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Chimeric antigen receptor T in the treatment of multiple myeloma – state of the art and future directions

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Dominik Dytfeld

Department of Hematology and Bone Marrow transplantation, University of Medical Sciences in Poznan, Poznan, Poland

Abstract

In spite of the introduction of several new drugs in the last 10 years, multiple myeloma (MM) remains incurable. Thus, an adoptive cellular therapy using chimeric antigen receptor T (CART), a strategy to increase the frequency of tumor-directed and functionally active T cells targeting antigens present on the cancer cell, might change the treatment in MM as it did in lymphoma and ALL. There are several targets for CART therapy in MM on different levels of development, which are discussed in the manuscript. B-cell maturation antigen (BCMA) being tested in the studies of phase 1–2 is the most promising, but so far CART has not been approved in the cure of MM and remains an experimental approach. The hematological society is facing a new technology which with its potential ability to cure MM, in spite of its complexity, cost, and toxicity, will definitely and soon change the landscape of myeloma in Europe and world-wide.

Keywords:
myeloma, CART, immunotherapy

Introduction

Multiple myeloma (MM) is diagnosed in around 1,600 new cases per year in Poland, with estimated population exceeding 10,000, despite recent improvements in treatment including proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies remains incurable and is associated with a high mortality rate [1]. In recent years, the development of immunotherapy has revolutionized the treatment of cancer. Therapeutic agents that induce the patients' immune system to activate the ability to kill tumor cells and to overcome the immunosuppressive mechanisms of the tumor microenvironment may improve clinical results. In this setting, cellular therapy using chimeric antigen receptor (CAR) might change significantly the treatment strategy for MM. CARs are artificial fusion proteins that incorporate an antigen recognition domain. T-cells expressing a CAR (CARTs) can precisely recognize a targeted antigen, which is an advantage over nonspecific cellular therapies such as allogeneic stem cell transplantation [2]. Additionally, to recognize the domain, CAR includes transmembrane region, one of two types of signaling domains (CD28 or 4-1BB) and T-cell activation domain (CD3ζ). Signaling region was introduced in the second generation of CARTs, which significantly improved the efficacy and the safety profile of this technology. Second generation CARTs are at the advanced stage of investigation, which led to the registration of antiCD19 CARTs for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL) in pediatric and young adults, and for diffuse large B-cell lymphoma (DLBCL) by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The first infusion in Poland was on November 28, 2019 [3, 4]. So far, there is no CART formally approved either by EMA or by FDA for the treatment of MM, but several constructs are being investigated. High efficacy of CART is unfortunately associated with life-threating toxicities. These toxicities include cytokine release syndrome (CRS) that manifests with fever, hypotension, and tachycardia; and immune effector cell-associated neurotoxicity syndrome (ICANS), which is related to different stages of encephalopathy including coma. CRS has been described to be more severe in patients with high disease burden and is associated with increase of serum cytokines such as interleukin 6 (IL-6) and interferon γ (IFN-γ). The treatment includes supportive care and the use of tocilizumab (IL-6 receptor antagonist) and steroids. Both ICANS and CRS are usually transient and fully reversible.

Antigen selection

One of the most important goals of the development of CART technology is to improve the efficacy-to-toxicity ratio, which can be achieved by improved construct of the receptor and the right choice of target. Thus, several different antigens are evaluated to understand the feasibility of introduction of CART in MM.

CD70

CD70, known as CD27 ligand, might be a good candidate for CART therapy in MM, as its presence is limited to lymphoid tissue when

Corresponding author: Dominik Dytfeld, Department of Hematology and Bone Marrow transplantation, University of Medical Sciences in Poznan, Szamarzewskiego 84, 60-569 Poznan, Poland, phone: +48 61 854 93 83, e-mail: dytfeld@icloud.com

administered. It is under investigation as a target in MM but has not been used in the clinical setting yet [5].

CD56

CD56 is surface glycoprotein mediating cell to matrix interactions. The construct of CART using CD56 as a target was assessed in preclinical studies; however, its potential neurotoxicity is a significant limitation to further studies [6].

CD38

CD38 is a transmembrane glycoprotein playing a significant role in cell adhesion and calcium metabolism. It is expressed on B cells, plasma cells, as well as natural killer (NK) cells and T cells. It is also present on prostate, muscles, and red blood cells. Despite the presence of CD38 on hematopoietic cells, due to the high efficacy of daratumumab and isatuximab (monoclonal antibodies with specificity to CD38), proven in clinical studies in MM, this antigen is a target for CART constructed with caspase-9 suicide gene and it is under investigation in preclinical setting [7].

CD138

CD138, known as syndecan-1, is heparin-sulfate proteoglycan present on plasma cells. Its expression on resistant cells is higher in newly diagnosed MM is the notable important characteristic. CART anti-CD138 was tested in phase 1 study in 6 patients with advanced disease. Four of them achieved stable disease (SD) and 1 progression (PD). Toxicity of the treatment was limited [8, 9].

CD19

Several studies suggested the significant role of cancer stem cells in the mechanism of the resistance in MM. It is postulated that $CD138^{-}CD45^{+}CD19^{+}CD20^{+}$ cells may elevate MM colonies and are considered as MM stem cells. Taking that into consideration, CART against CD19 was used in patients who failed to respond to high-dose therapy (autologous peripheral stem cell transplantation [auto-PBSCT]). Approximately 12–14 days after the second auto-PBSCT, 5×10^7 anti-CD19 autologous CART were infused. Out of 12 patients enrolled for the study, 10 patients who received CART have progressed with median progression-free survival (PFS) of 185 days [10].

Kappa light chain

Since some of the MM cells expressed light chains on the cell surface, construct of CART directed against kappa was used in phase 1 study in patients with relapsed/refractory MM (RRMM). Such construct was used in 7 patients with active MM. In those, 3 of them received salvage chemotherapy within 4 weeks before CART infusion, whereas those who did not receive chemotherapy and had lymphocyte count above 500/μl received cyclophosphamide. The best response was SD in 4 and PD in 3 patients [11].

Signaling lymphocyte-activating molecule F7

One of the most promising molecules targeted for immunotherapy is signaling lymphocyte-activating molecule F7 (SLAMF7), known also as a CD319 or CS1. It is present on the surface of plasma cells, dendritic cells, NK, and T cells [12]. As elotuzumab – monoclonal antibody directed against this antigen showed good results in combination with lenalidomide and pomalidomide in RRMM, this antigen is under investigation as a target for CART. An argument for such construct is lack of expression of SLAMF7 on non-hematological cells. In phase 1–2 study, CART against SLAMF7 with sleeping beauty transposon that can be stopped by rimiducin is investigated in RRMM (clinicaltrial.gov identifier: NCT03958656).

B-cell maturation antigen

B-cell maturation antigen (BCMA, also named TNFRSF17 or CD269) belongs to the family of tumor necrosis factors. It is present on plasma cells, but not on hematopoietic stem cells. Considering the strong expression of the BCMA on malignant plasma cells and its important mechanism of action, BCMA represents an ideal therapeutic target for CART therapy. In fact, the majority of CART constructs tested in clinical trials in MM are targeting BCMA.

There are two most advanced CARTs against BCMA in MM, which seem to be close to registration, which is expected by 2021: the first is bb2121 developed by Celgene/BMS and the second is JNJ-4528 by Janssen. Both are second generation CARTs but have slightly different design–bb2121 has one binding domain, whereas JNJ4528 has two (Fig. 1), which might have an impact on their efficacy and safety profile.

Bb2121 was investigated in phase 1 study with different doses of CART ($50–800 \times 10^6$ cells). All 33 patients had previously received both bortezomib and lenalidomide, and 79% were exposed to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. A total of 26 patients (79%) were refractory to both a proteasome inhibitor and an immunomodulatory agent; 6 patients (18%) were refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. After 6.2 months of observation, 85% of the patients achieved an objective response (at least SD). A total of 6 out of 15 patients who reached complete response have relapsed. The median PFS was 11.8 months for the active dose (150–800) and 2.7 for inactive dose (50), and the curve did not achieve plateau phase. All 16 patients who had a response (partial response or better) and who could be evaluated for minimal residual disease (MRD) had MRD-negative status with a sensitivity 10^{-4}. Hematologic toxicities were the most common events of grade (G) 3 or higher, including neutropenia (in 85% of the patients), leukopenia (in 58%), anemia (in 45%), and thrombocytopenia (in 45%). Around 76% had CRS, but mostly low grade. G3 (not seen in G4 or 5) was present in 2 patients only. ICANS was seen in 14 patients (42%), mostly G3. Only one patient experienced G4 reversible neurotoxicity [13]. In the phase 2 study that was assessing efficacy of bb2121 (KarMMA study) in 140 patients with RRMM in different doses ($150–450 \times 10^6$ cells) at least partial response (PR) was seen in 73.4% patients. The point of significance is the response was better in

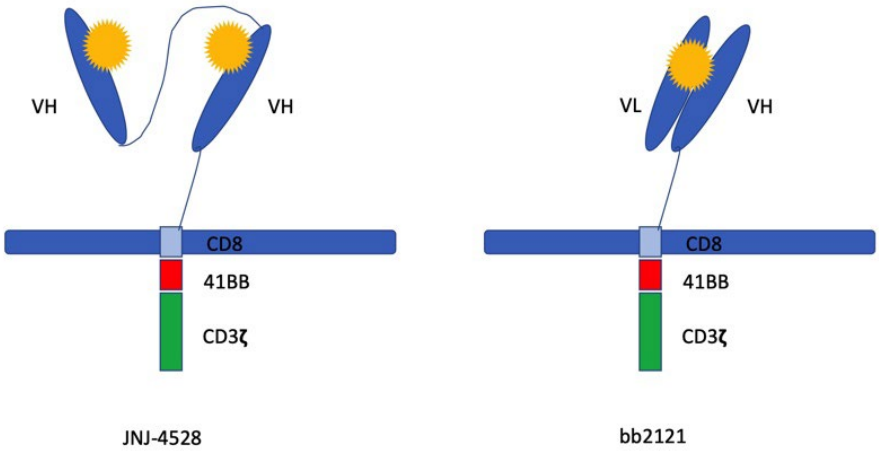

Fig. 1. The scheme of bb2121 and JNN4528 constructs

higher doses (ORR for 150 × 10^6 was 50%, 68.6% for 300 × 10^6, and 81.5 for 450 × 10^6). In another study, bb2121 was remodeled by the introduction of P13K inhibitor to enrich the drug product for memory-like T cells called as bb21217. After treatment of bb21217, 13 out of 22 patients developed mild CRS and only 1 developed G3. Five patients experienced ICANS but only one in G3 and one G4. Out of the evaluable 18 patients, 15 (83%) patients had response but eventually only 6 of them progressed [14].

A first-in-human phase 1 study (LEGEND-2) conducted in China of LCAR-B38M, an identical CAR to JNJ-4528, showed high overall response and manageable safety in 74 patients with RR MM. This construct is being assessed in phase 1b/2 CARTITUDE-1 study conducted in the US. Patients who were enrolled to this study had received a median of 5 (range 3–18) prior lines of treatment, 88% were triple-refractory to a proteasomes' inhibitor, immunomodulatory drug, and anti-CD38 antibody, 72% were penta-exposed, and 36% were penta-refractory. With a median follow-up of 3 months, an overall response rate of 91% was observed, with 4 stringent complete responses (sCRs), 2 CRs, 7 very good partial responses, and 6 PRs. Of the 15 evaluable patients, 10 were MRD-negative at the 10^{-5} sensitivity level, 2 at the 10^{-4} sensitivity level, and 3 had unidentified clones. No patient had progressed at the time of data cutoff. Most frequently reported adverse events were CRS (88%), neutropenia (80%), anemia (76%), and thrombocytopenia (72%). CRS was mostly mild (G1-2). There was one case of G3 CRS and one G5 at day 99, which raised from G4. Three patients developed ICANS: two in G1 and G3, which resolved within 2 days [15]. Common concerns regarding whether soluble BCMA present in serum might affect the efficacy anti-BCMA CART turned out to be not true. No correlation between expression of BCMA and response was noticed is what the most important observation is in both studies. Short summary of both studies is shown in table I.

Table I. Comparison of two phase 1 studies assessing bb2121 and JNJ-4528 in patients with RRMM

	bb2121	JNJ-4528
Investigator	Raje 2019	Madduri 2019
Number of patients	33	33
Number of antigen-binding domains	1	2
Median of number of prior therapies with range	7 (3–23)	5 (3–18)
Lymphodepletion	FluCy	FluCy
Number of cells infused	4 different doses (dose escalation phase) 50 × 10^6 cells 150 × 10^6 cells 450 × 10^6 cells 800 × 10^6 cells	Targeted dose: 0.75 × 10^6cells/kg with range 0.5–1.0 × 10^6
Bridging therapy allowed	Yes	Yes
PR + VGPR + CR	73% (all doses) 83% (150–800 × 10^6 cells)	91%
CRS ≥ G3	2 G3	1 G3
ICANS ≥ G3	1 G3	1 G3 and 1 G5

FluCy – fludarabine and cyclophosphamide; PR — partial response; VGPR – very good partial response; CR – complete response; CRS – cytokine release syndrome; G – grade; ICANS – immune effector cell-associated neurotoxicity syndrome

CARTs directed against BCMA are also being tested with gamma secretase inhibitor to increase BCMA expression on MM cells. In phase 1 study, 7 out of 8 enrolled for the study, who were eligible for evaluation, achieved at least PR and 5 out of 6 achieved MRD negativity. One patient died due to CRS [16].

Biclonal CART

Another way to improve efficacy is to combine two CARTs or use biclonal designs. The first approach was tested with anti-CD19 and anti-BCMA CARTs that were infused sequentially in 28 patients with RRMM. In all, 92% achieved at least PR, with median PFS of 8 months and median overall survival (OS) was 16 months. The treatment was well tolerated [17]. Biclonal constructs (anti-CD19 and BCMA) were tested in phase 1 study. All 5 patients that received it responded with no significant side effects (mild CRS was seen in 2 cases, no ICANS was observed) [18].

Summary and future directions

CART in MM is an emerging strategy that will definitely change the landscape of MM treatment in the near future. Available data on efficacy of CART in MM is limited mostly to one antigen (BCMA), with relatively short observation. Results so far are very promising in terms of unforeseen overall response rate reaching 90% in very advanced disease and toxicity much lower than that seen in lymphomas. Unfortunately, PFS curves do not reach plateau phase and thus CART, at least as of now, cannot be considered as curative method in MM. Definitely more data is needed to define the role of CART in the strategy of MM treatment. CART technology is being developed both in the research labs by improving CART constructs, as well as in the clinic by finding an optimal way to use it – probably in earlier stages of the disease with possible intention to treat. There are plenty of unanswered questions, but more than 70 recruiting studies focused on CART in MM, in different stages of the disease, in different construct including bi- and trispecific CARs will answer at least some of them. It should be kept in mind that CART is by far one of the most expensive therapies for hematologic malignancies, which needs to be included in long-term health policy planning. There is a strong interest in MM society as how, where, and on whom the CART therapy will be used. For sure academic studies on CART in MM are needed [19].

Authors' contributions

DD – the only author.

Conflict of interest

The author declares no conflict of interest related to this paper.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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