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Review

Chimeric Antigen Receptor T-cell Therapy in Multiple Myeloma: Potential Benefits and Key Challenges to Becoming a Standard Treatment

REVIEW

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ABSTRACT

Background: Multiple myeloma (MM) remains an incurable haematological malignancy, with most patients experiencing relapse owing to drug resistance despite advances in proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and autologous or allogeneic stem cell transplantation. Chimeric Antigen Receptor T-cell (CAR-T cell) therapy has emerged as a highly promising immunotherapeutic agent, particularly when targeting B-cell maturation antigen (BCMA).

Methods: A narrative literature review was conducted using PubMed, MEDLINE, and Embase to identify relevant studies published between 2013 and 2025. Search terms included 'CAR-T', 'multiple myeloma', 'BCMA', 'idecabtagene vicleucel', and 'ciltacabtagene autoleucel'. Additional grey literature was obtained from the National Institute for Health and Care Excellence (NICE), the Food and Drug Administration (FDA), and the cancer statistics database (SEER). Eligible studies included phase one to three clinical trials, systematic reviews, meta-analyses, review articles, and policy documents in English. Case reports, non-peer-reviewed conference abstracts, and non-English studies were excluded.

Results: FDA-approved, BCMA-directed CAR-T cell therapies such as idecabtagene vicleucel and ciltacabtagene autoleucel have shown unprecedented response rates in patients with relapsed and refractory multiple myeloma, with overall response rates of 73% and 98% respectively. However, challenges such as antigen escape, CAR-T cell exhaustion, high manufacturing costs and accessibility challenges have limited their widespread use. Adverse effects such as cytokine release syndrome, neurotoxicity, and prolonged immunosuppression further complicate their integration into clinical practice.

Discussion: CAR-T cell therapy represents potential for tangible improvement in the relapsed and refractory treatment landscape. Compared to conventional therapies, CAR-T cell therapy offers durable remission, particularly in heavily pretreated patients, and more precise targeting of tumour cells. Future research should focus on optimising CAR-T cell persistence, exploring dual- or multi-antigen targeting and developing more efficient, decentralised manufacturing processes. Bridging the gap between innovation and accessibility is critical for the feasible implementation of CAR-T cell therapy as a standard treatment for multiple myeloma. Broader integration into treatment algorithms requires addressing financial and ethical barriers to ensure equitable access.

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BACKGROUND

Multiple myeloma (MM) is the second most prevalent haematologic cancer in the United Kingdom (UK), with 5,900 people diagnosed on average annually. (1, 48) It is characterised by the clonal proliferation of abnormal plasma cells in the bone marrow, leading to excessive production of monoclonal immunoglobulins. multiple myeloma is a heterogeneous and complex disease associated with significant morbidity due to end-organ damage. This typically manifests as hypercalcaemia, renal impairment, anaemia, and bone lesions, which are collectively known as the CRAB criteria. (2-4) These clinical manifestations support clinicians in diagnosing and treating MM by distinguishing between active, symptomatic multiple myeloma and its precursor states, monoclonal gammopathy of undetermined significance (MGUS) and smouldering myeloma. (49)

Despite significant advances in treatment, such as proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and autologous or allogeneic stem cell transplantation, and a substantial improvement in survival outcomes, (5) multiple myeloma remains incurable. While novel agents have extended progression-free survival (PFS) and improved quality of life for patients with multiple myeloma, almost all eventually relapse (50) due to evolving drug resistance and clonal evolution. This problem is especially pronounced in those with high-risk cytogenetic profiles, of whom approximately 20% experience aggressive relapse, (54) and in patients with extramedullary disease. (5-7) These high-risk groups are also shown to have poorer and more limited treatment options (8), further highlighting the need for novel therapeutic strategies. Patients displaying clinical features at relapse have a worse overall and post-progression survival than those who relapse solely biochemically. (50) Combined with the fact that the five-year relative survival rate has plateaued over the past several years (Figure 1), there is an urgent need for innovative approaches that can overcome resistance and target relapsed and refractory disease. (9)

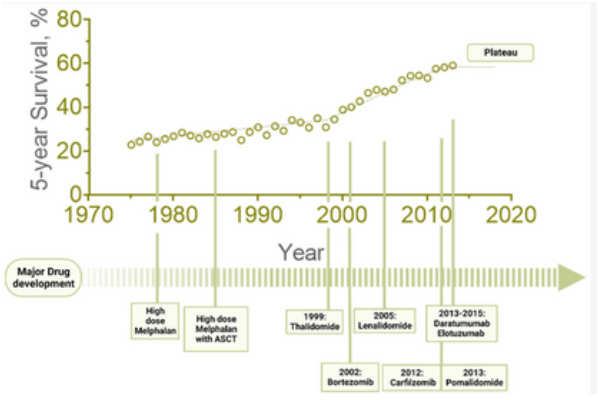

Figure 1: *Five-Year Relative Survival Percent, as reported at the Surveillance, Epidemiology, and End Results (SEER) Programme (9,10) - reproduced, licensed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/*

In recent years, Chimeric Antigen Receptor T-cell (CAR-T cell) therapy has emerged as a promising immunotherapy for relapsed and refractory multiple myeloma. By re-engineering a patient's T cells to target specific tumour antigens, CAR-T cell therapy offers the potential for an effective clinical response and durable remission periods, (11) even in patients with heavily pretreated multiple myeloma. CAR-T cell therapy has already transformed outcomes in other haematologic malignancies, such as large B-cell lymphoma and acute lymphoblastic leukaemia, where their introduction has led to higher complete response rates and reduced reliance on palliative or end-of-life care compared to standalone chemotherapy. (45)

The implementation of CAR T-cell therapy in the context of multiple myeloma would offer an additional line of therapy for patients with otherwise very limited options and potential improvement of long-term survival and quality of life. From a clinical perspective, understanding its efficacy, toxicity and logistical demands is essential for clinicians managing and treating advanced and relapsing haematologic disease, particularly as cellular therapies are becoming increasingly integrated into NHS oncology pathways. (46, 47) This highly specialised and tailored medicine has the potential to not only revolutionise outcomes for these patients but to introduce a new era of precision medicine into the National Health Service (NHS). (45)

However, the path to widespread clinical integration of CAR-T cell therapy presents many challenges, including antigen escape, CAR-T cell exhaustion, toxicity concerns and logistically complex and costly manufacturing, which limits its accessibility.

This review synthesises current evidence on CAR-T cell therapy in multiple myeloma and its potential to become a standard treatment, with emphasis on clinical efficacy, safety, barriers to implementation, and future research directions. In this context, "standard treatment" refers to therapies routinely used in first- or second-line clinical settings, supported by robust evidence of efficacy, manageable or mitigated toxicity, and feasible integration into the treatment guidelines.

METHODS

A narrative literature review was conducted using PubMed, MEDLINE, and Embase to identify relevant studies published between 2013 and 2025. Search terms included 'CAR-T', 'multiple myeloma', 'BCMA', 'idecabtagene vicleucel', and 'ciltacabtagene autoleucel'. Additional grey literature was obtained from the

National Institute for Health and Care Excellence (NICE), the Food and Drug Administration (FDA), and the cancer statistics database (SEER). Eligible studies included phase I-III clinical trials, systematic reviews, meta-analyses, review articles, and policy documents in English. Case reports, non-peer-reviewed conference abstracts, and non-English studies were excluded. References were screened for relevance, and findings were synthesised thematically.

RESULTS

Targeting multiple myeloma with CAR-T cells: Mechanisms, Benefits and Biological Barriers

The chimeric antigen receptor (CAR) is a fundamental component of CAR-T cell therapy. It is a tumour-specific receptor expressed on T cells following genetic modification and has a hybrid structure, comprised of extracellular antigen-recognition and intracellular signalling domains. The major histocompatibility complex (MHC)-independent design enables CAR-T cells to recognise and eliminate malignant cells without the need for human leukocyte antigen (HLA) compatibility, offering a significant advantage over other immunotherapies such as allogeneic stem cell transplantation, which requires donor matching and carries the risk of graft-versus-host disease (GVHD). (5, 7)

Among target antigens, BCMA has emerged as the most extensively researched and clinically validated target in multiple myeloma because of its high expression on malignant plasma cells and its limited expression on normal tissues. (9) Anti-BCMA CAR-T cell therapy is a rapidly evolving field that has shown safety and efficacy in heavily pretreated patients with multiple myeloma. (13)

Despite the promise of BCMA-targeted CAR-T cell therapy, several biological challenges continue to hinder its widespread implementation in multiple myeloma, the first of which is antigen escape. Tumour cells downregulate or lose BCMA expression, often through genetic mutations or epigenetic changes that can alter the tumour's antigen profile. Although relatively uncommon, this mechanism can lead to treatment resistance or relapse of multiple myeloma. When it does occur, it poses a significant obstacle, as it severely limits the reuse or sequencing of BCMA-targeted therapies. (14) This challenge is particularly problematic for CAR-T therapy because its cytotoxic efficacy is heavily dependent on sufficient surface antigen density on target cells. Therefore, reduced BCMA expression can significantly compromise CAR-T cell function by reducing cell-mediated cytotoxicity. (15) Although relatively rare, the consequences of antigen escape are profound, particularly when evaluating the feasibility of CAR-T therapy as a widely standardised treatment for multiple myeloma.

Further to this, traditional CAR-T cell therapies predominantly use single-antigen CAR designs, which, while effective, may not adequately address tumour adaptability and heterogeneity. This limitation has driven a push toward targeting dual or multiple antigens. (16, 17) By engaging with more than one target, these therapies aim to reduce the likelihood of tumour cells evading treatment through antigen escape.

Persistent antigen exposure creates another problem, termed T-cell exhaustion, which leads to progressive loss of T-cell function and response durability over time. From early stages of multiple myeloma, there is an association with a compromise in T-cell function, and this is further deepened in cases of relapse, (51) emphasising the need for multifaceted CAR-T strategies to achieve durable, long-lasting responses.

The third critical biological challenge in CAR-T cell therapy is the risk of on-target, off-tumour toxicity, where healthy tissues expressing low levels of the target antigen are inadvertently attacked. (9) This arises because current CAR-T constructs primarily target tumour-associated antigens (TTAs) which, are self-proteins like BCMA that are overexpressed on malignant tissues. (52) In contrast, neoantigens, derived from tumour-specific somatic mutations, are absent from normal tissues and would theoretically offer complete tumour selectivity and be a way to eliminate off-tumour toxicity. Neoantigens are, however, intracellular and rare in multiple myeloma, which limits their suitability. If BCMA targeting depends on the difference in expression and density between malignant and benign plasma cells, it highlights the need for strategies going forward that enhance tumour selectivity while preserving safety.

In terms of CAR development, CARs have undergone extensive modification over five generations. (11) Later-generation CARs incorporate co-stimulatory domains, such as CD28 or 4-1BB. These have been observed to improve T cell activation, persistence, and anti-tumour activity, (18) although the field currently lacks an understanding of how these co-stimulatory molecules can drive CAR-T exhaustion and reduce persistence. (19)

More recent strategies of interest include bispecific antibodies, which can bind to a tumour antigen expressed as well as CD3 on T cells, thus redirecting T cells to these myeloma cells with subsequent T cell activation. (11) Early studies also indicated that combining CAR-T cell therapy with checkpoint inhibitors or bispecific T-cell engagers may help overcome the above challenges and offer more durable

responses in multiple myeloma. (12)

Clinical Efficacy of CAR-T Cell Therapy in Real-World Settings

As of now, two anti-BCMA CAR-T cell products have been approved by the US Food and Drug Administration (FDA) for use in relapsing and refractory multiple myeloma: idecabtagene vicleucel (Ide-cel) and ciltacabtagene autoleucel (Cilta-cel). Figure 2 summarises the trial data relevant to each of these therapies. Both are approved for patients who have received at least four prior lines of therapy, including a proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal antibody. (20,21) This situates CAR-T therapy as a late-line option rather than a first- or second-line treatment for multiple myeloma. Nevertheless, clinical trial data and emerging real-world reports suggest that CAR-T therapies offer unprecedented disease control in highly treatment-resistant populations.

Figure 2: *Summary of pivotal trial data for ide-cel, (24) cilta-cel. (44) This graph was generated using PowerPoint.*

Demonstrating CAR-T's therapeutic potential, a 2020 five-year systematic review and meta-analysis (22) of BCMA-targeted CAR-T trials observed high overall response rates (ORRs) across twenty-three different CAR-T cell products, including a six-fold increase in median PFS in the treatment group compared to the control group's expected low PFS of approximately 2 months. More recent multi-institutional data (23) also support the superior therapeutic potential of anti-BCMA CAR-T cell therapy over existing drug options.

In the KarMMa phase 2 trial which evaluated the efficacy and safety of Ide-cel in patients with relapsing and refractory multiple myeloma, it reported an ORR of 73%, complete response (CR) ≥33%, median PFS of 8.8 months and median overall survival (OS) of 19.4 months in a heavily pretreated cohort. (24) Almost all patients had disease refractory to the last line of therapy, emphasising the significance of these results. It does, however, remain unclear whether the median PFS of 8.8 months translates to long-term durability or whether relapse remains inevitable, given that multiple myeloma becomes genetically complex and heterogeneous due to clonal evolution.

In the CARTITUDE-1 phase 1b/2 trial, Cilta-cel demonstrated remarkable efficacy, with an ORR of 98% and a median PFS 34.9 months. At 27 months, 66% of patients remained progression-free. These outcomes represent a striking improvement compared to Ide-cel, (29, 44) highlighting Cilta-cel's enhanced potency in heavily pre-treated multiple myeloma.

A 2023 multi-institutional study assessing outcomes of standard-of-care (SOC) Ide-cel outside the clinical trial setting found efficacy and safety profiling comparable to the KarMMA study results. (27) Most of the patients in this real-world cohort would have been ineligible for this trial due to co-morbidities or performance status, demonstrating the broader applicability of CAR-T cell therapy.

CAR-T cell therapy also significantly outperforms traditional late-line therapies such as pomalidomide and dexamethasone, which, while effective in some cases, often tend to offer lower ORRs (30-35%) and a median PFS of 4-6 months. (25, 26) This highlights the superior efficacy of CAR-T therapy in late-line settings, where conventional options are often limited and ineffective.

Despite these promising results, Ide-cel and Cilta-cel remain approved only for patients with multiple myeloma who have exhausted multiple prior therapies, limiting their use in earlier lines of treatment. However, broader access to CAR-T cell therapy has been gaining ground. As of February 2025, the National Institute for Health and Care Excellence (NICE) approved lisocabtagene maraleucel (Breyanzi) for adults with large B-cell lymphoma, (30) highlighting the growing confidence in CAR-T cell therapeutic implementation in clinical practice and suggesting that CAR-T's potential in myeloma may not be limited to late-line treatment, based on its broader efficacy in haematologic cancers.

Safety and Toxicity

Cytokine Release Syndrome (CRS) is one of the most prevalent and well-characterised toxicities associated with CAR-T cell therapy. Clinical presentation ranges from fever to life-threatening complications such as hypotension, capillary leak and end-organ dysfunction. (18, 31) The rates of CRS remain high, although the rates of higher grades are relatively low. (8) In clinical trials, CRS occurred in approximately 95% of patients treated with Cilta-cel and 84% of those receiving Ide-cel; however, severe CRS (grade ≥3) was observed in only around 5% of patients in both treatment groups (8, 18).

Immune effector cell-associated neurotoxicity syndrome (ICANS) is another frequent complication that occurs in 18-21% of patients and is severe in 10%. (32) The

underlying pathophysiology is thought to involve endothelial dysfunction and blood–brain barrier disruption (32, 33) but ultimately remains poorly understood. (18) Clinical manifestations range from confusion and tremor to seizures and, in occasional cases, rapid onset encephalopathy and features of cerebral oedema. (53)

While these adverse events are manageable with timely intervention, toxicity unpredictability challenges safe outpatient delivery. There is notably limited further analysis of haematologic cancer studies regarding the severity of side effects, as studies have rarely supplied grading of adverse events. (18) A systematic review has highlighted these adverse events as consistent barriers across CAR-T trials in haematologic malignancies, (34) emphasising the need for improved toxicity prediction, management, and patient selection before CAR-T cell therapy can be implemented in clinical practice as a standard treatment.

Logistical and Manufacturing Barriers

Beyond toxicity-related concerns, the complexity of CAR-T manufacturing presents a significant limitation to its clinical scalability. The process requires specialised centres, rigorous coordination, and a lengthy production timeline (Figure 3), which are vulnerable to significant delays and failure. (35) Current models rely on highly specialised facilities, with patient apheresis material often shipped internationally for modification and then returned for infusion, increasing the risk of logistical disruption. These delays are especially problematic for patients with aggressive disease, who may deteriorate during the "vein-to-vein" window. (11) While outpatient administration may reduce the system burden, its success depends on both tight proximity to centres and low-toxicity profiles - conditions that are not universally met. (35) Without more decentralised or rapid manufacturing solutions, these logistical barriers remain a challenge to the wider implementation of CAR-T cell therapy.

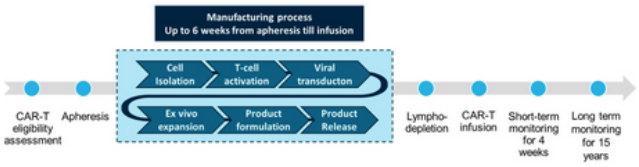

Figure 3: *Procedures before, during, and after CAR T cell therapy (11) - reproduced, licensed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/*

Emerging strategies to combat these barriers include decentralised manufacturing, simplified quality control, and automation to shorten production timescales. (43) These next-generation approaches are summarised in Table 1.

Strategy	Key Advantages	Key Limitations
Accelerated cell manufacturing	- Reduced vein-to-vein time - Less resource intensive - Increased manufacturing capacity - Less differentiated T cells in final product - Potential for reduced T-cell doses	- Higher risk of tumor cell contamination - T cells may show overly active phenotype → increased toxicity - Complexity in product-release testing
Process automation	- Reduced personnel and infrastructure costs - Lower probability of human error - Enables on-site production of fresh cell products	- Limited response to patient-specific cell behaviour - Difficult to maintain consistency across sites - Limited long-term testing for fresh products
In vivo cell manufacturing	- Eliminates need for ex vivo cell manufacturing (cost and time savings) - Potential for less differentiated T cells - Uses off-the-shelf reagents	- Unknown safety and durability - Potential for genotoxicity and immunogenicity - Risk of transgene insertion into non-T cells

Table 1: *Next-generation CAR-T cell manufacturing strategies. Adapted from Ceja Ayala et al (9,10,43) - reproduced, licensed under CC BY 4.0 https://creativecommons.org/licenses/by/4.0/*

Accessibility Challenges of CAR-T Cell Therapy

The high financial burden of CAR-T cell therapy is the most significant barrier to its widespread use in clinical practice. (37) The cost of CAR-T products alone is already prohibitively high, with current multiple myeloma three-drug regimens already costing at least $300,000 per patient annually in the United States (US). There are expectations that newer therapies could push these costs up to $500,000 annually. (37-40) This financial strain is amplified by the complex and patient-specific nature of CAR-T therapy, (39) which requires tailored cell manufacturing. These figures also do not account for costs related to drug costs, specialist centres, prolonged hospitalisation, and toxicity management, which all contribute significantly to overall expenditure. (37, 39) Given this, therapeutic access is often limited to only a small subset of patients, likely those with extensive insurance coverage or private resources.

Implementing a CAR-T programme also demands significant infrastructure investment, (40) which requires specialist staff, facilities, and intensive monitoring. Such requirements strain existing healthcare resources and limit the capacity of institutions to deliver CAR-T cell therapy at scale. (37, 39) For hospitals already strained by limited resources, these requirements can delay the adoption of CAR-T programmes or prevent their complete implementation, further widening disparities in access.

Disparities in access based on geography, socioeconomic status, and insurance create inequities in the delivery of CAR-T cell therapy. (41, 42) For many patients, CAR-T cell therapy remains a last-resort option only after

multiple traditional therapies have failed. (42) Access is further restricted by the need for an inpatient setting at highly specialised centres, making geographical proximity a determinant of eligibility. Even before this point in care, patient prioritisation is required due to the limited availability of treatment slots, further preventing equitable access.

DISCUSSION

While CAR-T offers hope for many patients with otherwise untreatable multiple myeloma, its cost threatens to create a two-tiered healthcare system. Ethically, the question shifts from when will patients receive CAR-T as a standard treatment? to who will receive it? Patients with access to comprehensive insurance or financial resources may have access, while others, marginalised by factors such as socioeconomic status and insurance status (42), may never get the chance. This disparity emphasises the moral challenge faced by healthcare systems worldwide: ensuring that access to groundbreaking therapies such as CAR-T is equitable and not determined solely by financial means or geographical location.

CAR-T cell therapy has reshaped outcomes for relapsed and refractory multiple myeloma, offering remission rates far superior to traditional therapies. (23, 29, 44) However, use is currently restricted to late-line treatment. Ongoing trials will determine whether earlier-line integration improves long-term survival. (25) These efforts could shift the treatment landscape for multiple myeloma from solely a last-resort intervention to a core component of early disease management.

Evidence supporting CAR-T cell efficacy is robust, with consistently high response rates demonstrated across pivotal trials (23, 29, 44) and further validation confirmed in real-world cohorts, (27) particularly in the case of Cilta-cel, which demonstrated to be more efficacious to Ide-cel with a similar toxicity profile. However, several limitations persist. Current studies are constrained by short follow-up periods, small patient cohorts and a lack of standardisation in toxicity grading, which complicates direct comparison across trials. (22, 34) It is also important to note that there are no current widely recognised prediction models for the known features that increase ICANS risk, (55) and research in this area would support safer implementation of CAR-T into clinical practice. Heterogeneity in manufacturing platforms introduces variability in product quality and outcomes, while publication bias tends to skew available evidence towards positive outcomes.

Future research should focus on optimising CAR-T design and delivery to improve both efficacy and safety. Dual and multi-antigen CAR-T constructs should be further developed to overcome antigen escape, (16) while novel CAR technologies have the potential to mitigate toxicity. (18) Combination therapies like checkpoint inhibitors or bispecific antibodies are being explored to enhance response durability. (19) Earlier-line use may maximise therapeutic benefit. (25) It is also critical that the interplay between intrinsic characteristics of the immune system and the tumour microenvironment is investigated further in the context of biomarker models, to see if patients who would have a better therapeutic response to CAR-T could be identified. (54) On the contrary, identifying and proactively managing those with increased toxicity risk is equally important for patient selection. (55)
Additionally, allogeneic "off-the-shelf" CAR-T platforms represent a promising way to address manufacturing delays and improve accessibility. (43) Economic innovation will also be crucial, with decentralised manufacturing and simplified production processes offering potential to reduce overall costs. (37, 39)
Despite research endeavours, several systemic challenges continue to prevent the adoption of CAR-T cell therapy. Equity of access remains arguably the most pressing moral and systemic issue. (41) High treatment costs and geographic constraints risk the development of a two-tier healthcare system in which only a subset of patients can benefit. Without co-ordinated policy reform and strategy investment to expand infrastructure, CAR-T cell therapy risks remaining a privilege of the few rather than a globally accessible standard of care. (42)

CONCLUSION

This review evaluates CAR-T cell therapy as a transformative immunotherapy with significant potential in revolutionising multiple myeloma treatment. Clinical trials and real-world studies confirm remarkable efficacy, (23, 29, 44) though durability, toxicity, and cost barriers remain unsolved. (18, 34, 39) Future implementation of CAR-T as a standard treatment depends not only on scientific advances, but also on systemic and ethical solutions. (41, 43) Addressing antigen escape, reducing toxicity, decentralising manufacturing, and ensuring equitable access will determine whether CAR-T becomes a standard of care rather than a specialist intervention.

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