Bispecific CAR-T vs. BCMA-Specific CAR-T: Advancing Treatment for Relapsed/Refractory Multiple Myeloma

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Abstract. Multiple myeloma (MM), despite therapeutic advances, remains an incurable disease. Therefore, the most patients eventually progress to relapsed/refractory multiple myeloma (RRMM). Chimeric antigen receptor (CAR) T-cell therapy targeting B-cell maturation antigen (BCMA) has shown remarkable efficacy in RRMM. However, limitations such as antigen escape, tumor heterogeneity, and T-cell exhaustion led to relapse. This review provides a comprehensive perspective on the transformative potential of bispecific CAR-T cell therapy as a promising strategy to overcome resistance and improve outcomes for patients with RRMM. The mechanisms of resistance to BCMA-targeted CAR-T therapy are comprehensively analyzed and categorized into BCMA-positive and BCMA-negative relapse/refractory mechanisms. The MIF/CD74 pathway as a potential contributor to BCMA CAR-T resistance was supported by single-cell RNA sequencing data and previous studies. The mechanistic advantages of dual-target are explored dual target CAR-T can prevent antigen escape and enhance T-cell activation. Clinical review of clinical trial data demonstrates the superior efficacy of bispecific CAR-T compared to BCMA CAR-T, including higher drug effect and more manageable side effects.

Keywords: Multiple myeloma, CAR T-cell therapy, B-cell maturation antigen (BCMA), bispecific CAR-T, antigen escape.

1. Introduction

Multiple myeloma (MM), the second most common hematological malignancy, characterized by abnormal clonal plasma cells in the bone marrow [1]. Over 5 hundred thousands of people are diagnosed as multiple myeloma each year in world. Clinically, over 70% of MM patients have anemia and osteolytic bone disease [2]. The past decade has witnessed transformative therapeutic advancements, driven by the development of immunomodulatory agents (e.g., lenalidomide), proteasome inhibitors (e.g., bortezomib), monoclonal antibodies (e.g., isatuximab), dexamethasone and autologous stem cell transplant (ASCT) [3, 4], have significantly improved overall survival. The median overall survival for patients eligible for ASCT is estimated to be approximately 10 years, compared with 4 years for those not eligible for ASCT. Unfortunately, despite these advancements, MM remains an incurable disease. Most of the patients will eventually processing to relapsed and refractory multiple myeloma (RRMM). The entire process of transforming MM to RRMM is complex and heterogeneous, evolving through multistep that involve genetic alternations as well as the changes in the tumor micro-environment [3]. For those RRMM patients, prognosis remains gloomy. The median overall survival (OS) is as low as 5.6 months for penta-refractory patients [5, 6]. In this context, chimeric antigen receptor (CAR) T-cell therapy has emerged as a breakthrough approach. B-cell maturation antigen (BCMA) is an ideal target antigen due to its high expression in MM cells and its absence in normal cells and tissues, enabling CAR-T cells to specifically target and eliminate abnormal plasma cells. BCMA CAR-T have showed remarkable efficacy in heavily pretreated RRMM patients. The overall response rates (ORR) ranging from 48% to 100% [6]. But limitations still exist. A phase I/II trial of BCMA-specific CAR-T cells reported a median progression-free survival (PFS) of only 11.8 months [6]. Approximately 30% of patients exhibit primary resistance to BCMA-targeted CAR-T therapy, and up to 33% experience relapse due to BCMA antigen downregulation or loss [5, 6]. Over 50% of patients relapse within 12 months due to antigen escape, tumor heterogeneity and T-cell exhaustion [7].

In recent years, bispecific CAR-T cell therapy has emerged as a promising approach to overcome the limitations of BCMA single target CAR-T. Dual-target CAR-T strategy aims to improve the efficacy of the treatment by reducing the chances of tumor escape due to antigen loss or downregulation and increasing the killing effect. By targeting two different surface markers, bispecific CAR-T cells may not only enhance tumor cell recognition but also reduce the risk of immune evasion, offering a more strong and durable response. In MM, combining BCMA targeting with another relevant antigen, such as CD38 and CD19, has shown promise in preclinical and early clinical studies. In summary, as the treatment of MM evolves from conventional therapy to advanced immunotherapeutic strategies, bispecific CAR T-cell therapy represents an important frontier. Addressing the challenges of antigen escape and tumor heterogeneity, bispecific CAR-T shows the potential of solving resistance problem in RRMM.

However, up to now, a comprehensive perspective on the role of bispecific CAR-T and its potential mechanism in RRMM is still lacking. Therefore, this study will discuss both the drug resistance mechanisms associated with BCMA and bispecific CAR-Ts' mechanism of effecting plasma cells. Clinical trials will be lifted for illustrating the effect and safety in bispecific CAR-T.

2. Relapse and Drug Resistance in BCMA-targeted CAR-T Therapy

2.1. BCMA+ Relapse and Resistance (R/R)

In this study the mechanism of BCMA CAR-T resistance is divided into BCMA negative R/R and BCMA positive R/R based on whether the BCMA expression is in effective expression level. BCMA+R/R related to the CAR-T cell exhaustion caused by TME and engineering manufacture of CAR-T cells. The high tumor burden and immunosuppressive cytokines (e.g., IL-10, TGF-β) also reduces therapeutic efficacy by limiting CAR-T proliferation. In MM micro-environment, myeloid-derived suppressor cells (MDSCs), regulatory T cells (Treg) and tumor-associated macrophages secrete inhibitory cytokines and express PD-L1 to decrease the CAR-T activity [8]. An important challenge in CAR-T cell therapy is ensuring their long-term persistence, which is primarily an industrial issue.

2.2. MIF/CD74 pathway, the potential pathway to solve the BCMA CAR-T R/R

The single cell sequencing cell-cell interactions show the potential probability of Macrophage migration inhibitory factor (MIF) and A Proliferation-Inducing Ligand (APRIL) pathway as a BCMA resistance mechanism [9]. In clinical and preclinical research, the TACI and BCMA target has been a CAR-T target for MM, but CD74 CAR-T is only in mantle cell lymphoma models [10]. In vitro co-culture study showed that CD74 expression significantly increased 12 hours after BCMA CAR-T treatment [11]. In this study, the GSE143317 data was downloaded from GEO database, which is a data from patient who shows BCMA resistance with the homozygous gene deletion [12]. The both of the expression of CD74 and MIF are significantly higher than BCMA in patient's B cells (Figure 1A-B). So, when the patient obtained the CAR-T therapy, expression of MIF and CD74 in B cells will be upregulated which cause the tumor proliferation and suppress the immune system by inhibiting T cells. So, MIF/CD74 pathway shows a potential ability in solving BCMA resistance, but there need more studies to verify it.

2.3. BCMA- Relapse and Resistance (R/R)

BCMA- R/R includes the loss or downregulation of BCMA expression. The very low levels of BCMA expression also considered as negative relapse and refractory in this study. Both of the loss and downregulation contribute to immune escape in MM. single cell sequencing shows the essential reason of BCMA loss is due to the BCMA biallelic loss in chromosome 16p13.13 [12, 13]. Also shows the BCMA+ R/R and BCMA- R/R will happen simultaneously [9]. This fact emphasize the importance to using bispecific CAR-T rather than single target BCMA CAR-T.

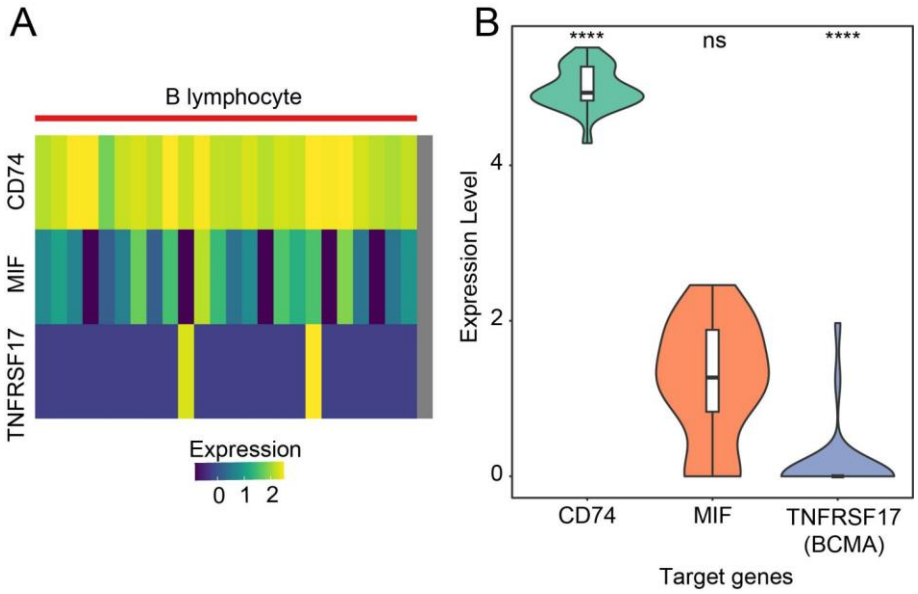

Figure 1. CD74/MIF and BCMA expression levels in B cells

Another type of BCMA- R/R is caused by the heterogeneity that patients shows primarily resistance to BCMA CAR-T or shows a clonal evolution after therapy. When the pretreatment BCMA expression density in patients is below 1000 ABC, relapse occurs earlier compared to those with higher BCMA expression levels. The unstable genetic MM cells rapidly acquire resistance mutations after treatment, especially the high-risk subtypes (e.g., del17p, t (4; 14)). Also, the prior BCMA-target therapies or other target therapies influencing the BCMA can cause the downregulate BCMA expression, γ-secretase can cut BCMA into soluble BCMA (sBCMA), reducing the density of BCMA on the cell membrane. This process also highlights the potential for CD19 monoclonal agents to induce drug resistance in CAR-T therapies and combining two different single agents might different to using multitarget CAR-T. When infused CAR-T cell, BCMA expression may temporarily decrease due to internalization or transcriptional downregulation, creating an antigen low state that allows residual MM cells to survive.

2.4. Mechanistic advantages of Dual-Target Engagement

Emerging evidence reveals distinct tumor escape mechanisms between dual-target and single-target CAR-T therapies [14]. In the CS1-BCMA trial, single-cell RNA sequencing of 4 relapsed patients demonstrated persistent co-expression of BCMA and CS1 in all remain myeloma cells, with no evidence of antigen-negative subclones. Compared with the BCMA single target CAR-T study, with 32% of relapses involved BCMA-negative clones not originally detected at baseline. The dual-target approach imposes an evolutionary bottleneck that simultaneous downregulation of both antigens would require catastrophic genomic reorganization, a phenomenon not observed in clinical specimens to date [5]. Single-target CAR-T cells, although can effectively against the dominant clones, will apply selective pressure that enriches BCMA- subpopulations, which cause the BCMA loss in 30–50%. The near-ubiquitous expression of CS1 (>95% of myeloma cells) ensures target redundancy. Preclinical models demonstrate that co-engagement of CS1 and BCMA triggers synergistic T-cell activation through SLAMF7-mediated ERK/NF-κB signaling, amplifying cytokine production (IFN-γ, IL-2) [15].

The CD19-BCMA CAR-T function in the contrary way. CD19, expressed in only 15-20% of myeloma cells at baseline, but becomes upregulated in 68% of patients after BCMA-targeted therapy [16]. Flow cytometric analyses of post-infusion marrow samples revealed CD19-BCMA CAR-T cells preferentially eliminated $CD19^{+}BCMA^{+}$ persisting clones responsible for late relapses in single-target cohorts. This dynamic targeting adaptiveness may explain the trial's unprecedented 19.7-month median progression-free survival (PFS), nearly doubling historical controls. After BCMA CAR-T therapy, there will re-emergence of CD19 in myeloma progenitor cells. Longitudinal single-cell RNA

sequencing reveals that 68% of post-BCMA CAR-T relapses exhibit CD19 upregulation. This dynamic adaptability is reflected in clinical outcomes, where CD19-BCMA CAR-T cells achieve 92% overall response rates (ORR) even in patients failing prior BCMA-directed therapies [17, 18].

3. Clinical evidence

3.1. Efficacy of Bispecific CAR-T Compared to BCMA Specific CAR-T

Table 1. Clinical Trials of Bispecific CAR-T in R/R MM

CAR-T type	Phase	N	CAR-T dose	Response Rates	Adverse Events
BCMA+CD19	I/II	50	NA	ORR (92%); median PFS (19.7 months)	≥3 grades CRS (8%); ≥1 grades ICANs (4%)
BCMA+CD19	II	62	1×10^6 cells/kg	ORR (92%); median PFS (18.3 months)	≥3 grades CRS (10%); ≥3 grades ICANs (10%)
BCMA+CD19	I	22	Low: 1×10^5 cells/kg Medium: 2×10^5 cells/kg High: 3×10^5 cells/kg	sCR (100%); MRD- (100%)	1-2 grades CRS (27%); ≥3 grades (0%)
BCMA+CD38	I	23	NA	ORR (87%); sCR (52%); median PFS (17.2 months)	1-2 grades CRS (65%); ≥3 grades CRS (22%)
BCMA+CD38	I	16	NA	ORR (87.5%); sCR (81.3%); 1-year PFS (68.8%); 1 year OS (75%)	1-2 grades CRS (43.8%); ≥3 grades CRS (31.3%)
BCMA+CS1	I/II	16	Low: 0.75×10^6 cells/kg Medium: 1.5×10^6 cells/kg High: 3.0×10^6 cells/kg	ORR (81%); sCR (38%); 1-year PFS (56.26%); 1-year OS (72.73%)	1-2 grades CRS (31%)
BCMA+GPRC5D	I	21	L1: 0.5 × 10^6 cells/kg, L2:1.0 × 10^6 cells/kg, L3: 2.0 × 10^6 cells/kg, L4: 4.0 × 10^6 cells/kg	ORR (92%); sCR (75%) in L3	1-2 grades CRS (71%)

The data from several clinical trials suggest that bispecific CAR-T therapies targeting BCMA and other antigens, such as CD19, CD38, CS1, and GPRC5D, exhibit strong anti-tumor activity in patients with RRMM (Table 1). In general, bispecific CAR-T therapies demonstrate high overall response rates (ORR) and extended progression-free survival (PFS) compared to traditional BCMA-targeted CAR-T therapy, though the degree of benefit may vary with different bispecific combination. Bispecific CAR-T therapies targeting BCMA and another antigen showed enhanced therapeutic efficacy over several historical BCMA monospecific CAR-T therapy. Pooled analysis of 190 patients from seven trials revealed an overall response rate (ORR) of 89.6% (range: 81-92%), exceeding the 73% ORR reported in the pivotal KarMMa trial of BCMA single targe. Stringent complete response (sCR) rates reached 52-81.3% in BCMA-CD38 constructs and 75% in high-dose BCMA-GPRC5D therapy, contrasting with the 33% sCR rate observed in BCMA monospecific therapies [7, 19-21].

The durability of response showed improvement. The median PFS extending to 17.2-19.7 months in bispecific comparing to 8.8 months in BCMA single target. BCMA-CD19 CAR-T maintained PFS beyond 18 months in two independent phase II trials [6, 22], showing enhanced T cell persistence through dual antigen engagement. Dose-response relationships emerged across different strategy of bispecific CAR-T. The highest efficacy observed at ≥2×10^6 cells/kg doses [5, 7, 23]. The BCMA-CD38 combination demonstrated exceptional 1-year survival metrics (68.8% PFS, 75% OS) [21], potentially reflecting synergistic targeting of plasma cell surface markers.

3.2. Safety profile relative to bispecific CAR-T

The safety profiles of bispecific CAR-T therapies were characterized primarily by cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS of grade ≥3 incidence ranged from 0% to 31.3% and ICANS of grade ≥3 were up to 10%. Targeting BCMA and CD19 reported grade ≥3 CRS in 8% to 10% of patients, with ICANS events occurring in 4% to 10%. The BCMA and CD38 dual-targeted trials exhibited higher rates of grade ≥3 CRS, ranging from 22% to 31.3%, with grade 1-2 CRS is in 43.8% to 65% of patients. The BCMA and CS1 study reported grade 1-2 CRS in 31% of patients with no grade ≥3 events. The BCMA and GPRC5D trial observed grade 1-2 CRS in 71% without higher-grade toxicities.

Importantly, the safety data indicate that bispecific CAR-T therapies can achieve high efficacy without a disproportionate increase in severe adverse events. The ability to target multiple antigens may allow for lower effective doses of each CAR-T cell population, potentially contributing to a more manageable toxicity profile. The absence of severe neurotoxicity in certain bispecific trials highlights the potential for these therapies to offer a safer therapeutic way.

4. Disscussion

The development of bispecific CAR-T therapy shows a potential of paradigm shift in MM immunotherapy. By addressing the critical limitations of BCMA specific CAR-T. This study shows that dual-antigen targeting (BCMA + CD19/CD38/CS1/GRPRC5D) achieves huge clinical efficacy in heavily pretreated RRMM, with ORR exceeding 80% and median PFS nearly doubling compared to BCMA-only CAR-T therapies. The observed durability of responses can be attributed to prolonged CAR-T persistence, increasing T-cell activity. Highlighting the mechanistic benefits of dual target therapy.

Longitudinal biomarker analyses demonstrated that dual-target CAR-T cells effectively eliminate remaining clones co-expressing both antigens. For instance, CD19-BCMA CAR-T cells using the post-treatment upregulation of CD19 observed in 68% of BCMA-resistant cases, transforming a resistance mechanism into a therapeutic opportunity. Safety outcomes were also important, with lower grade ≥3 CRS rates and neurotoxicity incidence. The differential toxicity between different CAR-T structure, the lower CRS in CS1-BCMA and CD19-BCMA may reflect the antigen-specific activation mechanism need more studies.

Despite having a promising outlook, challenges remain. Manufacturing and clinical application of bispecific CAR-T cells is still in potential. Research needs to ongoing to find the balance between efficacy and safety, as well as to verify the most effective combination of target antigens. Relapses in dual-target, although are rare, need more clinical trials to confirm. The more studies focusing on the MIF/CD74 pathway need to reveal the value of this pathway in handling the BCMA CAR-T relapse and resistance.

5. Conclusion

Bispecific CAR-T cell therapy shows a transformative potential in RRMM. By targeting two antigens such as BCMA plus CD19, CD38, or CS1, solving the antigen escape. Clinical evidence reveals in huge improvements, with overall response rates to 81-92% and median progression-free survival in 17-19 months, far surpassing the 8-12-months median PFS survival seen with BCMA-specific CAR-T. The safety profile showed lower rates of severe cytokine release syndrome (0-31%) and neurotoxicity (0-10%) compared to some single-target regimens. These outcomes signal that bispecific CAR-T could redefine treatment for RRMM, offering hope where options once dwindled. Questions for optimal antigen pairs, dosing precision, and the durability of responses demand further exploration to cement its place in clinical practice.

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