

CAR T-cell therapy: is it prime time in myeloma?

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Chimeric antigen receptor (CAR) T cells have shown promising activity in hematological malignancies and are being studied for the treatment of multiple myeloma, as well. B-cell maturation antigen, which is widely and almost exclusively expressed on plasma cells and B cells, is a promising target. Other targets being evaluated include CD19, CD38, CD138, signaling lymphocyte activation molecule or CS1, light chain, GPRC5D, and NKG2D. Early clinical studies have shown promising response rates in heavily pretreated patients, but relapses have occurred. Cytokine release syndrome and neurotoxicity have been observed in the majority of patients but are mostly grades 1 and 2. Relapse may be mediated by antigen escape and the limited persistence of CAR T cells. CAR T-cell constructs that target multiple antigens/epitopes or constructs with longer persistence due to a higher proportion of memory phenotype T cells may decrease the rates of relapse. Allogeneic CAR T cells that offer “off-the-shelf” options are also being developed. The challenges in integrating CAR T cells in myeloma therapy include disease relapse, adverse effects, cost, and identifying the right patient population. Longer-term data on efficacy and toxicity are needed before CAR T cells are ready for prime time in myeloma.

Clinical case

A 37-year-old man is seen in the office for management of relapsed refractory immunoglobulin A (IgA) κ multiple myeloma (MM). He is now 5 years from his initial diagnosis. He has previously received treatment with bortezomib, lenalidomide, and dexamethasone, followed by autologous stem cell transplantation (ASCT) and lenalidomide maintenance. He relapsed 1.5 years after initial ASCT, and subsequent therapies have included daratumumab, carfilzomib, pomalidomide, and venetoclax. He is now progressing with extramedullary disease at 2 sites. Fluorescence in situ hybridization studies show t(11;14) and MYC amplification. The last treatment was venetoclax based, with response lasting 12 months. The patient is working full time and has a robust performance status. He does not have any persistent nonhematologic toxicities and has grade 2 neutropenia. A matched sibling donor is available. He inquires about a chimeric antigen receptor (CAR) T-cell therapy clinical trial for treatment of his progressive MM, including the potential for response and expected toxicities.

Introduction

Despite recent improvements in survival with the development of several new agents, MM remains an incurable disease.¹ Furthermore, patients who have become refractory to proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibody have poor outcomes, with limited remaining treatment options.^{2,3} Therefore, there is an urgent unmet clinical need for newer therapeutic approaches for disease control in such patients.

Over the past several years, CAR T-cell therapy has emerged as a promising treatment for relapsed and refractory MM. CAR T cells are genetically modified T cells, with most containing an antigen-specific

Table 1. Results from selected studies of CAR T-cell therapy in MM

Site/developer	Target	Vector	Costimulatory molecule	scFv source	N	Median prior lines, n (highest dose)	CRS all grades/grade 3 or 4 (%)	Neurotoxicity all grades/grade 3 or 4 (%)	Response	MRD negative, % (sensitivity)	PFS	Comments
Data from published articles												
National Cancer Institute ²³	BCMA	Retrovirus	CD28	Murine	24, 16 highest dose	9.5 (highest dose)	Highest dose: 94/38	Highest dose: NA/19	Highest dose: ORR, 81%; CR, 13%	Highest dose: 69% (7×10^{-4})	Highest dose: 7.1 mo	BCMA expression required. Postinfusion increase in proportion of CD8 ⁺ cells noted.
Nanjing Legend LCAR-E38M (China) ²⁶	BCMA	Lentivirus	4-1BB	Non-scFv	57 of 74 in trial	3	90/7	2/0	ORR, 88%; CR, 68%	63% (1×10^{-4})	15 mo	Targets 2 BCMA epitopes; CAR T cells infused in 3 split doses.
Nanjing Legend LCAR-E38M (China) ²⁵	BCMA	Lentivirus	4-1BB	Non-scFv	17 of 74 in trial	≥3: 71%	100/41	NA	ORR, 88%; CR, 76%	NA	52.9% at 12 mo	No difference in toxicity/persistence of cells based on 3 vs 1 infusion. TLS seen in 3 patients.
University of Pennsylvania/Novartis CAR T BCMA ²⁴	BCMA	Lentivirus	4-1BB	Human	25, 11 in cohort 3	7	88/32	32/12	ORR, 48%; CR, 8%; Cohort 3: ORR, 64%; CR, 9%	16%; cohort 3: 9% (1×10^{-5})	Cohort 1: 2.1 mo; cohort 2: 1.9 mo; cohort 3: 4.1 mo.	BCMA intensity did not predict response. Responses correlated with CAR T-cell expansion, which was more likely with higher proportion of naive/memory phenotype cells. BCMA declined with treatment, more so in responders.
Bluebird/Celgene ²⁸	BCMA	Lentivirus	4-1BB	Murine	33	7-8	76/6	42/3	ORR, 85%; CR, 45%	94% (15/16 evaluable) (1×10^{-9} or deeper)	11.8 mo	Peak expansion correlated with response.
University of Pennsylvania/Novartis ⁹	CD19	Lentivirus	4-1BB	Murine	10	6	10/0	0	ORR, 80% with Mel, ASCT, and CAR T cells; 20% benefit rate from CART cells.	NA	6 mo	
Baylor ¹⁰	κ Light chain	Retrovirus	CD28	Murine	7	NA	0	0	0%	—	NA	
Dana-Farber Cancer Institute ²⁰	NKG2D	Retrovirus	None	Human	5	All ≥ 5	0	0	0%	—	NA	
Data from published abstracts												
JCARH125 Juno/Celgene ³⁰	BCMA	Lentivirus	4-1BB	Human	44	7	80/9	25/7	ORR, 82%; CR, 27%	NA	NA	1:1 CD4/CD8 ratio preselected prior to transduction and expansion. Response did not correlate with baseline serum BCMA level. Serum BCMA declined with treatment, more so in responders.
MCARH171 ³¹	BCMA	Retrovirus	4-1BB	Human	11	6	55/18	9/0	ORR, 64%; CR, 0%	NA	NA	No predefined CD4/CD8 ratio. Higher doses correlated with peak expansion. Peak expansion correlated with durability of response. Includes a truncated EGFR safety system.
FCARH143 ³⁶	BCMA	Lentivirus	4-1BB	Human	11	11	91/0	9/NA	ORR, 100%; CR, 36%	NA	NA	1:1 CD4/CD8 ratio after transduction and expansion. Encodes surface marker to analyze persistence. BCMA expression required. Includes a truncated EGFR safety system. BCMA antigen loss seen in 1 patient at time of relapse.

Data are current as of 2 May 2019.

CR, complete response; CRS, cytokine release syndrome; EMD, extramedullary disease; Mel, melphalan; MRD, minimal residual disease; NA, not available; ORR, overall response rate; PCL, plasma cell leukemia; PI3K, phosphoinositide 3 kinase; PFS, progression-free survival; tEGFR, truncated epidermal growth factor; TLS, tumor lysis syndrome.

Table 1. (continued)

Site/developer	Target	Vector	Costimulatory molecule	scFv source	N	Median prior lines, n	CRS all grades/grade 3 or 4 (%)	Neurotoxicity all grades/grade 3 or 4 (%)	Response	MRD negative, % (sensitivity)	PFS	Comments
P-BCMA - 101/Poseida ³⁶	BCMA	Nonviral (PiggyBac)	4-1BB	Human	23	6	9.5/0	4.8/4.8	ORR, 43-100% at various doses.	NA	NA	Nonviral PiggyBac DNA-delivery system: increases memory stem cells to increase persistence. It has a large cargo capacity, drug resistance gene for positive selection, proprietary safety switch. Peak expansion was delayed/slower (14-21 d); lower CRS.
BB21217 Bluebird/Celgene ²⁹	BCMA	Lentivirus	4-1BB	Murine	12	7	67/8	25/8	ORR, 83%; CR, 25%.	66% (4/6 evaluable) (NA)	NA	Same construct as bb2121. CAR T cells cocultured with PI3K inhibitor (bb007) to enrich for cells with memory phenotype to increase long-term CAR T-cell persistence.
HRAIN Biotechnology (China) ³²	BCMA	Retrovirus	4-1BB	NA	20	5.5	45/5	NA	ORR, 85%; CR, 45%.	NA	15 mo	tEGFR safety switch, BCMA expression required.
Tongji Hospital, Huazhong University (China) ³³	BCMA	NA	CD28, 4-1BB	Murine	30	4.5	97/20	3.3	ORR, 93%; CR, 50%.	NA	9.9 mo (no EMD or PCL), 4.6 mo (with EMD or PCL).	
CT053, Wenzhou University, Caragen (China) ³⁴	BCMA	NA	4-1BB	Human	17	4	29/6	NA	ORR, 100%; CR, 36%.	NA	NA	
SZ CART MM-02, Jiangsu Institute (China) ³⁷	CD19 and BCMA	Lentivirus	4-1BB (CD19) and CD28, OX40 (BCMA).	Murine (CD19) and human (BCMA)	10	—	100/0	0	ORR, 100%; CR, 70%.	60% (1 × 10 ⁻⁶)	NA	Tandem ASCT and separate infusions of CAR T cells targeted against CD19 and BCMA in high-risk MM. Lenalidomide maintenance post CAR T-cell therapy.

Data are current as of 2 May 2019.

CR, complete response; CRS, cytokine release syndrome; EMD, extramedullary disease; Mei, melphalan; MRD, minimal residual diseases; NA, not available; ORR, overall response rate; PCL, plasma cell leukemia; PI3K, phosphoinositide 3 kinase; PFS, progression-free survival; tEGFR, truncated epidermal growth factor; TLS, tumor lysis syndrome.

extracellular single-chain variable fragment (scFv) domain linked to a transmembrane component, followed by an intracellular costimulatory domain and the CD3 ζ part of the T-cell receptor (TCR) complex. The CD3 ζ portion leads to T-cell activation, whereas costimulatory molecules, such as CD-28, 41BB, and OX-40, enhance the T-cell response and can modify the phenotype of the CAR T cells. For example, 41BB is associated with a memory phenotype, theoretically enhancing the persistence of CAR T cells, whereas CD28 is associated with an effector T-cell phenotype.^{4,5}

Early clinical trials of CAR T-cell therapy have shown encouraging results in MM. In this article, we review the targets for CAR T-cell therapy in myeloma, the clinical data available to date, and strategies in development to improve the efficacy and optimize the safety of CAR T-cell therapy in myeloma.

Selection of targets

BCMA. B-cell maturation antigen (BCMA) is expressed on clonal and polyclonal plasma cells, as well as on a small subset of normal memory B cells, although the intensity of expression can vary with time due to the shedding of soluble BCMA in circulation after cleavage by a γ -secretase.^{6,7} Highly prevalent expression on plasma cells and exclusivity to the B-cell lineage has made BCMA an attractive target for CAR T-cell development in MM. Preclinical studies have shown promising activity of BCMA-directed CAR T cells, and soluble BCMA has not been a hindrance in efficacy.^{6,7} Several clinical trials with different BCMA-directed CAR T-cell constructs are ongoing, with encouraging preliminary data, as discussed in the BCMA-directed CAR T cells section and Table 1.

CD19. CD19-directed CAR T-cell therapy is approved by the U.S. Food and Drug Administration for acute lymphoblastic leukemia and large-cell lymphoma. CD19 is not widely expressed on malignant plasma cells; however, a minor subset of myeloma cells may express CD19 at low levels. It has been postulated that such cells are myeloma “stem cells,” responsible for propagating malignant plasma cells. It has been hypothesized that such cells can only be targeted after debulking of non-CD19-expressing myeloma cells by treatments like high-dose chemotherapy. This has been tested in a clinical trial; however, only modest clinical activity was observed.^{8,9}

Light chain. Igs, including light chains, are not typically expressed on the surface of myeloma cells. Similar to CD19, it has been proposed that myeloma “stem cells” have surface Ig expression. CAR T cells against κ light chains have been developed and tested in a clinical trial, with no myeloma response.¹⁰

CD38. CD38 is a potential target because of its high-intensity expression on plasma cells, with evidence of robust preclinical data using CD38-directed CAR T cells.¹¹ However, CD38 is also expressed on normal hematopoietic cells, such as red blood cells, natural killer (NK) cells, and other tissues, increasing the likelihood of “on-target, off-tumor” toxicity. Efforts to minimize off-tumor toxicity include developing affinity-optimized CD38 CAR T cells to preferentially target plasma cells, which have high CD38 expression, and spare normal cells with low CD38 expression.¹² A clinical trial with CD38 CAR T cells is ongoing (NCT03464916).

CD138. CD138 is expressed on plasma cells. However, it is also expressed on normal tissues, such as epithelial cells, potentially increasing “on-target, off-tumor” toxicity. In a preclinical study, CD138-directed CAR T cells were not toxic to epithelial cells.¹³ In a

clinical report of 5 patients treated with CD138-directed CAR T cells, no excess off-target effects were observed.¹⁴ A phase 1 clinical trial with CD138-directed CAR T cells is ongoing (NCT03672318).

SLAMF7 or CS1. SLAMF7 (signaling lymphocyte activation molecule F7) is widely expressed on plasma cells, as well as subsets of normal B and T cells, NK cells, monocytes, and dendritic cells and is already a therapeutic target of the monoclonal antibody elotuzumab. CAR T cells targeted against SLAMF7 have shown promising preclinical activity.¹⁵⁻¹⁷ However, because SLAMF7 is expressed on normal immune cells, these CAR T cells demonstrated selective fratricide of SLAMF7^{high+} B cells, T cells, and NK cells, while sparing the SLAMF7^{low} fraction in each subset. This may prove to be a challenge in the clinical application of such CAR T cells. A phase 1 clinical trial is underway (NCT03710421).

GPRC5D. GPRC5D is expressed on plasma cells, as well as some normal cells, such as hair follicle and lung tissue (expression is variable). Importantly, the expression on plasma cells is 500 to 1000 times that found on normal cells. CAR T cells developed against GPRC5D have shown encouraging preclinical activity.¹⁸

NKG2D. The NKG2D receptor activates NK cells and T-cell subsets after binding to a group of ligands that is expressed on infected cells and a variety of tumor cells, including MM. Importantly, no significant expression has been observed on normal healthy tissues.¹⁹ NKG2D-targeted CAR T cells have been studied in a small cohort of MM patients,²⁰ and NKG2D-directed CAR NK cells have also been developed with promising preclinical activity in MM.²¹

CAR T-cell products in clinical trials

Table 1 summarizes the results from selected clinical studies of CAR T-cell therapy in MM.

BCMA-directed CAR T cells. The first human clinical trial of CAR T cells targeting BCMA was conducted at the National Cancer Institute (NCT02215967).^{22,23} The BCMA CAR T-cell construct used in this phase 1 trial contained a CD28 costimulatory domain, and patients were required to have BCMA expression. Twenty-four patients were infused, including 16 patients at the highest dose level of 9×10^6 CAR T cells per kilogram. An additional 3 patients were enrolled but not infused because of a lack of BCMA expression, disease progression, or bacterial contamination of the product in 1 patient each. The median number of prior treatments in the highest dose cohort was 9.5. Overall response rate (ORR) in patients treated at the highest dose level was 81%, with a median event-free survival of 31 weeks. High peak CAR T-cell levels were associated with response, and responding patients were observed to have a decline in serum BCMA levels. Cytokine release syndrome (CRS) was seen in 94% of patients (15/16); it was grade 3 or higher in 38% of patients.

Another CAR T-cell construct targeting BCMA with 41BB as the costimulatory molecule was codeveloped by the University of Pennsylvania/Novartis and tested in a phase 1 trial.²⁴ Twenty-five patients, with a median of 7 prior lines of treatment, were treated in 3 cohorts. Patients in cohort 1 received 1 to 5×10^8 CAR T cells without lymphodepleting chemotherapy, whereas those in cohorts 2 and 3 received 1 to 5×10^7 and 1 to 5×10^8 CAR T cells, respectively, after cyclophosphamide (1.5 g/m²) lymphodepletion. CAR T-cell expansion and responses (ORR, 4/9) seen in cohort

1 suggested that lymphodepletion might not be absolutely required for CAR T-cell expansion and clinical activity. However, short-term CAR T-cell expansion was more consistently observed in cohort 3 vs cohort 1, suggesting a favorable impact of lymphodepletion on CAR T-cell expansion. BCMA expression was not a prerequisite, but it was identified in all patients by flow cytometry. CRS was seen in 88% of patients and was grade 3 or 4 in 32% of patients. Neurotoxicity was observed in 32% of patients and was grade 3 or 4 in 12% of patients. ORR was 48% in all patients and was 64% in cohort 3. Median duration of response was 124.5 days. Median overall survival for all patients was 502 days; it was not reached for patients in cohort 3. The preinfusion product was CD4⁺ predominant, whereas CD8⁺ T cells were predominant post-infusion. Baseline BCMA intensity did not correlate with expansion or response. Responders were noted to have a decline in BCMA expression on residual myeloma cells, which increased at the time of progression. In this trial, manufacturing was successful in all patients; however, 4 of the 29 enrolled patients progressed during product manufacturing and were not infused.

Results from a phase 1 multicenter study of LCAR-B38M CAR T cells (LEGEND-2; NCT03090659) conducted in China have been reported in 2 separate studies.^{25,26} This CAR T-cell construct targets 2 distinct BCMA epitopes derived from llama heavy chain antibodies, postulated to confer higher affinity toward BCMA. This construct, unlike many of the other CAR T-cell products, does not have a scFv domain. The first study reported data on 57 patients treated at 1 center, with a median of 3 prior lines of therapy. An ORR of 88% was observed. The complete response (CR) rate and the minimal residual disease (MRD)-negative disease rate by flow cytometry (1×10^{-4}) were 74% and 68%, respectively. Median time to response was 1 month. Median progression-free survival (PFS) was 15 months in all patients and 24 months in patients achieving MRD-negative CR. Median overall survival was not reached. Baseline BCMA expression did not correlate with response. CRS was seen in 89% of patients; rates of grades 3 and 4 CRS were 7% and 0%, respectively. Grade 1 neurotoxicity was observed in 1 patient.^{26,27} Similar results were observed in the study reporting on the remaining 17 patients (Table 1).²⁵

In a phase 1 study of bb2121 (NCT02658929), a BCMA-targeting CAR T-cell construct with 41BB as the costimulatory molecule, 33 of the 36 enrolled patients received CAR T cells after lymphodepleting chemotherapy. Three patients progressed during manufacturing, which was successful in all patients.²⁸ ORR was 85%, including a CR rate of 45%. Of the 16 patients with a hematologic response who were evaluated for MRD, 15 were MRD negative (1×10^{-5} or deeper). CRS occurred in 76% of patients and was grade 3 in 6%. Neurotoxicity occurred in 42% of patients, with grade 3 or 4 neurotoxicity in 3% of patients. Persistence of CAR T cells at 6 and 12 months was seen in 57% and 20% of patients, respectively.

There are several other ongoing studies of BCMA-directed CAR T cells with preliminary data presented in abstract form, as described in Table 1. Response rates have been high and are fairly comparable across trials. No new or unexpected toxicities have been observed.²⁹⁻³⁷

CD19 CAR T cells. CD19-directed CAR T cells have been infused in 10 heavily pretreated MM patients following a second ASCT.⁸⁻⁹ The PFS following this second ASCT was observed to be

significantly longer in 2 of the 10 patients compared with PFS after their first ASCT. Following progression, the disease course in these 2 patients was observed to be more indolent compared with pre-CAR T-cell therapy.

CAR T cells against other targets. Five MM patients were treated in a phase 1 trial of CAR T cells targeting NKG2D ligands. No CRS or neurotoxicity was observed. No objective tumor responses were seen.²⁰ A phase 1 trial of CAR T cells against κ light chain in 16 patients with various hematologic malignancies, including MM, showed stable disease in 4 of 7 myeloma patients. No significant toxicities were observed.¹⁰ Clinical trials with CAR T cells directed against other antigens expressed on myeloma cells, such as SLAMF7 (NCT03710421), CD38 (NCT03464916), and CD138 (NCT03672318), are ongoing.

Mechanism of resistance and strategies to improve efficacy

Mechanisms of resistance and relapse following CAR T-cell therapy in MM are poorly understood. Available data from clinical studies demonstrate that peak expansion of BCMA-directed CAR T cells generally correlates with response, whereas the extent of baseline BCMA expression does not, although most myeloma cells express BCMA.^{23,24,26} BCMA expression on residual myeloma cells generally decreases after CAR T-cell therapy, more so in responders than in nonresponders. At the time of progression, an increase in BCMA expression has been observed, potentially suggesting that additional BCMA-targeted therapies may be a future treatment option, at least in some patients. Persistence of CAR T cells has ranged from a few days in most patients to a few months in some patients, with some variability across studies.

One potential mechanism of relapse post-CAR T-cell therapy is antigen escape. Over time, tumor cells downregulate the target antigen expression or express a different epitope that is not targeted by the CAR T cells. This has been described in CD19-directed CAR T-cell therapy and has also been observed in myeloma.^{36,38} Positive selection of clonal cells that express, a priori, a different epitope has also been observed.³⁹ Similarly, tumors can exhibit trogocytosis, which refers to decreased antigen expression on target tumor cells and, in fact, transfer of the antigen to T cells, thereby mediating CAR T-cell-induced fratricide of T cells.⁴⁰ Strategies to mitigate antigen escape or epitope migration include targeting >1 antigen to increase efficacy. This can be achieved with dual CAR T cells (separate infusions of 2 different CAR T-cell products) or bispecific CAR T cells (CAR to >1 antigen in the same T cell).^{41,42} An ongoing study at the University of Pennsylvania is assessing the safety and efficacy of infusing BCMA CAR T cells in high-risk patients early in the disease course, with or without CD19 CAR T cells (NCT03549442). A phase 1 trial in China evaluated separate infusions of CD19- and BCMA-targeted CAR T cells after ASCT in high-risk patients early in the disease course. No excess or unusual toxicity was seen (NCT03455972). Preclinical data with CD19/CD20 CAR T cells in large cell lymphoma have shown that such bispecific CAR T cells are capable of overcoming CD19 antigen escape.⁴²

Another postulated mechanism of disease progression is the lack of long-term persistence of CAR T cells. This has been seen with myeloma and other malignancies. Several strategies are being developed to increase the proportion of long-lived T cells with a

memory phenotype in the infused product, which is expected to result in longer CAR T-cell persistence. BB21217 is a modified CAR T-cell product in which the T cells are cocultured with a phosphatidylinositol 3-kinase inhibitor to increase the proportion of memory-like phenotype T cells.²⁹ There are efforts to adjust the CD4/CD8 ratio to 1:1, before transduction (the JCARH125 product) or after (the FCARH143 product), to control the proportion of memory and effector T cells.^{30,36} Novel methods of CAR T-cell transduction, such as the nonviral PiggyBac transposon-based DNA-delivery system, are being used for the production of CAR T cells.³⁵ The CAR T-cell product created with this method has a larger number of memory T cells to theoretically increase long-term persistence. In a phase 1 trial with this product, peak expansion of CAR T cells was more gradual and was seen at days 14 to 21, compared with the usual 7 to 10 days, and it resulted in lower rates of CRS.

A third strategy is to combine CAR T-cell therapy with drugs that may enhance the activity of these cells. In preclinical studies, immunomodulation of CS1-directed CAR T cells with lenalidomide augmented their function with regard to antitumor activity and persistence.⁴³ γ -Secretase is an enzyme that cleaves BCMA off the surface of plasma cells. Inhibiting its activity may result in increased BCMA expression on malignant cells and may enhance the antitumor activity of BCMA CAR T cells. This would also decrease soluble BCMA, which may act as a possible decoy for BCMA CAR T cells. A clinical trial of BCMA-targeted T cells with a γ -secretase inhibitor is ongoing (NCT03502577).

Clinical case (continued)

Based on the patient's history, you determine that he is eligible to enroll in a BCMA CAR T-cell trial at your center. During the screening phase for the trial, his disease begins to progress further, with worsening calcium and increased bone pain. He is able to undergo leukapheresis to collect autologous cells but will have to wait 4 weeks for CAR T-cell manufacture.

Allogeneic CAR T-cell approaches

The time lag between the collection and manufacturing of autologous CAR T cells remains a challenge for patients with progressive disease. Allogeneic CAR T cells from healthy donors can provide readily available "off the shelf" CAR T cells. A BCMA-targeted allogeneic CAR T-cell product has shown promising preclinical activity in MM, in vitro and in mice xenografts.⁴⁴ To reduce the potential for graft-versus-host disease, these CAR T cells have been genetically edited using transcription activator-like effector nucleases (TALEN; Gelectis) to eliminate the TRAC gene. The CD52 gene has also been knocked out to allow for selective lymphodepletion of host lymphocytes with an anti-CD52 antibody.⁴⁴ Another allogeneic product under clinical development targets SLAMF7. This also uses TALEN gene-editing technology to inactivate TRAC to reduce graft-versus-host disease, as well as to knock out the expression of SLAMF7 on CAR T cells to reduce fratricide of SLAMF7-specific CAR T cells.⁴⁵

Clinical case (continued)

The patient receives a cycle of carfilzomib-based "bridging therapy" after leukapheresis, which is able to minimally slow his progression. Approximately 4 weeks after leukapheresis, he undergoes lymphodepleting chemotherapy with fludarabine and cyclophosphamide

and thereafter receives his CAR T cells. His course is complicated by a grade 2 CRS, which requires tocilizumab and a brief stay in the intensive care unit for low-dose vasopressor therapy. He is ultimately discharged 2 weeks after CAR T-cell infusion and eventually returns home. Within 4 weeks of CAR T-cell therapy, he has achieved a partial response, and his bone marrow is negative for disease morphologically. His course over the next few months is notable for profound hypogammaglobulinemia and intermittent neutropenia that are responsive to growth factor injections.

Safety of CAR T-cell therapy in MM

CRS is common in patients being treated with CAR T-cell therapy for myeloma, although the rates of grade 3 or 4 CRS have been low. CRS observed with myeloma CAR T-cell therapy is similar to other CAR T-cell settings and is generally manageable with tocilizumab and steroids, if necessary. Similarly, neurotoxicity has largely been low grade and steroid responsive. It has been hypothesized that toxicities like CRS and neurotoxicity from CAR T-cell therapies occur as a result of antigen recognition by the CAR receptor, which is synthetic in nature. An alternative receptor has been designed, called the T-cell antigen coupler, which recognizes antigens independent of MHC but engages the native TCR. The toxicity in preclinical models has been lower than that observed with CAR T cells, which has been attributed to the T-cell response being mediated by the native TCR.⁴⁶

Other toxicities that are becoming increasingly recognized include prolonged cytopenias, hypogammaglobulinemia, and an inflammatory condition similar in clinical picture to macrophage activation syndrome. These are all manageable by appropriate supportive care but do require close attention, even as the patient transitions to outpatient care. Antimicrobial prophylaxis, growth factor support, and, in some cases, IV Ig are necessary for several months after CAR T-cell infusion.

Conclusions

In conclusion, although CAR T-cell therapy in MM has shown promising clinical activity in early-phase trials, longer-term data on efficacy and toxicity are needed before CAR T cells are ready for prime time. We must better understand the underlying mechanisms of disease relapse to improve the duration of response. Additionally, the optimal patient population that may derive benefit from CAR T cells (upfront vs early relapse versus multiply relapsed) has not yet been identified. The safety of combining CAR T cells with drugs like lenalidomide for maintenance is also unknown. There are concerns about patients progressing during product manufacturing and unsuccessful manufacturing in some patients. All CAR T-cell clinical trials should report on the proportion of enrolled patients in whom CAR T cells were successfully manufactured, as well as patients who progressed during the manufacturing process. Although no CAR T-cell product is commercially available for MM, costs are anticipated to be high, and this may severely limit patient access. Clinicians, researchers, and regulators will have to continue to work together to optimize the product and the process, which will eventually yield appropriate access to this exciting new therapy.

Clinical case (continued)

Other treatment options that could have been considered for this patient include clinical trials of novel agents, such as

BCMA-targeted bispecific T-cell engagers⁴⁷ or BCMA-directed antibody drug conjugate,⁴⁸ which have shown promising activity in heavily pretreated patients and are available “off the shelf.” An allogeneic transplant could also have been considered. Although allogeneic stem cell transplantation (SCT) can result in durable remission in some patients, the transplant related mortality remains high, and relapses inevitably occur.⁴⁹ Co-occurrence of graft-versus-host disease may limit future treatment options in such patients. Additionally, several ongoing clinical trials of CAR T cells and other novel agents in MM exclude patients who have previously undergone an allogeneic SCT. After an in-depth discussion of the pros and cons of allogeneic SCT, the patient elected to enroll in a

CAR T-cell therapy clinical trial instead of pursuing an allogeneic SCT.

Authorship

Contribution: S.S. and N.S. both performed literature review; contributed to the conceptual design of the paper; wrote the paper; and have read the uploaded manuscript and consented to submission.

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References

1. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-2520.
2. Kumar SK, Dimopoulos MA, Kastritis E, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. *Leukemia*. 2017;31(11):2443-2448.
3. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. *Leukemia*. 2019;33(9):2266-2275.
4. Milone MC, Fish JD, Carpenito C, et al. Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo. *Mol Ther*. 2009;17(8):1453-1464.
5. Kawalekar OU, O'Connor RS, Fraietta JA, et al. Distinct signaling of coreceptors regulates specific metabolism pathways and impacts memory development in CAR T cells [published correction appears in *Immunity*. 2016;44(3)712]. *Immunity*. 2016;44(2):380-390.
6. Carpenter RO, Evbuomwan MO, Pittaluga S, et al. B-cell maturation antigen is a promising target for adoptive T-cell therapy of multiple myeloma. *Clin Cancer Res*. 2013;19(8):2048-2060.
7. Bu DX, Singh R, Choi EE, et al. Pre-clinical validation of B cell maturation antigen (BCMA) as a target for T cell immunotherapy of multiple myeloma. *Oncotarget*. 2018;9(40):25764-25780.
8. Garfall AL, Maus MV, Hwang WT, et al. Chimeric antigen receptor T cells against CD19 for multiple myeloma. *N Engl J Med*. 2015;373(11):1040-1047.
9. Garfall AL, Stadtmauer EA, Hwang WT, et al. Anti-CD19 CAR T cells with high-dose melphalan and autologous stem cell transplantation for refractory multiple myeloma [published correction appears in *JCI Insight*. 2019;4(4):127684]. *JCI Insight*. 2018;3(8):120505.
10. Ramos CA, Savoldo B, Torrano V, et al. Clinical responses with T lymphocytes targeting malignancy-associated κ light chains. *J Clin Invest*. 2016;126(7):2588-2596.
11. Mihara K, Bhattacharyya J, Kitanaka A, et al. T-cell immunotherapy with a chimeric receptor against CD38 is effective in eliminating myeloma cells. *Leukemia*. 2012;26(2):365-367.
12. Drent E, Themeli M, Poels R, et al. A rational strategy for reducing on-target off-tumor effects of CD38-chimeric antigen receptors by affinity optimization. *Mol Ther*. 2017;25(8):1946-1958.
13. Sun C, Mahendravada A, Ballard B, et al. Safety and efficacy of targeting CD138 with a chimeric antigen receptor for the treatment of multiple myeloma. *Oncotarget*. 2019;10(24):2369-2383.
14. Guo B, Chen M, Han Q, et al. CD138-directed adoptive immunotherapy of chimeric antigen receptor (CAR)-modified T cells for multiple myeloma. *J Cell Immuno*. 2016;2(1):28-35.
15. Chu J, He S, Deng Y, et al. Genetic modification of T cells redirected toward CS1 enhances eradication of myeloma cells. *Clin Cancer Res*. 2014;20(15):3989-4000.
16. Gogishvili T, Danhof S, Prommersberger S, et al. SLAMF7-CAR T cells eliminate myeloma and confer selective fratricide of SLAMF7⁺ normal lymphocytes. *Blood*. 2017;130(26):2838-2847.
17. Radhakrishnan SV, Bhardwaj N, Luetkens T, Atanackovic D. Novel anti-myeloma immunotherapies targeting the SLAM family of receptors. *Oncol Immunology*. 2017;6(5):e1308618.
18. Smith EL, Staehr M, Masakayan R, et al. Development and evaluation of an optimal human single-chain variable fragment-derived BCMA-targeted CAR T cell vector. *Mol Ther*. 2018;26(6):1447-1456.
19. Spear P, Wu MR, Sentman ML, Sentman CL. NKG2D ligands as therapeutic targets. *Cancer Immun*. 2013;13:8.
20. Baumeister SH, Murad J, Werner L, et al. Phase I trial of autologous CAR T Cells targeting NKG2D ligands in patients with AML/MDS and multiple myeloma. *Cancer Immunol Res*. 2019;7(1):100-112.
21. Leivas A, Rio P, Mateos R, et al. NKG2D-CAR transduced primary natural killer cells efficiently target multiple myeloma cells. *Blood*. 2018;132(suppl 1):590.

22. Ali SA, Shi V, Maric I, et al. T cells expressing an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma. *Blood*. 2016;128(13):1688-1700.
23. Brudno JN, Maric I, Hartman SD, et al. T cells genetically modified to express an anti-B-cell maturation antigen chimeric antigen receptor cause remissions of poor-prognosis relapsed multiple myeloma. *J Clin Oncol*. 2018;36(22):2267-2280.
24. Cohen AD, Garfall AL, Stadtmauer EA, et al. B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma. *J Clin Invest*. 2019;129(6):2210-2221.
25. Xu J, Chen L-J, Yang S-S, et al. Exploratory trial of a biepitopic CAR T-targeting B cell maturation antigen in relapsed/refractory multiple myeloma. *Proc Natl Acad Sci USA*. 2019;116(19):9543-9551.
26. Zhao WH, Liu J, Wang BY, et al. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. *J Hematol Oncol*. 2018;11(1):141.
27. Zhao W-H, Liu J, Wang B-Y, et al. Updated analysis of a phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B-cell maturation antigen, in patients with relapsed/refractory multiple myeloma. *Blood*. 2018;132(suppl 1):955.
28. Raje N, Berdeja J, Lin Y, et al. Anti-BCMA CAR T-cell therapy bb2121 in relapsed or refractory multiple myeloma. *N Engl J Med*. 2019;380(18):1726-1737.
29. Shah N, Alsina M, Siegel DS, et al. Initial results from a phase 1 clinical study of bb21217, a next-generation anti Bcma CAR T therapy. *Blood*. 2018;132(suppl 1):488.
30. Mailankody S, Htut M, Lee KP, et al. JCARH125, anti-BCMA CAR T-cell therapy for relapsed/refractory multiple myeloma: initial proof of concept results from a phase 1/2 multicenter study (EVOLVE). *Blood*. 2018;132(suppl 1):957.
31. Mailankody S, Ghosh A, Staehr M, et al. Clinical responses and pharmacokinetics of MCAH171, a human-derived Bcma targeted CAR T cell therapy in relapsed/refractory multiple myeloma: final results of a phase I clinical trial. *Blood*. 2018;132(suppl 1):959.
32. Liu Y, Chen Z, Fang H, et al. Durable remission achieved from Bcma-directed CAR-T therapy against relapsed or refractory multiple myeloma. *Blood*. 2018;132(suppl 1):956.
33. Li C, Wang Q, Zhu H, et al. T cells expressing anti B-cell maturation antigen chimeric antigen receptors for plasma cell malignancies. *Blood*. 2018;132(suppl 1):1013.
34. Jiang S, Jin J, Hao S, et al. Low dose of human scFv-derived BCMA-targeted CAR-T cells achieved fast response and high complete remission in patients with relapsed/refractory multiple myeloma. *Blood*. 2018;132(suppl 1):960.
35. Gregory T, Cohen AD, Costello CL, et al. Efficacy and safety of P-Bcma-101 CAR-T Cells in patients with relapsed/refractory (r/r) multiple myeloma (MM). *Blood*. 2018;132(suppl 1):1012.
36. Green DJ, Pont M, Sather BD, et al. Fully human Bcma targeted chimeric antigen receptor T cells administered in a defined composition demonstrate potency at low doses in advanced stage high risk multiple myeloma. *Blood*. 2018;132(suppl 1):1011.
37. Shi X, Yan L, Shang J, et al. Tandem autologous transplantation and combined infusion of CD19 and Bcma-specific chimeric antigen receptor T cells for high risk MM: initial safety and efficacy report from a clinical pilot study. *Blood*. 2018;132(suppl 1):1009.
38. Majzner RG, Mackall CL. Tumor antigen escape from CAR T-cell therapy. *Cancer Discov*. 2018;8(10):1219-1226.
39. Sotillo E, Barrett DM, Black KL, et al. Convergence of acquired mutations and alternative splicing of CD19 enables resistance to CART-19 immunotherapy. *Cancer Discov*. 2015;5(12):1282-1295.
40. Hamieh M, Dobrin A, Cabriolu A, et al. CAR T cell trogocytosis and cooperative killing regulate tumour antigen escape. *Nature*. 2019;568(7750):112-116.
41. Chen KH, Wada M, Pinz KG, et al. A compound chimeric antigen receptor strategy for targeting multiple myeloma. *Leukemia*. 2018;32(2):402-412.
42. Zah E, Lin MY, Silva-Benedict A, Jensen MC, Chen YY. T cells expressing CD19/CD20 bispecific chimeric antigen receptors prevent antigen escape by malignant B cells. *Cancer Immunol Res*. 2016;4(6):498-508.
43. Wang X, Walter M, Urak R, et al. Lenalidomide enhances the function of CS1 chimeric antigen receptor-redirected T cells against multiple myeloma. *Clin Cancer Res*. 2018;24(1):106-119.
44. Sommer C, Boldajipour B, Kuo TC, et al. Preclinical evaluation of allogeneic CAR T cells targeting BCMA for the treatment of multiple myeloma. *Mol Ther*. 2019;27(6):1126-1138.
45. Mathur R, Zhang Z, He J, et al. Universal SLAMF7-specific CAR T-cells as treatment for multiple myeloma. *Blood*. 2017;130(suppl 1):502.
46. Helsen CW, Hammill JA, Lau VWC, et al. The chimeric TAC receptor co-opts the T cell receptor yielding robust anti-tumor activity without toxicity. *Nat Commun*. 2018;9(1):3049.
47. Topp MS, Duell J, Zugmaier G, et al. Evaluation of AMG 420, an anti-BCMA bispecific T-cell engager (BiTE) immunotherapy, in R/R multiple myeloma (MM) patients: updated results of a first-in-human (FIH) phase I dose escalation study. *J Clin Oncol*. 2019;37(15 suppl):8007.
48. Trudel S, Lendvai N, Popat R, et al. Antibody-drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety and efficacy from dose expansion phase I study. *Blood Cancer J*. 2019;9(4):37.
49. Kuruvilla J, Shepherd JD, Sutherland HJ, et al. Long-term outcome of myeloablative allogeneic stem cell transplantation for multiple myeloma. *Biol Blood Marrow Transplant*. 2007;13(8):925-931.