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THE POTENTIAL ROLE OF CAR-T IN MULTIPLE MYELOMA TREATMENT: A REVIEW

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ABSTRACT

Background: Multiple myeloma (MM) is a hematologic malignancy causing the accumulation of plasma cells in bone marrow. The symptoms of MM are associated with organ dysfunction and include hypercalcemia, renal failure, anemia, and bone destruction. A relatively new and promising therapeutic option for MM is CAR-T therapy.

Aim of the study: This study aimed to outline the role of CAR-T therapy in MM treatment.

Material and methods: We conducted a literature review consisting of 24 articles. We described the role of CAR-T in MM therapy, its therapeutic points, the effectiveness of therapy, and its side effects.

Results: CAR-T cells transduced with CAR can recognize specific antigens and kill the cancer cells. For MM, these specific antigens include integrin β7, SLAMF7, CD138, BCMA, GPRC5D, and FCRL5. Integrin β7, in its active form, can be found in MM cells, whereas in other blood cells, integrin β7 remains in the inactive form. The expression of SLAMF7 on MM cells is high and uniform, but its function is not clear. The expression of SLAMF7 in MM is suspected to increase the survival and adhesion of MM cells to bone marrow stromal cells. CD138's strong expression on MM cells contributes to development and proliferation. BCMA expression was not detected in other human tissues, only in MM cells. GPRC5D is highly expressed in bone marrow samples from MM patients, and minimally expressed in other hematologic malignancies. FCRL5 is a protein marker found specifically on plasma cells in MM, its increased expression promotes B cell proliferation. The AlloCAR-T therapy also seems to be an effective method.
CAR-T therapy has adverse effects, including cytokine release syndrome, neurological toxicities, hematological disorders, and infusion fevers.

Conclusions: The effects of CAR-T therapy in MM are promising and give real benefits to patients. For this reason, it should be further developed and subjected to further research.

KEYWORDS: multiple myeloma, CAR-T, treatment

Background

Multiple myeloma (MM) is a hematologic malignancy triggered by the uncontrolled proliferation and accumulation of clonal plasma cells within the bone marrow. These cells produce monoclonal proteins found in the serum and urine of patients. MM causes organ dysfunction known by the CRAB acronym (hypercalcemia, renal failure, anemia, and bone destruction) [1]. MM accounts for 10% of all hematologic malignancies, its incidence varies from 0.1 per 100,000 to 5.3 per 100,000, depending on the country [2]. The median survival time of MM patients is 5–7 years. For this reason, to improve survival rates, remission rates, and the quality of life of patients, it is important to quickly introduce appropriate treatments (adjusted to the patient's age, condition, and stage of disease) [3,4]. Nowadays, MM treatment includes two or more drugs from the following classes: alkylating agents, corticosteroids, immunomodulatory drugs (e.g., thalidomide), and proteasome inhibitors. Additionally, biological drugs are used, such as daratumumab, elotuzumab, and histone deacetylase inhibitor (panobinostat) or exportin-1 inhibitor (selinexor) [5]. Another treatment option is stem cell transplantation, followed by maintenance therapy [6]. One of the new and interesting potential therapy methods is chimeric antigen receptor (CAR)-T therapy. CAR-T therapy seems to be useful when other methods are not effective. This therapy involves the generation of CAR-T cells from the blood of patients or donors. CAR-T cells, after propagation and genetic modification, are re-administered to patients [7] (Figure 1). A CAR is created by fusing the cancer-specific antigen recognition site of an antibody with co-stimulatory molecules, e.g., CD28. Because cells are transduced with CAR, they can recognize these specific antigens and kill the cancer cells [8].

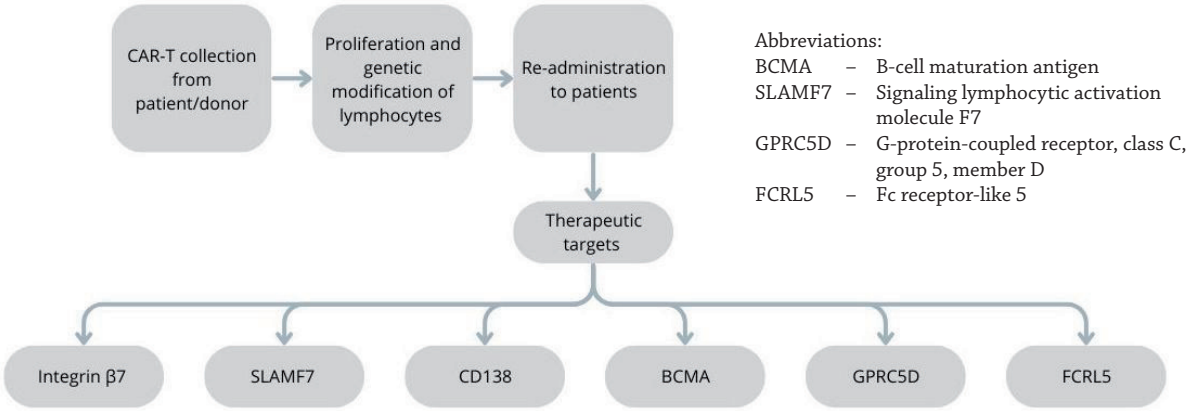


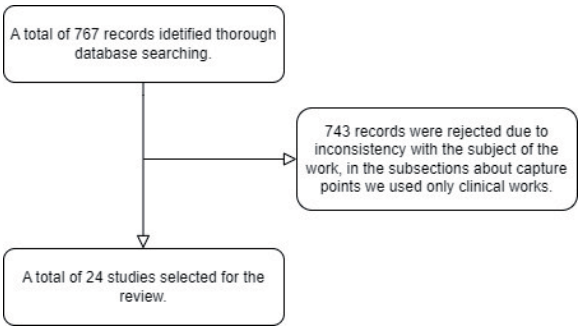
Figure 1. CAR-T formation and potential therapeutic targets

Aim of the study

This review aimed to outline the role of CAR-T therapy in MM treatment and to discuss the therapeutic targets of this therapy. We also discussed the side effects and effectiveness of CAR-T therapy.

Material and methods

We conducted a review of international articles in English available on the Pubmed platform. Our analysis used articles published between 2008 and 2024. Most of the articles described were published within the last 10 years. For scientific papers, we searched for terms containing the keywords: MM, CAR-T, integrin β7, SLAMF7, CD138, BCMA, GPRC5D, FCRL5, and alloCAR-T, which were combined using "AND". We focused on relevant international scientific journals available through the Pubmed platform. In this review, we discuss the use of CAR-T therapy in the treatment of MM and describe potential therapeutic points. We also paid attention to the side effects and effectiveness of the mentioned therapy. We present the current state of knowledge resulting from clinical research. We searched the Pubmed publications database using the keywords listed above. We selected free full texts. Starting from a total of 767 articles on the use of CAR-T in MM therapy, we excluded all unrelated articles. We selected articles containing information on the therapeutic points of CAR-T therapy,



the side effects, and the effectiveness of this therapy. In the subsections about capture points, we used only clinical studies. If articles contained the same type of information, we selected articles with the most up-to-date data. At the end, we collected 24 articles.

Results

We present the potential role of CAR-T in MM therapy and its therapeutic targets: integrin β7, SLAMF7, CD138, BCMA, GPRC5D, FCRL5, the role of alloCAR-T, adverse effects of using CAR-T, and its effectiveness.

Potential therapeutic targets

Integrin β7

CAR-T therapy seems to be effective in MM therapy. One of the therapeutic options is to use the MMG49 antibodies. It has been proven that this antibody binds to the protein - integrin β7 in its active form, which is present in MM cells, whereas in other blood cells, integrin β7 can be found in the inactive form. For this reason, healthy cells will not be damaged during therapy, only MM cells will be destroyed [9]. Expression of integrin β7 in MM was confirmed in a study carried out on a group of 137 patients. In 60 (44%) of them, the active form of β7 integrin was detected in > 80% of MM cells. Moreover, despite intensively treating the patients, this protein was highly expressed in MM cells [10].

SLAMF7

Another potential therapeutic target of CAR-T therapy in MM is the signaling lymphocytic activation molecule F7 (SLAMF7). The expression of SLAMF7 on MM cells is high and uniform compared to normal non-hematopoietic cells, where SLAMF7 is not expressed. The function of SLAMF7 in MM is not clear, but its expression is suspected to increase the survival and adhesion of MM cells to bone marrow stromal cells. Unfortunately, SLAMF7 is also expressed in cells such as NK cells or CD8+ T cells. For this reason, the therapy could cause cytopenias and related complications like severe infections. In the study carried out on mice, to prevent these side effects, the caspase-9 suicide gene was added. It was also considered which of the CD28 or 4-1BB co-stimulatory domains of CAR T cells would show higher anticancer activity. The better effect was in the case of CD28-containing CAR-T cells. Finally, T cells expressing anti-SLAMF7 CAR plus a suicide gene construct were shown to specifically recognize SLAMF7 in vitro and eradicate tumors in mice models [11].

CD138

In the study by Guo et al. [12], the effectiveness of therapy with T cells with modified CARs recognizing CD138 was confirmed. Due to CD138's strong expression on MM cells and contributing to their development and proliferation, this molecule seems to be an attractive therapeutic target. This study was carried out on 5 patients with resistance to treatment: 4 of them had regressed MM during the study for more than 3 months, also one patient who was treated for advanced plasma cell leukemia had a reduction of MM cells in peripheral blood from 10.5% to <3% [12].

BCMA

Potential usefulness also presents CAR-T bb2121 targeting B-cell maturation antigen (BCMA) therapy. In a 1st phase study carried out on patients with resistance to treatment or recurrence of MM, this therapy resulted in a positive response in 85% of the subjects, moreover, 45% (15 patients) reached the overall response [13]. BCMA seems to be a suitable target for CAR-expressing T cells because its expression was not detected in other human tissues, only in MM cells. The study carried out on 5 patients confirmed that all 5 MM patients showed expression of BCMA [14]. The next study carried out on 12 patients also showed the effectiveness of this therapy. Ali S et al. [15] used different doses of CAR-BCMA T cells. It was found that a lower dose was associated with a more limited anti-myeloma effect and milder myeloma toxicity. Whereas 1 patient reached partial remission after the 3rd level of doses. The 4th level of doses ($9 \times 10^{(6)}$ CAR(+) T cells/kg body weight) was used in two patients: the first patient, whose bone marrow was 90% occupied by MM cells before the start of treatment, and second whose bone marrow was 80% occupied by MM. After treatment in both patients, bone marrow plasma cells were undetectable by flow cytometry [15]. Another study showed, that in therapy with BCMA, complete responses were confirmed in 44.8% of patients, moreover, the median progression-free survival was, on average, 12.2 months, which is significantly better compared to the expected 1.9 months [16]. There were also attempts to combine therapy with BCMA and CD38 CAR-T cells (BCMA-CD38) in patients with relapsed or refractory MM. The results showed that BCMA-CD38 CAR-T cells have an increased anti-myeloma effect in combination compared to single use, which is a promising therapeutic effect. The research was carried out on

16 patients, 87.5% responded to treatment (including 13 rigorous, complete responses and 1 partial response). The one-year progression-free survival rate was 68.8%, and the overall one-year survival rate was 75.0%. The effects of this therapy are really promising and should be further developed and subjected to further research [17].

GPRC5D

G-protein-coupled receptor, class C, group 5, member D (GPRC5D) is a surface receptor that is highly expressed in bone marrow samples from MM patients, minimally expressed in other hematologic malignancies, and restricted to the hair follicle in normal tissues. Therefore, it seems to be a promising therapeutic target. A study was conducted in which 17 patients received CAR-T cell therapy targeting the GPRC5D receptor. These patients were heavily pre-treated for MM, including 8 who received BCMA CAR-T cell therapy. Four dose levels were studied and clinical responses were reported at all. The maximum tolerated dose was set at 150×106 CAR-T cells. A response was observed in 71% of patients, and the median duration was 7.8 months. Only 6 patients progressed after the initial response, of which 4 had no GPRC5D expression at the time of progression, and 2 had a reduced expression. Seven of ten patients who had previously received BCMA-directed therapies experienced a partial or better response [18]. Another study confirming the effect of CAR-T therapy targeting GPRC5D was conducted in China in patients diagnosed with relapsed or refractory MM who were previously treated and were positive for GPRC5D. All patients (n=10) had an overall response, 6 of whom had a close complete response, and 4 had a very good partial response. Only 2 patients experienced disease progression [19]. In a Phase II study, 33 patients were infused with anti-GPRC5D CAR T cells. A response rate was observed in 91% of participants. However, all patients who previously received CAR-T cell therapy against BCMA experienced a partial or better response [20]. These studies suggest that GPRC5D CAR-T can be used not only as an alternative to other CAR-T therapies but also after CAR-BCMA T cell treatment and the occurrence of disease relapse (in people resistant to this treatment) [18–20].

FCRL5

A new potential target of CAR-T cells for use in MM immunotherapy may also be Fc receptor-like 5 (FCRL5), a protein marker found specifically on plasma cells in MM. FCRL5, in addition to increased expression in this disease, promotes B cell proliferation. In a study conducted both in vitro on MM cell lines and in vivo on mouse xenograft models, BCMA- and FCRL5-CARs were designed. It was proven that FCRL5 CAR-T cells led to increased death of MM cells expressing FCRL5 compared to BCMA CAR-T cells. Additionally, higher production of interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) was observed in FCRL5 cells. However, when evaluating FCRL5 CAR-T cells in the dispersed MM xenograft model, their growth was inhibited, which resulted in the extension of the lifespan of the mice. However, when examining the effectiveness of inhibiting tumor growth alone, the effect was temporary (14 days), and all mice relapsed and died within 60 days. To improve therapeutic durability, FCRL5 CAR-T cells were engineered to secrete Interleukin-15 (IL-15). The use of FCRL5 CAR/IL-15 resulted not only in inhibition of tumor growth but also in reduced tumor burden in the spleen and bone marrow. An increase in body weight was also noted on day 14 of treatment, and survival time was longer until the end of the study [21].

AlloCAR-T therapy

The AlloCAR-T therapy, which uses T lymphocytes from a healthy donor, which are modified and targeted to BCMA also seems to be an effective method. The positive results were seen in a study carried out on mice. Allogeneic BCMA CAR-T elicited sustained antitumor responses in mice models. Importantly, it was discovered that they maintained their potency after scale-up manufacturing. The advantage of AlloCAR-T therapy over autogenic is that AlloCAR-T would be easily available because of using ready-to-use products. On the other hand, a disadvantage of the therapy could be considered a higher risk of graft-versus-host disease, but TALEN (transcription activator-like effector nucleases)-mediated knockout of the TRAC and CD52 genes prevented this adverse effect in mice models [22].

Adverse effects

However, like other therapeutic methods, CAR-T therapy also causes adverse effects (Figure 2). The most clinically important and potentially life-threatening complication, which was predominant among all treatments, is cytokine release syndrome (CRS) [23]. The first symptom of CRS is fever, followed by hypotension, hypoxia, cardiac dysfunction, arrhythmias, and renal and other organ failure [24]. After BCMA therapy was carried out on 640 patients, 80.3% (n=514) had CRS, and 10.5% (n=67) had symptoms of neurotoxicity (16). Neurological toxicity is variable and includes encephalopathy, delirium,

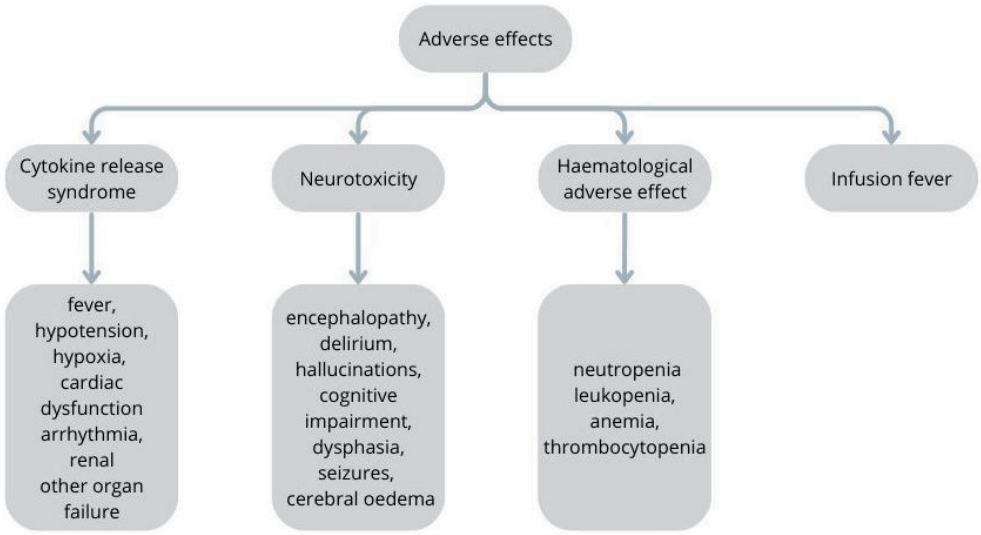


Figure 2. Adverse effects of CAR-T therapy

hallucinations, cognitive impairment, dysphasia, seizures, and cerebral edema [24]. The most common hematological adverse effect is neutropenia but also leukopenia, anemia, and thrombocytopenia were observed [13]. After therapy with T cells recognizing CD138, the most common side effect was an infusion fever, which occurred after the second infusion of T cells, with the highest temperature recorded being 39.6 degrees Celsius [12].

Conclusions

MM is a common hematological malignancy, which usually has a poor prognosis. Remission of the disease is not usually possible, however, the rapidly progressing development of new treatment methods like CAR-T therapy gives hope for changes. CAR-T therapy utilizes the ability of modified T lymphocytes to recognize tumor-specific antigens. For MM, these specific antigens include integrin β, SLAMF7, CD138, and BCMA. Despite the occurrence of adverse effects such as CRS, neurotoxicity, and hematological toxicities, the use of CAR-T gives real benefits to patients, which is an extension in survival time. This therapy should be subjected to further research, improved and developed with new branches, such as the thriving AlloCAR-T therapy.

Abbreviations

BCMA – B-cell maturation antigen
CAR – Chimeric antigen receptor
CRS – cytokine release syndrome
FCRL5 – Fc receptor-like 5
GPRC5D – G-protein-coupled receptor, class C, group 5, member D
IFN-γ – Interferon-gamma
IL-15 – Interleukin-15
MM – Multiple Myeloma
SLAMF7 – Signaling lymphocytic activation molecule F7
TALEN – Transcription activator-like effector nucleases
TNF-α - – Tumor necrosis factor-alpha

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