CAR T-Cell Therapy in Multiple Myeloma

Angelo Maiolino[1*], Mariana Nassif Kerbauy[2], Roberto José Pessoa de Magalhães[3], Fernando Vieira Pericole de Souza[4,9], João Tadeu Damian Souto Filho[5], Edvan de Queiroz Crusoé[6], Abrahão Elias Hallack Neto[7], Vânia Tietsche de Moraes Hungria[8]

1. Universidade Federal do Rio de Janeiro – Departamento de Clínica Médica – Rio de Janeiro (RJ), Brazil.
2. Hospital Israelita Albert Einstein – São Paulo (SP), Brazil.
3. Universidade Federal do Rio de Janeiro – Departamento de Hematologia – Rio de Janeiro (RJ), Brazil.
4. Universidade Estadual de Campinas – Hemocentro – Campinas (SP), Brazil.
5. Faculdade de Medicina de Campos – Campos dos Goytacazes (RJ), Brazil.
6. Universidade Federal da Bahia – Departamento de Medicina Interna – Salvador (BA), Brazil.
7. Universidade Federal de Juiz de Fora – Departamento de Clínica Médica – Juiz de Fora (BH), Brazil.
8. Clinica São Germano – São Paulo (SP), Brazil.
9. Universidade de São Paulo – Faculdade de Medicina – Bauru (SP), Brazil.

***Corresponding author:** angelomaiolino@gmail.com

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ABSTRACT

The introduction of CAR (chimeric antigen receptor) T-cell therapy into clinical practice has revolutionized the treatment landscape of relapsed/refractory multiple myeloma (RRMM). At present, two B-cell maturation antigen (BCMA)-targeted CAR T-cell therapies, idecabtagene vicleucel and ciltacabtagene autoleucel, are used in clinical practice, but only ciltacabtagene autoleucel is approved in Brazil. In this review, we explore the advantages and challenges of integrating CAR T-cell therapy earlier in the RRMM treatment course.

Keywords: Car-T cell; Immunotherapy; Multiple myeloma.

INTRODUCTION

Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by the uncontrolled proliferation of malignant plasma cells within the bone marrow microenvironment, resulting in bone destruction, anemia, renal dysfunction, hypercalcemia, and progressive immune dysregulation. Over the past two decades, major therapeutic advances have substantially improved outcomes for patients with multiple myeloma. The introduction of proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies has transformed treatment strategies and significantly prolonged survival. Despite these advances, multiple myeloma remains largely incurable, and most patients ultimately experience disease relapse after successive lines of therapy. Patients who become refractory to these three principal drug classes—proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies—historically have had poor outcomes and limited treatment options.[1,2]

High-dose melphalan followed by autologous hematopoietic cell transplantation (HCT) continues to represent a cornerstone of therapy for transplant-eligible patients with newly diagnosed disease and remains an important component of modern treatment algorithms. Nevertheless, even with contemporary

induction regimens and maintenance strategies, relapse remains inevitable for most patients. Consequently, the development of novel immunotherapeutic approaches capable of inducing deeper and more durable responses has become a major focus of research in multiple myeloma.[1]

Among emerging immunotherapeutic strategies, therapies targeting B-cell maturation antigen (BCMA) have demonstrated particularly promising clinical activity. BCMA is a member of the tumor necrosis factor receptor superfamily that plays a critical role in plasma cell survival and differentiation. Importantly, BCMA expression is largely restricted to plasma cells and malignant myeloma cells, with minimal expression in other tissues, making it an attractive and highly specific therapeutic target.[3] BCMA signaling promotes plasma cell survival through interactions with its ligands APRIL and BAFF within the bone marrow microenvironment, further supporting the biological rationale for therapeutic targeting.

Several BCMA-directed therapeutic platforms have been developed in recent years, including antibody-drug conjugates, bispecific antibodies, and chimeric antigen receptor (CAR) T-cell therapies. Among these approaches, CAR-T therapy has demonstrated particularly profound antitumor activity and has emerged as one of the most transformative therapeutic advances in the management of relapsed or refractory multiple myeloma.[3]

CAR-T therapy involves the collection of autologous T lymphocytes through leukapheresis followed by genetic modification to express a synthetic receptor capable of recognizing tumor-associated antigens. The CAR construct typically consists of an extracellular antigen-binding domain derived from a monoclonal antibody, a transmembrane domain, and intracellular signaling domains that activate T-cell cytotoxic function upon antigen recognition. Following genetic modification and ex vivo expansion, CAR-T cells are reinfused into the patient after lymphodepleting chemotherapy, most commonly consisting of fludarabine and cyclophosphamide. This preparative regimen enhances CAR-T expansion by reducing competing lymphocytes and increasing cytokine availability. Once infused, CAR-T cells undergo rapid in vivo expansion and can mediate potent cytotoxic activity against malignant plasma cells expressing BCMA.[4]

MATERIALS AND METHODS

Literature review on BCMA-targeted chimeric antigen receptor (CAR) T-cell therapy for relapsed/refractory multiple myeloma using the two main available agents: idecabtagene vicleucel and ciltacabtagene autoleucel.

RESULTS/ DISCUSSION

The first CAR-T therapy approved for multiple myeloma was idecabtagene vicleucel (ide-cel), based on the phase II KarMMa study. In this trial, patients with relapsed or refractory multiple myeloma who had previously received a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody were treated with ide-cel. The overall response rate reached approximately 73%, with complete responses observed in approximately one-third of patients. Minimal residual disease (MRD) negativity was achieved in a substantial proportion of responders, and the median progression-free survival was 8.8 months.[5]

Subsequently, the randomized phase III KarMMa-3 study evaluated ide-cel in patients with relapsed disease who had received two to four prior lines of therapy. In this study, ide-cel significantly improved outcomes compared with standard-of-care regimens. Median progression-free survival was 13.3 months in the ide-cel arm compared with 4.4 months in the control group, confirming the clinical benefit of CAR-T therapy in this patient population.[6]

A second BCMA-directed CAR-T therapy, ciltacabtagene autoleucel (cilta-cel), has demonstrated particularly remarkable efficacy in clinical trials. Cilta-cel incorporates two BCMA-binding domains designed to enhance antigen-binding avidity, potentially contributing to the profound antitumor activity observed in clinical studies.[7]

The pivotal phase Ib/II CARTITUDE-1 trial evaluated cilta-cel in heavily pretreated patients with relapsed or refractory multiple myeloma who had received a median of six prior lines of therapy. Treatment with cilta-cel

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resulted in an overall response rate of approximately 97%, representing one of the highest response rates ever reported in relapsed myeloma. Deep responses were frequently observed, with stringent complete responses achieved in approximately 67% of patients. Importantly, MRD negativity at a sensitivity of 10^{-5} was achieved in the majority of patients achieving complete response.[7,8]

Initial analyses demonstrated a 12-month progression-free survival rate of approximately 77% and an overall survival rate approaching 89%. Long-term follow-up of CARTITUDE-1 has confirmed the remarkable durability of these responses. With follow-up exceeding five years, median progression-free survival has reached approximately 34–35 months, while median overall survival approaches 60 months.[9] Notably, long-term survival analyses demonstrate a plateau in the progression-free survival curve, suggesting that a subset of patients may achieve prolonged disease control after a single CAR-T infusion. Approximately one-third of treated patients remain progression-free five years after treatment without additional therapy, an unprecedented finding in heavily pretreated multiple myeloma. These observations have generated considerable interest in the possibility that CAR-T therapy may achieve long-term remission or functional cure in selected patients.[9]

Encouraged by these results, CAR-T therapy has been evaluated earlier in the disease course. The phase III CARTITUDE-4 trial investigated cilta-cel in patients with lenalidomide-refractory multiple myeloma who had received one to three prior lines of therapy. In this randomized study, cilta-cel demonstrated significantly superior efficacy compared with standard-of-care regimens consisting of pomalidomide- or daratumumab-based combinations. The overall response rate exceeded 84% in the CAR-T arm compared with approximately 67% in the control group. Deep responses were also significantly more frequent with CAR-T therapy, with complete response rates approaching 73% compared with approximately 22% in the control arm.[10] Minimal residual disease negativity rates exceeded 60% among patients treated with cilta-cel compared with approximately 15% in the standard therapy group (8,10). Median progression-free survival was not reached in the CAR-T arm, whereas it was 11.8 months in the control arm, corresponding to a hazard ratio of approximately 0.26 and representing a 74% reduction in the risk of disease progression or death.[10] Overall survival also favored cilta-cel (HR 0.55; 95% CI, 0.39–0.79).[11] These findings strongly support the integration of CAR-T therapy earlier in the treatment algorithm of multiple myeloma.

An important practical aspect of CAR-T therapy is the use of bridging therapy. Because the manufacturing process for autologous CAR-T products typically requires several weeks, disease progression may occur between leukapheresis and CAR-T infusion. Bridging therapy is therefore frequently used to maintain disease control during this interval.[12] Bridging regimens are individualized according to disease aggressiveness, prior therapies, patient characteristics and the planned collection and infusion dates. Common strategies include proteasome inhibitor-based combinations, immunomodulatory drugs, corticosteroids, monoclonal antibodies, or localized radiotherapy.

Despite its remarkable efficacy, CAR-T therapy is associated with unique toxicities that require specialized management. Cytokine release syndrome (CRS) is the most common complication and results from rapid immune activation and cytokine release following CAR-T infusion. CRS typically presents with fever, hypotension, and hypoxia within the first few days following treatment and can be effectively managed with supportive care and anti-interleukin-6 therapy such as tocilizumab.[13]

Neurological toxicity may occur early after CAR-T infusion and is referred to as immune effector cell-associated neurotoxicity syndrome (ICANS). In addition to early neurotoxicity, delayed neurological events have been described following BCMA-directed CAR-T therapy, particularly with cilta-cel. These events may occur several weeks after infusion and have been described as movement and neurocognitive treatment-emergent adverse events.[14]

Prolonged or recurrent cytopenias, hypogammaglobulinemia, and serious infections can extend well beyond initial recovery. Patients will need immunoglobulin replacement for a while, besides antimicrobial prophylaxis, revaccination planning, and close hematologic and infectious monitoring.[15]

In addition to CAR-T therapy, BCMA-directed bispecific antibodies such as teclistamab and elranatamab have demonstrated substantial clinical activity in patients with relapsed or refractory multiple myeloma. These agents redirect endogenous T cells toward malignant plasma cells through simultaneous binding to BCMA and CD3.[16,17] Clinical trials evaluating these therapies have reported overall response rates ranging from approximately 60% to 70% in heavily pretreated patients. Unlike CAR-T therapy, bispecific antibodies are available as off-the-shelf treatments and do not require individualized manufacturing, an advantage when prompt disease control is needed. This convenience must be considered alongside repeated dosing and their distinct toxicity profile, including higher infection risk. By contrast, a single CAR T-cell infusion may provide a prolonged treatment-free interval, although leukapheresis, manufacturing, lymphodepletion, and specialized care are required. The optimal sequence of CAR-T cells and bispecific antibodies, particularly after prior BCMA-directed treatment, remains unsettled.

CONCLUSION

The therapeutic landscape of multiple myeloma continues to evolve rapidly. BCMA-directed CAR T-cell therapy has reshaped the treatment of RRMM, with randomized evidence supporting its use earlier in relapse and the possibility of prolonged treatment-free remission after a single infusion. Timely referral, disease control during the interval before infusion, and long-term monitoring for toxicity are necessary for safe and effective use. Further studies and longer follow-up are needed to determine whether deep responses and durable remissions will translate into cure for a subset of patients.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data will be available upon request.

AUTHOR´S CONTRIBUTIONS

Conceptualization: Maiolino A, Kerbauy MN, Magalhães RJP, Souza FVP, Souto Filho JTD, Crusoé EQ, Hallack Neto AE, Hungria VT; **Investigation:** Maiolino A, Kerbauy MN, Magalhães RJP, Souza FVP, Souto Filho JTD, Crusoé EQ, Hallack Neto AE, Hungria VT; **Methodology:** Maiolino A, Kerbauy MN, Magalhães RJP, Souza FVP, Souto Filho JTD, Crusoé EQ, Hallack Neto AE, Hungria VT; **Formal Analysis:** Maiolino A, Kerbauy MN, Magalhães RJP, Souza FVP, Souto Filho JTD, Crusoé EQ, Hallack Neto AE, Hungria VT; **Data Curation:** Maiolino A, Kerbauy MN, Magalhães RJP, Souza FVP, Souto Filho JTD, Crusoé EQ, Hallack Neto AE, Hungria VT; **Writing:** Maiolino A, Kerbauy MN, Magalhães RJP, Souza FVP, Souto Filho JTD, Crusoé EQ, Hallack Neto AE, Hungria VT; **Final Approval:** Maiolino A, Kerbauy MN, Magalhães RJP, Souza FVP, Souto Filho JTD, Crusoé EQ, Hallack Neto AE, Hungria VT.

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DECLARATION OF USE OF ARTIFCIAL INTELLIGENCE TOOLS

The authors declare that they used the Artificial Intelligence tool (Claude), version [v 5.1231.2], in the preparation, correction, or specific stages of the manuscript production and evaluation process, for [to format the text and improve english language]. All content generated with the help of AI was critically reviewed by the responsible author(s) to ensure its accuracy, integrity, and scientific compliance. No Artificial Intelligence tool was included as an author, nor did it have access to unpublished raw data, except as explicitly described and in accordance with [the standard/policy adopted by the journal].

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