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Leading article

CAR-T cell therapy: Transforming the landscape in the treatment of haematological malignancies

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Abstract

Chimeric Antigen Receptor T-cell (CAR-T) therapy represents one of the most significant advances in cancer treatment of the 21st century. This revolutionary therapeutic modality, which utilizes the adoptive cellular immunity has made a paradigm shift in the outcome of relapsed/ refractory haematological malignancies. Initiated as simple laboratory experiments, it has developed into multiple FDA-approved products, making a strong impact on current haematological practice.

CAR-T therapy is available for regular use widely across the world, including some countries in Asia. India made history in 2023, when it approved its first locally manufactured CAR-T product, NexCAR19. Sri Lanka has yet to implement this potentially life-saving treatment.

This review discusses the mechanism of action, clinical applications, safety profile, and future directions of CAR-T therapy, with particular attention to its potential implementation in Sri Lankan healthcare settings.

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Introduction

The theoretical concept of CAR-T therapy began in the early 1990s, and has evolved in to a life-saving treatment modality, which changed the landscape of today's haemato-oncology practice. The outcome of patients with relapsed refractory haematological malignancies, which was once very dismal, is redefined with the invent of CAR-T therapy.

CAR-T therapy is a powerful example of translational medicine, beginning in the laboratory, paving its way to the bedside. The ability of T lymphocytes to be genetically modified to recognize tumor specific antigens was demonstrated in initial experiments in the 1990s[1]. The true potential of this approach became evident with the pioneering work done in the 2000s at the university of Pennsylvania. The very first clinically successful story emerged in 2010, where a patient with chronic lymphocytic leukemia achieved complete remission following treatment with CD19 targeting CAR-T cells[2]. This seminal case paved the way for the FDA approval of tisagenlecleucel (Kymriah) in 2017, marking the beginning of a new era in cancer therapy.

CAR-T therapy is no longer an experimental treatment today, but an established treatment modality for various haematological malignancies. Many renowned cancer centres around the world, have embraced this technology. India approved its first locally manufactured CAR-T product in 2023, marking a historic milestone for South Asia[3]. Sri Lanka is yet to experience and introduce this remarkable transformative therapy to its patients.

The science behind CAR-T therapy

The principle behind CAR-T therapy is reprogramming the body's own immune cells to find and destroy cancer cells, turning the patient's defense system into a personalized treatment.

The manufacturing process is complexed, but the primary elements have been standardized with stringent quality control measures to ensure safety and potency of the final product. The manufacturing process can be divided into four main stages. These being, isolation and enrichment of T cells, followed by activation and expansion of T cells, gene transfer of a vector, and finally, ex-vivo expansion of CAR-T cells and cryopreservation. The process begins with the collection of T lymphocytes from the patient through apheresis. These T cells then undergo genetic modification in specialized manufacturing facilities. Viral vectors such as lentiviruses or retroviruses serve as the delivery vehicles for the genetic instructions, by introducing synthetic genes which encode for the chimeric antigen receptors[4]. These receptors incorporate the specificity of antibodies with the cytotoxic capability of T cells. The CAR-T cells produced, then undergo ex-vivo expansion in bioreactors for about 10-14 days, in order to achieve a sufficient number of Car-T cells required for patient administration. The complete process from collection of T cells from the patient to producing the final product usually takes up to 3-4 weeks.

The structure of a CAR molecule is a superb creation of biological engineering. Starting with the first-generation basic structure CAR, it has expanded to several generations in the current era (Figure 1). The second-generation CARs consist of several critical components working together to bring about the desired effects and are the backbone of all approved therapies[5].

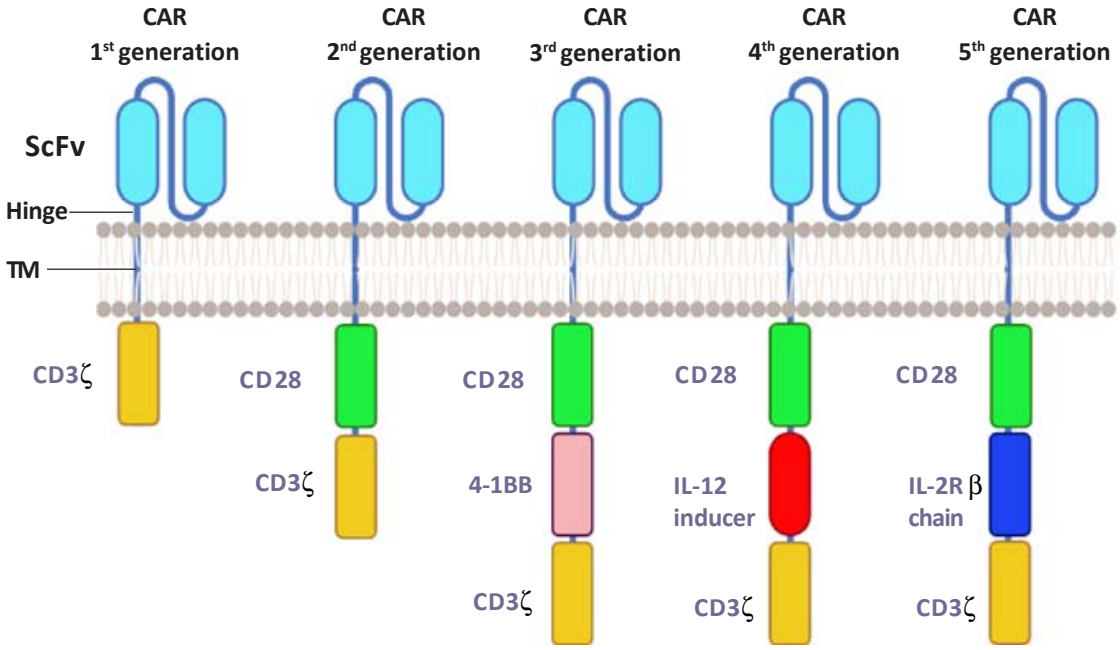

Figure 1. Basic structural differences in the five generations of CAR constructs.
(This figure was created by Y. Alvitigala using Biorender.com)

All generations of CAR constructs have a common basic structure composed of 3 domains and a hinge region. An extracellular domain that targets tumour-specific antigens [ScFV], a transmembrane domain and an intracellular domain. The intracellular domain reflects the generation of the CAR and its functional activity. For example, CD3 domain initiates signal transduction pathways, while CD28 and 4-1BB domains act as co-stimulatory signals. The IL-12 inducer prompts cytokine release within the TEM and IL-2R mimics IL-2 signalling enhancing survival, proliferation and persistence of CAR-T cells.

A CAR has three domains, namely the extracellular domain, transmembrane domain and the intracellular domain. The extracellular domain is composed of a single-chain variable fragment (scFv) which is derived from monoclonal antibodies. It allows the CAR-T cell to recognize specific antigens on tumor cells independent of HLA presentation, in contrast to natural T cells, which require antigen presentation through HLA molecules. The intracellular domain contains an activation domain (typically CD3ζ) and a co-stimulatory domain (such as CD28 or 4-1BB). The main function of the activation domain is to initiate the T cell activation and cytotoxicity, while the co-stimulatory domain enhances T cell expansion, persistence, and survival. Robust and sustained anti-tumor activity is ensured by this dual signal system (Figure 2).

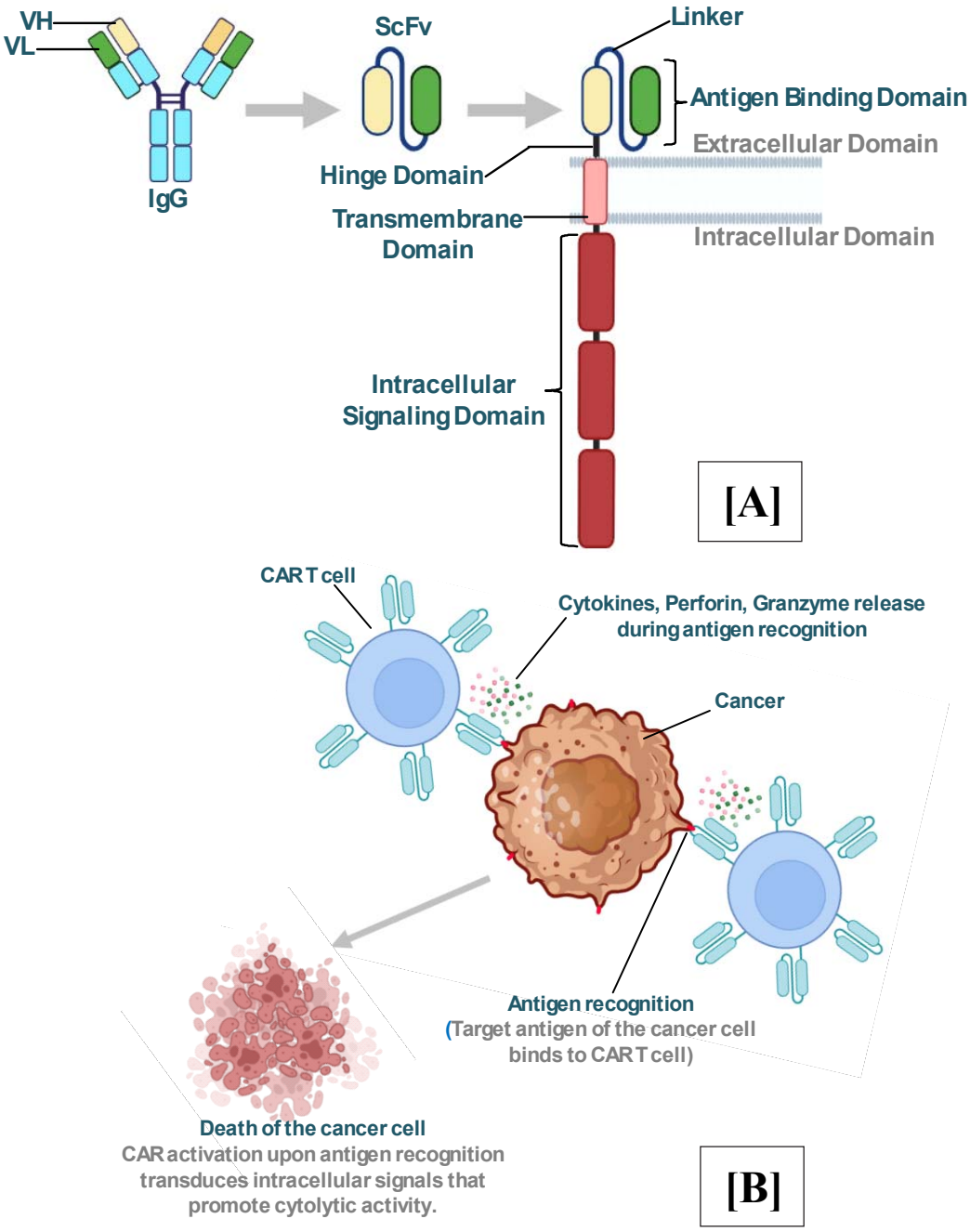

Figure 2. CAR structure [A] and function in killing cancer cells [B].
(This figure was created by Y. Alvitigala using Biorender.com)

Clinical applications and approved indications

CAR-T therapy has shown its greatest clinical impact in the treatment of B-cell malignancies, with CD19 becoming the most widely targeted antigen. By January 2025, the FDA had approved seven distinct CAR-T cell products, each authorised for particular indications based on a steadily expanding body of clinical evidence[6,7] (see Table 1).

Tisagenlecleucel (Kymriah) was the first CAR-T therapy to receive regulatory approval. It was initially introduced for relapsed or refractory B-acute lymphoblastic leukaemia (B-ALL) in children and young adults. Over time, its approved use has broadened to include adults with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL). This approval was driven by impressive clinical trial outcomes, with complete remission observed in over 80% of B-ALL patients who had no remaining standard treatment options[8].

Axicabtagene ciloleucel (Yescarta) was approved soon after, gaining authorisation for the treatment of several B-cell lymphomas. Its effectiveness was first established in the landmark ZUMA-1 trial, which showed a 54% complete response rate and an overall response rate of 83% in patients with relapsed or refractory large B-cell lymphoma[9]. Further clinical studies have expanded its approved uses to include follicular lymphoma and its role as a second-line option for patients with high-risk diffuse large B-cell lymphoma (DLBCL).

Table 1. CAR-T cell products approved for clinical use

CAR-T product	Commercial name	Target antigen	Approved indications
Tisagenlecleucel (Tisa-cel)	Kymriah	CD19	B-ALL (<25 years) R/R DLBCL (adults)
Axicabtagene ciloleucel (Axi-cel)	Yescarta	CD19	R/R DLBCL after ≥2 prior therapies R/R FL after ≥2 therapies DLBCL refractory to 1st-line or relapsing <12 months
Brexucabtagene autoleucel (Brexu-cel)	Tecartus	CD19	R/R Mantle Cell Lymphoma R/R B-ALL (adults ≥26 yrs)
Lisocabtagene maraleucel (Liso-cel)	Breyanzi	CD19	R/R DLBCL after ≥2 prior therapies DLBCL refractory/relapsing early post 1st-line R/R CLL/SLL after BTK + BCL-2 inhibitors
Idecabtagene vicleucel (Ide-cel)	Abecma	BCMA	R/R Multiple Myeloma after ≥2 prior therapies (incl. IMiD, PI, and anti-CD38)
Ciltacabtagene autoleucel (Cilta-cel)	Carvykti	BCMA	R/R Multiple Myeloma after ≥1 prior therapy IMiD, PI, and refractory to lenalidomide)
Obecabtagene autoleucel (Obe-cel)	Aucatzyl	CD19	R/R B-ALL

The introduction of CAR-T therapy for multiple myeloma marks another significant advancement in the field of cancer treatment. Two therapies, idecabtagene vicleucel (Abecma) and ciltacabtagene autoleucel (Carvykti), which target B cell maturation agent (BCMA) have shown promising outcomes in multiply relapsed myeloma patients. The KarMMa trial reported a 73% overall response rate, including 33% complete responses and led to the approval of Abecma[10]. CARTITUDE-1 trial showed even more striking results, with all patients responding to treatment and 83% achieving complete remission[11].

CAR-T therapy has begun to shift into earlier stages of treatment more recently. Better outcomes were seen with CAR-T as a second line option for DLBCL compared to traditional salvage chemotherapy and stem cell transplantation in the ZUMA-7 and TRANSFORM trials[12,13] which supported the approval of CAR-T for second line use.

The treatment journey: from consultation to recovery

The process of delivering CAR-T therapy needs thorough coordination with collaboration across various medical specialties and careful selection of suitable patients. A detailed assessment of the patient needs to be done to establish the suitability of the patient for CAR-T. The overall physical condition, organ functions and the disease extent and approval for the disease need to be evaluated.

Once the patient is selected for CAR-T, the next step involves apheresis, a procedure to collect T cells. This procedure usually takes 4 to 6 hours and the patient's blood is passed through an apheresis machine that isolates T lymphocytes while returning the remaining blood components. The collected immune cells are then frozen and shipped to specialised manufacturing centres.

The manufacturing phase introduces several logistical and clinical challenges. Patients must remain stable during the 3 to 4 weeks it takes to produce their customised cell therapy. Some may require interim treatment to manage disease activity during this waiting period. This is known as bridging therapy and can include chemotherapy or radiation. These treatments are carefully chosen to control the disease without interfering with the effectiveness of the upcoming CAR-T infusion.

Once the CAR-T cells are ready, patients undergo a preparatory treatment known as lymphodepletion. This step is essential to allow the infused cells to grow and function effectively within the body. Typically, it involves a three-day course of chemotherapy using fludarabine and cyclophosphamide, which temporarily weakens the immune system to create a more favourable environment for the incoming CAR-T cells.

The frozen cells are thawed at the bedside and delivered through an intravenous line over a period of 15 to 30 minutes. Close observation is required afterwards to identify and manage the potential serious side effects. Patients are usually monitored intensively for at least 10 days, with many institutions opting to keep them in hospital for two to three weeks during this critical period.

Safety profile and toxicity management

CAR-T therapy comes with a distinct set of adverse effects that demand experienced clinical management. Among the most serious and potentially life-threatening complications are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)[14]. Recognising and responding to these conditions early is essential to ensure patient safety.

CRS is the most frequently encountered severe side effect, affecting 70% to 90% of patients to varying degrees. It occurs when the infused CAR-T cells become highly activated and trigger a surge in inflammatory molecules, especially interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). Symptoms usually appear within the first few days following treatment and can range from mild, flu-like discomfort to critical, multi-organ complications. Timely identification and treatment are key to preventing the condition from escalating.

A well-structured approach, based on the severity grading is used in the management of CRS. Supportive care with antipyretics and fluid management alone will be adequate for mild cases, while moderate cases typically warrant treatment

with tocilizumab, a monoclonal antibody that blocks IL-6 receptors. Severe cases may require corticosteroids and intensive care support[15].

ICANS typically present between three to seven days following the CAR-T cell infusion, a few days after CRS. It is thought to be caused by inflammatory cytokines affecting the central nervous system. Patients may experience symptoms such as confusion, difficulty speaking, seizures, or other neurological changes. Tools like the ICE (Immune Effector Cell-Associated Encephalopathy) score are used by healthcare teams to assess and track the severity of these neurological effects[16].

Managing ICANS involves careful monitoring and preventive strategies, including the use of anti-seizure medications before symptoms appear. The primary treatment is with corticosteroids, particularly high-dose methylprednisolone. In contrast to CRS, tocilizumab is typically avoided in cases of ICANS due to the risk that it may worsen neurological side effects.

Additional notable side effects of CAR-T therapy include prolonged cytopenias that can last for several months, leaving patients more vulnerable to infections.

B-cell aplasia is an anticipated consequence of therapies targeting CD19. Patient may require regular immunoglobulin replacement to support the immune system.

The overall immunosuppressed state also raises the likelihood of opportunistic infections, making preventive antimicrobial treatment and close clinical monitoring essential for patient safety[17].
Long-term outcomes and survival data

The long-term follow-up data from CAR-T therapy trials have provided increasingly encouraging results, establishing this treatment as a curative option for many patients with previously incurable diseases. B-cell acute lymphoblastic leukemia, which is the most successful story, long-term remission rates exceed 60% in pediatric patients, with many achieving durable cures[18].

Data continue to mature for aggressive B cell lymphomas, but show promise for long-term disease control. Five-year follow-up of ZUMA-1 trial demonstrated that approximately 43% of patients remained in remission, with many considered functionally cured[19]. Importantly, patients who achieved complete remission at three months had a high likelihood of maintaining long-term disease-free survival.

The multiple myeloma experience, while shorter in duration, has been equally impressive. Early data from the KarMMa trial showed that patients achieving complete response had excellent progression-free survival, with many maintaining remissions beyond two years[20]. The CARTITUDE-1 trial results for ciltacabtagene autoleucel have been even more encouraging, with minimal progression events in patients achieving complete response[21].

Quality of life assessments have shown that patients who achieve remission following CAR-T therapy experience significant improvements in physical function, emotional well-being, and overall quality of life[22]. This is particularly meaningful given that many patients had exhausted conventional treatment options and faced poor prognoses.

Real life data

There is a growing body of real-world evidence supporting the efficacy of CAR-T therapy.

Few studies in relapsed/ refractory (R/R) myeloma have mirrored the promising results from pivotal clinical trials. Largest real world multi-centre study on ide-cel in R/R myeloma with the inclusion of 821 patients who received ide-cel, showed comparable results to the pivotal trials with an overall response rate of 73% with a complete response rate of 25% after a median follow-up of 11.6 months[23]. Grade ≥3CRS was seen in 3% while grade ≥3 ICANS was seen in 5%. Treatment related mortality was 8%. 77% of the patients in this study had significant comorbidities, and would have been ineligible for the registrational KarMMA trail, which highlights the efficacy and safety of CAR-T in this group of patients as well. A large German registry-based study involving 343 patients treated with ide-cel or cilta-cel also reported overall response rates (ORR) of 82% and 94% respectively,

with complete responses (CR) in up to 61% of cilta-cel recipients[24]. These findings align with those from the CARTITUDE-1 trial, and importantly, were observed even in patients who would not have qualified for clinical trials. Similarly, U.S. real-world data on cilta-cel reported ORRs around 89% and CR rates up to 70%, with most patients experiencing only low-grade cytokine release syndrome (CRS) and manageable neurotoxicity[25].

Similarly encouraging real world experiences are noted with the B cell lymphomas, particularly with axi-cel and tisa-cel in DLBCL. Multiple observational studies have demonstrated ORRs between 76%-90%, CRs in about 40%-50% of patients, median progression-free survival (PFS) of 8-12 months and overall survival (OS) exceeding 17 months in many cohorts[26]. Toxicities such as CRS and ICANS were common but largely manageable with standard supportive care.

The ALL studies have also demonstrated substantial benefit with CD19 directed CAR-T therapy in real world setting. Data from early phase studies show ORRs of over 80%, with event-free survival (EFS) at 6 months exceeding 70%, mirroring results from the ELIANA trial[27].

Challenges and limitations

Despite its remarkable success, CAR-T therapy continues to face several significant challenges limiting its widespread adoption and effectiveness.

The most pressing concern is the cost, where per patient expenses exceed $400,000 in many healthcare systems[28]. This is a significant economic burden, which extends beyond the initial treatment cost to include hospitalization, supportive care, and long-term monitoring expenses.

India's recent approval of its first locally manufactured CAR-T product, NexCAR19 in 2024, represents a significant milestone for the region which demonstrates the potential for cost-effective local manufacturing[29]. The second CAR-T therapy, varnimcabtagene autoleucel (var-cel) by the trade name Qartemi was also approved few months later by India's Central Drugs Standard Control Organization for adult patients with relapsed or refractory B-cell non-Hodgkin's lymphoma (B-NHL).

Another major challenge faced is the manufacturing limitation. Individualized production is needed for each patient with the autologous approach, and this limits the manufacturing capacity. Additionally, some patients with rapidly progressive disease can deteriorate during the 3-4 week manufacturing timeline, before receiving treatment.

Another significant biological challenge is immune escape, where tumor cells lose expression of the target antigen (such as CD19) as a mechanism of resistance[30]. As a resolution to this, dual targeted CAR-T products are developed, that target multiple antigens simultaneously, such as CD19/CD22.

The success of CAR-T therapies for acute myeloid leukaemia (AML) has lagged behind its B-cell counterpart. The main challenge in the development of a CAR-T therapy, for the most common acute leukaemia in adults and the elderly, is the lack of a specific target antigen that is both effective and safe. Most surface antigens expressed by AML cells are shared with healthy haematopoietic stem cells and progenitor cells. Therefore, when these antigens are targeted simultaneously it may result in potentially fatal on-target/off-tumour toxicities. A prolonged period of myeloablation is one of them. In addition, the tumour microenvironment (TME) in AML is comparatively immunosuppressive. This too could have a negative impact on the immune response[31].

While CAR-T therapy has transformed treatment for haematological malignancies, success in solid tumors has been less progressive due to the immunosuppressive TME, limited tumor-specific antigens, and trafficking challenges[32]. In addition to being highly immunosuppressive the TME is hypoxic and fibrotic, thereby creating a biological and physical barrier to CAR-T cells reaching tumor cells[31].

Future directions and innovations

The future of CAR-T therapy depends on overcoming existing challenges while broadening its use to treat additional diseases. Several

innovative strategies are underway to transform this field and to explore further horizons.

Creation of allogeneic or "off-the-shelf," CAR-T products is one such key area of focus. Utilization of donor T cells that can be produced in advance and stored for immediate use, can help lower costs and reduce wait times. Early clinical trials have shown encouraging results despite some concerns such as graft-versus-host disease and shorter persistence[32].

An emerging innovation in the field is the development of fourth and fifth-generation CAR-T cells, often referred to as "armored" CAR-T cells. These modified cells are designed with additional features, enabling them to produce supportive cytokines, persist longer in the body, and more effectively migrate to tumour sites. These enhancements aim to boost therapeutic impact and may help extend the use of CAR-T therapy to solid tumours, an area where success has so far been limited[33].

In vivo CAR T therapy is another recent advance, where the T cells are engineered into CAR T cells directly, within the patient by using delivery vehicles incorporated with gene editing tools[34]. This has the potential to reduce manufacturing costs, achieve faster turnaround times and offer greater convenience for patients.

Another important area of research is developing safety mechanisms that allow CAR-T cells to be turned off if serious side effects arise. These safety switches aim to make the therapy safer and easier to control[35].

Exploring the possibility of other immune cells such as natural killer (NK) cells, macrophages, and γδ T cells offers further therapeutic opportunities. CAR-NK cells have shown promise due to their potentially lower toxicity and suitability as off-the-shelf treatments[36].

Conclusion

CAR-T cell therapy marks a major breakthrough in the treatment of haematological cancers, providing renewed hope for individuals with relapsed or treatment-resistant disease. With increasing data supporting its long-term effectiveness and a manageable safety profile, CAR-T is poised to become a regular part of cancer care protocols.

Sri Lanka has not yet been able to offer this scientific advancement as a treatment option that is accessible to those who need it. Reaching this goal will demand significant improvements in healthcare infrastructure, comprehensive training for medical professionals, the establishment of well-defined regulatory systems, and allocation of a sizable budget. While these challenges are considerable, the potential to enhance patient care and strengthen the country's medical landscape makes this a valuable and necessary pursuit.

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Conflict of interests

Authors declare that there is no conflict of interests.

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