Review Article

Advancing Multiple Myeloma Immunotherapy: A Review of Chimeric Antigen Receptor T-Cell and Bispecific T-Cell Engagers Cell Therapies in Revolutionizing Treatment

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Abstract

Multiple Myeloma (MM) is a hematologic malignancy characterized by clonal plasma cell development, leading to serious complications. Despite traditional treatments, MM remains incurable, necessitating innovative therapeutic approaches. Chimeric Antigen Receptor (CAR) T-cell therapy and Bispecific T-cell engagers (BiTEs) are emerging immunotherapies showing promise in MM treatment. CAR T-cell therapy involves modifying patient T-cells to target specific antigens, primarily B Cell Maturation Antigen (BCMA). BiTEs, on the other hand, are non-IgG-like bispecific antibodies designed to engage both CD3 and tumor-associated antigens. These therapies exhibit impressive efficacy in clinical trials, leading to FDA approvals for specific MM patient populations. Despite their successes, these therapies come with unique challenges and adverse effects, such as cytokine release syndrome (CRS) and neurotoxicity. This narrative review explores the mechanisms, efficacy, challenges, and potential benefits of CAR T-cell and BiTE therapies for MM patients, shedding light on their roles in addressing this complex disease.

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Keywords ● Multiple myeloma ● CAR T-cell therapy ● Bispecific antibodies ● Immunotherapy

What's Known

- Immunotherapy for multiple myeloma (MM), an incurable cancer affecting bone marrow plasma cells, has been a focal point of research for the last four decades, with Chimeric Antigen Receptor (CAR) T-cell therapy and Bispecific T-cell engagers (BiTEs) emerging as promising approaches for relapsed/refractory MM.

What's New

- Both targeting B Cell Maturation Antigen (BCMA) and BiTE therapy provide readily available options. While CAR T-cell therapy requires intricate cell manipulation and lymphodepletion, presenting hurdles, it also demonstrates promise in early-stage MM treatment.
- The difference lies in their administration speed, efficacy, clinical outcomes, safety profile, availability, and cost.

Introduction

Multiple Myeloma (MM) ranks as the second most common hematologic malignancy globally, characterized by aberrant clonal plasma cell proliferation in the bone marrow, leading to severe complications such as anemia, hypercalcemia, renal impairment, and bone lesions.[1] Its prevalence is notably increasing, notably in regions such as the US, Australia, and Western Europe, contributing to over 2% of cancer-related deaths in the US alone.[2] Despite a steady annual incidence, with around four new cases per 100,000 people reported annually in the US, MM remains a challenge with significant mortality and morbidity. Risk factors include age, ethnicity, family history, and precursor plasma cell abnormalities such as Monoclonal Gammopathy of Undetermined Significance (MGUS).[3] Symptoms include bone pain, nausea, fatigue, and neurological symptoms.[4] While traditional treatments include chemotherapy, radiation, and hematopoietic stem cell

transplantation (HSCT), the need for novel therapies persists, given MM's incurable nature.[5] Recent advancements such as proteasome inhibitors, emerging immunomodulatory drugs, monoclonal antibodies (mAbs), antibody-drug conjugates (ADC), bispecific T-cell engagers (BiTE), chimeric antigen-T-cell therapy (CAR-T), peptide-drug conjugates, and small-molecule targeted therapies offer new hope.[6]

T-cell therapies stand out among emerging treatments for their distinct mechanism of action.[7] Particularly, Anti-B-cell Maturation Antigen (BCMA) CAR-T cell therapy has shown promise in Relapsed/Refractory (R/R) MM due to BCMA's selective expression on MM cells.[8, 9] It can only be found in plasma cells and is not present in T lymphocytes, hematopoietic stem cells, memory or naive B cells, or other B cells. Limited rare BCMA-positive cell expression has been observed in normal tissue cells, including lymph nodes, spleen, lungs, and stomach.[10] Other possible target antigens, including CD38 and CD138, are also being researched and can be coupled with additional targets, such as BCMA, to create bispecific CAR T-cells. [5] While challenges such as cytokine-release toxicity and relapse post-treatment exist, ongoing research explores additional target antigens and bispecific CAR T-cells to enhance efficacy.[10]

In parallel, Bispecific Antibodies (BsAbs or BiAbs or BispAbs), first developed in 1985, offer a rapidly evolving approach, enabling T cell-mediated cancer cell destruction without genetic modification.[11, 12] BiTE therapies activate the patient's T-cells to target and destroy cancer cells without altering their genetic makeup or requiring *ex vivo* expansion. These treatments establish a direct link between endogenous T-cells and tumor-expressed antigens.[13] Originally designed to tackle challenges in relapsed/refractory diseases, T-cell-based immunotherapies such as CAR T-cell and BiTE are now being investigated as earlier-line therapies in MM patients.[14] Despite the increasing use of combination therapies in MM, relapse remains common among patients. For those under 60, the 10-year survival rate is approximately 30%. Additionally, patients often undergo triple-class exposure earlier in their treatment course.[10]

The main goal of this narrative review is to fully grasp the therapeutic approaches involving CAR T-cell and BiTE treatments for patients with MM. This review aims to offer clinicians and researchers insights into how these innovative immunotherapies address MM, along with their effectiveness, challenges, and potential benefits.

Mechanisms of CAR T-cell in MM

CAR T-cell therapy is an innovative and personalized approach to treating MM. It can reconfigure the host's immune system to attack tumor cells without requiring Human Leukocyte Antigen (HLA) presentation.[15] CARs are artificial fusion proteins that comprise an antigen-recognition domain connected to a T-cell activation domain (e.g., CD3 CD247) and to a costimulatory domain (e.g., CD28 or 4-1BB TNFRSF9, also called CD137).[10] CARs consist of an extracellular and intracellular region (figure 1) linked by a transmembrane domain 16. It also consists of a single-chain variable fragment (scFv), hinge, and transmembrane sections that connect the extracellular antigen-recognition domain to cytoplasmic signaling domains, in addition to an antigen-recognition domain.[7] The primary function of CARs is to bind antigens and to activate T-lymphocytes independently of Major Histocompatibility Complex (MHC).[16]

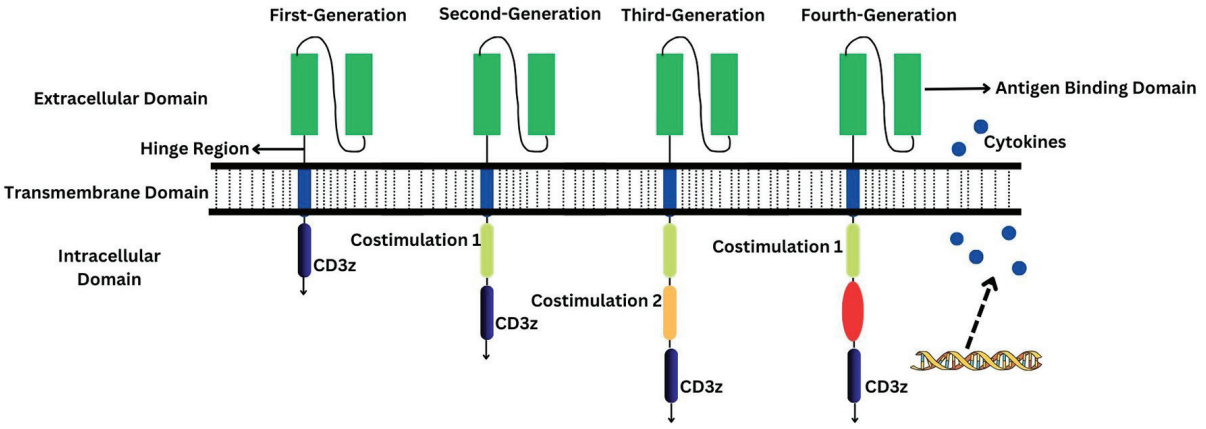

Figure 1: A diagrammatic representation of different generations of CARs. First-generation CARs possess an extracellular antigen recognition domain coupled with intracellular CD3z for signal transduction. Second-generation CARs are equipped with one costimulatory domain, and third-generation CARs include a second costimulatory domain. Fourth-generation CARs are built upon second-generation CAR cells by incorporating cytokine-expressing CAR T-cells.

CAR T-cell treatment for MM targets the BCMA (figure 2), a transmembrane glycoprotein belonging to the tumor necrosis factor (TNF) receptor superfamily.[17] Other CAR T-cell therapy targets include the Kappa-light chain, CD19, CD138, CD38, SLAMF7, GPRC5D, NY-ESO-1, and NKG2D.[18] CAR T-cells have the lethal properties of cytotoxic T-cells, but they are engineered to be highly specific to their target antigen(s) and do not require MHCs or co-stimulation.[19]

In CAR T-cell therapy, the patient's T-cells are isolated by a process called leukapheresis (figure 3) followed by T-cell proliferation induced by culturing the cell, and expansion is achieved by exposure to various pro-growth cytokines, including anti-CD3 antibodies, and interleukin-2 (IL-2). [19] T-cells can be genetically modified to express a CAR through the use of retroviruses, lentiviruses, or transposons. Genetic material encoding a CAR protein sequence is included in CAR vectors.[7] It may take up to 6 weeks to manufacture CAR T-cells.[19] Most patients receive lymphodepletion chemotherapy with fludarabine (30 mg/m^2 per day) plus cyclophosphamide (300 mg/m^2 per day) before receiving CAR-T-cell infusions.[18] After re-infusion to induce MM cell death, CAR T-cells can bind to antigens, proliferate, release tumor antigens, and induce epitope spreading; and T-cells will initiate signaling cascades (CD3 provides primary signal for T-cell activation and the subsequent signal by costimulatory domain) that stimulate the release of pro-inflammatory cytokines such as TNF, IFN-y, IL2, and IL6, resulting in cytolysis (figure 4).[15] CAR-engineered T-cells grow and attack numerous cancer cells through repeated lysis. For the treatment of R/R MM, the Food and Drug Administration (FDA) has approved two CAR T-cell products: idecaptagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel); these drugs are second-generation autologous CAR T-cell products designed for to attack BCMA. Cilta-cel possesses dual-BCMA binding domains that bind to two unique BCMA epitopes, whereas ide-cel receptors comprise a single BCMA binding domain. Each is dispensed 5-7 days after daily lymphodepletion with cyclophosphamide and fludarabine for 3 days.[19]

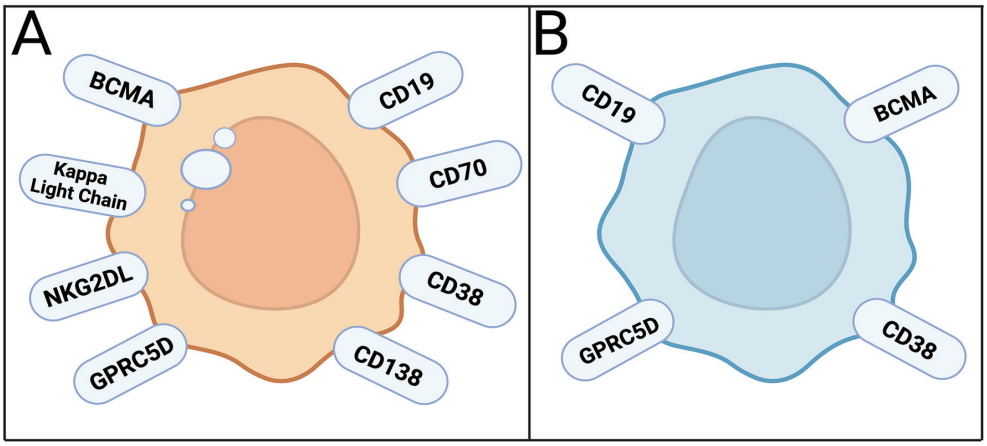

Figure 2: Surface antigens in MM Cells. A) CAR T-cells encompass BCMA, CD19, CD70, CD38, CD138, GPRC5D, NKG2DL, and Kappa Light Chain. B) BiTE cells include CD19, BCMA, CD38, and GPRC5D. Crafted using BioRender.com.

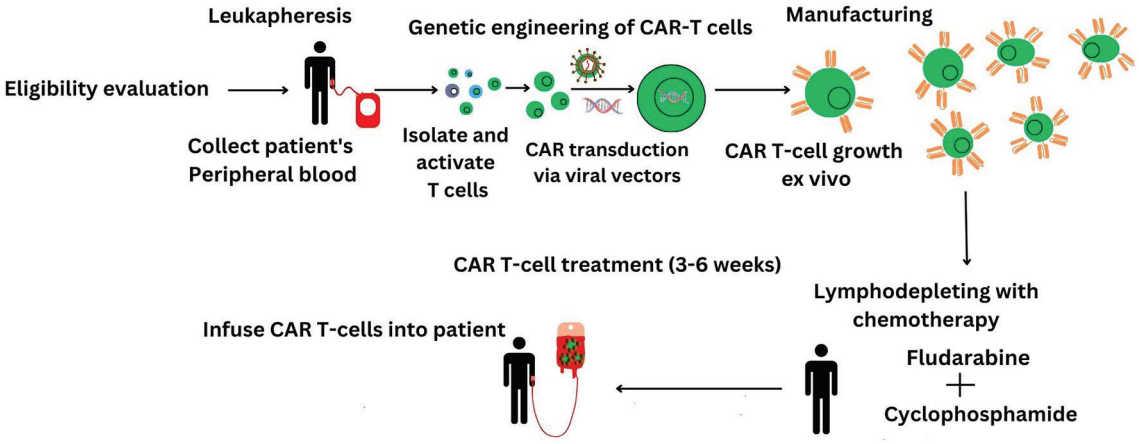

Figure 3: An illustration of the CAR T-cell therapy manufacturing process. CAR T-cells are manufactured by isolating patient T-cells, genetically modifying them to express CARs targeting specific antigens, expanding them *ex vivo*, administering lymphodepleting chemotherapy, and infusing the CAR T-cells back into the patient.

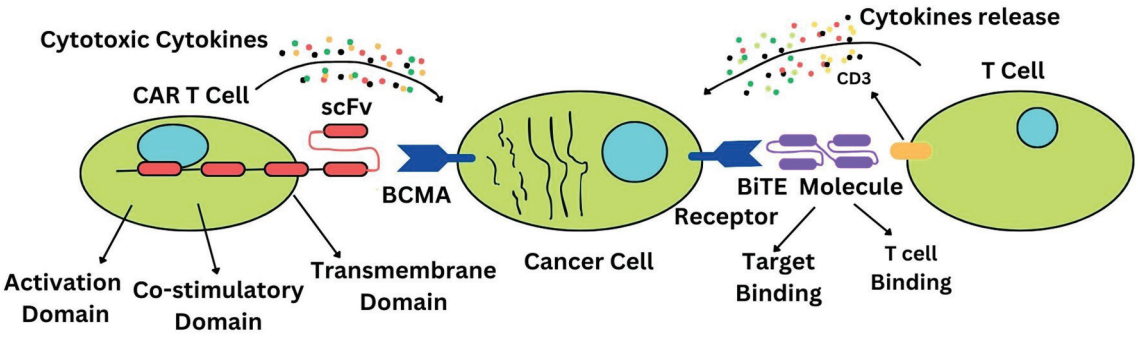

Figure 4: A representation of the CAR T-cell and BiTE therapy mechanisms in MM. CAR T-cells recognize tumor antigens via chimeric receptors, activating cytotoxicity upon binding. BiTE cells link T-cells and tumor cells, inducing T-cell-mediated killing through simultaneous antigen engagement.

Mechanism of BiTE Therapy in MM

BiTEs are non-IgG-like BsAbs subtypes composed of two antigen recognition domains (scFv from monoclonal antibodies) joined by a linker.[16] BiTEs can target CD3 and tumor-associated antigens (e.g., BCMA, CD19) (figure 2) simultaneously, attracting cytotoxic T-cells to cancer cells and has emerged as a highly promising therapy approach for MM.[18] ScFvs connect to MM cells and T-cells by binding the particular MM antigen and the T-cell receptors CD3 subunit, respectively.[20] The primary scFv binding domain can be changed to target any surface antigen, enabling off-the-shelf, rapid therapy against a variety of tumors as well as permitting retreatment. The second scFv binding domain is time-specific for CD3, an invariable component of the T-cell receptor complex.[13] The dual BCMA- and CD3-scFv-containing BiTE attaches to CD3 and BCMA simultaneously, allowing T-cell/MM cell crosslinking, followed by CD4+/CD8+ T-cell activation and cytotoxic cytokine release (figure 4), leading to cancer cell death.[21] BiTE molecules can engage any T-cell because there is no need for co-stimulation or usual MHC methods.[21] Pacanalotamab (AMG 420, BI 836909) and teclistamab-cqyv (Tecvayli) are the BiTE therapy drugs approved by the FDA for treating MM. They attach to both BCMA (on MM cells) and CD3 (on cytotoxic T-cells), whereas talquetamab (JNJ-64407564) is another bispecific antibody drug targeting GPRC5D on MM cells and CD3 on T-cells.[16, 22] Being available in an off-the-shelf manner, BiTE molecules offer superior production reliability and availability.[22]

Discussion

MM treatment is advancing swiftly, driven by therapeutic innovation in cellular and immunotherapy. Treatments such as CAR T-cell therapy and BiTEs are showing promising outcomes. Two decades after the first engineered chimeric receptor antigen, CAR T-cell therapy first received FDA approval in 2017 and has shown commendable efficacy in various hematological malignancies.[23]

Efficacy of CAR T-Cell Therapy in MM

Ide-cel received FDA approval on March 26, 2021, following results from phase 2 of the KarMMa trial. In this trial, Ide-cel was given to 128 out of 140 enrolled patients with triple-class exposed and refractory MM, i.e., patients receiving the three main classes of myeloma therapy: immunomodulatory agents, proteasome inhibitors, and anti-CD38 antibodies. Ide-cel demonstrated an overall response rate (ORR) and a complete response (CR) in 73% and 33% of patients, respectively. The median progression-free survival (mPFS) was 8.8 months (95% CI: 5.6 to 11.6), with 26% of treated patients achieving minimal residual disease (MRD)-negative status.[24] It demonstrated exceptional efficacy when compared with the newly approved drugs at that time, such as exportin-1 inhibitor, selinexor,[25, 26] and anti-BCMA monoclonal antibody belantamab mafodotin, which showed an ORR of 21% and 34%, respectively.[27] In the KarMMa-3 phase 3 trial, 386 RR MM patients were randomized, with 254 participants to ide-cel and 132 to a standard regimen. Compared to the standard regimen, patients receiving ide-cel demonstrated an mPFS of 13.3 months vs 4.4 months and a CR rate of 39% vs 5%, although adverse events were more often seen with ide-cel (93% vs 75%).[28] After ide-cel, another second-generation CAR T-cell therapy, cilta-cel received FDA approval in 2022, following the CARTITUDE-1 trial. Among 97 patients in this trial, cilta-cel demonstrated an ORR of 97%, and PFS was not reached.[29, 30] Recently, two-year follow-up of CARTITUDE-1 showed 7-month PFS and Overall Survival (OS) rates of 54.9% (95% CI, 44.0 to 64.6) and 70.4% (95% CI, 60.1 to 78.6), respectively.[28] While cilta-cel exhibited superior ORR and mPFS compared

to ide-cel, the OS rate remained statistically similar.[26] Owing to the high efficacy in these trials among refractory/relapsing MM, there has been growing curiosity regarding the use of CAR T-cell therapy as earlier-line therapies in MM patients. The success of CAR-T therapies in earlier-line treatments has been previously demonstrated in lymphomas, as evident in the BELINDA, TRANSFORM, and ZUMA7 trials.[31-33] CARTITUDE-4, a phase 3 trial, showed improved outcomes over the standard-of-care (SOC) of pomalidomide, bortezomib, and dexamethasone (PVd) or daratumumab, pomalidomide, and dexamethasone (DPd) in patients with lenalidomide-refractory MM who received one to three prior lines of therapy. Compared to standard therapy, the ORR was 84.6% (vs. 67.3%), and the mPFS was not reached (vs 11.8 months) with a hazard ratio of 0.26 (CI, 0.18 to 0.38).[34]

Efficacy of BiTE Therapy in MM

Bite therapy's efficacy in MM was demonstrated in 2020 when 70% of 42 patients responded to AMG420 (pacanalotamab) with a median PFS of 23.5 months.[35] Two years later, teclistamab-cqyv, a BsAb against BCMA, demonstrated strong efficacy in the phase I/II MajesTEC-1 trial, which led to its FDA approval on October 25, 2022, being the first BiTE therapy in MM to do so. In this trial of 165 RR MM patients, ORR was 63%, and mPFS and OS rates were 11.3 and 18.3 months, respectively.[36] Another BiTE therapy, talquetamab-tgvs, a bispecific IgG4 antibody targeting GPRC5D, was assessed in the MonumenTAL-1 trial.[37] Currently, trials are underway evaluating talquetamab in combination with other drugs, such as RedirecTT-1 (with teclistamab) and TRIMM-2 (with daratumumab/TalD). MonumenTAL-3 study is a phase 3 ongoing trial comparing Tal-D (with or without pomalidomide P) versus DPd (daratumumab+pomalidomide +dexamethasone) in patients with RRMM with ≥1 prior line of therapy.[38] There are ongoing trials for other BiTE therapies, including the anti-FcRH5 drug, cevostamab,[39] and anti-BCMA BsAbs, elranatamab,[40] ABBV-383, and alnuctamab.[41] Cevostamab targets and offers hope for patients who are refractory to anti-BCMA treatment. CAMMA 2 is an ongoing phase I/II trial evaluating its efficacy in RR MM patients with prior anti-BCMA therapy.[42]

Limitations of CAR T-Cell and BiTE Therapies

Although CAR T-cell therapy is highly effective, some considerations must be taken into account when selecting patients for it. Its administration in active Human immunodeficiency viruses (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infections is contraindicated. Moreover, the preceding lymphodepletion chemotherapy dose needs to be adjusted in patients with reduced renal function, particularly for fludarabine.[43]

Despite the efficacy of both of these therapies in treating RR/MM patients, they are not without adverse events, including cytokine release

Table 1: General comparison of CAR T-cell and BiTE therapy

Features	CAR T-cell therapy	BiTE therapy
Structure	A synthetic receptor, including a target antigen-binding domain (scFv), a hinge region, a transmembrane domain, and an intracellular signaling domain.[22]	It consists of two connected scFvs, one of which targets CD3 and another targets the MM antigen.[22]
Design	CAR T-cells transduction via viral vectors.[45]	Reconstituted soluble protein.[45]
Availability	Takes >3 weeks for manufacturing. It can be potentially overcome in the future by using non-conventional allogeneic CAR T-cells.[46]	Available off-the-shelf.
Preparation	Autologous CAR T-cells grow *ex-vivo*.	Recombinant, more production reliability.
Treatment administration	Delay of 3 to 5 weeks for the CAR T-cells to expand, a disadvantage for the patient in crisis. One-time therapy.	Treatment given continuously. Tecvayli: QW can be switched to Q2W.[47]
Lymphodepletion treatment	Treatment with drugs like fludarabine and cyclophosphamide is necessary.	Lymphodepletion is not required.
Loss of Target Antigen	More risk.[22]	Lesser risk. Targeting different antigens sequentially or simultaneously can potentially overcome antigenic shifting.[22]
FDA Approval	Idecaptagene vicleucel (ide-cel/ABECMA): March 27, 2021 Ciltacabtagene autoleucel (cilta-cel/CARVYKTI): February 28, 2022	Teclistamab-cqyv (TECVAYLI): October 25, 2022 Talquetamab-tgvs (TALVEY): August 9, 2023.[48]
Treatment cost	High (around $500,000 per treatment).[20]	High (around $2,000 per unit, $500,00 per year of QW dosing).[49]

CAR: Chimeric antigen receptor; BiTE: Bispecific T-cell Engagers; scFv: Single chain fragment variable; MM: Multiple Myeloma; FDA: Food and Drug Administration; QW: Once weekly; Q2W: every-other-week

syndrome (CRS), neurotoxicity such as immune effector cell-associated neurotoxicity syndrome (ICANS), cytopenia, and so on. To minimize the incidence of CRS, the European Myeloma Network recommends using corticosteroids, antihistamines, and antipyretic drugs as a premedication regimen.[43] They also advise step-up dosing for several BsAbs and some CAR T-cell therapies, using tocilizumab and assessing patients twice daily. Other anti-IL-6 drugs, high-dose corticosteroids, and anakinra might be considered in refractory cases. Neurological evaluation is recommended every 8 hours, and ICANS is managed with steroids, anakinra, and anticonvulsants if convulsions occur. Preventive measures against infections include antiviral and antibacterial drugs and administration of immunoglobulins.[35] These side effects are more pronounced in CAR T-cells than in BiTE therapy. Due to this and the requirement of a conditioning regimen, CAR T-cell therapy is less preferred in patients over 75 years.[16]

Unlike BiTE therapy, CAR T-cell therapy poses additional challenges, including the inability to quickly halt treatment for severe adverse effects, high cost per quality-adjusted life years (QALY), logistic complexities, and a manufacturing failure risk of less than 10%.[44, 45] This is because much time is required for engineering and lymphodepletion before infusion.

Table 2: Comparison of efficacy and safety profile

Features	CAR T-cell therapy	BiTE therapy
Neurotoxicity risk	Higher risk Ide-cel: 15%; (G3/4=3%)[28] 18%; (G3/4=6%)[50] Cilta-cel=21.6%[51]	Lesser risk Teclistamab: 9 ICANS events (all gr 1/2; all resolved) in 3% i.e., 5 patients Neurotoxic events in 14.5% of patients[36] Talquetamab ICANS 11% Elranatamab ICANS (3.4%)[41]
Other adverse effects	Ide-cel Neutropenia in 117 patients (91%), anemia in 89 (70%), and thrombocytopenia in 81 (63%)[24] Cilta-cel Neutropenia 95.9% Anemia 81.4% Thrombocytopenia 79.4% Fatigue 37.1% Other: cough, transaminitis, GI side effects, dyselectrolytemia	Teclistamab Neutropenia 72%; grade 3 or 4, 65% Anemia 54%; grade 3 or 4, 38% Thrombocytopenia 42%; grade 3 or 4, 22% Infections 78%; grade 3 or 4, 52% Talquetamab (QW, Q2W) Skin-related AEs (56%, 71%) Nail-related AEs (54%, 53%), Dysgeusia (50%, 48%) Infections (58%, 65%); grade 3/4: (22%, 16%) Elranatamab Anemia (56%), Neutropenia (53%), Thrombocytopenia (33%), Lymphopenia (32%) Fatigue 40% G3/4, 3% Infections 61.8% (G3/4: 31.7%) Peripheral neuropathy 17.1%[41]
Median duration of response (mDOR)	Ide-cel: 10.7 mo[24] Cilta-cel: not reached at 27 mo	Teclistamab: 24 mo[52] Talquetamab QW: 9.5 mo Q2W: not reached at 6 mo
ORR	Ide-cel: 73%;[24] 84%[50] cilta-cel: 97.9%	Teclistamab: 63%[52] Talquetamab QW: 74% Q2W: 73% Elranatamab (n=123): 61-64%[41]
mPFS (and mOS)	Ide-cel: 8.8 mo[24] Cilta-cel: not reached at 27 mo[51]	Teclistamab: 12.5 mo (OS 21.9 mo)[52] Talquetamab QW: 7.5 mo Q2W: 11.9 mo Elranatamab: not reached at 15 mo[41]
Complete response (CR) and stringent complete response (sCR)	Ide-cel: 33%;[24] 42%[50] Cilta-cel: sCR rate was 82.5% (no patient was CR only.)	Teclistamab=43%[52] Talquetamab: very good partial response or better (≥VGPR) in 59% (QW) and 57% (Q2W) Elranatamab: CR=19.5%; sCR=15.4%[41]

CAR: Chimeric antigen receptor; BiTE: Bispecific T-cell Engagers; ICANS: immune effector cell-associated neurotoxicity syndrome; QW: once weekly; G3/4: Grade 3 or 4; Q2W: every-other-week; ORR: overall response rate; mPFS: median progression-free survival; mOS: median overall survival; VGPR: Very good partial response

Although there are similarities between CAR T-cell therapy and BiTE therapy, including activating T-cells against tumor cells, often targeting BCMA, and having similar side effects such as grade 1/2 CRS, fatigue, cytopenia, and neurotoxicity, these therapies differ in many ways (tables 1 and 2).

Conclusion

MM is an incurable cancer of bone marrow plasma cells that produces a lot of antibodies or proteins that damage various organs, particularly the kidneys and bones. CAR T-cell and BiTE therapies targeting BCMA have dramatically changed the treatment in the past few years in patients with R/R MM. BiTE therapy provides an off-the-shelf approach, whereas CAR T-cell therapy necessitates weeks of cell engineering and lymphodepletion before infusion, posing challenges in patients requiring urgent treatment. Ongoing research suggests the potential for rapid CAR T-cell production, enhancing accessibility and efficacy for their usage in the early stages of MM. Resistance to these therapies remains a significant challenge, and ongoing clinical trials are aiming to overcome it by combining two different CAR T-cells to target multiple different antigens (e.g., SLAMF7, CD138, GPRC5D) and also combining these with multiple standard therapies to increase their effectiveness. The impact of these therapies, whether implemented individually or in combination with the standard of care, can reshape the patient outcomes in MM, presenting possibilities for better results for those under care.

Authors' Contribution

R.N., P.F., and V.K.: Conceptualization, Data acquisition following literature review, original draft writing; J.V. and R.B.G.: Conceptualization, Final paper editing, and proofreading; R.J.: Conceptualization, Methodology, Supervision, Reviewing and editing of the manuscript. All authors have reviewed and approved the manuscript's final draft and consented to be accountable for all aspects of the work, ensuring that any questions regarding the accuracy or integrity of any part of the work are appropriately addressed and resolved.

Conflict of Interest: None declared.

References

1 Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and Management of Multiple Myeloma: A Review. JAMA. 2022;327:464-77. doi: 10.1001/jama.2022.0003. PubMed PMID: 35103762.

2 Padala SA, Barsouk A, Barsouk A, Rawla P, Vakiti A, Kolhe R, et al. Epidemiology, Staging, and Management of Multiple Myeloma. Med Sci (Basel). 2021;9. doi: 10.3390/medsci9010003. PubMed PMID: 33498356; PubMed Central PMCID: PMCPMC7838784.

3 Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95:548-67. doi: 10.1002/ajh.25791. PubMed PMID: 32212178.

4 Janssens R, Lang T, Vallejo A, Galinsky J, Plate A, Morgan K, et al. Patient Preferences for Multiple Myeloma Treatments: A Multinational Qualitative Study. Front Med (Lausanne). 2021;8:686165. doi: 10.3389/fmed.2021.686165. PubMed PMID: 34295912; PubMed Central PMCID: PMCPMC8289885.

5 Zhang X, Zhu L, Zhang H, Chen S, Xiao Y. CAR-T Cell Therapy in Hematological Malignancies: Current Opportunities and Challenges. Front Immunol. 2022;13:927153. doi: 10.3389/fimmu.2022.927153. PubMed PMID: 35757715; PubMed Central PMCID: PMCPMC9226391.

6 Soekojo CY, Chng WJ. Treatment horizon in multiple myeloma. Eur J Haematol. 2022;109:425-40. doi: 10.1111/ejh.13840. PubMed PMID: 35880395.

7 Mikkilineni L, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for multiple myeloma. Blood. 2017;130:2594-602. doi: 10.1182/blood-2017-06-793869. PubMed PMID: 28928126; PubMed Central PMCID: PMCPMC5731088.

8 Carpenter RO, Evbuomwan MO, Pittaluga S, Rose JJ, Raffeld M, Yang S, et al. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. Clin Cancer Res. 2013;19:2048-60. doi: 10.1158/1078-0432.CCR-12-2422. PubMed PMID: 23344265; PubMed Central PMCID: PMCPMC3630268.

9 Bu DX, Singh R, Choi EE, Ruella M, Nunez-Cruz S, Mansfield KG, et al. Pre-clinical validation of B cell maturation antigen (BCMA) as a target for T cell immunotherapy of multiple myeloma. Oncotarget. 2018;9:25764-80. doi: 10.18632/oncotarget.25359. PubMed PMID: 29899820; PubMed Central PMCID: PMCPMC5995247.

10 van de Donk N, Usmani SZ, Yong K. CAR T-cell therapy for multiple myeloma: state of the art and prospects. Lancet Haematol.

2021;8:e446-e61. doi: 10.1016/S2352-3026(21)00057-0. PubMed PMID: 34048683.
11 Perez P, Hoffman RW, Shaw S, Bluestone JA, Segal DM. Specific targeting of cytotoxic T cells by anti-T3 linked to anti-target cell antibody. Nature. 1985;316:354-6. doi: 10.1038/316354a0. PubMed PMID: 3160953.
12 Brinkmann U, Kontermann RE. The making of bispecific antibodies. MAbs. 2017;9:182-212. doi: 10.1080/19420862.2016.1268307. PubMed PMID: 28071970; PubMed Central PMCID: PMCPMC5297537.
13 Einsele H, Borghaei H, Orlowski RZ, Subklewe M, Roboz GJ, Zugmaier G, et al. The BiTE (bispecific T-cell engager) platform: Development and future potential of a targeted immuno-oncology therapy across tumor types. Cancer. 2020;126:3192-201. doi: 10.1002/cncr.32909. PubMed PMID: 32401342.
14 Du J, Zhuang J. Major advances in the treatment of multiple myeloma in American Society of Hematology annual meeting 2020. Chronic Dis Transl Med. 2021;7:220-6. doi: 10.1016/j.cdtm.2021.08.003. PubMed PMID: 34786541; PubMed Central PMCID: PMCPMC8579022.
15 Teoh PJ, Chng WJ. CAR T-cell therapy in multiple myeloma: more room for improvement. Blood Cancer J. 2021;11:84. doi: 10.1038/s41408-021-00469-5. PubMed PMID: 33927192; PubMed Central PMCID: PMCPMC8085238.
16 Kegyes D, Constantinescu C, Vrancken L, Rasche L, Gregoire C, Tigu B, et al. Patient selection for CAR T or BiTE therapy in multiple myeloma: Which treatment for each patient? J Hematol Oncol. 2022;15:78. doi: 10.1186/s13045-022-01296-2. PubMed PMID: 35672793; PubMed Central PMCID: PMCPMC9171942.
17 Wang Z, Chen C, Wang L, Jia Y, Qin Y. Chimeric antigen receptor T-cell therapy for multiple myeloma. Front Immunol. 2022;13:1050522. doi: 10.3389/fimmu.2022.1050522. PubMed PMID: 36618390; PubMed Central PMCID: PMCPMC9814974.
18 Choi T, Kang Y. Chimeric antigen receptor (CAR) T-cell therapy for multiple myeloma. Pharmacol Ther. 2022;232:108007. doi: 10.1016/j.pharmthera.2021.108007. PubMed PMID: 34582835; PubMed Central PMCID: PMCPMC8930424.
19 Rendo MJ, Joseph JJ, Phan LM, DeStefano CB. CAR T-Cell Therapy for Patients with Multiple Myeloma: Current Evidence and Challenges. Blood Lymphat Cancer. 2022;12:119-36. doi: 10.2147/BLCTT.S327016. PubMed PMID: 36060553; PubMed Central PMCID: PMCPMC9439649.
20 Alhallak K, Sun J, Jeske A, Park C, Yavner J, Bash H, et al. Bispecific T Cell Engagers for the Treatment of Multiple Myeloma: Achievements and Challenges. Cancers (Basel). 2021;13. doi: 10.3390/cancers13122853. PubMed PMID: 34201007; PubMed Central PMCID: PMCPMC8228067.
21 Yu B, Jiang T, Liu D. BCMA-targeted immunotherapy for multiple myeloma. J Hematol Oncol. 2020;13:125. doi: 10.1186/s13045-020-00962-7. PubMed PMID: 32943087; PubMed Central PMCID: PMCPMC7499842.
22 Cho SF, Yeh TJ, Anderson KC, Tai YT. Bispecific antibodies in multiple myeloma treatment: A journey in progress. Front Oncol. 2022;12:1032775. doi: 10.3389/fonc.2022.1032775. PubMed PMID: 36330495; PubMed Central PMCID: PMCPMC9623099.
23 Mullard A. FDA approves first CAR T therapy. Nat Rev Drug Discov. 2017;16:669. doi: 10.1038/nrd.2017.196. PubMed PMID: 28959944.
24 Munshi NC, Anderson LD, Jr., Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021;384:705-16. doi: 10.1056/NEJMoa2024850. PubMed PMID: 33626253.
25 Vogl DT, Dingli D, Cornell RF, Huff CA, Jagannath S, Bhutani D, et al. Selective Inhibition of Nuclear Export With Oral Selinexor for Treatment of Relapsed or Refractory Multiple Myeloma. J Clin Oncol. 2018;36:859-66. doi: 10.1200/JCO.2017.75.5207. PubMed PMID: 29381435; PubMed Central PMCID: PMCPMC6905485.
26 Chari A, Vogl DT, Gavriatopoulou M, Nooka AK, Yee AJ, Huff CA, et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. N Engl J Med. 2019;381:727-38. doi: 10.1056/NEJMoa1903455. PubMed PMID: 31433920.
27 Martin T, Usmani SZ, Berdeja JG, Agha M, Cohen AD, Hari P, et al. Ciltacabtagene Autoleucel, an Anti-B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CARTITUDE-1 2-Year Follow-Up. J Clin Oncol. 2023;41:1265-74. doi: 10.1200/JCO.22.00842. PubMed PMID: 35658469; PubMed Central PMCID: PMCPMC9937098.
28 Rodriguez-Otero P, Ailawadhi S, Arnulf B, Patel K, Cavo M, Nooka AK, et al. Idecel or Standard Regimens in Relapsed

and Refractory Multiple Myeloma. N Engl J Med. 2023;388:1002-14. doi: 10.1056/NEJMoa2213614. PubMed PMID: 36762851.
29 Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398:314-24. doi: 10.1016/S0140-6736(21)00933-8. PubMed PMID: 34175021.
30 Martin T, Usmani SZ, Schecter JM, Vogel M, Jackson CC, Deraedt W, et al. Matching-adjusted indirect comparison of efficacy outcomes for ciltacabtagene autoleucel in CARTITUDE-1 versus idecabtagene vicleucel in KarMMa for the treatment of patients with relapsed or refractory multiple myeloma. Curr Med Res Opin. 2021;37:1779-88. doi: 10.1080/03007995.2021.1953456. PubMed PMID: 34256668.
31 Bishop MR, Dickinson M, Purtill D, Barba P, Santoro A, Hamad N, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. N Engl J Med. 2022;386:629-39. doi: 10.1056/NEJMoa2116596. PubMed PMID: 34904798.
32 Kamdar M, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet. 2022;399:2294-308. doi: 10.1016/S0140-6736(22)00662-6. PubMed PMID: 35717989.
33 Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022;386:640-54. doi: 10.1056/NEJMoa2116133. PubMed PMID: 34891224.
34 San-Miguel J, Dhakal B, Yong K, Spencer A, Anguille S, Mateos MV, et al. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. N Engl J Med. 2023;389:335-47. doi: 10.1056/NEJMoa2303379. PubMed PMID: 37272512.
35 Topp MS, Duell J, Zugmaier G, Attal M, Moreau P, Langer C, et al. Anti-B-Cell Maturation Antigen BiTE Molecule AMG 420 Induces Responses in Multiple Myeloma. J Clin Oncol. 2020;38:775-83. doi: 10.1200/JCO.19.02657. PubMed PMID: 31895611.
36 Moreau P, Garfall AL, van de Donk N, Nahi H, San-Miguel JF, Oriol A, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2022;387:495-505. doi: 10.1056/NEJMoa2203478. PubMed PMID: 35661166; PubMed Central PMCID: PMCPMC10587778.
37 Chari A, Minnema MC, Berdeja JG, Oriol A, van de Donk N, Rodriguez-Otero P, et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. N Engl J Med. 2022;387:2232-44. doi: 10.1056/NEJMoa2204591. PubMed PMID: 36507686.
38 Cohen YC, Moreau P, Tolbert J, Qin X, Ma X, Vieyra D, et al. MonumenTAL-3: Phase 3 trial of talquetamab+ daratumumab±pomalidomide versus daratumumab+ pomalidomide+ dexamethasone in relapsed/refractory multiple myeloma following≥ 1 prior line of therapy. Blood. 2022;140:4418-9. doi: 10.1182/blood-2022-162733.
39 Lesokhin AM, Richter J, Trudel S, Cohen AD, Spencer A, Forsberg PA, et al. Enduring responses after 1-year, fixed-duration cevostamab therapy in patients with relapsed/refractory multiple myeloma: early experience from a phase I study. Blood. 2022;140:4415-7. doi: 10.1182/blood-2022-157547.
40 Mohty M, Tomasson MH, Arnulf B, Bahlis NJ, Rodríguez-Otero P, Martinez-Lopez J, et al. S196: Elranatamab, A B-Cell Maturation Antigen (BCMA)-Cd3 Bispecific Antibody, For Patients with Relapsed/Refractory Multiple Myeloma: Extended Follow Up and Biweekly Administration from Magnetismm-3. HemaSphere. 2023;7:e1309654. doi: 10.1097/01.hs9.0000967696.13096.54.
41 Bahlis NJ, Tomasson MH, Mohty M, Niesvizky R, Nooka AK, Manier S, et al. Efficacy and safety of elranatamab in patients with relapsed/refractory multiple myeloma naïve to B-cell maturation antigen (BCMA)-directed therapies: results from cohort a of the magnetismm-3 study. Blood. 2022;140:391-3. doi: 10.1182/blood-2022-162440.
42 Kumar S, Bachier CR, Cavo M, Corradini P, Delforge M, Janowski W, et al. CAMMA 2: A phase I/II trial evaluating the efficacy and safety of cevostamab in patients with relapsed/refractory multiple myeloma (RRMM) who have triple-class refractory disease and have received a prior anti-B-cell maturation antigen (BCMA) agent. American Society of Clinical Oncology. 2023. doi: 10.1200/JCO.2023.41.16_suppl.TPS8064.
43 Ludwig H, Terpos E, van de Donk N, Mateos

MV, Moreau P, Dimopoulos MA, et al. Prevention and management of adverse events during treatment with bispecific antibodies and CAR T cells in multiple myeloma: a consensus report of the European Myeloma Network. Lancet Oncol. 2023;24:e255-e69. doi: 10.1016/S1470-2045(23)00159-6. PubMed PMID: 37269857.

44 Kapinos KA, Hu E, Trivedi J, Geethakumari PR, Kansagra A. Cost-Effectiveness Analysis of CAR T-Cell Therapies vs Antibody Drug Conjugates for Patients with Advanced Multiple Myeloma. Cancer Control. 2023;30:10732748221142945. doi: 10.1177/10732748221142945. PubMed PMID: 36651055; PubMed Central PMCID: PMCPMC9869188.

45 Subklewe M. BiTEs better than CAR T cells. Blood Adv. 2021;5:607-12. doi: 10.1182/bloodadvances.2020001792. PubMed PMID: 33496755; PubMed Central PMCID: PMCPMC7839370.

46 Du Z, Zhu S, Zhang X, Gong Z, Wang S. Non-Conventional Allogeneic Anti-BCMA Chimeric Antigen Receptor-Based Immune Cell Therapies for Multiple Myeloma Treatment. Cancers (Basel). 2023;15. doi: 10.3390/cancers15030567. PubMed PMID: 36765526; PubMed Central PMCID: PMCPMC9913487.

47 Usmani SZ, Karlin L, Benboubker L, Nahi H, San-Miguel J, Trancucci D, et al. Durability of responses with biweekly dosing of teclistamab in patients with relapsed/refractory multiple myeloma achieving a clinical response in the majesTEC-1 study. American Society of Clinical Oncology. 2023. doi: 10.1016/S2152-2650(23)01410-6.

48 Center for Drug Evaluation and Research [Internet]. Talquetamab-tgvs for relapsed or refractory multiple myeloma. U.S. Food and Drug Administration. [Cited 10 August 2023]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-talquetamab-tgvs-relapsed-or-refractory-multiple-myeloma

49 Hua G, Scanlan R, Straining R, Carlson DS. Teclistamab-cqyv: The First Bispecific T-Cell Engager Antibody for the Treatment of Patients With Relapsed or Refractory Multiple Myeloma. J Adv Pract Oncol. 2023;14:163-71. doi: 10.6004/jadpro.2023.14.2.7. PubMed PMID: 37009408; PubMed Central PMCID: PMCPMC10062534.

50 Hansen DK, Sidana S, Peres LC, Colin Leitzinger C, Shune L, Shrewsbury A, et al. Idecabtagene Vicleucel for Relapsed/Refractory Multiple Myeloma: Real-World Experience From the Myeloma CAR T Consortium. J Clin Oncol. 2023;41:2087-97. doi: 10.1200/JCO.22.01365. PubMed PMID: 36623248; PubMed Central PMCID: PMCPMC10082273.

51 van de Donk NWCJ, Garfall A, Benboubker L, Uttervall K, Groen K, Rosiñol Dachs L, et al. P911: Evaluation of Prophylactic Tocilizumab (TOCI) For the Reduction of Cytokine Release Syndrome (CRS) To Inform the Management of Patients (Pts) Treated with Teclistamab In Majestec-1. HemaSphere. 2023;7:e43149cb. doi: 10.1097/01.HS9.0000970548.43149.cb.

52 van de Donk NW, Moreau P, Garfall AL, Bhutani M, Oriol A, Nooka AK, et al. Long-term follow-up from MajesTEC-1 of teclistamab, a B-cell maturation antigen (BCMA) x CD3 bispecific antibody, in patients with relapsed/refractory multiple myeloma (RRMM). American Society of Clinical Oncology. 2023. doi: 10.1016/S2152-2650(23)00857-1.