v. 4, n. 74, 2024

International Journal of Health Science

CAR-T CELLS IN THE TREATMENT OF MULTIPLE MYELOMA: RECENT ADVANCES AND PROSPECTS

Rafael Soares Barbosa
Student of medicine course, University: Dom Bosco University: UNDB, Brazil

Antônio Coelho e Silva Neto
Student of medicine course, University: Dom Bosco University: UNDB, Brazil

Roberta Lima Silva
Student of medicine course, University: Dom Bosco University: UNDB, Brazil

Fábio de Almeida Teixeira
Student of medicine course, University: Dom Bosco University: UNDB, Brazil

Victor Botelho de Araújo Faustino
Student of medicine course, University: Dom Bosco University: UNDB, Brazil

Luiz Paulo Barros Leite da Cunha Dias
Student of medicine course, University: Dom Bosco University: UNDB, Brazil

José Nilo Ribeiro Neto
Student of medicine course, University: Dom Bosco University: UNDB, Brazil

José Eduardo Santos Machado
Student of medicine course, University: Dom Bosco University: UNDB, Brazil

Sthefany de Sousa Alves Campos
University: UNDB, Brasil Student of medicine course, University: Dom Bosco

Yasmin Nunes Santos
Student of medicine course, University: Dom Bosco University: UNDB, Brazil

Nicole Peres Soeira
Student of medicine course, University: Dom Bosco University: UNDB, Brazil

Thiago Henrique Ferreira Matos
Student of medicine course, University: Dom Bosco University: UNDB, Brazil

Abstract: Immunotherapy with CAR-T cells (Chimeric Antigen Receptor T Cells) has proven to be a revolutionary approach in the treatment of refractory multiple myeloma. Therapies targeting B cell maturation antigen (BCMA) have demonstrated high efficacy, including in high-risk situations. In this context, several CAR-T therapies focused on BCMA are in clinical development, and their clinical approval is imminent. The research carried out was based on a time frame from 2019 to 2023, all in English, which dealt with the management of traditional and pioneering approaches using CAR-T cells in the treatment of multiple myeloma. Therefore, this literary review made use of recognized books in the health area, as well as the Scientific Electronic Library Online (SciELO) and Pubmed platforms as a basis for all scientific articles used in this research. Therefore, the great perception was that recent years were marked by advances in research into chimeric cell therapy for the treatment of multiple myeloma, due to factors such as legal approvals and discoveries of effective working mechanisms, having already indicated impact on the therapeutic options available for multiple myeloma.
Keywords: CAR-T cells; Therapy; Multiple myeloma; T lymphocytes; BCMA.

INTRODUCTION

Multiple myeloma (MM) is a type of hematological cancer characterized by the uncontrolled and clonal proliferation of plasma cells in the bone marrow. Plasma cells are cells that originate in the bone marrow and play a crucial role in the immune system, producing antibodies that help fight infections and other diseases. The clinical manifestations of MM result from the unrestrained multiplication of malignant plasma cells, excessive production of monoclonal immunoglobulin and suppression of the normal immune defense system (Guedes; Becker; Teixeira, 2023).

Referring to the working mechanisms of excision and manipulation of the body's anti-tumor defense cells, T lymphocytes can be obtained from the blood or areas of tumor infiltration in the patient, and are then multiplied in culture with the help of growth factors. before being reinserted into the same patient who will undergo the targeted treatment in question (Abbas; Pillai; Lichtman, 2019).

These concepts relate to one of the most effective modern treatments targeting multiple myeloma: CAR-T cells. These stand out for having high specificity and potency, culminating in cellular dynamics that prevent the production of toxic effects on patients who use them.

Clinical studies are investigating the possibility of using CAR-T therapies, including as initial treatment in the first instance, in patients with high-risk multiple myeloma (Rendo et al., 2022).

Therefore, as research advances towards discovering new intervention methods in the treatment of multiple myeloma, the results converge towards the use of CAR-T cells. In this sense, this article's central objective is to present recent advances in the field of chimeric T-cells, as well as what is expected from these new therapies and how they can be applied in different pathological contexts of multiple myeloma.

LITERATURE REVIEW

Multiple myeloma is a type of cancer that affects plasma cells in the bone marrow, and traditional treatment methods involve the use of chemotherapy, stem cell transplantation and other interventions that specifically target cancer cells. At this juncture, CAR-T cells appear as the most promising treatment for multiple myeloma in recent years, having this unique character due to recent scientific and legal advances regarding their use.

According to Martino et al. (2021), multiple myeloma has pathophysiological consequences, among others, hypercalcemia, bone destruction, kidney failure and suppression of blood cell production. With this in mind and given the metabolic repercussions of this condition, the great challenge to establishing CAR-T therapy in refractory cases of multiple myeloma scientific advances is the toxicity caused by the action of chimeric cells in the body.

However, available data on anti-BCMA CART cell therapy (BCMA markers: B Cell Maturation Antigen) have demonstrated efficacy and manageable toxicity in patients previously undergoing multiple treatments. The close relationship between CAR-T cells and BCMA receptors is noted, in the sense that the therapy is based on the usefulness that such receptors have in identifying cancer cells idiosyncratic to multiple myeloma, so that they can act directly on their elimination.

BCMA is found at much higher levels in cancerous plasma cells from patients with multiple myeloma compared to normal bone marrow cells from healthy donors. Several studies have investigated whether BCMA can be used as an indicator for diagnosis, prognosis and/or to predict how a patient will respond to treatment. Overexpression and activation of BCMA are linked to the progression of multiple myeloma in laboratory studies and in real patients, making BCMA an attractive therapeutic target (Shah et al., 2020).

According to the American Journal of Hematology (2022), survival in multiple myeloma has improved significantly over the past 15 years, and particularly over the past decade, where chimeric T-antigen receptor therapies have been approved by the Food and Drug Administration (FDA). for the treatment of recurrent multiple myeloma, which promise to further improve treatment results. (Rajkumar, 2022).

Furthermore, the introduction of malleable techniques in which CAR-T cells are useful is of paramount importance and demonstrates positive results in tests carried out over recent years. However, there are still gaps regarding the widespread use of this resource in the treatment of multiple myeloma, since several adverse factors are found in patients who use it - especially because it is the newest and least known and described of the interventions. emerging strategies to combat multiple myeloma.

METHODOLOGY

This is a bibliographical review, of a quantitative nature, which used the platforms PubMed, Scientific Electronic Library On-line (SciELO) and Google Scholar as a database for searching scientific articles. Literature published from 2019 to 2023 was used. Articles from all languages were selected, but only the materials found were in full English language, which addressed advances in the treatment of multiple myeloma through the use of CAR-T cells.

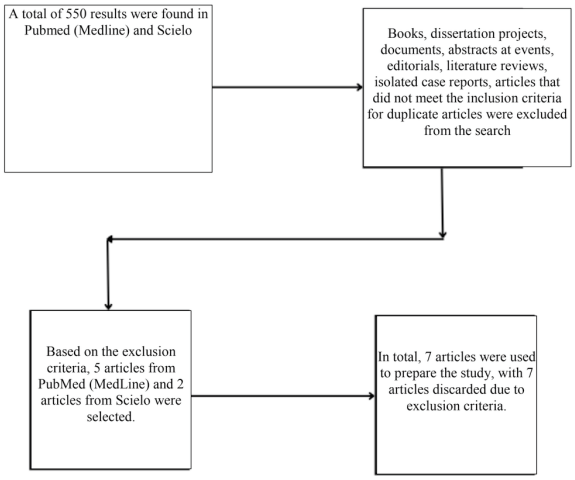
The descriptors used followed the description of the terms DeCs (Health Descriptors) and Medical Subject Headings (MeSH) in the English language, as shown in Table 1.

("CAR-T cell" [MeSH terms] AND "Therapy" [MeSH terms] AND "Multiple Myeloma" [MeSH terms]

Table 1-Search strategy for the study.

Source: Authors (2023)

In this review, the inclusion criteria designed to filter the search were three: "CAR-T cell"; "Therapy" and "Multiple Myeloma". The use of these terms is justified by their relevance to the subject and how the three terms interrelate, but in a non-exclusive way, thus justifying their position as inclusion criteria. The exclusion criteria used were books, dissertation project documents, event summaries, editorials, literature reviews, isolated case reports, articles that did not meet the inclusion criteria and duplicate articles, according to Flowchart 1.



Flowchart 1: Systematization of filtering articles to prepare the study

Source: Authors (2023)

RESULTS AND DISCUSSION

The choice of articles to be used in this review was carried out by reading the title, summary and, finally, reading the article in full, with a careful analysis of the articles based on the aforementioned inclusion and exclusion criteria.

According to the search engine, 505 results were found, in the PubMed database and in the Scielo database (Table 2). There are 503 results in the PubMed database and 02 in the Scielo database. Of the 505 works obtained as a result, 14 articles were selected from the PubMed platform. However, only 5 addressed objective issues and followed the exclusion criteria, so these 5 articles were used in the preparation of the study. Furthermore, 2 works were selected from the Scielo platform, from a universe of 2. The works used in the study will be displayed in Table 2, following the order of year of publication.

TITLE	AUTHOR, YEAR	OBSERVATIONS
Recent updates on CAR T clinical trials for multiple myeloma	LIN et al. 2019	BCMA-targeted CAR T cells have high efficacy in refractory myeloma. CAR T therapies for BCMA are in development. Clinical approval is expected. CAR T for CD138, CS1 and light chains show promise. CAR T for CD19, with autologous transplantation, is active. Dual-target CAR T is evaluated. Cellular immunotherapy must improve myeloma treatment.
CAR T-cell therapy in multiple myeloma: more room for improvement	TEOH; CHNG, 2021	Immunotherapy has evolved from a concept to a practical cancer treatment, revolutionizing therapy in the last decade. CAR-T therapy is a promising option that prolongs survival and remission in B-cell malignancies even after conventional treatments fail.
Brazilian Association of Hematology, Hemotherapy and Cellular Therapy Consensus on genetically modified cells. IV: CAR-T cell therapy for multiple myeloma patients	MAIOLINO et al. 2021	CAR-T cell therapies are crucial for treating hematological malignancies, including myeloma. Initially, recommended after exposure to conventional treatments. Earlier use is being explored, including in high-risk myeloma. The challenge in Brazil is access to public and private systems due to cost. Accurate patient selection is key to success, considering criteria and history. Relevant in the Brazilian scenario where equitable access is challenging.
Chimeric Antigen Receptor (CAR) T cell therapy for multiple myeloma	CHOI; KANG, 2022	Impressive response rates and clinical efficacy in heavily treated myeloma patients led to FDA approval of the first CAR-T therapy for myeloma in March 2021
CAR-T cell therapy for multiple myeloma: a practical toolkit for treatment in Brazil	HUNGRIA et al. 2022	BCMA is a promising target in the treatment of multiple myeloma. Two CAR-T therapies, ide-cel and cilta-cel, targeting BCMA have been approved by the FDA. The KarMMa study evaluated ide-cel in patients with refractory myeloma, with a response rate of 73%, including 33% complete responses, and a median progression-free survival of 8.8 months.
CAR-T cell therapy in multiple myeloma: Current limitations and potential strategies	ZHANG et al. 2023.	Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal proliferation of malignant cells in the bone marrow, accompanied by excessive production of monoclonal immunoglobulin (called M protein) and subsequent organ damage, accounting for approximately 10% of hematological malignancies.
Long-term outcomes following CAR T cell therapy: what we know so far	CAPPEL; KOCHEN-DERFER, 2023.	Chimeric antigen receptors (CAR) are fusion proteins designed to target T cells to antigens expressed on cancer cells. CAR T cells are now an established treatment for patients with relapsed and/or refractory B-cell lymphomas, B-cell acute lymphoblastic leukemia, and multiple myeloma

Table 2: Articles selected from the PubMed and Scielo databases

Source: Authors (2023)

Lin et al. (2019) states that CAR T therapies targeting BCMA show high efficacy in patients with refractory multiple myeloma, and CAR T cell therapy products targeting BCMA are in constant clinical development. Clinical approval of these therapies is expected soon, and CAR T cells targeting CD138, CS1 (SLAMF7) and light chains demonstrate promising results. Furthermore, CAR T cells targeting CD19, when combined with autologous stem cell transplantation, have demonstrated significant activity in the setting of refractory MM.

CAR T cell approaches that target two targets simultaneously are being evaluated in clinical trials for this type of myeloma, with the expectation that advances in cellular immunotherapy will have a significant impact on improving therapeutic options for this purpose. According to Teoh; Chng (2021), the evolution of immunotherapy, from a promising concept to a practical cancer treatment, is visible and palpable. CAR-T therapy with chimeric antigen receptor (CAR) T cells has emerged as a promising option in B-cell malignancies, conferring remarkable results in terms of prolongation of survival and remission.

According to Maiolino et al. (2021), CAR-T therapies are gaining prominence as essential tools in the treatment of hematological malignancies, including multiple myeloma.

Initially, these therapies are recommended for patients who have already undergone proteasome inhibitors, immunomodulators, and anti-CD38 treatments. The possibility of using CAR-T therapies earlier is currently being evaluated, including as initial treatment for high-risk MM patients. However, an important challenge in the Brazilian context will be to ensure access to these therapies, both in the public health system and in private health plans.

Choi; Kang (2022) portrays that CAR-T therapies and their respective innovations require evaluation, especially regarding costs versus clinical benefits. It is worth remembering that careful patient selection is crucial to your success. Furthermore, the approval of CAR T therapy for multiple myeloma was approved by the FDA in 2021, that is, it is a relatively short period since its approval. BCMA is a promising target for treatment, as ide-cel and cilta-cel have also been approved. According to Hungary et al. (2023), of the patients treated, the overall response rate was 73.0%, with 33.0% achieving at least one effective response. The median progression-free survival was 8.8 months.

Adding to this, Zhang et al. (2023) states that MM is a malignancy characterized by the proliferation of excess M protein, causing damage to organs, corresponding to around 10% of hematological malignancies.

For Cappel; Kochenderfer (2023), chimeric antigen receptors (CAR) are designed to direct T cells to antigens on cancer cells. CAR T cells are an established treatment for refractory B-cell lymphomas, B-cell acute lymphoblastic leukemia, and multiple myeloma.

FINAL CONSIDERATIONS

In recent years, CAR-T cell therapy targeting the BCMA antigen has achieved remarkable results in the treatment of multiple myeloma, and the side effects of this treatment can generally be controlled. However, there are still several challenges that need to be addressed. As can be seen, disease relapses continue to occur after anti-BCMA CAR-T cell therapy, and barriers such as high production costs and the time-consuming manufacturing process of CAR-T cells limit their accessibility. Therefore, it is necessary to seek additional improvements in this context.

Therefore, possible therapeutic strategies are being investigated, which include the search for improvement of the structure of the chimeric antigen receptor (CAR) and methods of genetic modification of T cells, the exploration of CAR-T cell therapy directed at multiple targets, in addition combination with other therapeutic approaches. However, advances in science and medicine regarding CAR-T cells are already significant and have already proven useful for treating patients affected by multiple myeloma.

REFERENCES

ALBAGOUSH, S. A.; SHUMWAY, C.; AZEVEDO, A. M. **Multiple Myeloma.** 2023. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30521185/. Acesso em: 12/09/2023.

CAPPEL, K. M.; KOCHENDERFER, J. N. **Long-term outcomes following CAR T cell therapy: what we know so far**. 2023. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10100620/pdf/41571_2023_Article_75 4.pdf. Acesso em: 26/08/2023.

CHOI, T; KANG, Y. **Chimeric Antigen Receptor (CAR) T-cell therapy for multiple myeloma.** 2022. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8930424/pdf/nihms-1745831.pdf. Acesso em: 26/08/2023.

GUEDES, A.; BECKER, R. G.; TEIXEIRA, L. M. E. **Mieloma múltiplo (Parte 1) – Atualização sobre epidemiologia, critérios diagnósticos, tratamento sistêmico e prognóstico.** 2023. Disponível em: https://www.scielo.br/j/rbort/a/r6fGKw4rsScqFw3wHtmHmDh/?format=pdf&lang=pt. Acesso em: 12/09/2023.

HUNGRIA, V. *et al.* **CAR-T cell therapy for multiple myeloma: a practical toolkit for treatment in Brazil.** 2022. Disponível em: https://www.scielo.br/j/htct/a/TtdMdwkzVF4PLGjKmJjDrXz/?lang=en&format=pdf. Acesso em: 26/08/2023.

LIN, Q. *et al.* **Recent updates on CAR T clinical trials for multiple myeloma**. 2019. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6829852/pdf/12943_2019_Article_109 2.pdf. Acesso em: 26/08/2023.

MAIOLINO, A. *et al.* **Associação Brasileira de Hematologia, Hemoterapia e ~ Terapia Celular Consensus on genetically modified cells. IV: CAR-T cell therapy for multiple myeloma patient**s. 2021. Disponível em: https.://www.scielo.br/j/htct/a/KbF4cn7KJFpJcPfn4J6pdDH/?lang=en&format=pdf. Acesso em: 26/08/2023.

MARTINO, M. *et al.* **CART-Cell Therapy: Recent Advances and New Evidence in Multiple Myeloma.** 2021. Disponível em: https://pubmed.ncbi.nlm.nih.gov/34072068/. Acesso em: 12/09/2023.

RAJKUMAR, S. V. American Journal of Hematology. **Multiple myeloma: 2022 update on diagnosis, risk stratification, and management.** 2022. Disponível em: https://onlinelibrary.wiley.com/doi/10.1002/ajh.26590. Acesso em: 12/09/2023.

RENDO, M. J. *et al.* **CAR T-Cell Therapy for Patients with Multiple Myeloma: Current Evidence and Challenges.** 2022. Disponível em: https://pubmed.ncbi.nlm.nih.gov/36060553/. Acesso em: 12/09/2023.

SHAH, N. *et al.* **B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches.** 2020. Disponível em: https://pubmed.ncbi.nlm.nih.gov/32055000/. Acesso em: 12/09/2023.

TEOH, P. J.; CHNG, W. J. **CAR T-cell therapy in multiple myeloma: more room for improvement**. 2021. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8085238/pdf/41408_2021_Article_469. pdf. Acesso em: 26/08/2023.

ZHANG, X.; *et al.* **CAR-T cell therapy in multiple myeloma: Current limitations and potential strategies**. 2023. Disponível em: Frontiers | CAR-T cell therapy in multiple myeloma: Current limitations and potential strategies (frontiersin.org). Acesso em: 26/08/2023.