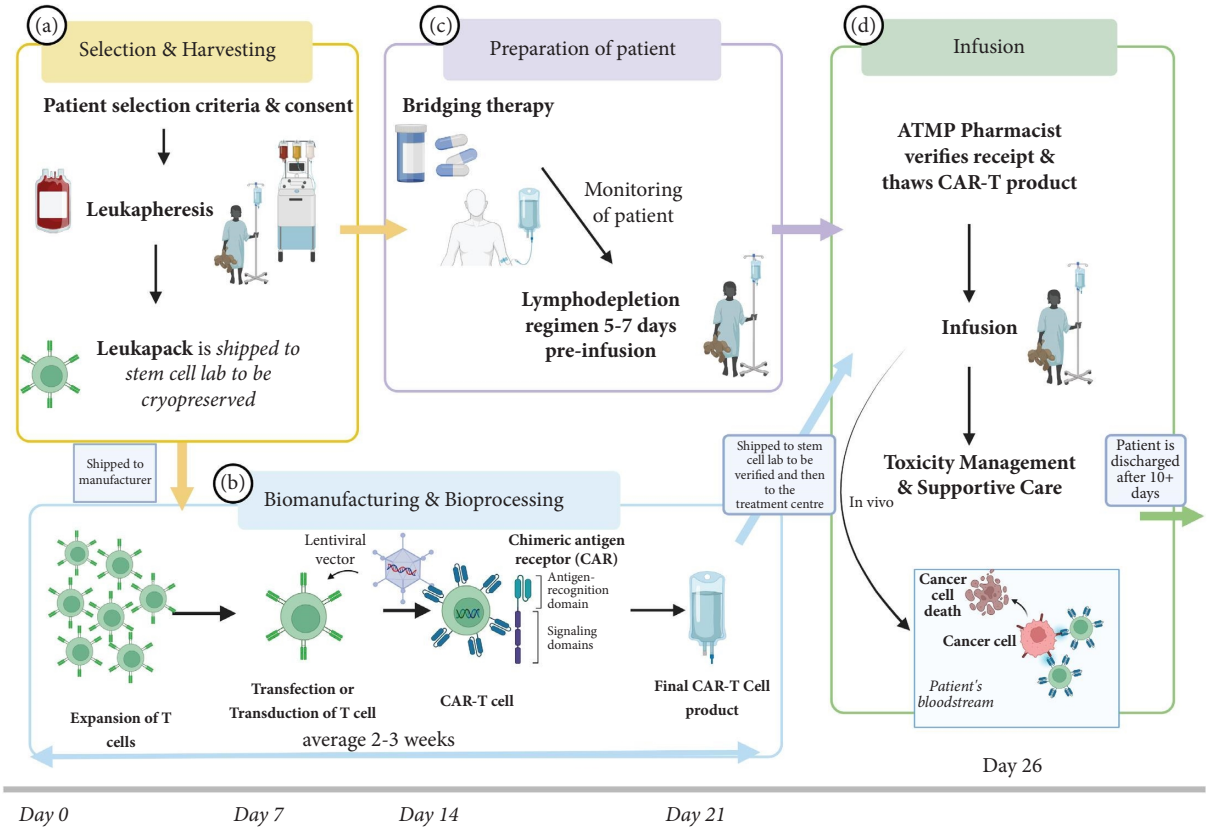

Figure 3: CAR-T cell treatment cycle. The "vein-to-vein" process of CAR-T therapy is complex and lengthy. (a) Once the patient meets selection criteria and patient consent is obtained, clinical staff send a consent form and cell collection request form to the stem cell lab and apheresis unit and the manufacturer is notified. A blood sample from the patient or donor must be tested for infectious diseases and a precount of their cell composition is performed. Once all conditions are met, harvesting begins. The patient undergoes leukapheresis and the starting material is directly sent fresh to the manufacturing facility or sent to the stem cell lab to be cryopreserved and shipped to the manufacturer. (b) The CAR-T cells are manipulated by genomic transduction and expanded in a culture medium and formulated into the final product. The final product undergoes QC/QA tests, is released by a Qualified Person (QP), and is cryopreserved and sent to the stem cell lab to be verified and stored and released upon receipt of the product form. (c) During the time required for bioprocessing, the patient is being prepared to receive the CAR-T cells with bridging chemotherapy, to ensure minimal tumour burden if required, and lymphodepletion prior to anticipated infusion of the final product. (d) In the treatment centre, the ATMP pharmacist or Qualified Person from blood bank or the cell processing centre receives the product, verifies it, and issues the product for infusion. The product is thawed and infused. The patient is monitored for 10+ days and supportive care and toxicity management are issued with patient follow-up postinfusion. Key: CAR = chimeric antigen receptor.

drawback, particularly in patients with aggressive cancers [44]. During this waiting period, patients may require bridging therapies to control the disease and reduce the tumour burden, which is associated with increased toxicities. A current area of development is to reduce "vein-to-vein" time, from when the patient's blood is taken to when the reprogrammed T cells are reinfused back to the patient [45]. To ensure safety and decrease variability in the final product, the manufacturing of CAR-T cell products is highly controlled and good manufacturing practice- (GMP-) compliant with processes undergoing rigorous quality control checkpoint testing [46, 47].

At the point of relapse, the patient is referred for CAR-T cell therapy and assessed against predetermined selection criteria, and mandatory pre-CAR-T cell therapy investigations are undertaken (Figure 3). The pharmacist reviews the CAR-T cell order and verifies patient approval as per manufacturer requirements and that the patient meets criteria for reimbursement. A comprehensive medication review is conducted to identify and discontinue medications that could potentially impact the number and functionality of harvested T cells, such as corticosteroids, immunosuppressants, and chemotherapy. Additionally, drugs that might interfere with the apheresis process, such as antihypertensives, are evaluated, and a washout period for certain medications may be initiated. During the leukapheresis process, the blood leukocyte compartment is procured, and the remainder of the blood is simultaneously reinfused back to the patient. The process can take 3–6 hours (over 1-2 harvests, 3–6 hours per harvest) for sufficient leukocyte numbers to be harvested (as per collection requirements for different manufacturers) [48]. The harvested leukocytes are processed, packaged, and labelled with an apheresis ID and or manufacturer's batch ID to ensure chain of custody. For

instance, in the EU, the starting cells must be collected within an authorised Tissue Establishment (TE) and in accordance with EU directive 2004/23/EC, precollection mandatory viral markers are required within 30 days of collection, with mandatory sterility testing at source, and products must have a Single European Code (SEC) assigned for shipment; thus, the product is shipped to manufacturer as a starting TE-compliant cell product and returns as a drug. The starting product may be shipped fresh on the day of collection or cryopreserved, depending on manufacturer's requirement.

The biomanufacturing of the starting material (patient or donor leukocytes) begins with removal of contaminating cells by enrichment of the T cells by isolation of lymphocytes by size and density and promotion of certain biomarkers associated with persistence and antitumour activity via counterflow centrifugal elutriation [49]. Activating T cells to proliferate using CD3- and CD28-antibody-coated paramagnetic beads is required for transfection/transduction of the CAR into the T cells as they proliferate using vectors, such as lentiviral or gammaretroviral vectors [45], or more novel nonviral technology. This allows the CAR to be expressed on the T cell surface after permanent integration into the proliferating T cell genome. The transduced T cells are then expanded in a bioreactor, such as WAVE (Cytiva), G-Rex (Wilson Wolf), Cocoon (Lonza), or CliniMACs Prodigy (Miltenyi), using cell-based artificial antigen presenting cell- (aAPC-) coated beads, expansion media, sera, and cytokines (e.g., IL-2) [50]. The culture conditions are carefully considered to ensure the quality and polarization of CAR-T cells. Determining the ratio of $CD4^+ : CD8^+$ T cells is becoming more relevant since there are now significant data to support a correlation with the incidence of adverse effects, such as CRS and ICANS, as well as with improved efficacy of treatment [50–52]. The expansion process typically takes 4–11 days before the CAR-T cells are formulated into the final product and cryopreserved in a solution with 10% DMSO. Each clinical batch, generally 1–3 bags of product, undergoes rigorous release testing with final product release by a Qualified Person (may be a pharmacist with relevant expertise) before it is transported cryopreserved to the stem cell lab for separate GMO storage in vapour phase liquid nitrogen as a medicinal product on behalf of pharmacy (at which point a pharmacist ensures that the product is within specification); multiple stakeholders are involved requiring excellent communication.

The manufacturing process and scheduling of the patient for therapy must be well coordinated; chain of custody is critical here requiring that the returned cells have the same full ID as shipped starting cells. Bridging therapy (if required) is administered following leukapheresis and prior to lymphodepletion to ensure disease control prior to infusion. Five to seven days prior to CAR-T cell administration, the patient undergoes lymphodepletion for three consecutive days to ensure endogenous lymphocytes are removed to enhance the levels of homeostatic cytokines. A rest period of 48 h is allowed after lymphodepletion before CAR T infusion. Once the cryopreserved CAR-T cell product integrity is confirmed along with original chain of custody ID, it undergoes clinical thawing at the bedside by scientific or clinical staff according to institutional and manufacturer's standard operational procedures (SOPs) in recognised CAR-T cell treatment centres, authorised by a haematologist, and is administered to the patient. Two doses of tocilizumab (anti-IL-6 receptor monoclonal antibody therapy) must be readily available and administered (if required) within two hours in the case of CRS, according to common grading criteria and SOPs (beyond the scope of this review). The patient is hospitalised for up to 10 days postinfusion to monitor for adverse events (infection, CRS, and ICANS), and long-term follow-up continues following patient discharge. EBMT regulation requires that patients are followed up for 15 years after CAR-T cell therapy to ensure there are no long-term undefined toxicities.

5. The Challenges and Potential Solutions

CAR-T cell immunotherapy is a major advance in the treatment of relapsed and refractory B-cell malignancies. However, the application of CAR-T cells is limited by a multitude of challenges such as efficacy and safety, severe toxicities, applicability to treating solid tumours [35], logistics, and related costs (Figure 4).

5.1. Efficacy and Persistence of CAR-T Cells. Poor persistence and exhaustion of the CAR-T cell product can negatively affect clinical efficacy (Figure 4(a)). The TME is a hostile environment for T cells and other immune cells in which they compete for key nutrients required to drive metabolism, such as glucose, glutamine, and fatty acids [25, 26]. Furthermore, the TME recruits immunosuppressive cells and aerobic glycolysis through the Warburg effect which promotes hypoxic conditions resulting in dampened differentiation and cytokine production of T cells. Within the TME, there is an accumulation of toxic metabolites such as kynurenine, reactive oxygen species [27], tryptophan [28], and adenosine [29] and expression of immune checkpoint modulators such as CTLA4 and PDL1 [30]. These actions contribute to T cell dysfunction and exhaustion, resulting in poor CAR-T cell persistence. The enrichment of less differentiated T cell subsets such as T_n, T_{scm}, and T_{cm} during the bioprocess can improve the persistence of CAR-T cells; this can be achieved by the promotion of oxidative phosphorylation, e.g., by modulating the CAR construct or the optimisation of biomanufacturing [44]. For instance, the integration of more specific co-stimulatory signals in the CAR construct, such as CD28, CD19, 41BB or CD27 can enhance CAR-T cell functionality and persistence [43]. CAR-T cell culture conditions can also be optimised through the use of exogenous cytokines such as IL-7 and IL-15 and through nutritional optimisation of culture media to promote T_{scm} [43, 53]. In addition, targeting mitochondrial biogenesis through exogenous cytokines can enhance less exhausted phenotypes [35] and maintain ROS balance to preserve effector function and prevent T cell exhaustion [54, 55], enabling more durable drug responses and disease remission.

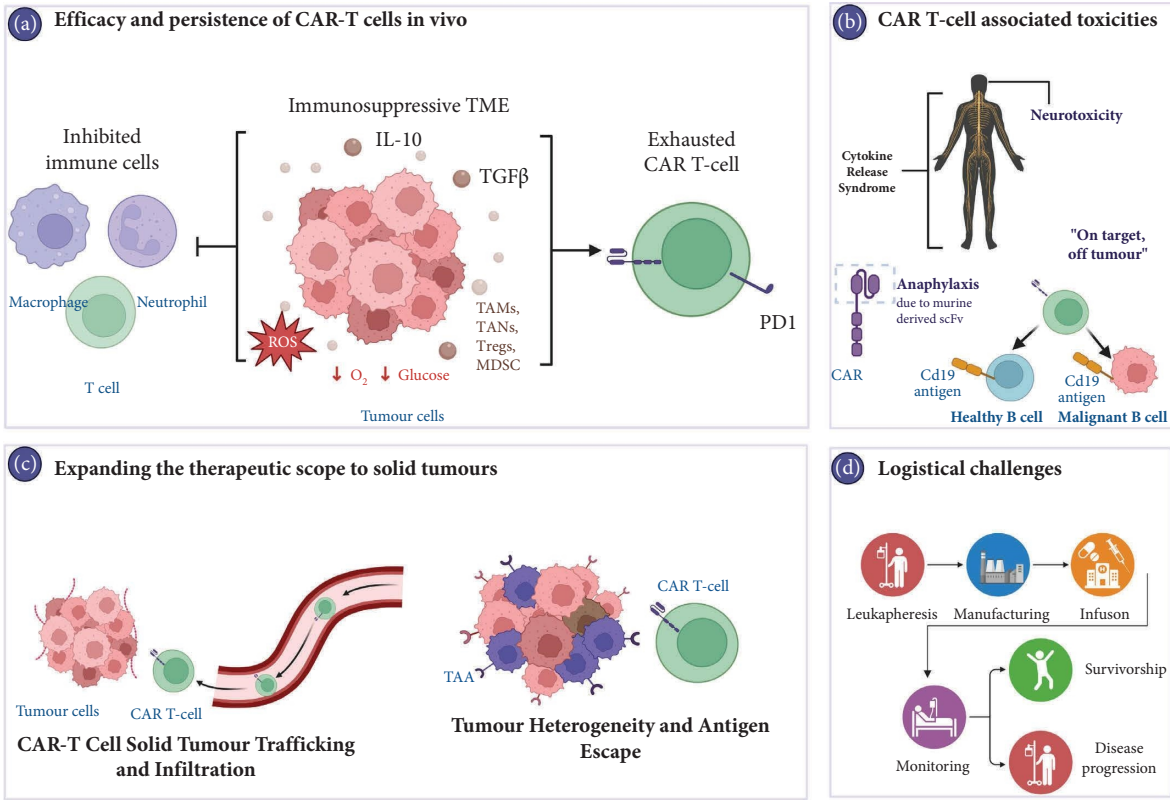

FIGURE 4: Challenges for CAR-T cell immunotherapy. CAR-T cell therapy is a complex treatment process. While outcomes are promising, there are associated challenges that must be addressed to assure continued success. (a) The efficacy and persistence of CAR-T cells in vivo is limited by the immunosuppressive TME, which impairs CAR-T cell function and reduces their anti-tumour effects. (b) CAR-T cell immunotherapy is associated with serious adverse effects such as cytokine release syndrome, neurotoxicity, anaphylaxis, and "on-target, off-tumour" toxicities. There are efforts in place to manage these toxicities and new CAR engineering strategies to offset these effects. (c) Expanding the therapeutic scope to solid tumours is needed to meet the unmet clinical need for treatment options for solid malignancies. There are many strategies being employed to overcome evasive solid tumour cells such as manipulation of CAR-T cell trafficking and combined TCR CAR-T profiles to limit antigen escape. (d) There is a significant logistical challenge associated with CAR-T cell therapy. Pharmacists are heavily involved in the logistical orchestration of this therapy from the leukapheresis process, to communicating with the other sites involved to coordinate timelines for instance. Key: IL-10 = interleukin 10, TGF-B = transforming growth factor-B, TAMs = tumour-associated macrophages, TANs = tumour-associated neutrophils, T_{regs} = regulatory T cells, MDSC = myeloid-derived suppressor cells, ROS = reactive oxygen species, PD1 = programmed cell death protein 1, scFv = single chain variable fragment, and TAA = tumour-associated antigen.

5.2. CAR-T Cell-Associated Toxicities. CAR-T cell therapies are unfortunately associated with serious adverse effects including on-target, off-tumour toxicities, anaphylaxis, and most commonly CRS and ICANS (Figure 4(b)) [56, 57]. On-target, off-tumour toxicities occur when CAR-T cells attack normal cells also expressing tumour-associated antigens (TAAs) that can result in normal cell aplasia, e.g., normal B-cell aplasia observed with anti-CD19 CAR-T cell therapies [56]. In addition, anaphylaxis can be induced due to the immunogenicity of murine-derived scFv of the antigen-binding domain of CAR-T cell products. These risks may be partially mitigated by employing more specifically targeted antigens and by humanising the scFv, respectively [57].

CRS, which manifests early postinfusion, is the most frequently reported toxicity [56]. It is mediated by imbalanced supraphysiologic cytotoxic cytokine release due to extensive T cell proliferation and tumour cell cytotoxicity *in vivo*, potentially exacerbated by myeloid infiltration and activation at the tumour site. The pathophysiology of CAR-T cell-related CRS is associated with the release of IL-6, which is treated with tocilizumab and in refractory cases with anakinra (IL-1 antagonist). Biomarkers associated with severe CRS (sCRS) include peak levels of several serum cytokines such as IFNγ, tumour necrosis factor-α (TNFα), IL-2, IL-6, IL-10, ferritin, and C-reactive protein (CRP) [58]. Patients who develop sCRS are at higher risk for developing ICANS, which can manifest following CRS [59]. Risk factors include higher disease burden, high CAR-T cell infusion dose, preexisting neurological conditions, and cyclophosphamide/fludarabine-based pre-lymphodepleting regimens (which enhances expansion of CAR-T cells *in vivo*). Uniquely, endothelial cell activation plays a role in the pathophysiology of ICANS with potential treatment options in future targeting endothelial cell stabilisation reducing the permeability of the blood-brain barrier (BBB) [60]. In

addition, safety mechanisms, such as "off-switches" and "suicide genes," are being explored to deactivate CAR-T cells in the event of "on-tumour, off-target" and CRS toxicities [39].

5.3. Expanding the Therapeutic Scope to Solid Tumours. Expanding the scope of CAR-T cell therapy beyond B-cell malignancies to solid tumours is a tremendous challenge due to poor trafficking and infiltration to the solid tumour, in part due to the hostile TME, tumour heterogeneity of tumour cells, and antigen escape (Figure 4(c)) [61]. For CAR-T cells to act in tumour sites, they require the expression of adhesion molecules on both T cells and tumour vasculature, appropriate homing signals, and binding to TAAs to become activated with expansion to relevant therapeutic densities. There is marked difficulty in identifying TAAs due to the innate heterogeneity of solid tumour cells. Furthermore, the relevant antigens expressed are at low levels (or not effectively expressed) or they may be widely expressed on off-target cells resulting in toxicity. Tumour cells are also responsible for the downregulation and masking of immunogenic epitopes. There is an active area of research exploring TAAs unique to solid tumours and mechanisms to overcome antigen escape, such as multitargeted CAR-T cell therapeutic approaches [39].

5.4. Logistics Challenges. There are complex logistics associated with the provision of CAR-T cell therapy despite progress in the design and operation of the CAR-T cell supply chain (Figure 4(d)). Access to CAR-T cell therapy is currently limited to eligible patients who have been heavily pretreated with up to at least two lines of previous traditional therapy; the complex manufacturing process of CAR-T cells takes up to several weeks further restricting availability [62]. Biomanufacturing of individualised autologous CAR-T cells must be under GMP-compliant conditions in an accredited facility, and timelines between the patient and manufacturing facility must be predefined and coordinated [63]. Biomanufacturing failures and shortages in manufacturing slots may result in patients waiting up to several months for treatments; this timeline may not be sustainable for those with aggressive conditions who may ultimately become ineligible during the waiting period. There are efforts being made to find alternative sources of T cells and to scale up the manufacturing process to shorten the lead time, for instance, point-of-care manufacturing of CAR-T cells in specialist centres.

5.5. Are Allogeneic CAR-T Cells the Way Forward? There are many drawbacks associated with current clinical manufacturing processes, for instance, the vein-to-vein manufacturing time is not appropriate for patients with rapidly proliferative diseases such as B-cell acute lymphoblastic leukaemia (B-ALL), where the progression of the disease can worsen prognosis and result in treatment ineligibility. A significant complicating factor is that these patients generally have a paucity of good quality T cells due to previous treatments and/or the nature of their disease. As the demand for CAR-T cell therapy increases, logistically there is a marked need for more readily available treatment options and shorter lead times [47]. The development of allogeneic CAR-T cells provides a potential solution, to provide readily available "off-the-shelf" cryopreserved batches of universal CAR-T cells, as shown in Table 1.

Allogeneic CAR-T cell therapy is an active area of research, with 143 clinical trials currently underway as per https://ClinicalTrials.gov; none have reached phase III (accessed on May 18, 2023). Allogeneic CAR TCR$\alpha\beta$ T cell therapy is a form of allogeneic CAR-T cell therapy currently in phase I clinical development whereby the T cell is engineered to express both the CAR and the TCR. The process involves PBMCs procured from healthy donors with immune cells unimpacted from previous cancer treatments and the immune effects of cancer, enabling standardisation of product and redosing of patients with the same batch and multiple batches of different HLA subtypes [64]. Despite the myriad of potential benefits of "off-the-shelf" CAR-T cell treatments, there is an increased risk of alloreactivity and GvHD which impede any anti-tumour activity [69]. GvHD is mediated by the TCR$\alpha\beta$ of the allogeneic T cells recognising HLA mismatch and inducing host rejection. Many mechanisms are investigated to produce allogeneic CAR T cells with a reduced risk of GvHD by the generation of TCR-deficient CAR-T cells. These strategies include the knockout of the T cell receptor α constant (TRAC) locus by gene editing using Zinc Finger Nucleases, CRISPR-Cas9, and TALEN technology. The TRAC locus is targeted as only a single gene encodes for α chain, whereas two genes encode for β chain, therefore disrupting the TCR$\alpha\beta$ and preventing the recognition of HLA mismatch reducing alloreactivity and thus GvHD. MHC edits targeted by genetic ablation can also reduce the immunogenicity of allogeneic CAR-T cells. Autologous CAR-T cells remain superior due to their longer persistence *in vivo* and need for less intensive preconditioning regimens. However, allogenic CAR-T cell therapy allows for cheaper and "off-the-shelf" availability. The optimisation of allogenic CAR-T cell therapy to avoid rejection is an active area of research with clinical trials ongoing to assess the safety, efficacy, and feasibility of such treatment [70]. One such example which is further along the drug pipeline is UCART19, a "first-in-class" allogeneic anti-CD19 CAR that is non-HLA matched and transduced with TALEN, disrupting the expression of endogenous surface TCRs and CD52 (highly expressed on T cells and associated with GvHD) [71]. Preconditioning using an anti-CD52 monoclonal antibody, alemtuzumab, is required to produce an ideal environment for expansion in this case and is associated with a lower incidence of GvHD. There are further ongoing preclinical and clinical trials with allogeneic CAR-T cells underway [72] with different allogeneic technologies in development. The advent of universal CAR-T cells will remarkably revolutionise CAR-T cell therapy increasing its accessibility and applicability.

Table 1: Autologous versus allogeneic CAR-T cell therapy [64].

	Autologous	Allogeneic
Origin	Patient	Healthy donor
Production and manufacturing	Long lead time from leukapheresis to CAR-T cell administration Variability in the starting T cell product difficulty to control quality parameters Greater persistence of CAR-T cells	Scaled-up process allows the production of a greater number of products from a single donor "Off-the-shelf" availability Standardised processes Standardised HLA-matched batches
Clinical indication	Haematological malignancies (demonstrated) Solid tumours	Haematological malignancies (research underway) Solid tumours
Application and patient selection	Slow disease progression Use of standard lymphodepletion regimens Successful manufacturing and expansion Absence of T cell paucity Previous lines of therapy	Rapid disease progression Use of enhanced lymphodepletion regimens Manufacturing failure due to T cell paucity or failed ex vivo expansion Autologous manufacturing logistic issues
Associated issues and risks	Frequent severe grade ≥3 CRS and ICANS CAR-related gene modifications Long-term side-effects such as B-cell aplasia with B-cell associated CAR-T cells Limited by the number of cells High cost	CRS CAR and/or gene-editing modifications GvHD Allo-rejection Toxicities related to enhanced lymphodepletion Reduced therapeutic efficiency upon standard lymphodepletion Shorter persistence Increased risk of alloimmunisation requiring redosing Moderate cost (expected)
Persistence	Intermediate to long (months to years)	Short to intermediate (weeks to months)
Products	Approved: Kymriah [65] Tecartus [63] Yescarta [66] Breyanzi [67] Abecma [63] Carvykti [68]	Approaching approval: UCART-19 [64] PBCAR0191 [64] CARCIK-CD19 [64] CTX110 [64] ALLO-715 [64] ALLO-501 [64]

Key: CAR = chimeric antigen receptor; HLA = human leukocyte antigens; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome; GvHD = graft versus host disease.

6. The Clinical Pharmacist Perspective of CAR-T Cells

CAR-T cell agents are now approved for patients with relapsed/refractory B cell lymphoma, B-ALL, and multiple myeloma (MM), having demonstrated enhanced overall response rates (ORRs) and CRs [73]. There are six CAR-T cell products currently approved by the EMA, on a conditional approval basis (Table 2): tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, idecabtagene vicleucel, and ciltacabtagene autoleucel.

6.1. Disease Considerations. Non-Hodgkin Lymphoma (NHL) is a heterogeneous group of lymphomas, for which CAR-T cells are considered in patients with B-cell NHL who have failed at least two lines of standard therapy, as per ZUMA-1 [66], ZUMA-5 [76], JULIET [65], TRANSCEND NHL 001 [67], and ZUMA2 [79] trials, or after second-line therapy [73] (Table 2). B-ALL, the most common childhood malignancy, has a poor prognosis for those over the age of 50 years and in children following relapse [83]. Tisagenlecleucel is indicated for refractory/relapsed B-ALL in children and young adults (<26 years) [84] and brexucabtagene autoleucel is indicated for use in adults >26 years with relapsed/refractory disease. CAR-T cell therapy targeting the B-cell maturation antigen (BCMA) has improved outcomes for patients with relapsed MM, a plasma cell neoplasm with high rates of relapse and resistance due to mutations driven by clonal evolution [85]. Two CAR-T cell products are approved for adult patients with this indication, idecabtagene vicleucel and ciltacabtagene autoleucel, after four failed lines of standard therapy (Table 2).

6.2. How Patients Are Prepared for Treatment. The selection of patients for CAR-T cell therapy is based on disease status, treatment history, fitness, and EBMT-EHA and national recommendations to ensure they meet criteria. Patients can experience worsening of their condition while waiting for CAR-T therapy, and approximately 7% of patients do not survive to completion of CAR-T cell manufacturing [84], highlighting the importance of bridging therapy [68, 74, 75, 77, 78, 80–82, 86]. Bridging therapy is anticancer treatment which is administered from the point of collection of leukocytes until the initiation of lymphodepleting therapy to maintain disease control [87] (Figure 3). Therapy is selected based on a disease- and patient-specific basis and may involve chemotherapy, radiotherapy, or immunotherapy. This period mandates frequent monitoring of the patient to effectively manage complications. Prior to CAR-T cell infusion, the patient undergoes lymphodepleting conditioning, such as cyclophosphamide and fludarabine, to promote enhanced expansion and engraftment of CAR-T cells after infusion *in vivo*. These conditioning treatments can also be associated with superior disease-free survival and CAR-T cell persistence *in vivo* [88, 89]. The lymphodepletion process is scheduled 3–5 days prior to CAR-T cell administration enabling a favourable immune environment for CAR-T cell expansion. CAR-T cell treatment involves the collaboration of a multidisciplinary team, with the clinical pharmacist performing an integral role.

6.3. Clinical Pharmacist Role in the Provision of CAR-T Cell Therapy. Pharmacists play an intrinsic role in all steps of the CAR-T treatment cycle (Figure 5) including governance and operational and clinical aspects, particularly toxicity management and postinfusion care [13, 90].

There are three levels of *governance* protocols which must be adhered to in the provision of CAR-T cell therapy: (1) those by the Foundation for the Accreditation of Cellular Therapy (FACT) and the Joint Accreditation Committee of International Society for Cellular Therapy (ISCT) and European Society for Blood and Marrow Transplantation (EBMT) (FACT-JACIE) International standards, (2) National, and (3) Local governance. Pharmacists should be cognisant of the unique governance which underpins CAR-T cells as ATMPs via priority medicines, PRIME scheme. The quality, safety, and efficacy of these products are annually reviewed and classified under the conditional authorisation by the EMA, and the ATMP status mandates CAR-T cell product compliance with GMP standards [31, 91]. GMP assures the manufacture of a high-quality product, in a reproducibly controlled, auditable, and GMP-accredited facility with GMP-accredited equipment and appropriately trained personnel [46]. There are extensive documentation requirements and guidelines to ensure compliance with GMP. All treatment centres must be accredited by FACT-JACIE competent authorities [2, 92]. All treatment centres are invited to participate in a data collection initiative to report their findings to the EBMT contributing towards Post Authorisation Studies (PAS) mandated by the EMA.

The operational role of pharmacists in the provision of CAR-T cell therapies is multifaceted and critical to the success of these innovative treatments and as per FACT-JACIE standards (Figure 5). Pharmacists are responsible for ensuring the provision and implementation of relevant policies by serving on drugs and therapeutics committees and by providing recommendations and developing guidelines and standard operating procedures (SOPs) regarding the transportation and handling of CAR-T cell products, administration of the product, risk management plan (RMP) management, and toxicity management [13]. Pharmacists should implement such guidelines by developing electronic medical records (EMRs) documenting patient treatment plans, lymphodepletion regimens, and toxicity management plans in conjunction with treating haematologists and provide patient and staff education and wallet card provisions (detailing patient information and health care professional (HCP) information which they can present to HCPs if needed: emergency department, pharmacy, and medical visits). Pharmacists have a critical role to play in storage, handling, and inspection of the product upon receipt, ensuring the chain of identity and that the product is stored in a time- and temperature-specific manner with clear temperature monitoring SOPs in place and ensuring that biohazard signage and spill kits are

Table 2: Overview of approved CAR-T cell products.

	Tisagenlecleucel	Axicabtagene ciloleucel	Brexucabtagene autoleucel	Lisocabtagene maraleucel	Idecabtagene vicleucel	Ciltacabtagene autoleucel
Proprietary name	Kymriah™	Yescarta™	Tecartus™	Breyanzi™	Abecma™	Carvykti™
Biological	CTL019 [65, 74, 75]	KTE-C19 [66, 76–78]	KTE-X19 [79]	JCAR017 [67, 80]	bb2121 [81]	LCAR-B38M [68, 82]
Target	CD19	CD19	CD19	CD19	BCMA	BCMA
Costimulation	4-1BB	CD28	CD28	4-1BB	4-1BB	4-1BB
Signalling domain	CD3ζ	CD3ζ	CD3ζ	CD3ζ	CD3ζ	CD3ζ
Vector	Lentiviral	Retroviral	Retroviral	Lentiviral	Lentiviral	Lentiviral
Indication	Paediatric 3L+ B-ALL Young adult 3L+ B-ALL 3L+ DLBCL 3L+ FL	3L+ DLBCL 3L+ PMBCL 4L+ FL	3L+ MCL Adult 3L+ B-ALL	3L+ DLBCL 3L+ PMBCL 3L+ FL	4L+ MM	4L+ MM
MA trial	ELIANA JULIET	ZUMA-1 ZUMA-5	ZUMA-2 ZUMA-3	TRANSCEND NHL 001	KarMMa-3	CARTITUDE-1
Approval	2017 (FDA) 2018 (EMA)	2017 (FDA) 2018 (EMA)	2020 (FDA) 2020 (EMA)	2021 (FDA) 2022 (EMA)	2021 (FDA) 2022 (EMA)	2022 (FDA) 2022 (EMA, positive CHMP opinion received)

Key: 3L+ = three or more lines of failed treatment; B-ALL = B-cell acute lymphoblastic leukaemia after three lines or more lines of therapy; 4L+ = four or more lines of failed treatment; DLCBL = diffuse large cell B cell lymphoma; FL = follicular lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; MCL = mantle cell lymphoma; MM = multiple myeloma; EMA = European Medicines Agency; FDA = Food and Drug Administration.

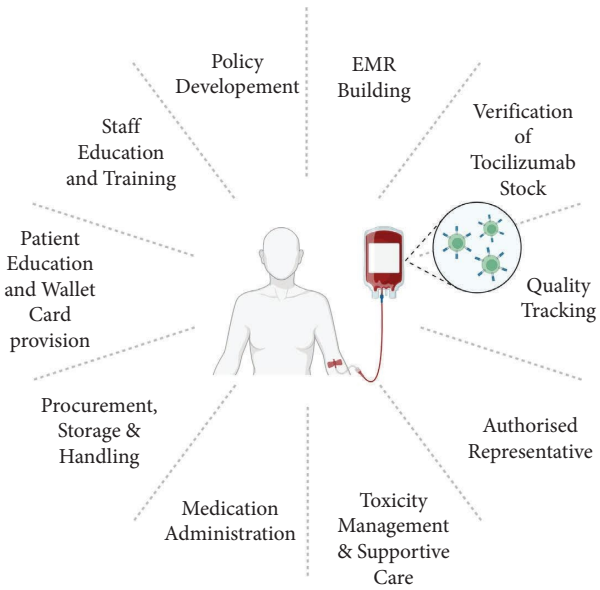

Figure 5: Provision of CAR-T cell therapy from a pharmacist's perspective. The ATMP clinical pharmacist plays an important role in the multidisciplinary team for the safe and effective provision of CAR-T cell therapy. They have a variety of responsibilities, including development of SOPs and guidelines within their institution, the building of treatment plans within the patient electronic medical record (EMR), ensuring the availability of at least two doses of tocilizumab for immediate treatment of CRS, and quality tracking of CAR-T cell therapy quality metrics. Pharmacists help manage CAR-T cell-associated toxicities, provide supportive care, verify medication prescriptions, ensure the chain of identity of the product and correct time and temperature storage, assist in logistics, provide patient and staff education, and furnish patients with a treatment wallet card.

available throughout, with recommended record keeping throughout the transport chain up until administration.

The pharmacist must review (1) the treatment plan and oversee and ensure the appropriate dosage (per kg or m^2/body surface area, or flat, single versus split dose or based on tumour load) and dose adjustments based on hepatic and renal function, (2) the schedule of bridging therapy and/or lymphodepletion regimen, (3) the CAR-T cell therapy, (4) the supportive care (emetogenic, gastro-protection, oral care, fungal, PJP, and HSV prophylaxis), (5) premedications (paracetamol and diphenhydramine or another H1 antagonist), and (6) the wash-out period prior to leukapheresis if suitable. The pharmacist should perform a medication reconciliation and medication review prior to treatment for drug-drug interactions and ensure the restriction of medications such as glucocorticoids and live vaccines (avoided six weeks prior to lymphodepletion conditioning and treatment). It is also the responsibility of the pharmacist to undertake a risk assessment, which includes record keeping and reporting, notification of intended use of a biological agent, protective measures (e.g., PPE), and appropriate disinfectant and waste policy. An important aspect of the risk assessment is verification and documentation of the availability of at least two doses of tocilizumab for emergency administration to treat CRS following infusion of product. It is notable that waste disposal of the infusion bags, giving sets, and anything that was in direct contact with the CAR-T cell product has specific GMO waste handling requirements.

CAR-T cell therapy-associated life-threatening toxicities, i.e., CRS and ICANS, can be disease-related or CAR-T cell-related, and such complications are managed on a short-term, medium-term, and long-term basis. The pharmacist is directly involved in helping to manage these toxicities and postinfusion care through the development of SOPs and review of drugs and recommended dosages for treatment.

In the *short-term monitoring* phase (infusion to day 28), patients are required to remain in hospital for up to 10 days postinfusion for monitoring of CRS, ICANS, septic shock, and other adverse reactions. CRS is the most common toxicity with an overall incidence of 74–94% [93], a median onset of 2-3 days (dependent on the type/generation of CAR-T cell infused), and a median duration of 7-8 days. CRS is characterised as a systemic inflammatory response which can manifest as fevers, hypotension, hypoxia, tachycardia, chills, hepatic/renal/cardiac dysfunction, coagulopathy, and haemophagocytic lymphohistiocytosis. The severity varies and is assessed by a standardised grading scale (I–IV) [94]. Treatment management involves the administration of tocilizumab (a monoclonal antibody that targets the IL-6 receptor), and staff should be educated on the two-hour window administration. Pharmacists should also be aware of the limitation of use of myeloid growth factors, particularly granulocyte-macrophage colony-stimulating factor (GM-CSF) for three weeks following infusion as it may worsen CRS. ICANS is the second most common adverse effect with an overall incidence of 58–87% [94], a median onset of 4–6 days, and a median duration of 6–17 days. ICANS can develop concurrent with CRS or following resolution. It can be identified early through the deterioration in handwriting and impaired concentration, though any neurological impairment can be considered treatment related. Neurotoxicity assessment for CAR-T cell therapy involves the American Society for Transplantation and Cellular Therapy (ASTCT) ICANS Consensus Grading. This accounts for different domains such as the immune effector cell-associated encephalopathy (ICE) score, which should be performed at least every 8 hours, assessing the level of consciousness, presence of seizures, motor skill findings, and elevated ICP/cerebral oedema, with a 0–4 grading scale for each domain. Management of toxicities for CRS and ICANS and their treatment algorithm should be included in CAR-T cell therapy SOPs.

The *medium-term follow-up phase* (day 28 to day 100 postinfusion) involves monthly monitoring for toxicities, such as delayed macrophage activation syndrome and CRS, B-cell aplasia, GvHD, and infections. The *long-term follow-up phase* (day 100 onwards postinfusion) includes the monitoring of complications such as hypogammaglobulinemia and prolonged cytopenia and secondary malignancies, genotoxicity, immunogenicity, and other neurological complications. Since CAR-T cell therapy is a novel immunotherapy, long-term effects are still being investigated and the implementation of standardised protocols and policies for ongoing

follow-up is required [95]. Parameters which should be monitored include disease status, further treatments, late effects, infections, immunological status, new malignancies, autoimmune disease, endocrine, reproductive and bone health, neurological status, psychological status, cardiovascular status, respiratory status, and gastrointestinal and hepatic status. Pharmacists may also be responsible within the MDT for the development of a comprehensive pharmacovigilance CAR-T cell therapy program.

6.4. Future Developments from a Clinical Pharmacist Perspective. The field of CAR-T cell therapy is an active area of research in which there is a global effort to design CAR-T cell products with improved response rates, persistence *in vivo*, tumour targeting, and reduced toxicity [41, 96]. There is ongoing research into potential biomarkers and early interventions to identify, manage, and potentially prevent toxicities. The combination of CAR-T cell therapy with other anticancer agents or armoured with immunomodulators is being explored to offset "on-target, off-tumour" effects [58] and to synergistically enhance therapeutic efficacy [97]. There are currently different cell therapy products undergoing clinical trials targeting solid tumours [35, 58, 59, 98] (Supplementary Table 1), T-cell and myeloid malignancies [99] and other non-cancer conditions, such as autoimmunity [100]; multitargeted CARs [42, 101] are also being evaluated to overcome tumour antigen escape mechanisms. Emerging strategies being explored to overcome safety and efficacy issues include switch-based control systems, combinatorial antigen recognition technology to circumvent on-target, off-tumour toxicities [39], and stimuli-based activation of CARs at tumour sites [59, 96, 102, 103]; the next generation of CAR-T cells will exhibit multitargeted recognition regulated by intrinsic signals and harness gene editing to improve persistence and resistance to the suppressive factors within the TME and the integration of fail-safes or "suicide-switches" in the event of toxicities [102, 103]. Understanding the pathophysiology of toxicities associated with treatment will enable more targeted and effective treatment options to be developed. Scaling-out of the manufacturing process to shorten manufacturing time and increase the availability of "off-the-shelf" allogeneic products is being explored to allow for readily available CAR-T cell products with reduced side effects such as GvHD [42]. Allogeneic sources of CAR-T cells would enable a readily available and cost-effective treatment option, allowing immediate access to these life-changing therapies.

The increased demand for CAR-T cell immunotherapy necessitates optimised administrative and logistical strategies for workflow, scaling, and coordination in which the specialist pharmacist plays a fundamental role [104]. As this type of therapy uses "living drugs," there is a need for a concerted logistical effort to ensure the chain of identity is upheld, the process of collection, manufacturing, and infusion is orchestrated efficiently between the different sites involved, and that there is marked consideration for the logistics associated with patient access. For instance, optimising ordering platforms, transportation, supply chain visibility, and effective communication between sites of care (clinical site, manufacturer, and stem cell lab) is crucial to ensure the successful operation of this time-sensitive and potentially lifesaving/curative therapy [104]. Effectively, the implementation of safe and effective CAR-T cell therapy depends on the collaboration of the multidisciplinary team (MDT), in which there is an increasing need for specialised CAR-T cell/ATMP pharmacists and standardised responsibilities of the pharmacist within the MDT regarding ordering, product receipt, storage, preparation, and dispensing [12].

7. Conclusions and Recommendations for Further Research

CAR-T cell therapy has become standard of care in some forms of blood cancers and a promising treatment modality against other types of neoplasms and potentially immune and infectious diseases. As these products are "first-in-class" with increasingly more clinical trial data and ongoing research, a thorough understanding of their biophysical properties, control of heterogeneity, overall efficacy, and long-term safety will allow for the development of safer and more efficacious CAR-T cell products and release criteria for improved outcomes. The current body of literature highlights knowledge gaps and potential areas for further investigation including (1) comprehensive and integrated multiomics analysis of CAR-T cells that may enable novel strategies to improve CAR-T cell efficacy, persistence, and metabolism to enhance clinical outcomes; (2) continuous refinement and enhancement of the evidence base for allogeneic CAR-T cells for the realisation of more cost-effective and broader applications; and (3) streamlined manufacturing processes to minimise "vein-to-vein" time, including the incorporation of the clinical pharmacist in a comprehensive MDT throughout this process to implement CAR-T cell therapy in personalised clinical practice. In this review, we have placed special emphasis on the perspective of the clinical pharmacist within this team, incorporating distinctive expertise in medication management, patient care, quality control and tracking, education for patients and caregivers, MDT collaboration, and research and quality improvement initiatives required to successfully place novel therapeutics into practice. There is an urgent need to develop harmonised international practical guidelines that delineate the role and integration of pharmacists in the management, safety, and delivery of CAR-T cell therapy, including the role of the Qualified Person in releasing cellular products where they are manufactured (and in dispensing at point-of-care). We hope that this review has successfully identified relevant knowledge gaps and has highlighted the role of the pharmacist within the MDT for CAR-T cell therapy.

Data Availability

There are no primary data associated with this review. All sources are cited in the References section.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Supplementary Table 1: potential target antigens being studied for different cancer types. (*Supplementary Materials*)

References

[1] M. Piñeros, L. Mery, I. Soerjomataram, F. Bray, and E. Steliarova-Foucher, "Scaling up the surveillance of childhood cancer: a global roadmap," *Journal of the National Cancer Institute: Journal of the National Cancer Institute*, vol. 113, no. 1, pp. 9–15, 2021.

[2] A. Hernandez-Lopez, M. A. Tellez-Gonzalez, P. Mondragon-Teran, and A. Meneses-Acosta, "Chimeric antigen receptor-T cells: a pharmaceutical scope," *Frontiers in Pharmacology*, vol. 12, Article ID 720692, 2021.

[3] D. T. Debela, S. G. Muzazu, K. D. Heraro et al., "New approaches and procedures for cancer treatment: current perspectives," *SAGE Open Medicine*, vol. 9, Article ID 205031212110343, 2021.

[4] N. Vasan, J. Baselga, and D. M. Hyman, "A view on drug resistance in cancer," *Nature*, vol. 575, no. 7782, pp. 299–309, 2019.

[5] N. E. Papaioannou, O. V. Beniata, P. Vitsos, O. Tsitsilonis, and P. Samara, "Harnessing the immune system to improve cancer therapy," *Annals of Translational Medicine*, vol. 4, no. 14, p. 261, 2016.

[6] C. Hayes, "Cellular immunotherapies for cancer," *Irish Journal of Medical Science*, vol. 190, no. 1, pp. 41–57, 2021.

[7] M. W. Rohaan, S. Wilgenhof, and J. Haanen, "Adoptive cellular therapies: the current landscape," *Virchows Archiv*, vol. 474, no. 4, pp. 449–461, 2019.

[8] S. Tan, D. Li, and X. Zhu, "Cancer immunotherapy: pros, cons and beyond," *Biomedicine and Pharmacotherapy*, vol. 124, Article ID 109821, 2020.

[9] O. Pasvolsky, P. Kebriaei, B. D. Shah, E. Jabbour, and N. Jain, "Chimeric antigen receptor T-cell therapy for adult B-cell acute lymphoblastic leukemia: state-of-the-(C)ART and the road ahead," *Blood Advances*, vol. 7, no. 14, pp. 3350–3360, 2023.

[10] M. L. Schubert, M. Schmitt, L. Wang et al., "Side-effect management of chimeric antigen receptor (CAR) T-cell therapy," *Annals of Oncology*, vol. 32, no. 1, pp. 34–48, 2021.

[11] D. J. Baker, Z. Arany, J. A. Baur, J. A. Epstein, and C. H. June, "CAR T therapy beyond cancer: the evolution of a living drug," *Nature*, vol. 619, no. 7971, pp. 707–715, 2023.

[12] M. B. Marzal-Alfaro, V. Escudero-Vilaplana, J. L. Revuelta-Herrero, R. Collado-Borrell, A. Herranz-Alonso, and M. Sanjurjo-Saez, "Chimeric antigen receptor T cell therapy management and safety: a practical tool from a multidisciplinary team perspective," *Frontiers in Oncology*, vol. 11, Article ID 636068, 2021.

[13] J. P. Booth, C. L. Kusoski, and J. M. Kennerly-Shah, "The pharmacist's role in chimeric antigen receptor T cell therapy," *Journal of Oncology Pharmacy Practice*, vol. 26, no. 7, pp. 1725–1731, 2020.

[14] M. Galassi and M. E. Moreno-Martínez, "Role of pharmacists," in *The EBMT/EHA CAR-T Cell Handbook*, N. Kröger, J. Gribben, C. Chabannon, I. Yakoub-Agha, and H. Einsele, Eds., pp. 215–217, Springer International Publishing, Cham, Switzerland, 2022.

[15] D. G. M. Tantalo, A. J. Oliver, B. von Scheidt et al., "Understanding T cell phenotype for the design of effective chimeric antigen receptor T cell therapies," *Journal for ImmunoTherapy of Cancer*, vol. 9, no. 5, Article ID e002555, 2021.

[16] R. I. Klein Geltink, R. L. Kyle, and E. L. Pearce, "Unraveling the complex interplay between T cell metabolism and function," *Annual Review of Immunology*, vol. 36, no. 1, pp. 461–488, 2018.

[17] R. J. Kishton, M. Sukumar, and N. P. Restifo, "Metabolic regulation of T cell longevity and function in tumor immunotherapy," *Cell Metabolism*, vol. 26, no. 1, pp. 94–109, 2017.

[18] M. Ben Khelil, Y. Godet, S. Abdeljaoued, C. Borg, O. Adotévi, and R. Loyon, "Harnessing antitumor $CD4^+$ T cells for cancer immunotherapy," *Cancers*, vol. 14, no. 1, p. 260, 2022.

[19] L. M. E. Janssen, E. E. Ramsay, C. D. Logsdon, and W. W. Overwijk, "The immune system in cancer metastasis: friend or foe?" *Journal for ImmunoTherapy of Cancer*, vol. 5, no. 1, p. 79, 2017.

[20] Y. Zheng, X. Wang, and M. Huang, "Metabolic regulation of CD8(+) T cells: from mechanism to therapy," *Antioxidants and Redox Signaling*, vol. 37, no. 16-18, pp. 1234–1253, 2022.

[21] J. B. Wing, A. Tanaka, and S. Sakaguchi, "Human FOXP3+ regulatory T cell heterogeneity and function in autoimmunity and cancer," *Immunity*, vol. 50, no. 2, pp. 302–316, 2019.

[22] G. O. Rangel Rivera, H. M. Knochelmann, C. J. Dwyer et al., "Fundamentals of T Cell metabolism and strategies to enhance cancer immunotherapy," *Frontiers in Immunology*, vol. 12, Article ID 645242, 2021.

[23] A. Teijeira, S. Garasa, I. Etxeberria, M. Gato-Cañas, I. Melero, and G. M. Delgoffe, "Metabolic consequences of T-cell costimulation in anticancer immunity," *Cancer Immunology Research*, vol. 7, no. 10, pp. 1564–1569, 2019.

[24] E. J. Wherry, S.-J. Ha, S. M. Kaech et al., "Molecular signature of CD8+ T cell exhaustion during chronic viral infection," *Immunity*, vol. 27, no. 5, pp. 824–884, 2007.

[25] J. Rieusset, "The role of endoplasmic reticulum-mitochondria contact sites in the control of glucose homeostasis: an update," *Cell Death and Disease*, vol. 9, no. 3, p. 388, 2018.

[26] E. L. Carr, A. Kelman, G. S. Wu et al., "Glutamine uptake and metabolism are coordinately regulated by ERK/MAPK during T lymphocyte activation," *The Journal of Immunology*, vol. 185, no. 2, pp. 1037–1044, 2010.

[27] A. Angelin, L. Gil-de-Gómez, S. Dahiya et al., "Foxp3 reprograms T cell metabolism to function in low-glucose, high-lactate environments," *Cell Metabolism*, vol. 25, no. 6, pp. 1282–1293.e7, 2017.

[28] G. López-Cantillo, C. Urueña, B. A. Camacho, and C. Ramírez-Segura, "CAR-T cell performance: how to improve their persistence?" *Frontiers in Immunology*, vol. 13, Article ID 878209, 2022.

[29] A. D. Waldman, J. M. Fritz, and M. J. Lenardo, "A guide to cancer immunotherapy: from T cell basic science to clinical practice," *Nature Reviews Immunology*, vol. 20, no. 11, pp. 651–668, 2020.

[30] Y.-C. Lu and X.-J. Wang, "Harnessing the power of the immune system in cancer immunotherapy and cancer prevention," *Molecular Carcinogenesis*, vol. 59, no. 7, pp. 675–678, 2020.

[31] A. Holzinger and H. Abken, "Treatment with living drugs: pharmaceutical aspects of CAR T cells," *Pharmacology*, vol. 107, no. 9-10, pp. 446–463, 2022.

[32] S. Feins, W. Kong, E. F. Williams, M. C. Milone, and J. A. Fraietta, "An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer," *American Journal of Hematology*, vol. 94, no. S1, pp. S3–s9, 2019.

[33] H. Dana, G. M. Chalbatani, S. A. Jalali et al., "CAR-T cells: early successes in blood cancer and challenges in solid tumors," *Acta Pharmaceutica Sinica B*, vol. 11, no. 5, pp. 1129–1147, 2021.

[34] L. C. Fleischer, H. T. Spencer, and S. S. Raikar, "Targeting T cell malignancies using CAR-based immunotherapy: challenges and potential solutions," *Journal of Hematology and Oncology*, vol. 12, no. 1, p. 141, 2019.

[35] B. Cao, M. Liu, L. Wang et al., "Remodelling of tumour microenvironment by microwave ablation potentiates immunotherapy of AXL-specific CAR T cells against non-small cell lung cancer," *Nature Communications*, vol. 13, no. 1, p. 6203, 2022.

[36] Y. Wu, Z. Huang, R. Harrison et al., "Engineering CAR T cells for enhanced efficacy and safety," *APL Bioengineering*, vol. 6, no. 1, Article ID 011502, 2022.

[37] H.-M. Cho, P.-H. Kim, H.-K. Chang et al., "Targeted genome engineering to control VEGF expression in human umbilical cord blood-derived mesenchymal stem cells: potential implications for the treatment of myocardial infarction," *Stem Cells Translational Medicine*, vol. 6, no. 3, pp. 1040–1051, 2017.

[38] M. Hudecek, M.-T. Lupo-Stanghellini, P. L. Kosasih et al., "Receptor affinity and extracellular domain modifications affect tumor recognition by ROR1-specific chimeric antigen receptor T cells," *Clinical Cancer Research*, vol. 19, no. 12, pp. 3153–3164, 2013.

[39] S. Rafiq, C. S. Hackett, and R. J. Brentjens, "Engineering strategies to overcome the current roadblocks in CAR T cell therapy," *Nature Reviews Clinical Oncology*, vol. 17, no. 3, pp. 147–167, 2020.

[40] M. C. Jensen and S. R. Riddell, "Designing chimeric antigen receptors to effectively and safely target tumors," *Current Opinion in Immunology*, vol. 33, pp. 9–15, 2015.

[41] K. E. Ruppel, S. Fricke, U. Köhl, and D. Schmiedel, "Taking lessons from CAR-T cells and going beyond: tailoring design and signaling for CAR-NK cells in cancer therapy," *Frontiers in Immunology*, vol. 13, Article ID 822298, 2022.

[42] A. Dimitri, F. Herbst, and J. A. Fraietta, "Engineering the next-generation of CAR T-cells with CRISPR-Cas9 gene editing," *Molecular Cancer*, vol. 21, no. 1, p. 78, 2022.

[43] M. Hong, J. D. Clubb, and Y. Y. Chen, "Engineering CAR-T cells for next-generation cancer therapy," *Cancer Cell*, vol. 38, no. 4, pp. 473–488, 2020.

[44] N. Watanabe, F. Mo, and M. K. McKenna, "Impact of manufacturing procedures on CAR T cell functionality," *Frontiers in Immunology*, vol. 13, Article ID 876339, 2022.

[45] B. L. Levine, J. Miskin, K. Wonnacott, and C. Keir, "Global manufacturing of CAR T cell therapy," *Molecular Therapy-Methods and Clinical Development*, vol. 4, pp. 92–101, 2017.

[46] A. P. Gee, "GMP CAR-T cell production," *Best Practice and Research Clinical Haematology*, vol. 31, no. 2, pp. 126–134, 2018.

[47] M. Abou-El-Enein, M. Elsallab, S. A. Feldman et al., "Scalable manufacturing of CAR T cells for cancer immunotherapy," *Blood Cancer Discovery*, vol. 2, no. 5, pp. 408–422, 2021.

[48] X. Wang and I. Riviere, "Clinical manufacturing of CAR T cells: foundation of a promising therapy," *Molecular Therapy- Oncolytics*, vol. 3, Article ID 16015, 2016.

[49] C. Priesner, K. Aleksandrova, R. Esser et al., "Automated enrichment, transduction, and expansion of clinical-scale CD62L+ T cells for manufacturing of gene therapy medicinal products," *Human Gene Therapy*, vol. 27, no. 10, pp. 860–869, 2016.

[50] C. J. Turtle, L.-A. Hanafi, C. Berger et al., "CD19 CAR–T cells of defined CD4+: CD8+ composition in adult B cell ALL patients," *Journal of Clinical Investigation*, vol. 126, no. 6, pp. 2123–2138, 2016.

[51] K. A. Hay, L.-A. Hanafi, D. Li et al., "Kinetics and biomarkers of severe cytokine release syndrome after CD19 chimeric antigen receptor–modified T-cell therapy," *Blood*, vol. 130, no. 21, pp. 2295–2306, 2017.

[52] E. S. Allen, D. F. Stroncek, J. Ren et al., "Autologous lymphapheresis for the production of chimeric antigen receptor T cells," *Transfusion*, vol. 57, no. 5, pp. 1133–1141, 2017.

[53] N. Cieri, B. Camisa, F. Cocchiarella et al., "IL-7 and IL-15 instruct the generation of human memory stem T cells from naive precursors," *Blood*, vol. 121, no. 4, pp. 573–584, 2013.

[54] T. W. Mak, M. Grusdat, G. S. Duncan et al., "Glutathione primes T cell metabolism for inflammation," *Immunity*, vol. 46, no. 6, pp. 1089-1090, 2017.

[55] T. Huan, D. Chen, G. Liu et al., "Activation-induced cell death in CAR-T cell therapy," *Human Cell*, vol. 35, no. 2, pp. 441–447, 2022.

[56] J. N. Brudno and J. N. Kochenderfer, "Recent advances in CAR T-cell toxicity: mechanisms, manifestations and management," *Blood Reviews*, vol. 34, pp. 45–55, 2019.

[57] R. Elahi, E. Khosh, S. Tahmasebi, and A. Esmaeilzadeh, "Immune cell hacking: challenges and clinical approaches to create smarter generations of chimeric antigen receptor T cells," *Frontiers in Immunology*, vol. 9, Article ID 1717, 2018.

[58] N. Panoskaltsis, "Are all cytokine storms the same?" *Cancer Immunology, Immunotherapy*, vol. 70, no. 4, pp. 887–892, 2021.

[59] V. S. Sheth and J. Gauthier, "Taming the beast: CRS and ICANS after CAR T-cell therapy for ALL," *Bone Marrow Transplantation*, vol. 56, no. 3, pp. 552–566, 2021.

[60] C. L. Flugel, R. G. Majzner, G. Krenciute et al., "Overcoming on-target, off-tumour toxicity of CAR T cell therapy for solid tumours," *Nature Reviews Clinical Oncology*, vol. 20, no. 1, pp. 49–62, 2023.

[61] N. Tokarew, J. Ogonek, S. Endres, M. von Bergwelt-Baildon, and S. Kobold, "Teaching an old dog new tricks: next-generation CAR T cells," *British Journal of Cancer*, vol. 120, no. 1, pp. 26–37, 2019.

[62] A. Gajra, A. Zalenski, A. Sannareddy, Y. Jeune-Smith, K. Kapinos, and A. Kansagra, "Barriers to chimeric antigen receptor T-cell (CAR-T) therapies in clinical practice," *Pharmaceutical Medicine*, vol. 36, no. 3, pp. 163–171, 2022.

[63] S. R. Bailey, T. R. Berger, C. Graham, R. C. Larson, and M. V. Maus, "Four challenges to CAR T cells breaking the glass ceiling," *European Journal of Immunology*, vol. 53, no. 11, Article ID 2250039, 2023.

[64] S. Depil, P. Duchateau, S. A. Grupp, G. Mufti, and L. Poirot, "Off-the-shelf allogeneic CAR T cells: development and challenges," *Nature Reviews Drug Discovery*, vol. 19, no. 3, pp. 185–199, 2020.

[65] S. J. Schuster, C. S. Tam, P. Borchmann et al., "Long-term clinical outcomes of tisagenlecleucel in patients with relapsed

or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study," *Lancet Oncology*, vol. 22, no. 10, pp. 1403–1415, 2021.

[66] F. L. Locke, A. Ghobadi, C. A. Jacobson et al., "Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial," *Lancet Oncology*, vol. 20, no. 1, pp. 31–42, 2019.

[67] J. S. Abramson, L. I. Gordon, M. L. Palomba et al., "Updated safety and long term clinical outcomes in TRANSCEND NHL 001, pivotal trial of lisocabtagene maraleucel (JCAR017) in R/R aggressive NHL," *Journal of Clinical Oncology*, vol. 36, p. 7505, 2018.

[68] L. Chen, J. Xu, S. W. Fu et al., "Updated phase 1 results of a first-in-human open-label study of Lcar-B38M, a structurally differentiated chimeric antigen receptor T (CAR-T) cell therapy targeting B-cell maturation antigen (Bcma)," *Blood*, vol. 134, p. 1858, 2019.

[69] O. Pasvolsky, M. Daher, G. Alatrash et al., "CARving the path to allogeneic CAR T cell therapy in acute myeloid leukemia," *Frontiers in Oncology*, vol. 11, Article ID 800110, 2022.

[70] C. Graham, A. Jozwik, A. Pepper, and R. Benjamin, "Allogeneic CAR-T cells: more than ease of access?" *Cells*, vol. 7, no. 10, 2018.

[71] H. Lin, J. Cheng, W. Mu, J. Zhou, and L. Zhu, "Advances in universal CAR-T cell therapy," *Frontiers in Immunology*, vol. 12, 2021.

[72] J. N. Brudno, R. P. Somerville, V. Shi et al., "Allogeneic T cells that express an anti-CD19 chimeric antigen receptor induce remissions of B-cell malignancies that progress after allogeneic hematopoietic stem-cell transplantation without causing graft-versus-host disease," *Journal of Clinical Oncology*, vol. 34, no. 10, p. 1112, 2016.

[73] L. W. Buie, "Balancing the CAR T: perspectives on efficacy and safety of CAR T-cell therapy in hematologic malignancies," *American Journal of Managed Care*, vol. 27, 2021.

[74] S. L. Maude, T. W. Laetsch, J. Buechner et al., "Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia," *New England Journal of Medicine*, vol. 378, no. 5, pp. 439–448, 2018.

[75] T. W. Laetsch, S. L. Maude, S. Rives et al., "Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA trial," *Journal of Clinical Oncology*, vol. 41, no. 9, pp. 1664–1669, 2023.

[76] C. A. Jacobson, J. C. Chavez, A. R. Sehgal et al., "Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial," *Lancet Oncology*, vol. 23, no. 1, pp. 91–103, 2022.

[77] S. S. Neelapu, F. L. Locke, N. L. Bartlett et al., "Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma," *New England Journal of Medicine*, vol. 377, no. 26, pp. 2531–2544, 2017.

[78] C. Jacobson, F. L. Locke, A. Ghobadi et al., "Long-term (≥4 year and ≥5 year) overall survival (OS) by 12-and 24-month event-free survival (EFS): an updated analysis of ZUMA-1, the pivotal study of axicabtagene ciloleucel (axi-cel) in patients (pts) with refractory large B-cell lymphoma (LBCL)," *Blood*, vol. 138, p. 1764, 2021.

[79] M. L. Wang, J. Munoz, A. Goy et al., "KTE-X19, an anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in patients (Pts) with relapsed/refractory (R/R) mantle cell lymphoma (MCL): results of the phase 2 ZUMA-2 study," *Blood*, vol. 134, p. 754, 2019.

[80] J. S. Abramson, M. L. Palomba, L. I. Gordon et al., "High durable CR rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort," *Blood*, vol. 130, p. 581, 2017.

[81] N. Raje, J. Berdeja, Y. Lin et al., "Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma," *New England Journal of Medicine*, vol. 380, no. 18, pp. 1726–1737, 2019.

[82] D. Madduri, J. G. Berdeja, S. Z. Usmani et al., "CARTITUDE-1: phase 1b/2 study of ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T cell therapy, in relapsed/refractory multiple myeloma," *Blood*, vol. 136, pp. 22–25, 2020.

[83] S. P. Hunger and E. A. Raetz, "How I treat relapsed acute lymphoblastic leukemia in the pediatric population," *Blood*, vol. 136, no. 16, pp. 1803–1812, 2020.

[84] L. Amini, S. K. Silbert, S. L. Maude et al., "Preparing for CAR T cell therapy: patient selection, bridging therapies and lymphodepletion," *Nature Reviews Clinical Oncology*, vol. 19, no. 5, pp. 342–355, 2022.

[85] Z. Wang, C. Chen, L. Wang, Y. Jia, and Y. Qin, "Chimeric antigen receptor T-cell therapy for multiple myeloma," *Frontiers in Immunology*, vol. 13, 2022.

[86] L. J. Nastoupil, M. D. Jain, J. Y. Spiegel et al., "Axicabtagene ciloleucel (axi-cel) CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: real world experience," *Blood*, vol. 132, no. Supplement 1, p. 91, 2018.

[87] M. D. Jain, M. T. Jacobs, L. J. Nastoupil et al., "Characteristics and outcomes of patients receiving bridging therapy while awaiting manufacture of standard of care axicabtagene ciloleucel CD19 chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory large B-cell lymphoma: results from the US Lymphoma CAR-T Consortium," *Blood*, vol. 134, no. Supplement_1, p. 245, 2019.

[88] C. J. Turtle, K. A. Hay, L.-A. Hanafi et al., "Durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor–modified T cells after failure of ibrutinib," *Journal of Clinical Oncology*, vol. 35, no. 26, pp. 3010–3020, 2017.

[89] S. S. Neelapu, S. Tummala, P. Kebriaei et al., "Chimeric antigen receptor T-cell therapy—assessment and management of toxicities," *Nature Reviews Clinical Oncology*, vol. 15, no. 1, pp. 47–62, 2018.

[90] A. B. Clemmons, M. Alexander, K. DeGregory, and L. Kennedy, "The hematopoietic cell transplant pharmacist: roles, responsibilities, and recommendations from the ASBMT pharmacy special interest group," *Biology of Blood and Marrow Transplantation*, vol. 24, no. 5, pp. 914–922, 2018.

[91] M. C. Galli, Y. Zhao, C. Quintarelli et al., "CAR-T Cell Therapy Development: Regulatory Issues and Challenges to Harmonize Translation from Bench to Bedside," 2021, https://www.aiatris.it/media/1109/eurecart_whitepaper_final.pdf.

[92] J. Buechner, M. J. Kersten, M. Fuchs, F. Salmon, and U. Jager, "Chimeric antigen receptor-T cell therapy: practical considerations for implementation in europe," *Hemasphere*, vol. 2, no. 1, p. e18, 2018.

[93] E. C. Morris, S. S. Neelapu, T. Giavridis, and M. Sadelain, "Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy," *Nature Reviews Immunology*, vol. 22, no. 2, pp. 85–96, 2022.

[94] D. W. Lee, B. D. Santomasso, F. L. Locke et al., "ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells," *Biology of Blood and Marrow Transplantation*, vol. 25, no. 4, pp. 625–638, 2019.

[95] I. Yakoub-Agha, C. Chabannon, P. Bader et al., "Management of adults and children undergoing chimeric antigen receptor T-cell therapy: best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE)," *Haematologica*, vol. 105, no. 2, pp. 297–316, 2020.

[96] T. R. Abreu, N. A. Fonseca, N. Gonçalves, and J. N. Moreira, "Current challenges and emerging opportunities of CAR-T cell therapies," *Journal of Controlled Release*, vol. 319, pp. 246–261, 2020.

[97] J. Fan, A. Adams, N. Sieg et al., "Potential synergy between radiotherapy and CAR T-cells- A multicentric analysis of the role of radiotherapy in the combination of CAR T cell therapy," *Radiotherapy and Oncology*, vol. 183, Article ID 109580, 2023.

[98] Y. Gong, R. G. J. Klein Wolterink, J. Wang, G. M. J. Bos, and W. T. V. Germeraad, "Chimeric antigen receptor natural killer (CAR-NK) cell design and engineering for cancer therapy," *Journal of Hematology and Oncology*, vol. 14, no. 1, p. 73, 2021.

[99] W. Wei, D. Yang, X. Chen, D. Liang, L. Zou, and X. Zhao, "Chimeric antigen receptor T-cell therapy for T-ALL and AML," *Frontiers in Oncology*, vol. 12, Article ID 967754, 2022.

[100] T. Riet and M. Chmielewski, "Regulatory CAR-T cells in autoimmune diseases: progress and current challenges," *Frontiers in Immunology*, vol. 13, Article ID 934343, 2022.

[101] V. Luginbuehl, E. Abraham, K. Kovar, R. Flaaten, and A. M. S. Müller, "Better by design: what to expect from novel CAR-engineered cell therapies?" *Biotechnology Advances*, vol. 58, Article ID 107917, 2022.

[102] L. Labanieh, R. G. Majzner, and C. L. Mackall, "Programming CAR-T cells to kill cancer," *Nature Biomedical Engineering*, vol. 2, no. 6, pp. 377–391, 2018.

[103] S. Vandghanooni, M. Eskandani, Z. Sanaat, and Y. Omidi, "Recent advances in the production, reprogramming, and application of CAR-T cells for treating hematological malignancies," *Life Sciences*, vol. 309, Article ID 121016, 2022.

[104] P. Karakostas, N. Panoskaltsis, A. Mantalaris, and M. C. Georgiadis, "Optimization of CAR T-cell therapies supply chains," *Computers and Chemical Engineering*, vol. 139, Article ID 106913, 2020.