Chimeric Antigen Receptor T Cells in Multiple Myeloma

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KEYWORDS

• Multiple myeloma • CAR-T • BCMA • GPRC5D • BiTEs

KEY POINTS

- Chimeric antigen receptor (CAR)-T in multiple myeloma is a rapidly evolving field.
- Unlike most other malignancies, several markers are in advanced stages of clinical investigation in multiple myeloma, with several having a unique side effect profile.
- Alternate sources of CARs such as allogeneic CARs and the use of combination therapy will be critical in optimizing their use in myeloma therapy.

BACKGROUND

Multiple myeloma (MM) is the second most common hematological malignancy with an approximate incidence of up to 8.5 cases per 100,000 persons per year.[1–4] Despite considerable advances in treatment options, including new generations of proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, MM remains incurable with most patients relapsing and eventually dying of disease-related complications.[5]

A substantial proportion of patients either do not respond to current therapies or acquire resistance to treatment. Patients who are triple-class or penta-class refractory have an overall survival (OS) of 9.2 and 5.6 months, respectively, highlighting the need for improved therapeutic options for patients with MM.[6] It is well accepted that MM develops in a dysfunctional immune environment, evidenced by the fact that most active anti-MM therapies target the immune microenvironment in addition to neoplastic plasma cells.[7] This includes the immunomodulatory imide drugs (IMiDs), which upregulate IL-2 in T cells, proteosome inhibitors that induce immunogenic cell death, and monoclonal antibodies that promote antibody-dependent cellular toxicity and natural killer (NK)-cell-mediated tumor cell killing.[8] New treatment approaches

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Hematol Oncol Clin N Am 37 (2023) 1089–1105
https://doi.org/10.1016/j.hoc.2023.05.008 **hemonc.theclinics.com**

have continued to focus on immune modulation as a mechanism of anti-MM activity, including the development of antibody–drug conjugates (ADCs),[9] bispecific T-cell engaging antibodies (BiTEs), and chimeric antigen receptor (CAR) T cells. In particular, CAR-T cells and BiTEs have demonstrated high overall and durable responses leading to their recent approvals by the FDA.[10–14]

CAR-T cells are genetically engineered T cells modified ex vivo to express a chimeric receptor constituted by an antigen receptor containing a single-chain variable fragment (scFv) and an intracellular T-cell receptor (TCR) signaling domain.[15] The scFv is the recognition domain directed to target unique antigens on tumor cells. The intracellular domain of the CAR contains signaling components including domains from CD3-zeta (first generation), in addition to a costimulatory domain such as CD28 or 41bb (second generation) or both (third generation).[16] Of note, CAR-T target cell recognition and activation does not require major histocompatibility complex (MHC)-mediated presentation of antigens. During manufacturing, the patient's own T cells or donor-derived T cells, in the case of allogeneic CAR-T, are isolated and genetically modified to express the CAR. Adoptively transferred CAR-T cells are therefore equipped to induce and sustain long-lasting remissions through a synergy of antibody-based target cell recognition and the memory and effector function of T cells.[17] This approach differs from BiTEs, which serve as a molecular bridge bringing tumor cells into close proximity of native T cells and activating them.[18]

Here, we review recent data on targets in MM, approaches to developing cell therapies targeting them and the future outlook for this developing field.[19–22]

Chimeric Antigen Receptor T Sources

CAR-T cells are currently derived from 1 of 2 sources, either autologous or allogeneic T cells.[23] Autologous CARs have the advantage of limited risk of immune rejection, and no risk of inducing graft versus host disease, thus limiting potential toxicity. However, this approach does have several limitations including the ability to harvest T cells of adequate quality and quantity as many patients have been exposed to multiple lines of cytotoxic and anti-lymphocytic therapy that may alter T-cell function and numbers.[24] Also, the relatively long times needed to manufacture cells, often 4 to 6 weeks, can limit use in patients with aggressive or rapidly progressive disease.[25]

Efforts are ongoing to develop novel manufacturing approaches to decrease the time in culture (10–14 days for standard CARs), decrease vein-to-vein time, and potentially improve the quality of the CAR T-cell product by selecting cells with more favorable T-cell phenotypes. These approaches have used shortened ex vivo manufacturing time completed in as little as 2 days with cell expansion occurring in vivo. Preliminary results have demonstrated promising response rates and evidence of selection for CAR T-cell products enriched for stem and central memory phenotypes.[26–28] Whether these approaches will lead to improved outcomes for patients remains to be seen.

Allogenic CAR-T cells represent an off-the-shelf alternative to traditional CAR manufacturing. The potential immunogenicity and the short persistence of the product remain the main challenges to using allogenic CAR-T cells.[29,30] A second issue is the potential for graft versus host disease (GVHD) driven by the infused T cells. A principal driver of GVHD following allogeneic CAR T-cell administration is thought to be the presence of $\alpha\beta$ T cells, the cell type mostly commonly used to generate CAR-T cells. Two main strategies have been developed to reduce the risk of GVHD: the selection of virus-specific T cells that do not target host antigens and the genetic ablation of the endogenous TCR locus.[31,32] The use of virus-specific memory T cells during hematopoietic stem cell transplantation was able to control viral infections without occurrence

of GVHD.[33,34] A small clinical trial using allogeneic virus-specific T cells expressing the anti-CD19 CAR construct demonstrated that these were safe and capable of anti-tumor activity without clinical manifestation of GVHD. New clinical trials are ongoing using anti-CD19 and anti-CD30 CAR-T cells engineered with Epstein–Barr virus-specific allogeneic T cells.[30] To overcome host recognition and rejection, allogeneic CAR-T manufacturing strategies have used the deletion of antigens like CD52 such that anti-CD52 antibodies can be used during lymphodepletion to selectively remove host T cells.[30]

Targets in Multiple Myeloma

In the ideal world, the target for cell therapies would be expressed at a high level on malignant plasma cells, not be expressed on any normal tissues, and be required for MM cell viability thus limiting the risk of antigen loss. Much work has focused on identifying such targets and most trials for CAR-T in MM have primarily focused on the B-cell maturation antigen (BCMA). BCMA is the target for the 2 FDA-approved CAR T-cell products in MM.[35] It is predominantly expressed on differentiated B cells and has high expression on malignant plasma cells.[19] BCMA, also known as TNF receptor superfamily 17 (TNFRSF17), is a cell surface receptor and functions to promote prosurvival signals upon binding to its ligands—B-cell activator of the TNF family (BAFF) and a proliferation inducing ligand (APRIL)—participating in the proliferation of MM cells.[20] The extracellular domain of BCMA can be cleaved off of the surface of cells by the membrane-bound protease γ-secretase and a soluble portion can thus be shed from MM cells (sBCMA). sBCMA serves as a biomarker of MM tumor burden and shedding may limit therapeutic efficacy by decreasing the concentration of antigen on the membrane of MM cells.[21]

In addition to BCMA, other agents under development target myeloma-specific antigens including G protein-coupled receptor class C group 5 member D (GPRC5D) and Fc receptor homolog 5 (FcRH5) and have shown initial promise in patients with MM, even among those who have previously been exposed to BCMA-targeting drugs.[22] GPRC5D is normally expressed only in the hair follicle and some epithelial cells and is not expressed on normal plasma cells.[36] However, it was identified because of its high expression in neoplastic plasma cells and MM cell lines. Its function in normal skin cells and in neoplastic plasma cells is unknown. Importantly, its expression is independent of BCMA, potentially allowing dual targeting of these antigens.[36,37,38] GPRC5D-based CAR-T cells as well as a BiTEs are undergoing advanced stages of development and are discussed more below.[36,37–39]

FcRH5 is a type I membrane protein that is expressed on B cells and plasma cells and is found on myeloma cells with near 100% prevalence.[40] The function of FcRH5 is unknown, but its expression is higher on neoplastic as compared to normal plasma cells.[41] ADCs and BiTEs have been developed to target this antigen. BFCR4350 A, a humanized bispecific antibody, targets the most membrane-proximal domain of FcRH5 on MM cells and CD3 on T cells. Initial safety and activity data with BFCR4350 A have been encouraging in heavily pretreated myeloma patients.[40,42]

CD138 has been a target of interest in myeloma for many years as it is used as one of the pathologic hallmarks of plasma cells. A CAR-T targeting CD138 demonstrated modest activity but the broad expression of CD138 in epithelial, endothelial, and vascular smooth muscle cells, continues to be a concern in utilization of this target.[43,44]

Although CD19 is expressed in only a subset of patients with MM, the availability of highly active CARs targeting this antigen has led to their use in patients with MM with mixed results.[45] Although there have been reports of deep and durable responses, it is unclear how generalizable this is. Initial efforts to utilize co-infusion of anti-BCMA and

anti-CD19 CARs have not demonstrated improved activity over anti-BCMA CARs alone.[46] However, interest still remains in this approach and dual CARs such as GC012 F targeting BCMA and CD19 manufactured in under 36 hours have also made it to early phase clinical trials.[28]

In addition to these well-validated targets, a number of other antigens are being explored in patients with MM.[25] Dual targeting CARs against BCMA and CD38, the antigen targeted by monoclonal antibodies daratumumab and isatuximab, have shown evidence of activity and long-term persistence in initial studies.[22,25] The CARAMABA project is currently utilizing anti-SLAMF7, the antigen targeted by elotuzumab, CARs developed using a sleeping beauty transposon-based manufacturing strategy and is currently recruiting patients.[47] However, preclinical data have looked promising results from the first-in-human study that has not been publicly presented. Kappa and Lambda light chain, which are expressed on the surface of most MM cells, have also been targeted by CAR-T cells in preclinical models and remain a promising approach.[48] Finally, other mature B-cell sell surface molecules such as APRIL are potential targets in MM and CAR-T cells against these targets are being developed.[49,50]

Autologous Chimeric Antigen Receptor T Cells

Several autologous CAR T-cell products have been studied in clinical trials and 2 were recently FDA approved, fundamentally changing the treatment paradigm for patients with relapsed and refractory MM (**Table 1**). Idecabtagene vicleucel (ide-cel, bb2121) is a BCMA-directed CAR T-cell therapy with a humanized scFv and a 41BB costimulatory domain.[13] In the phase 1/2 KaRRMa-1 study, 140 patients with heavily pretreated relapsed and refractory MM were enrolled and 128 patients were infused with ide-cel at doses ranging from 150 to 450 million cells following standard lymphodepletion with fludarabine and cyclophosphamide. With a median follow-up of 13.3 months, 94 of 128 patients (73%) had a response, and 42 of 128 (33%) achieved a complete response (CR) or better. The side effect profile was consistent with other CAR-T products with hematologic adverse events (AE) being most common: neutropenia (91%), anemia (70%), and thrombocytopenia (63%) were the most common events. Cytokine release syndrome (CRS) was reported in 84% of patients with only 7 (5%) being grade 3 or higher. Neurotoxic effects manifested as the immune effector cell-associated neurotoxicity syndrome (ICANS) developed in 18% of patients and were grade 3 in 4 patients (3%). The median time to the onset of CRS was 1 day (range, 1–12), with a median duration of 5 days (range, 1–63). Management of CRS and ICANS included use of IL-6 blocking agents such as tocilizumab in 52% and glucocorticoids in 15% of patients. Three patients (2%) died within 8 weeks of infusion from ide-cel related AEs (bronchopulmonary aspergillosis, gastrointestinal hemorrhage, and CRS). One patient (1%) died between 8 weeks and 6 months from an ide-cel related AE (cytomegalovirus pneumonia).[13] These data led to the FDA-approval of ide-cel in 2021 for patients with MM relapsed after at least 4 prior lines of therapy.

Data from the confirmatory phase 3 randomized KaRMMa-3 trial were recently published.[51] A total of 386 patients with MM relapsed after at least 3 prior lines underwent randomization: 254 to ide-cel and 132 to standard-of-care chemotherapy. At a follow-up of 18.6 months, the median progression-free survival was 13.3 months in the ide-cel group, as compared with 4.4 months in the control group (hazard ratio for disease progression or death, 0.49). The overall response rate (ORR) was 71% in the ide-cel group and in 42% in the standard-regimen group ($P < 0.001$); a complete response occurred in 39% and 5% of patients, respectively. Data on OS are still immature.[51]

Efforts have been made to promote the production of CAR-T cells with favorable characteristic, including increased number of stem and central memory like T cells.

Table 1
Clinical trials of autologous chimeric antigen receptor T cells and their outcomes

	Ide-cel KARMMA[13] (n = 128)	Cilta-cel CARTITUDE- 1[12] (n = 97)	bb21217 CRB- 4029[54] (n = 69)	P-BCMA 101 PRIME[84] (n = 53)	Orva-cel EVOLVE[85] (n = 62)	CT053[7] (n = 20)	ALLO-715 UNIVERSAL[63,11] (n = 31)	MCARH109 (n = 17)
Phase	II	Ib/II	I	I/II	I/II	I	I	I
Target/Costim	BCMA/41BB	BCMA/4-1BB	BCMA/41BB	BCMA/41BB	BCMA/4-1BB	BCMA/4- 1BB	BCMA/4-1BB	GPRC5D/4-1BB
scFv	Chimeric mouse	Chimeric llama	Chimeric mouse	Chimeric mouse	Human	Human	Human	
Specificity	Autologous	Autologous	Autologous - PI3K inhibitor	Autologous—piggyBac	Autologous	Autologous	Allogenic CD52 & TCR Kos	Autologous
No. of infused CAR-T cells	150–450 M	0.75 M/kg	150–450 M	51–1178 M	150–600 M	50–180	40–180 M	24–450 M
Population age, median (range) years of prior lines, median (range)	61 (33–78)	61 (43–78)	62 (33–76)	60 (42–74)	61 (33–77)	55 (39–67)	65 (46–76)	60(38–76)
# of prior lines, median (range)	6 (3–16)	6 (3–18)	6 (3–17)	8 (2–18)	6 (3–18)	4 (2– 11)	5 (3– 11)	5
Triple-/Penta- refractory	84%/26%	86%/28%	64%/NR	60%/NR	94%/48%	NR	NR	94%/NR
Efficacy	@450 M:							
ORR	82%	98%	60%	50%–75%	92%	100%	50%–75%	44%–90%
CR, rate	39%	80%	28%	NR	36%	35%	NR	35%
PFS, median months	12.1	66%	NR	NR	NR	NR	NR	NR
CRS All grade/grade $\geq$ 3	96%/6%	95%/5%	70%/4%	17%/0%	89%/3%	79%/0%	45%/0%	88%/5%
Median onset, days (range)	1 (1– 10)	7 (1–12)	2 (1– 20)	NR	2 (1–4)	2 (1–4)	NR	NR
Median duration, days (range)	7 (1–63)	4 (1–97)	4 (1–28)	NR	4 (1–10)	4 (1–8)	NR	NR
Tocilizum ab/steroid use	67%/22%	69%/22%	45%/15%	7%/6%	76%/52%	32%/21%	19/10	53%/24%
ICANS All Grade / Grade 3	@450M: 20% / 6% Rest : 17% / 1%	12% / 9%	16% / 4%	4% / 4%	13% / 3%	NR	11% / 0%	0% / 0%

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Table 1
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Median onset, days (range)	2 (1–10)	8 (3–12)	27 (11–108)	7 (2–24)	NR	4 (1–6)	NR	NA	NR
Median duration, days (range)	5 (1– 22)	4 (1–12)	75 (2–160)	2 (1–188)	NR	4 (1–10)	NR	NA	NR

Main reported clinical trials of CAR-T cells in multiple myeloma. Data of efficacy and safety are shown.

Abbreviations: Costim, costimulatory domain; CR, complete remission; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ORR, overall response rate; PFS, progression free survival; scFv, single-chain variable fragment.

The use of PI3K inhibitors has been shown to alter T-cell differentiation in vitro.[52,53] This was the basis of the CRB-402 trial of bb21217, which used the same primary CAR-T construct as in the KaRMMa studies with the addition of a PI3K inhibitor (bb007) during ex vivo culture to enrich the product for memory-like T cells and decrease the proportion of highly differentiated or senescent T cells. Seventy-two patients received bb21217 at doses ranging from 150 to 450 million CAR-T cells with a median follow-up for all patients of 9.0 months. Toxicity and overall response rates were similar to that seen in the KaRMMa-1 study. Analysis of peripheral blood samples collected 15 days post bb21217 infusion demonstrated that patients with higher than the median number of CD8+ CAR-T cells expressing CD27 and CD28 had significantly longer duration of response (DOR) compared to patients with lower than the median values.[54] However, this did not result in improved overall outcomes and development of this product has been stopped.

The CARTITUDE-1 study utilized ciltacabtagene autoleucel (cilta-cel), a CAR T-cell therapy that differs from other products due to the presence of 2 BCMA-targeting single-domain antibodies in its extracellular domain, thus increasing the avidity for BCMA. One-hundred thirteen patients with relapsed and refractory MM were enrolled in this study, 97 of whom received a cilta-cel infusion at the recommended phase 2 dose of 0.75×10^6 CAR + viable T cells per kilogram. Median follow-up was 12.4 months and ORR was 97% with 67% achieving a CR or better. The median time to first response was 1 month and responses deepened over time. The median DOR was not reached (95% CI 15.9—not estimable), nor was the PFS (16.8—not estimable). The 12-month progression-free rate (PFR) was 77% and OS rate was 89%. Fourteen deaths occurred in the study: 6 due to treatment-related AEs, 5 due to progressive disease, and 3 due to treatment-unrelated AEs. CRS occurred in 95% of patients, with 6% grade 3. Median time to CRS onset from cilta-cel infusion was 7 days and median duration was 4 days (excluding 1 patient with 97-day duration). Patients received tocilizumab (67%), corticosteroids (22%), and anakinra (19%). Neurotoxicity after cilta-cel infusion, including ICANS, occurred in 21% of 97 patients, but only 2 patients had grade 3 events.

The median time to ICANS onset was 8 days, and the median duration was 4 days. ICANS resolved in all 16 patients.[12] In a small number of patients, late neurotoxicity following cilta-cel was observed with development of gait disturbance and parkinsonian-like symptoms. The mechanism by which this occurs is unknown but has been hypothesized to be related to low-level expression of BCMA in the substantia nigra.[55] Efforts to prevent this devastating complication have focused on minimizing the degree of CAR-T expansion by minimizing disease burden at the time of infusion. Recent updated data showed that at a median follow-up of 27.7 months, the median PFS and OS were still not reached; 27-month PFS and OS rates were 54.9% and 70.4% (95% CI, 60.1–78.6), respectively.[56] Overall response rates and DOR have clearly been higher with cilta-cel as compared to ide-cel, albeit with increased rates of CRS and ICANS, but the reasons for this remain unclear and are an important area of further investigation. A confirmatory phase 3 study is underway.

Resistance to anti-BCMA therapies has been attributed a number of mechanisms including downregulation of BCMA, mutation or deletion of the *TNFRSF17* gene, as well as lack of persistent or activity of the engineered T cells.[57–60] Thus, novel therapies targeting new MM antigens and approaches to overcoming T-cell exhaustion and senescence will be needed in the future to combine with BCMA-targeting agents.[38]

One such approach is the use of CAR-T cells targeting GPRC5D. A phase I trial of a GPRC5D targeting CAR-T cell, MCARH109, enrolled 17 patients with relapsed and refractory MM, some of whom had been previously exposed to anti-BCMA therapy.[37] A

response was reported in 71% of the patients in the entire cohort. Importantly, patients who had received prior anti-BCMA therapy also showed responses. At the 450×10^6 CAR T-cell dose, 1 patient had grade 4 CRS and ICANS, and 2 patients had a grade 3 cerebellar disorder of unclear cause. No cerebellar disorders, ICANS of any grade, or CRS of grade 3 or higher occurred in the 12 patients who received doses of 25×10^6 to 150×10^6 cells. As expected, based on the normal tissue expression of GPRC5D, on-target but off-tumor toxic effects included transient rash (18%), dysgeusia (12%), and nail changes (65%), all of which were limited to grade 1 or 2. As compared with the bispecific GPRC5D T-cell engager talquetamab, the frequency and severity of rash and dysgeusia were lower with MCARH109.[37,39]

CD19 CAR-T cells have been utilized in the treatment of myeloma with examples of patient responses leading to the idea of targeting both CD19 and BCMA in the same patients.[45]

Approaches to dual targeting of CAR-T cells are in early stages. GC012 F is an autologous CAR-T therapeutic dual-targeting BCMA and CD19 using a next-day manufacturing platform. Sixteen transplant-eligible newly diagnosed patients with high-risk MM received GC012 F infusion in a phase 1 clinical trial. The ORR was 100% and 87.5% of patients achieved a CR or better with all evaluable patients achieving minimal residual disease (MRD) negativity in all dose levels. Because patients also received standard MM induction therapy prior to CAR-T infusion the role of GC012 F in mediating these responses and the importance of the CD19-targeting component cannot be assessed. Only 25% of patients experienced grade 1 to 2 CRS. No cases of ICANS or other neurotoxicity of any grade were observed.[25,28]

A phase I clinical trial of anti-BCMA chimeric antigen receptor T cells (CAR-T-BCMA) with or without anti-CD19 CAR-T cells (huCART19) in patients with MM with low burden of disease responding to third- or later-line therapy (N = 10) or high-risk patients responding to first-line therapy (N = 20), followed by IMiD maintenance was conducted by the group at UPenn. No high-grade CRS and only one instance of low-grade neurologic toxicity was observed. Data on responses were limited and difficult to interpret; however, these data do provide additional evidence for the safety of administering CAR-T cells in earlier lines of therapy.[46] Multiple efforts are currently underway to provide CAR-T cells to patients at earlier stages in disease treatment including in newly diagnosed patients, possibly as a replacement for autologous transplantation, as consolidation for patients who do not achieve an adequate response to induction and in high-risk patients who relapse quickly after first-line therapy.[61]

Other novel approaches to developing antigen recognition domains have also shown activity and may provide unique methods for making dual-targeting CAR-T cells in the future. CART ddBCMA is an autologous anti-BCMA CAR T-cell therapy with a unique, synthetic binding domain targeting BCMA. Instead of the typical scFv approach, the binding domain is a small stable protein, called a D-Domain, comprising only 73 amino acids. The small size of the domain allows for high expression on the surface of T cells and related technology allowing separate infusion of CAR-T cells and the antigen-specificity domain may provide flexible binding domains with the ability to target multiple antigens. Initial data utilizing CART-ddBCMA in 31 patients showed an ORR of 100%. Ninety percent of patients had CRS, with most cases being low grade. No neurologic side effects were noted.[62]

Allogeneic Chimeric Antigen Receptor T Cells

Allogeneic CAR-T cells have been of great interest given the potential ease of use and rapid availability for patients with aggressive and rapidly progressive disease. To bring

Table 2
Allogeneic chimeric antigen receptor T cells in multiple myeloma

Developer	CAR T-Cell Product	Target Antigen	Allogeneic Technology	Tools and Vectorization	Development Phase and Trial Reference
Allogene Therapeutics	ALLO715	BCMA	*TRAC* and *CD52* KO	TALEN mRNA (KO)	Preclinical
Celyad	CYAD-101	NKG2D	Expression of a TRAC-inhibitory molecule peptide consisting of a truncated form of CD3ζ	Retroviral vector (co-expression of TRAC-inhibitory molecule with CAR)	Phase I in CRC (NCT03692429, alloSHRINK)
Poseida Therapeutics	P-BCMAALL01	BCMA	*TRAC* and MHC class I KO	CRISPR gRNA and dead Cas9 fused to Clo51 nuclease (Cas-CLOVERTM) (KO)	Preclinical

Abbreviations: AAV6, adeno-associated virus 6; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BCMA, B-cell maturation protein (also known as TNFRSF17); BPDCN, blastic plasmacytoid dendritic cell neoplasm; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CLL1, C-type lectin-like molecule 1; CRC, colorectal cancer; CTL, cytotoxic T cell; CTLA4, cytotoxic T-lymphocyte-associated antigen 4; EBV, Epstein–Barr virus; gRNA, guide RNA; iPSC, inducible pluripotent stem cell; IND, investigational new drug; KO, knockout; MHC, major histocompatibility complex; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; PDC1, programmed cell death protein 1 (gene); PEBL, protein expression blocker; shRNA, short hairpin RNA; TALEN, transcription activator-like effector nuclease; TCR, T-cell receptor; TI, targeted integration; TRAC, T-cell receptor alpha constant chain; ZFN, zinc-finger nuclease.

these to the clinic a variety of constructs and production modalities are being developed (Table 2).

In the UNIVERSAL phase I trial a single dose of ALLO-715 was infused into patients with MM following lymphodepletion with a regimen containing fludarabine, cyclophosphamide and ALLO647, which is an anti-CD52 monoclonal antibody. The lymphodepletion chemotherapy used for this allogeneic CAR-T was significantly more intensive than that used for most autologous CARs with fludarabine being administered at 90 mg/m^2 and cyclophosphamide at 900 mg/m^2. Fifty-three patients were enrolled, all of whom received product. CRS requiring the use of tocilizumab and/or corticosteroids across all patients was 19% and 15%, respectively. ICANS was identified in 11% of patients. The most common grade greater than or equal to 3 AEs were anemia (41.2%), neutropenia (41.2%), lymphopenia (29.4%), and thrombocytopenia (29.4%) which were likely enhanced due to the higher doses of lymphodepletion used in this study. Infectious complications occurred in 56% of patients, 29% of which were grade greater than or equal to 3. Of all infections, viral infections or low-grade viral reactivation were most common, potentially attributable to the use of an anti-CD52 antibody in the lymphodepletion regimen. Among patients who received the highest dose (320×10^6 CAR + T cells), responses were highest among those who also received higher doses of lymphodepleting chemotherapy. In this group, the ORR was 80% with 50% achieving a very good partial response or better (VGPR) and 20% achieving a CR.[63]

P-BCMA-ALLO1 is an allogeneic CAR-T manufactured using a nonviral transposon-based integration system that introduces a humanized anti-BCMA CAR producing a highly enriched T stem cell memory product. The endogenous TCR and the beta-2 microglobulin gene are eliminated via use of a Cas-CLOVER site-specific gene editing system to eliminate GVHD and reduce MHC class I expression.[64] Seven patients have been treated with P-BCMAALLO1 with 1 patient achieving a VGPR and 2 patients with a partial response.[65]

Other products have been less successful, including CYAD-101, a NKG2D-based allogeneic CAR-T product that was being evaluated in patients with relapsed and refractory MM. Although initial data suggested activity, this study was paused and the product was discontinued on account of patient deaths related to pulmonary complications.[66]

Early results utilizing allogeneic CAR-T therapy in patients with MM have shown promising results, but limitations related to short persistence and the requirement for intensive lymphodepleting regimens that leave patients susceptible to atypical infections remain major obstacles to their use. Significant work is needed to overcome these challenges, better manage infectious complications, improve persistence and long-term outcomes, and bring these agents to the clinic.

Natural Killer-Based Chimeric Antigen Receptor Cells

NK cells are unique innate immune cells that can manifest rapid and potent cytotoxicity of pathogens and cancer cells without the requirement of prior sensitization or recognition of classical peptide antigens. CAR-transduced NK (CAR-NK) cells may be able to simultaneously improve efficacy and control adverse effects including CRS, neurotoxicity, and GVHD. Moreover, because of the inherent properties of NK cells, allogeneic CAR-NK cells could represent an off-the-shelf product satisfying the clinical demand for large-scale manufacture for cancer immunotherapy attribute to the cytotoxic effect via both NK cell receptor-dependent and CAR-dependent signaling cascades.[25,67,68] Currently, no human data for CAR-NK cells have been reported in patients with MM but preclinical studies have shown promising results for the therapeutic efficacy of NKs expressing anti-BCMA CARs with a soluble form

of the tumor necrosis factor-related apoptosis-inducing ligand (sTRAIL).[67] This remains an exciting area for future development.

Induced Pluripotent Stem Cell-Derived Chimeric Antigen Receptor Cells

T cells derived from differentiated induced pluripotent stem cells (iPSCs) may offer a platform to produce a virtually endless number of off-the-shelf allogeneic T cells. Several advances have been made recently in the establishment of systems for iPSC-based CAR T-cell generation including the use of feeder free platforms for differentiating T cells in a sustainable manner for a variety of applications. Phase I clinical data utilizing FT576, an iPSC-derived anti-BCMA CARNK cell that can be combined with daratumumab to promote antibody-directed cellular cytotoxicity, showed activity in patients with relapsed and refractory MM.[69,70]

Dendritic Cell-Based Vaccination for Multiple Myeloma

Tumor vaccines in which patient derived MM cells are fused with autologous dendritic cells (DCs) such that a broad array of tumor antigens are presented in the context of the antigen presenting machinery of the DC fusion partner has shown preliminary evidence of activity in MM. Thirty-six patients with newly diagnosed MM received serial vaccinations with DC/MM fusion cells either prior to or following autologous transplantation. Seventy-eight percent of patients achieved a response of at least VGPR and 47% achieved a CR. Remarkably, 24% of patients who achieved a partial response following transplant converted to CR after vaccination consistent with possible vaccine-mediated effects on residual disease. Significant work is ongoing to develop approaches to potentially improve cell selection to increase antitumor response. In addition, work is ongoing to combine DC vaccines with other immune modulators such as the IMiD drugs to alter the tumor and immune microenvironment.[71–74] There is rationale to combine this approach with CAR T-cell therapy to improve T-cell-mediated killing and promote a bystander effect, and preclinical work is ongoing to test this approach.[75]

Combination Approaches

As discussed above, many of the agents used during standard of care therapy for MM have immune-mediated effects. Thus, combinations of cell therapies with both standard approved agents as well as novel immune modulators represent an exciting opportunity to improve patient outcomes.

Gamma Secretase Inhibitors

Downregulation or biallelic loss of BCMA on MM cells following CAR T-cell therapy is a known mechanism of relapse.[57] The multi-subunit γ-secretase complex (GS), an intramembrane protease, reduces CAR T-cell function via cleavage of BCMA and subsequent shedding of the soluble BCMA (sBCMA) extracellular domain into the circulation. Multiple inhibitors of gamma secretase have been developed, initially as therapies for Alzheimer's disease, and are now being tested for combinatorial efficacy with BCMA-targeting agents.[76] A recent phase 1 first inhuman trial of escalating doses of BCMA targeted CAR-T cells in combination with a GS inhibitor (JSMD194) for patients with relapsed or refractory MM. All 18 treated patients completed the 5-day run-in with JSMD194. The only patient who did not demonstrate an increase in BCMA antibody binding capacity after GS inhibitor run-in had previously received BCMA targeted therapy and BCMA expression at screening was virtually absent. With follow-up of 20 months, the median PFS was 11 months. Among patients without prior exposure to BCMA targeted therapy (n = 11), the median PFS has not been

reached, whereas among those previously exposed to BCMA targeted therapy (n = 7), the median PFS was 2 months.[67,77] These GS inhibiting agents may be able to be combined with currently approved anti-BCMA drugs, although the optimal order and timing of dosing, and approaches to managing toxicity have yet to be worked out.

Immunotherapeutic Drugs

Regulation of the T-cell phenotypes post CAR-T Infusion has been thought to significantly affect CAR-T activity and clinical outcomes. Thalidomide analogs, such as lenalidomide, have long been known to alter T-cell function and promote secretion of IL2, thought to mediate their immune modulatory effects.[78] Thus, there is significant rationale for combining thalidomide analogs with other immune targeting therapies. In a study combining lenalidomide with CS1 CAR-T cells, in tumor bearing mice, it was found that lenalidomide potentiated the cytotoxicity and memory maintenance of the CARs along with an increase in Th1 cytokine production and immune synapse formation.[79] Lenalidomide has long been used for post-transplant maintenance in MM and potentially could continue to play a similar immunomodulatory role in the post CAR-T setting.[80] Trials are underway to test the use of thalidomide analogs as maintenance following CAR T-cell infusion. Other combination therapies with bispecific antibodies, CAR-T cells and monoclonal antibodies that lead to immune checkpoint inhibition have also shown promise in preclinical models.[81,82,83] Further studies to evaluate rational combinations of checkpoint inhibitors with anti-MM cell therapies are in development.

SUMMARY

In just a short few years a tremendous amount of work has been done toward developing cell therapies for MM, yielding the first approvals for these therapies and fundamentally changing the course of treatment for patients with relapsed and refractory MM. However, patients still uniformly relapse; thus, continued work is needed to develop rational combinations of therapies to improve outcomes and to develop novel cell therapy approaches that may eventually produce cures for this disease.

CONFLICTS OF INTEREST

P. Shah reports no relevant conflicts of interest. A.S. Sperling reports consulting fees from Adaptive Technologies, Novartis, and Roche.

DISCLOSURE

Dr P. Shah reports no relevant conflicts of interest.

ACKNOWLEDGMENTS

P. Shah was supported by the Holland Leukemia Research Fund. A.S. Sperling was supported by grants from the NCI, United States (K08CA252174) and DOD, United States (CA210827).

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