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Review article

From spear to trident: Upgrading arsenal of CAR-T cells in the treatment of multiple myeloma

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ABSTRACT

Multiple myeloma (MM), marked by abnormal proliferation of plasma cells and production of monoclonal immunoglobulin heavy or light chains in the majority of patients, has traditionally been associated with poor survival, despite improvements achieved in median survival in all age groups since the introduction of novel agents. Survival has significantly improved with the development of new drugs and new treatment options, such as chimeric antigen receptor T-cell therapy (CAR-T), which have shown promise and given new hope in MM therapy. CARs are now classified as first-, second-, and third-generation CARs based on the number of monovalent to trivalent co-stimulatory molecules incorporated into their design. The scope of this review was relatively narrow because it was mainly about a comparison of the literature on the clinical application of CAR-T therapy in MM. Thus, our goal is to provide an overview of the new advances of CAR-T cells in the cure of MM, so in this review we looked at the progress of the clinical use of CAR-T cells in MM to try to provide a reference for their clinical use when managing MM.

1. Introduction

Multiple myeloma (MM) is an incurable type of malignant plasma cell tumor characterized by the uncontrolled proliferation of clonal plasma cells that often occurs in the elderly. With new drugs and treatment regimens, control of MM has gradually and dramatically been improved. Among the treatment regimens available for MM, immunotherapy is one of the most promising developments in terms of therapeutic efficacy in hematologic malignancies. Significant progress has been made in chimeric antigen receptor T cell therapy (CAR-T), which is distinctly different from traditional drugs. Therefore, to critically summarize advances in CAR-T therapy in MM, we purposefully conducted a review, combining a large number of articles and review articles that were closely related to the topic we framed from the beginning. The review paper does not attempt to systematically review the entire literature on CAR-T therapy. Instead, only those studies meeting the inclusion criteria we set as using CAR-T in MM were eventually selected, narrowing down to approximately 110 studies that appeared to meet our criteria. Most articles dealing with CAR-T therapy for solid tumors were excluded, except for a few that introduced trivalent CAR-T therapy for solid tumors. Therefore, the review is developed based on the 110 literatures we focused on, starting first with a simple introduction to what MM is, followed by the pathophysiological etiology of MM, and then a simple description of a common treatment regimen of MM. We then mainly looked at monovalent, bispecific and trispecific targeting of CAR-T cells in the cure of MM, especially relapsed and refractory multiple myeloma (RRMM). It

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should be noted that this review is unlikely to address all aspects of CAR-T cell progression. Rather, we presented the story surrounding CAR-T cell cutting-edge MM therapy.

2. What is multiple myeloma (MM)?

Multiple myeloma (MM), like cancer in general, is characterized in most patients by abnormal proliferation of plasma cells and production of monoclonal immunoglobulin heavy chains (abbreviated as M protein) or light chains [1]. Originally documented by Waldenstrom J in 1960 [2], the presence of M protein in the blood of asymptomatic patients was from the beginning called "essential hypergammaglobulinemia". When it was later clinically discovered that patients with monoclonal gammopathy have a greater tendency to develop plasma cell malignancies, ie. mainly MM, Kyle RA concluded that such gammopathy may not be benign [3]. Thus, they coined the term MGUS, short for monoclonal gammopathy of undetermined significance [4], a precursor that consistently precedes MM in pathogenesis, if not all, as demonstrated by many recent studies [5–7].

With multiple genetic hits and branching disease evolution, MM, genetically, is a complex disease. Much previous work investigating the molecular mechanism of MM has established clear and close relationships between chromosomal aberrations, somatic mutations, activation of signaling pathways and RNA expression, as extensively reviewed elsewhere [8–10]. The emergence of technologies to define MM, such as high-throughput RNA sequencing and single-cell sequencing analysis [11–13], will greatly contribute to the understanding of MM pathogenesis. In addition, studies involving microRNA, circular RNA, alternative splicing and epigenetic profiling are also ongoing. Until now, the outcome of MM has been dismal, despite the fact that survival has more or less been prolonged after the clinical use of new regimens or agents such as thalidomide, lenalidomide and bortezomib, which have been successfully combined with each other and/or with cytotoxic drugs to form various regimens that have been thoroughly and clinically investigated [14].

3. Prognosis of MM

Prognostic factors in MM may be related to patients, tumor clone, and/or tumor mass. As previously shown [15], old age and poor performance are two independent prognostic factors that have consistently been shown to play a key role in predicting MM. Especially in the last ten years, the survival ability of people under 60 has improved significantly. In addition, current studies seem to support the view that renal function [16], heart rate and hypertension [17] are also unneglectable factors when evaluating the survival of MM, which were found to be associated with shorter survival. Nevertheless, by contrast, the most important factor related to prognosis is the cytogenetic abnormal status chiefly assessed by fluorescence in situ hybridization [18–21], including but not limited to abnormalities of chromosome 1 (1q gains, 1p losses),t (4, 14) (p16, q32), t(14, 16) (q32, q23), deletion of 17p13 and chromosome 22, which are associated with worse prognosis. Of note, cytogenetic abnormalities were not necessarily associated with shortened survival. A particularly informative example supporting this notion involves the translocation t(11,14)(q13,q32) [22], which has been reported to be associated with a favorable outcome in MM. However, a recent publication [23] tends to question the conclusion that translocation t (11, 14) does not show a favorable result in MM. Therefore, the prognostic significance of translocation t (11, 14) is still controversial [24] and requires further studies. Tumor mass is another well-accepted factor affecting survival. First defined by Durie BG and Salmon SE [25] using a mathematical model in 1975, the relationship between tumor mass and M protein has been widely accepted. A simpler classification method was recently proposed [26] and validated in a large cohort of 10,750 patients with MM at diagnosis. It required only two biochemical scores, namely serum albumin and β2-microglobulin. However, the effectiveness of this staging method seems to be questioned [27].Considering these limitations, further research and standard genomic classification are needed [28].

4. Conventional treatment of MM

Although major advances were achieved in the treatment of MM, relapse after therapy tends to occur in the majority of patients and hence strives for further treatment. Immunomodulatory drugs such as lenalidomide and thalidomide and the proteasome inhibitor bortezomib are a new regimen in the treatment of relapsed and refractory MM (RRMM), which has remained a major challenge in the last decade due to the development of greatly improved antitumor drugs. Not only does them directly target MM, but also exerts a dramatic inhibitory effect on tumor cells interacting with the bone marrow microenvironment. The advent of novel therapies targeting the tumor microenvironment has remarkably improved the prognoses for patients with RRMM. Good supporting examples [29,30] include bortezomib, a proteasome inhibitor, and the immunomodulatory agents thalidomide and lenalidomide, which are key agents in this setting. Combinations of these new agents with each other or with standard anti-MM agents are in clinical trials to further improve outcomes for RRMM patients. Conventional treatments for RRMM include dexamethasone, standard chemotherapy, and autologous hematopoietic stem cell transplantation (HSCT). High-dose chemotherapy salvaged by ASCT is now considered the standard of care for younger newly diagnosed patients. This treatment was originally developed to overcome the resistance of MM to conventional chemotherapy and was initially evaluated in patients with RRMM, contributing to improved response rates. A retrospective analysis performed of all patients undergoing first ASCT for MM between 1995 and 2019 in the European Society for Blood and Marrow Transplantation centers [31] revealed that despite continued progress in the treatment of MM, HSCT may seem to challenge the future role of MM. HSCT; However, HSCT remains central and indispensable in the MM treatment paradigm. To date, this approach has not been prospectively evaluated as part of a randomized trial in the setting of RRMM.

In RRMM, high-dose therapy combined with HSCT has been reported to be able to achieve pronounced progress-free survival but at the expense of substantial toxicity and even mortality brought about by treatment as such [32]. In addition, there is debate about the

optimal timing of HSCT, which remains to be determined [33]. Allogeneic transplantation has been regarded as a potential therapeutic approach after myeloablative induction. Although this approach may be able to achieve durable response rates, it was associated with gravely high mortality caused by treatment [34]. Because of this drawback, this treatment modality has been abandoned as a viable treatment option for most patients with MM [35]. Apart from the conventional curative approaches reviewed above, some novel agents have been developed, including thalidomide, lenalidomide and bortezomib. Extensive investigations have been carried out surrounding the monotherapy of these three novel agents or exploration of different combination regimens of each other or combinations with conventional agents, for instance, dexamethasone in the RRMM context, namely, triplet or doublet treatment approaches [36], demonstrating significant response rates and prolonged survival, either alone or in combination in patients with RRMM.

5. CAR-T therapy as a new therapy for MM after bone marrow transplantation

In spite of noteworthy advancements within the result of patients with MM and cutting edge treatment getting to be progressively viable and drawing out infection control [37], MM remains serious, and backslide remains unavoidable for the larger part of patients. Hence, with an expansive body of restorative choices being accessible [38], it is still pivotal to undertake to set up prescribed treatment alternatives for RRMM. In addition, the improvement of unused specialists with interesting antimyeloma action remains a tall need in this field. A great illustration is the accessibility of the monoclonal antibodies daratumumab and elotuzumab [39], which have significantly changed the treatment worldview and extended the alternatives for patients with RRMM. In expansion, modern approaches to MM administration, counting chimeric antigen receptor (CAR) T-cell treatment [40] and novel monoclonal antibodies with unique targets, are breakthroughs that are profoundly likely to alter the treatment landscape [41] within the year that takes after. Exceptionally as of late, significant advance has been made in controlling and curing relapsed/refractory huge B-cell lymphomas [42] by the clinical application of CAR treatment and checkpoint receptor inhibitory drugs. These extraordinary innovations have stimulated considerable intrigued within the field of immunotherapy, and inquire about patterns have driven to a multiplication of writing with respect to CARs within the immunotherapy of cancers. Considering these, here, in passages that follow, we are going primarily center on the new development of CAR T treatment within the MM setting. Other novel treatments, counting novel monoclonal antibodies or Bcl-2 restraint with venetoclax [43], will be disregarded.

6. Off-the-shelf CARs used for RRMM

While CAR-T therapy can be said to have changed the treatment paradigm for highly pretreated B-cell malignancies such as large B-cell lymphoma and MM, another important milestone achieved by CAR-T therapy was the development of a CAR therapy product such as Ciltacabtagene autoleucel (cilta-cel) [44], which has received Food and Drug Administration (FDA) approval and has been used in patients with RRMM. Several evidence from a multicenter study [45–48] showed that cilta-cel has a better potential to maximize effective therapy and minimize non-tumor toxicity, highlighting Cilta-cel as a new therapy that addresses unmet needs in patients with RRMM. Idecabtagene vicleucel (ide-cel) [49] is another CAR product approved by the FDA for the treatment of patients with RRMM. Multiethnic clinical trials have shown and highlighted the increased therapeutic potential of RRMM patients treated with Cilta-cel [50]. As much as prolonged and improved effect brought about by cilta-cel, it is not necessarily perfect. Considering the adverse side effects, such as hematologic toxic effects and cytokine release syndrome [51], caused by the use of ide-cel in RRMM, additional real-world data will be needed [47] to help provide further insights into the comparative efficacy and safety profiles of these treatments in RRMM as these treatments become more widely available. In addition to the two CAR-T products described above, the U.S. Food and Drug Administration approved 6 CAR-T-cell products [44], and the remaining four included tisagenlecleucel (tisa-cel), axicabtagene ciloleucel (axi-cel), brexucabtagene autoleucel (brexu-cel) and lisocabtagene maraleucel (liso-cel) in the last 5 years. These CARs have shown significantly improved outcomes for patients with B-cell non-Hodgkin lymphoma (NHL) and multiple

Table 1
Target used by CAR-T cells in the treatment of MM.

Antigen target	Expression on the surface of normal cells	Expression on the surface of MM cells	ClinicalTrials.gov Identifier
GPRC5D [61]	Hardly detected	Overexpressed	NCT04555551
BCMA [51]	Plasma and a few of mature B cells	Overexpressed	Approved by FDA
CD38 [62]	Pro-B, plasma, T, NK, myeloid progenitor cells	Highly expressed	NCT03464916 NCT03754764
CS1(CD319, CRACC or SLAMF7) [63]	A fraction of plasma, NK, DC,CD8+ and B cells	Overexpressed	NCT03958656 NCT04499339
CD138 [64]	Plasma cells	Highly expressed	NCT03672318
Kappa light chain [56]	Mature B cells		NCT00881920
CD56 [56]	NK, T, neuron cells	Strongly expressed on 70 % MM	NCT03473496 NCT03271632
CD19 [54]	B cells	A fraction of MM	NCT02135406
CD44v6 [65] CD174 (Lewis Y) [66]	Activated T cells, monocytes	43 % developmental MM	NCT04097301
CD229 [67]	B and T lymphocytes	strongly expressed	
NY-ESO-1 [56]	Hardly detected	Strongly expressed	
NKG2D [68]	Plasma, follicle, lung	Strongly expressed	NCT02203825

myeloma (MM). However, relapse and progression can occur after an initial response due to several mechanisms. On the other hand, CAR T cell therapy has not been widely used in solid tumors due to various obstacles. As a result, "younger generation" CAR T cells are developed and persist [44], overcoming these challenges to expand their applications.

7. Monovalent CAR T strategy

Despite continued dramatic improvements in MM outcomes, MM remains incurable and relapse is inevitable for the majority of MM patients, as previously noted. Recently, the use of chimeric antigen receptor engineered T-cell therapy (CAR-T) has shown great promise in the treatment of MM, including approaches targeting B-cell maturation antigen (BCMA) [52], CD138 [53], CD19 [54], orphan G protein-coupled receptor, class C group 5 member D (GPRC5D) [55], which showed significantly improved activity, including a sustained and profound response. For targets currently being investigated in preclinical or clinical trials for MM, see the comprehensive review by previous researchers [56–58] where the authors provided a comprehensive overview of CAR-T targets for MM, which include CD138, CD38, CS1, CD19, kappa light chain, CD56, CD44v6, Lewis Y, NY-ESO-1, CD229 (Table 1). Therefore, we omit this information here to avoid repeating its already published content. In addition to these well-used targets in CAR-T cell therapy, a number of new targets including CCR10, TXNDC11 and LILRB4 have been discovered, but have yet to be evaluated by integrating proteomic data with transcriptomic data [59]. Although this type of promising therapy is changing the paradigm of cancer treatment, especially for MM, CAR-T cells still have some limitations that have significantly compromised their safety and efficacy. An example is that CAR-T cells can cause on-target or off-target tumor toxicity [60] due to the induction of an autoimmune response caused by their antigen reactivity. In addition, CAR-T cells have a certain probability of losing antigen-specific reactivity *in vivo* due to antigen escape and may also lack *in vivo* persistence. Based on these defects that can occur when using monovalent CAR-T cells to treat cancer, concerted efforts are underway to overcome these limitations to make monovalent CAR-T cell therapy more effective and safer.

8. Bivalent CAR-T strategy

Killing two birds with one stone, which is also workable in CAR-T. With single target specificity, conventional CARs used in MM therapy can lead to tumor escape due to tumor heterogeneity [69]. Moreover, CAR-T cells can grow up to as high as ten thousand times in response to their antigen, which can cause serious side effects. The most important of these side effects is cytokine release syndrome (CRS), which can worsen in patients. Under these circumstances, there is a clinical need for continued improvement and optimization of CAR-T therapies for MM. A number of strategies have been proposed to boost the efficacy and safety of current CAR-T therapies. Dual-target CAR-T cells targeting combinations of two different genes, for example, BCMA and CD19 [70] or BMCA and GPRC5D [71], are now being assessed in clinical trials. Indeed, to overcome the specificity of CAR-T cells in MM, dual antigen targeting of CAR-T cells can be established using a split-dual CAR-T cell strategy. Kloss CC et al. first established this concept and demonstrated that it is fully functional [72]. Based on this concept, colleagues have since done a lot of extensive work in both solid and non-solid tumors. Compared to solid tumors [73], there have been few efforts to investigate the effects of dual-target CAR-T cell strategies in the treatment of MM (Table 2). For example, a recent article investigated bidirectional CAR-T cell therapy in MM [71]. This finding was so important and impressive that it was highlighted and commented upon [74]. In this study, Fernandez de Larrea C and associates [71] showed that CAR-T cells simultaneously target B-cell maturation antigen (BCMA) [39] and G protein coupled receptor class C group 5D (GPRC5D) in preclinical models of multiple myeloma, providing insight into the optimization of dual targeting designs for cellular therapy of MM. Given that targeting only BCMA, although exciting, experimental data revealed that the duration of response was always short, especially in individuals with low or negative BCMA expression [75]. To address this problem, the authors optimized conventional CAR-T cells targeting BCMA together with GPRC5D, another attractive target in MM, and compared dual targeting with monospecific BCMA or GPRC5D in MM in an *in vivo* tumor xenograft model.

and deliberately compared the dual-targeting approach with monospecific BCMA or GPRC5D in an *in vivo* tumor xenograft model of MM, attesting to the superiority of BCMA/GPRC5D dual-target approach over monospecific BCMA or GPRC5D CAR-T cells in the treatment of MM. Similarly, in another MM study using a dual-target approach, Zah E and colleagues [78] systematically optimized tandem design CARs targeting BCMA and CS1 antigens (also called SLAMF7 or CD319) in a mouse model of MM; showing that BCMA/CS1 bispecific CAR offers a promising therapeutic approach to prevent antigen escape in CAR-T cell therapy against MM. bidirectional CAR-T cells therefore deserve more research. Accordingly, van der Schans JJ et al. [83] reviewed the literature related to dual-target CAR T-cell therapy in MM and noted that the use of two or more target antigens can change the treatment paradigm for MM; However, more research is needed to determine which approach would work best in a particular situation.

Table 2
Dual targets used by TanCAR-T cells in the treatment of MM.

Bispecific target	Neurotoxicity	Hematologic toxicity	Chictr.org.cn Identifier
CD38+BCMA [76,77]	Not observed	Commonly seen	ChiCTR1800018143
CS1+BCMA [78]	Undisclosed	Undisclosed	
CD19+BCMA [79]	Undisclosed	Undisclosed	
GPRC5D + BCMA [71]	Undisclosed	Undisclosed	
CD38+CD138 [80]	Undisclosed	Undisclosed	
CD19+CD138 [81]	Undisclosed	Undisclosed	
CD19+CD22 [82]	Not mentioned	Not mentioned	

9. Trivalent CAR-T strategy

Following the success of bispecific targeting strategies, trispecific CAR-T cells are being investigated and evaluated for cancer therapy. The initial report specifically addressing trivalent CAR-T cell therapy was from glioblastoma [84]. Although this new study was not relevant to the MM around which we designed the review, it is still worth mentioning here for completeness and to mention the main results and significance of this study. Considering that combined targeting of two glioma antigens can overcome antigenic escape and improve T-cell effector functions, the therapeutic effect would be compromised by the high inter-patient variability of surface antigen expression, which seriously hinders the clinical effect of dual targeting. antigens In this scenario, the authors proposed the possibility of simultaneously targeting three target antigens in glioblastoma, namely HER2, IL13Rα2, and EphA2, generating trivalent CAR-T cells equipped with the three aforementioned CAR molecules. The findings showed that trivalent CAR-T cells targeting HER2, IL13Rα2 and EphA2 were able to successfully overcome the therapeutic effect, which is compromised by inter-patient variability, which tends to capture almost one hundred percent of tumor cells in most tumors tested in the study. The study was a major breakthrough because it made it possible to upgrade the arsenal of fully functional CAR-T cells from bivalent to trivalent. Despite these, there were also some limitations that the authors did not consider; therefore, this study received some challenges and comments from peers [85] and these comments were addressed in another separate letter [86]. Another large study in solid tumors [87] showed well-engineered CAR-T cells that simultaneously targeted three antigens (PSCA, TGFβ, and IL4) to enhance the function of transgenic T cells, as well as enhance safety. in the immunosuppressive tumor microenvironment.

With the exception of glioma above, tri-specific CAR-T cells have been studied in the treatment of hematological malignancies. At the same time, a trispecific CAR-T targeting CD19, CD20, and CD22 was developed by Schneider D et al. [88] to address the antigenic escape problem that often occurs when CAR-T treatment is used for B cells. malignant tumors. The authors compared the killing effect of monovalent CAR-T cells (targeting only CD19), bispecific CAR-T cells (targeting CD19 and CD20), and tri-specific CAR-T cells, demonstrating their superiority and robustness in killing malignant cells compared to their monovalent counterparts. At the time of writing, rather limited data exist exploring tri-specific CAR-T cells in the cure of MM.

10. Endless challenges faced in CAR-T therapy

Most CARs designed to target tumor-associated antigens inevitably result in some form of on-target/off-target toxicity (OTOT) [89]. In addition, the potential for cytokine-related toxicities [90] may be another overlooked but expected outcome of OTOT reactions. Based on these, we review some of the more common toxicity risks [90], including OTOT toxicities, cytokine release syndrome and certain neurological events associated with CAR therapy.

11. OTOT toxicity

By targeting tumor-associated self-antigens, CARs can cause the destruction of healthy tissues expressing the target antigen. Therefore, it was necessary to pay special attention to limit possible adverse OTOT effects. It seems possible that reduced affinity may direct CAR T cells to tumor cells that express high levels of tumor-associated self-antigens while sparing normal tissues that express low levels of tumor-associated self-antigens. However, a reduction in CAR target-binding affinity may compromise the overall antitumor activity. Faced with this problem, Drent E et al. [91] proposed and optimized a CAR-T strategy by introducing the co-stimulatory domain of CD28. This combinatorial co-stimulatory design not only enabled the use of very low-affinity binding domains to engineer safe CAR-T cells, but also maintained optimally effective CAR-T cells in the treatment of MM. such examples are numerous and readily available for other type of tumors. In addition to CD28, other costimulatory molecules used to enhance CAR-T cells function include ICOS, OX40 and CD27, as reviewed elsewhere [92]. We will not go into much detail here in these examples. However, combining these studies may provide a good indication that the choice of tumor-associated antigen for CAR targeting is still the most important factor in achieving tumor antigen-specific killing and avoiding OTOT toxicity in light of tumor-associated self-CAR-antigens that may present a risk of severe extratumoral toxicity that may be invisible in preclinical models. This issue must be considered when discussing the avoidance of OTOT toxicity achieved during CAR-T cell therapy. How can antigen-specific killing of a tumor be maximized while minimizing damage to healthy tissues? To answer this question, Flugel CL et al. [93] systemically analyzed and summarized almost all existing interventions that can be applied to overcome the challenge of OTOT toxicity in solid tumors. In actual fact, these OTOT mitigation strategies can be transferred and extended to MM.

12. Cytokine release syndrome (CRS)

Aside from OTOT, cytokine release syndrome (CRS) is another side effect that has been frequently seen in CAR-T clinical trials. CRS seen with CAR therapy can be more severe when mentioned in the same breath as the same type of syndrome seen with tumor infiltrating autologous T cells (TILs) or T-cell receptor (TCR) therapy. This may be because, unlike TILs or TCRs that react with the cognate antigens in their native binding specificity, artificial antigen-binding domains engineered into CARs may bind with altered affinities that cannot be accurately predicted. Thus, CRS is not only observed with CARs but also with other synthetic anticancer antibodies such as blinatumomab [94]. Inflammatory cytokines [95] elevated during CRS included, but not limited to, IL6, IL8, IL10, MCP1, TNFα, IFNγ, etc. The clinical features observed in CRS share many similarities with macrophage activation syndrome and hemophagocytic lymphohistiocytosis (HLH) [96]. In addition to the common clinical features observed between HLH and CRS [90], the main cytokines that are increased in HLH [97] are mild to severe, including multi-organ damage, IL10, IL6 and IFNγ. Increased

levels of these cytokines after CAR-T infusion indicate macrophage activation and a possible role for macrophages in driving certain aspects of CRS. Therefore, a better understanding of the biology of CRS in needed to improve the clinical management of CRS.

13. Neurotoxicity

Emerged as an unexpected outcome linked with CAR therapy, neurotoxicity has been observed in relation to CRS or immediately after the development of CRS and following the resolution of CRS or without any CRS. Neurologic toxicities caused by CAR therapy are diverse and include encephalopathy, cognitive defects, dysphasias, seizures, and cerebral edema [90,98]. Requiring intubation and mechanical ventilation, these neurological complications may become severe. Fortunately, some of these neurological complications can be reversible. The underlying mechanism resulting in neurological complications is currently unknown; however, several lines of evidence exist [99,100] indicating that neurotoxicity in animal models seems to be associated with elevated levels of inflammatory cytokines present in the cerebrospinal fluid. Furthermore, cellular infiltrates, including anti-CD20 CAR and unmodified T cells, have built up in the cerebrospinal fluid and brain parenchyma [101], which could partly account for the neurotoxicity engendered by CAR-T therapy. First observed and described in patients with refractory multiple myeloma receiving anti-CD19 CAR therapy [102], neurotoxicity has developed. The complications arising on account of neurotoxicity range from being mild to severe [103]. The adverse events caused by neurotoxicity can be assessed following the national cancer institute common toxicity criteria for adverse events (NCI CTCAE version 5) [104]. Management of CAR-T-associated CRS neurologic toxicity comprises an important component of contingency protocols in CAR therapy. In addition to neurotoxicity, acute kidney injury [105] is another endless challenge which is commonly seen after CAR-T-cell infusion. Of course, acute kidney injury is not exclusive to CAR-T therapy that can cause it. With respect to the cause and cure of acute kidney injury brought about by CAR-T, we will not dwell on it; instead, consultation can be made in reviews [106,107] published previously.

14. Iterative CAR-T cells

It can be perceived that significant challenges appear to be endless in the upgrading of CARs in that an optimal mono/bi/tri-valent CAR-T structure has not been established. As it stands, no evident effect of one plus one more than two in terms of overall survival has been achieved in clinical trials, regardless of mono/bi/tri-valent CAR-T therapy, suggesting that further optimization is required. It should be noted that particular attention [108] should be given to the optimization of CAR-T cells with di- or tri-valents, for example, finding the optimal antigen target, appropriate spatial structure, and suitable linker for single-chain fragment variables (scFvs), to improve the persistence and efficacy of CAR-T cells. Nevertheless, with the development of new technology, these scientific challenges discussed above will eventually be addressed and conquered. Therefore, in the near future, from off-the-shelf to customized design, there will be many CARs available that are always right for those with MM.

15. Perspectives of CAR-T

Transformed the treatment paradigms for hematological malignancies and MM, CAR-T therapy's evolution has been under way. Although exciting clinical efficacy has preliminarily been observed and achieved, some problems, including loss of antigen loss and downregulation of targeting receptor, remain in the CAR-T therapy of MM. Dual targeting or trivalent targeting simultaneously of more than one tumor antigen on MM cells is being investigated both clinically or experimentally to enhance the efficacy and lessen side effects. The ideal combination of different antigens to target in the curing of MM remains a big deal to explore.

Ethical approval and consent to participate

Not applicable.

Consent for publication

All authors were consent for publication in the current form.

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CRediT authorship contribution statement

Jin Zhao: Writing – original draft. **Meijing Zheng:** Writing – original draft. **Li Ma:** Writing – review & editing. **Tao Guan:** Writing – review & editing. **Liping Su:** Writing – review & editing, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

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