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BCMA CAR-T therapy combined with pomalidomide is a safe and effective treatment for relapsed/refractory multiple myeloma

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Abstract

Background B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor T-cell (CAR T-cell) therapy has exhibited remarkable efficacy in refractory or relapsed multiple myeloma (R/R MM), but recurrence and rapid progression of disease are still observed within a short time after treatment. Long-term pomalidomide therapy, which potentiates T-cell functionality, might enhance the efficacy of BCMA CAR T-cell therapy.

Methods We performed a single-center retrospective clinical study. Patients with relapsed or refractory multiple myeloma who received BCMA CAR T-cell infusion were enrolled in our study, and were followed by long-term pomalidomide treatment (4 mg/day) or not one month after infusion. The response and adverse events were assessed after infusion. The effect of pomalidomide on BCMA CAR T-cells was assessed in vitro.

Results The objective response rate (ORR) of BCMA-CART was 100%. Three months following CAR T-cell infusion, of the 8 patients receiving pomalidomide, except for 2 patients who stopped maintenance therapy and were lost to follow-up, all patients (6/6) achieved VGPR (very good partial response) or CR (complete response), while only 5 patients (5/8) who did not receive pomalidomide treatment achieved VGPR or better. At a median follow-up of 27 months, for the 8 patients who did not receive pomalidomide administration, the median TTP (time to progression) was 5.85 (1–14) months, while the OS (overall survival) was 10.7 (1.2–16) months. Of the 8 patients who received pomalidomide therapy after CAR T-cell infusion, the median TTP was 13 (7–13) months, while the OS was not reached. Moreover, neither long-term hematological toxicity nor drug-induced liver damage was observed during the follow-up period. Mechanistically, pomalidomide promotes antimyeloma efficacy of BCMA CAR T-cells by inhibiting cell apoptosis and enhancing cytoxicity.

Conclusions Our results confirmed that BCMA CAR T-cell therapy combined with long-term pomalidomide had a low recurrence rate and manageable therapy-related side effects, providing a promising option for treating R/R MM.

Keywords Relapsed/Refractory multiple myeloma (R/R MM), BCMA CAR T-cell therapy, Pomalidomide, Combination therapy

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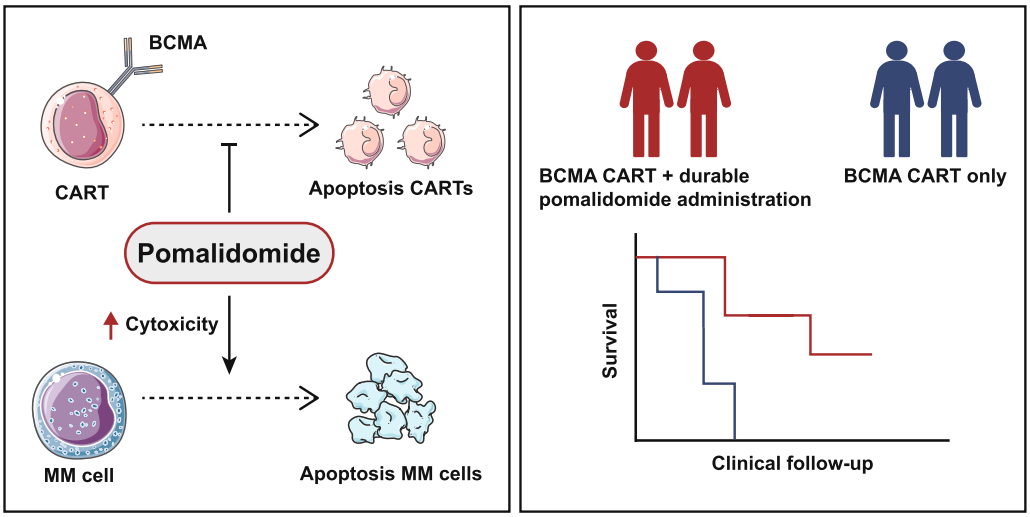
Graphical Abstract



Background

Multiple myeloma (MM) is a plasma cell malignancy, accounting for 13% of hematologic malignancies [1]. Although myeloma patients have benefited from the advent of proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs) [2, 3], myeloma remains incurable, and nearly all patients eventually relapse and become refractory to available therapies [2, 3]. B cell maturation antigen (BCMA), a member of the tumor necrosis factor superfamily, were mainly expressed on plasma cells and plasmacytoid dendritic cells, which is a reasonable target for MM. BCMA-targeted chimeric antigen receptor (CAR) T-cell therapy has shown encouraging activity in relapsed or refractory multiple myeloma (R/R MM) patients, with an objective response rate (ORR) of 81%-97%. Furthermore, the progression-free survival (PFS) of R/R MM patients who received BCMA CAR T-cell therapy was 6 ~ 17.4 months [3–8]. However, in 45% (27% ~ 64%) of R/R MM patients, recurrence and rapid progression of disease were still observed within a short time after BCMA CAR T-cell infusion [9].

Notably, the antitumor effects and persistence of CAR T-cells, which are limited by product quality and structure design, significantly affect clinical outcomes. Combination with chemotherapeutics or immunomodulatory drugs has been employed to enhance the response to CAR T-cells in high-risk patients. Anti-PD-1 monoclonal antibodies can directly promote the cytotoxicity of CAR T-cells, and BTK (Bruton's tyrosine kinase) inhibitors promote persistence of CAR T-cells in vivo. Additionally, antitumor chemotherapy exerts synergistic effects to achieve deeper remission in patients with hematological malignancies [10–13]. A series of clinical studies of BCMA CAR T-cell therapy have shown that only combination with lenalidomide has demonstrated benefits in R/R MM patients [14, 15]. Lenalidomide, a second-generation IMiD, has been demonstrated to promote T-cell proliferation in an IL-2-dependent manner and accelerate the formation of immune synapses between CAR T-cells and targets after contact, through which the efficacy of CAR T-cell killing is amplified [12, 13]. Nevertheless, the hematological toxicity of lenalidomide cannot be ignored for clinical use [16, 17]. As a third generation IMiD, pomalidomide has stronger antimyeloma activity and is widely applied in the treatment of MM patients refractory to lenalidomide. To increase safety, a low dose of pomalidomide can be administered to effectively kill myeloma cells [18, 19]. Although pomalidomide and BCMA CAR T-cell infusion play a significant role in R/R MM patient treatment, there are no clinical studies on the benefit of the combination of these two treatments in R/R MM patients.

In this study, we found that R/R MM patients who received long-term pomalidomide therapy after BCMA CAR T-cell infusion achieved deeper clinical remission and longer progression-free survival. These benefits might be explained by the enhanced cytotoxic capability of CAR T-cells and the durable pomalidomide-mediated tumor-killing effect. Our results provide a rational clinical combination strategy based on BCMA CAR T-cell therapy that may significantly improve the prognosis of patients with R/R myeloma.

Methods

Patient population

We conducted a single-center retrospective study with a small sample size at the Third Xiangya Hospital of Central South University, which was registered with the Chinese Clinical Trail Registration Center (ChiCTR2000036350). Key eligibility criteria included an age of 18 to 75 years; a diagnosis of relapsed or refractory multiple myeloma with three or more previous lines of treatment, including proteasome inhibitors and immunomodulatory agents[20–22]; measurable disease (defined as any of the following: a serum level of monoclonal protein of ≥ 5 g per liter, a urinary level of monoclonal protein of ≥ 200 mg per 24 h, a serum level of involved free light chains of ≥ 10 g per liter with an abnormal free light-chain ratio, plasma cell infiltration in bone marrow of ≥ 5%, or one or more biopsy-proven extramedullary plasmacytomas measuring ≥ 2 cm in diameter); positive expression of BCMA on the surface of plasma cells detected by immunohistochemistry or flow cytometry; received BCMA CAR T-cell therapy at our center between May 2017 and December 2021; and adequate organ function. R/R MM patients who had previously received CAR T-cell therapy or BCMA-targeted therapy were excluded from this study. As shown in Fig. 1, nine patients received BCMA CAR T-cell infusion without maintenance therapy, and one of them, who died from septic shock in the acute phase of CAR T-cell infusion, was excluded.

Prior to CAR T-cell infusion, all patients were administered standard lympho-depleting chemotherapy (fludarabine (25 mg/m^2/day) and cyclophosphamide (250 mg/m^2)) for three consecutive days. Autologous BCMA CAR T-cells were generated and amplified by Shanghai Yucardi Biopharmaceuticals [23]. In the pomalidomide arm, drug administration was started from one month after infusion, except for Patient 3 who received oral pomalidomide treatment two months after BCMA CAR T-cell infusion. According to the guideline of CSCO (the Chinese Society of Clinical Oncology), the standard

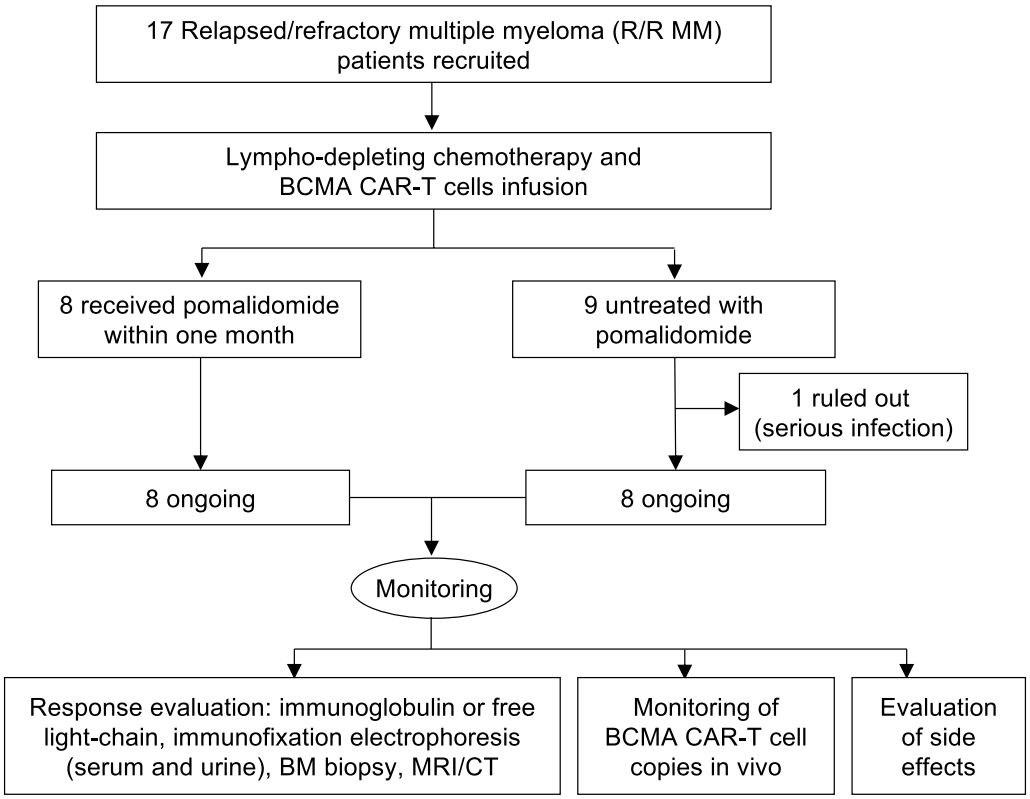


Fig. 1 Clinical study design. Seventeen R/R MM patients were included in this study, following with standard lympho-deleting chemotherapy and BCMA CAR T-cells infusion. One patient in the control arm was excluded because of unexpected serious infection after CAT T-cells infusion. Eight R/R MM patients received standard pomalidomide therapy one month after BCMA CAR T-cell infusion, while the other 8 patients did not receive pomalidomide maintenance treatment. Disease related examinations, such as examination of immunoglobulin or free light-chain levels, BM biopsy, and routine blood test, were completed and documented. Additionally, BCMA CAR T-cell CAR copy numbers in peripheral blood after cell infusion were monitored at the indicated timepoints. *BCMA* B cell maturation antigen, *CAR T-cells* Chimeric antigen receptor-modified T cells, *MRI* magnetic resonance imaging, *CT* computed tomography

dose of pomalidomide for R/R MM patients is defined as 4 mg/day for 21 days of a 28-day cycle, which should be adjusted to 3 mg/day for patients with hepatic or renal dysfunction (Patient 1). Patients in the pomalidomide arm received persistent pomalidomide therapy until death. All patients were followed up at regular intervals. The data cutoff date for follow-up was 31 July 2023.

Evaluation of *CAR* T-cell therapy efficacy and safety

According to the IMWG criteria for response and minimal residual disease assessment in multiple myeloma, clinical responses to different therapeutic plans were evaluated at the indicated time points after CAR T-cell infusion [23]. If necessary, magnetic resonance imaging (MRI) or computed tomography (CT) was employed to assess extramedullary involvement, that the IMWG requires the disappearance of soft-tissue masses for CR or VGPR, and a decrease $\geq$ 50% for PR. Overall survival (OS) and TTP (time to progression) were (overall survival) was defined as the time from the start of randomization to death (for any reason), while TTP (time to progression) was defined as the time from the start of randomization to tumor progression (in any form) or death (due to progression of disease). Based on the criteria proposed by Lee et al. [24], cytokine release syndrome (CRS) was graded from 0 to 4. Grade 3 or higher was regarded as severe CRS. Additionally, monitoring of the levels of interleukin-6 (IL-6), C-reactive protein (CRP) and ferritin was performed to evaluate the severity of CRS. Immune effector cell-associated neurotoxicity syndrome (ICANS) was evaluated according to ASTCT consensus guidelines [25]. Adverse events (AEs) were graded using the Common Terminology Criteria for AEs 5.0 [26]. Long-term hematological and hepatic toxicities were monitored following BCMA CAR-T infusion. R/R MM patients were required to be monitored weekly within 2 months after BCMA CAR-T cell infusion, followed by monthly monitoring for the next 4 months, and the median follow-up duration for assessing long-term toxicity was 9 [7–21] months.

Immunohistochemistry assay

The formalin-fixed, paraffin-embedded extramedullary lesion tissues were sectioned to 4-μm thickness. For immunohistochemical staining of CD38, CD138, lambda-chain and kappa-chain expression, we used the BenchMark ULTRA (Ventana Medical Systems, Oro, AZ, USA) automated slide stainer to stain sections with the anti-CD38, CD138, lambda-chain and kappa-chain antibody (MXBiotechnologies) according to the instructions. The positive control (meningioma) and negative control samples were run simultaneously with each specimen.

Tracking of circulating *CAR* T-cell numbers

As described previously, absolute quantification of the circulating CAR gene copy numbers was performed by quantitative polymerase chain reaction (qPCR) [27, 28]. DNA was extracted from PB samples using the TIANamp Blood DNA Kit (TIANGEN, China) following the manufacturer's instructions and was further amplified by using primers and probes complementary to specific sequences within the lentiviral vector. The standard curve was constructed with serial dilutions of the plasmid encoding the transgene. Amplifications were carried out with the ABI 7500 Real-Time PCR System (Applied Biosystems, Thermo Fisher Scientific, USA) using the protocol provided by the manufacturer. The copy numbers were determined in reference to the standard curve.

Cell culture

The BCMA-expressing cell line K562 (an erythroleukemia cell line) and BCMA CAR T-cells were obtained from Yucardi. The expression of BCMA on the K562 cell surface was confirmed by FACS. They were both cultured in RPMI 1640 medium supplemented with 10% FBS (Gemini) and 1% penicillin/streptomycin (P/S, Gibco, Life Technologies). For CAR T-cell cultivation, human IL-2 (50 IU/mL) were included in the culture medium. The pomalidomide (CAT#CC-4047, Selleck) used in this study was dissolved in DMSO to a concentration of 2 mg/mL and further diluted to the indicated concentrations (1, 2.5, 5, 10 μg/mL) with cell culture medium.

Flow cytometry

Multiparameter FACS was performed to assess the apoptosis of hematopoietic tumor cells and BCMA CAR T-cells. After four days of pomalidomide treatment, ARP1 cells, BCMA-K562 cells, and BCMA CAR T-cells were harvested and further incubated with anti-Annexin V-APC antibody (BioLegend) (2.5 μg/ml) for 25 min at room temperature (RT). The cells were washed once with 1X binding buffer (Annexin V-FITC/PI Apoptosis Detection kit), and propidium iodide (PI) solution (CAT#A211-01/02, Calbiochem) (500 mg/mL, 2 μL per sample) was added before loading the samples into the FACS machine. The percentages of apoptotic (Annexin V^+) cells were quantified by FACS. In addition, an anti-BCMA-PE antibody (CAT# 357503, BioLegend) was used to verify BCMA expression in the K562 cell line by FACS analyses. For the proliferation assay, BCMA CAR T-cells were stained with CFSE dye (CAT#65-0850-84, eBioscience) (5 μM) for 10 min in a cell incubator, washed three times with PBS before being seeded into culture plates (1×10^6/200 μl), and then activated by anti-CD3 (CAT#317325, BioLegend) and anti-CD28 (CAT#302933,

BioLegend) monoclonal antibodies. After 4 days of culture in RPMI 1640 medium supplemented with 10% FBS, 1% P/S, and 50 IU/mL human IL-2 (CAT#202-IL-010, R&D SYSTEMS), BCMA CAR T-cells were collected and stained with anti-CD3-PE Texas Red and anti-CD45-Krome Orange (CAT#A96416, Beckman) antibodies for 15 min at RT. The mean fluorescence intensity of CFSE was quantified by FACS.

CAR T-cell cytotoxicity assay

Prior to the specific killing assay, BCMA CAR T-cells were pretreated with pomalidomide at gradient concentrations (1, 2.5, 5, 10 μg/mL) for 18 h in an incubator and then mixed with BCMA-expressing K-562 cells at an effector-to-target ratio of 1:1 in RPMI 1640 medium supplemented with 10% FBS and 1% P/S in the presence of pomalidomide at the indicated concentrations (1, 2.5, 5 μg/mL). The cell mixtures were cocultured for 2 h at 37 °C in 5% CO_2. Then, the supernatants of the coculture system were collected, and the cytotoxicity was measured by the LDH Cytotoxicity Assay Kit (CAT#C0016, Beyotime) following the manufacturer's instructions. In brief, the maximum LDH release group and the control group (RPMI 1640 medium) were prepared in advance. The supernatant (60 μL) was mixed with 20 μL of LDH release reagent (1×) and further incubated at room temperature for 30 min. The absorbances were then determined at 490 nm, and the optical density (OD) values were documented. The killing efficiency for each well was calculated as follows: [(OD value of samples to be tested—OD value of control group) / (OD value of maximum LDH release group—OD value of control group)] × 100%.

Statistics

Descriptive analyses are primarily used in clinical studies, owing to the limited number of cases. For Kaplan–Meier survival analysis, the log-rank (Mantel–Cox) test was used to determine statistical significance. Categorical variables were summarized as number and percentage and compared using unpaired T-test or Fisher's exact test, as appropriate. Data are presented as the mean ± S.D. of all experiments in this study. There was a minimum of three samples per group, as indicated in the figure legends. Unpaired two-tailed Student's t test was used to evaluate statistical significance: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; N.S., not statistically significant.

Results

Patient chracteristics

A total of 16 patients were included in this study. The median age of the enrolled R/R MM patients was 57.5 years [44], and 6 of them were males. Overall, 8 of 16 (50%) R/R MM patients received pomalidomide administration after BCMA CAR T-cells infusion. The clinical characteristics of enrolled patients are summarized in Table 1. Of the 8 R/R MM patients in the pomalidomide arm, 4 (50%) had high-risk cytogenetic abnormalities (IGH rearrangement, 1q21 amplification, and P53 deletion) prior to the BCMA CAR T-cells infusion, while 3 (37.50%) patients in the control group were detected

Table 1 Clinical characteristics of patients with R/R MM in two arms

	Total (n = 16)	Patients treated with Pom after CAR T-cells infusion (n = 8)	Patients without Pom administration after CAR Tcells infusion (n = 8)	*p*-Value
Age, years, median (range)	57.5 (44–71)	56 (46–71)	59 (44–65)	0.7158
Male, n (%)	6 (37.50%)	3 (37.50%)	3 (37.50%)	> 0.9999
High-risk cytogenetics, n (%)	7 (43.75%)	4 (50%)	3 (37.50%)	> 0.9999
EMD, n (%)	7 (43.75%)	5 (62.5%)	2 (25%)	0.3147
Prior lines of therapy, n (%)				
3	7 (43.75%)	3 (37.50%)	4 (50%)	> 0.9999
4	6 (37.5%)	3 (37.50%)	3 (37.50%)	> 0.9999
≥ 5	3 (18.75%)	2 (25%)	1 (12.50%)	> 0.9999
Previous treatment with IMiDs, n (%)	16 (100%)	8 (100%)	8 (100%)	> 0.9999
Previous ASCT, n (%)	10 (62.50%)	5 (62.5%)	5 (62.5%)	> 0.9999
KPS < 60 prior to CAR T-cells infusion	7 (43.75%)	4 (50%)	3 (37.50%)	> 0.9999
Diseases status prior to CAR T-cells infusion, PD, n (%)	16 (100%)	8 (100%)	8 (100%)	> 0.9999
Diseases status one month after CAR T cells infusion, n (%)				
PR	8 (50%)	4 (50%)	4 (50%)	> 0.9999
VGPR	8 (50%)	4 (50%)	4 (50%)	> 0.9999

EMD extramedullary disease, *IMiDs* immunomodulatory drugs, *ASCT* autologous stem cell transplantation, *PD* progressive disease, *PR* partial response, *VGPR* very good partial response, *KPS* Karnofsky performance status

with these cytogenetic abnormalities (Table 1 and Supplementary Table 1). Soft tissue masses in extraosseous locations (extramedullary disease, EMD) with or without bone lesions were examined before CAR T-therapy in 5 (62.5%) of 8 R/R MM patients in the "pomalidomide" group and in 2 (25%) of 8 R/R MM patients in the control arm (Supplementary Table 1). All patients enrolled in this study received more than third-line therapy prior to CAR T-therapy, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), or anti-CD38 monoclonal antibodies (Supplementary Table 2). Five (62.5%) of 8 R/R MM patients in the pomalidomide arm, had undergone prior ASCT, while 62.5% of the patients in the control group had ($p > 0.9999$) (Table 1 and Supplementary Table 1). All patients in both groups were in progressive disease (PD) at the time before CAR T-cell infusion (Table 1).

Long-term pomalidomide administration improves the antitumor efficacy of BCMA *CAR* T-cell therapy.

According to the IMWG criteria, all the 16 enrolled patients achieved different degrees of remission 1 month after CAR T-cell infusion, and the overall objective response rate (ORR) was 100% (Table 1 and Fig. 2a). Three months following CAR T-cell therapy, of the 8 patients who did not receive pomalidomide administration, only 5 patients (62.50%) achieved very good partial response (VGPR) or better. Notably, except for 2 patients who discontinued the maintenance therapy on their own and were lost to follow-up within the first cycle of pomalidomide administration, all patients (6/6) who received long-term pomalidomide treatment after BCMA CAR T-cell infusion achieved VGPR or CR at the same time (Fig. 2a). Among the 6 R/R MM patients who received long-term pomalidomide, responses were noted: 4 patients (4/6) achieved complete response (CR) at 2 months, 3 months, 8 months, and 9 months after CAR T-cell infusion. Patient 5 achieved optimal VGPR within 1 month following CAR T-cell infusion but relapsed at 9.7 months after CAR T-cell infusion (Fig. 2a). Of the 8 patients who only received BCMA CAR T-cell therapy without any maintenance therapy, 5 patients (5/8) achieved VGPR, and 3 patients (3/8) just achieved partial response (PR) during follow-up. All patients who only received BCMA CAR T-cell therapy progressed during the follow-up period and eventually died after infusion (Fig. 2a). At the data cutoff date (July 31, 2023), the median follow-up time was 27 months. The median TTP (time to progression) was 5.85 (range, 1–14) months in the control arm, while the OS was 10.7 (1.2–16) months (Fig. 2b, c). Of the 8 patients who were administered pomalidomide therapy after CAR T-cell infusion, the median TTP was 13 (range, 7–31) months, while the OS was not reached. Notably, there were significant differences in TTP and OS between the groups (the *p*-Values were 0.0166 and 0.0068, respectively) (Fig. 2b, c). Taken together, these results show that pomalidomide maintenance therapy after BCMA CAR T-cell infusion resulted in a significant benefit in patients with R/R MM, slowing disease progression and prolonging overall survival.

Representative cases of treatment responses

Patient 2, a 57-year-old woman, was diagnosed with IgG-κ MM in June 2018 and assessed as R-ISS stage III, without any high-risk cytogenetic features at the time of diagnosis. She received induction chemotherapy with 4 cycles of bortezomib, lenalidomide, and dexamethasone (VRD) and was assessed as VGPR according to IMWG response criteria, but biochemical relapse was observed in the consolidation therapy stage. Then, she received other chemotherapy regimens, including IT, ICD, and IRD (Supplementary Table 2), and eventually achieved PR. She relapsed again in October 2020 and had newly detected high-risk cytogenetic alterations, such as 1q21 amplification, RB1 deletion, D13S319 deletion, P53 deletion, and a complex karyotype. Given her poor response and disease recurrence, BCMA CAR T-cell therapy was initiated in January 2021. No CAR T-cell treatment-related acute toxicity (CRS or ICANS) was observed. The patient was assessed as VGPR one month after CAR T-cell infusion and started to receive oral pomalidomide (4 mg per day for 21 days of a 28-day cycle). Two months later, the karyotype returned to normal, and she eventually achieved CR 8 months after CAR T-cell therapy. At the end of the follow-up, no disease progression had been observed.

Patient 3, a 71-year-old man, was diagnosed with IgG-κ MM in April 2020 and further assessed as R-ISS stage III; he also lacked high-risk clinical features. After 3 cycles of VRD and one cycle of IRD (ixazomib, lenalidomide and dexamethasone), a new mass on the chest wall was identified with multiple myeloma extramedullary lesions, which was confirmed by pathological biopsy (Supplementary Fig. 1). Considering the poor prognosis for extramedullary MM, one cycle of bortezomib, pomalidomide and dexamethasone (VPD), one cycle of dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE), and even salvage ASCT were given. However, the extramedullary mass did not shrink, and the patient retained stable disease (SD). Therefore, he received BCMA CAR T-cell infusion in May 2021. He achieved PR one month after CAR T-cell therapy, and long-term pomalidomide treatment (4 mg per day for 21 days of 28-day cycle) has been administered since then. The best response was CR, which was achieved 9 months after infusion.

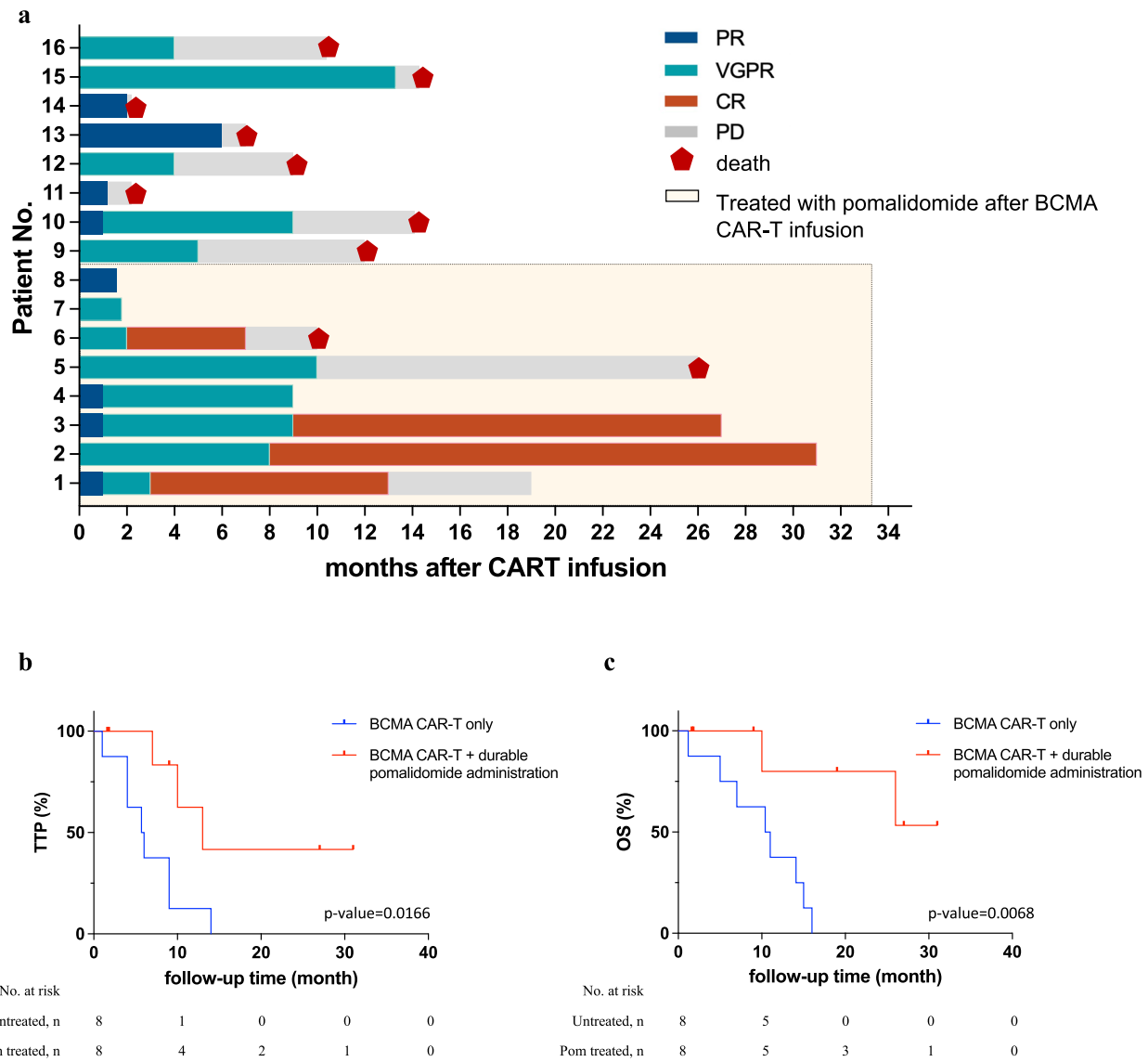


Fig. 2 Combination with oral pomalidomide treatment enhances the efficacy of BCMA CAR T-cell therapy. **a** Swimlane plot showing the response of 16 R/R MM patients who received BCMA CAR T-cells infusion, and eight patients received standard pomalidomide therapy one month after cell infusion. **b**, **c** TTP (**b**) and OS (**c**) of R/R MM patients who received oral pomalidomide treatment (n = 8) and those who did not receive pomalidomide maintenance therapy (n = 8). *PR* partial response, *VGPR* very good partial response, *CR* complete response, *PD* progressive disease, *TTP* time to progression, *OS* overall survival

After follow-up for 15 months, no recurrence has been detected.

Safety and side effects of BCMA *CAR* T-cell infusion in patients

Immune disorders, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), are the most common adverse events in the acute phase of CAR T-cell infusion [29]. Most of the patients enrolled in this study (7/16, 43.75%) developed CRS of grade II and below, with major symptoms of fever and fatigue, while 5 patients (5/16, 31.25%) developed severe CRS (grade III and above) (Table 2). Only one patient in the pomalidomide arm, developed ICANS (Table 2). Moreover, the acute toxicities induced by CAR T-cell infusion were relieved by administration of tocilizumab (8 mg/kg), glucocorticoids, and other related symptomatic and supportive treatments. Hematologic toxicities of grade III or above were also observed, including neutropenia (14/16), lymphopenia (12/16), anemia (10/16), and thrombocytopenia (7/16), which were rapidly resolved within one month after CAR T-cell

Table 2 Safety and side effects of BCMA CAR-T-cell infusion in patients

Adverse events	Total (n = 16)	Patients treated with Pom after CAR T-cells infusion (n = 8)	Patients without Pom administration after CAR T-cells infusion (n = 8)	*p*-Value
Cytokine release syndrome, CRS*				
All grades, n (%)	12 (75%)	4 (50%)	8 (100%)	0.0769
Grade 1–2, n (%)	7 (43.75%)	3 (37.5%)	4 (50%)	> 0.9999
Grade ≥ 3, n (%)	5 (31.25%)	1 (12.5%)	4 (50%)	0.2821
Immune effector cell-associated neurotoxicity syndrome, ICANS*				
All grades, n (%)	1 (6.25%)	1 (12.5%)	0 (0)	> 0.9999
Grade 1–2, n (%)	1 (6.25%)	1 (12.5%)	0 (0)	> 0.9999
Grade ≥ 3, n (%)	0 (0)	0 (0)	0 (0)	> 0.9999
Hematological toxicities (Grade ≥ 3)				
Neutropenia, n (%)	14 (87.5%)	6 (75%)	8 (100%)	0.4667
Lymphopenia, n (%)	12 (75%)	5 (62.5%)	7 (87.50%)	0.5692
Anemia, n (%)	10 (62.5%)	3 (37.5%)	7 (87.50%)	0.1189
Thrombocytopenia, n (%)	7 (43.75%)	4 (50%)	3 (37.50%)	> 0.9999
Other				
Pyrexia, n (%)	12 (75%)	4 (50%)	8 (100%)	0.0769
Fatigue, n (%)	6 (37.5%)	3 (37.5%)	3 (37.50%)	> 0.9999
Elevated transaminase levels, n (%)	5 (31.25%)	2 (25%)	3 (37.50%)	> 0.9999
Elevated bilirubin levels, n (%)	1 (6.25%)	0 (0)	1 (12.50%)	> 0.9999
Coagulopathy, n (%)	6 (37.5%)	2 (25%)	4 (50%)	0.6084
Respiratory infection, n (%)	5 (31.25%)	3 (37.5%)	2 (25%)	> 0.9999
Diarrhea, n (%)	2 (12.5%)	1 (12.5%)	1 (12.50%)	> 0.9999

CRS and ICANS were evaluated according to the ASTCT consensus guidelines and the modified criteria by Lee, et al. All adverse events were graded by the Common Terminology Criteria for Adverse Events version 5.0

infusion. No death was attributed to treatment-related toxicities. There was no statistically significant difference in acute adverse effects between the two groups (Table 2). Transient elevations in transaminases were observed in the acute phase after CAR T-cell infusion and then rapidly resolved. Notably, no persistent suppression of bone marrow hematopoiesis or hepatotoxicity caused by long-term pomalidomide administration was observed during follow-up (Fig. 3a-f).

Monitoring of chimeric antigen receptor (*CAR*) transgene copy numbers after BCMA *CAR* T-cell infusion

The abundance of circulating BCMA CAR T-cells in patients was detected at the indicated time points after CAR T-cell infusion, and the dynamic changes were monitored as shown in Fig. 4. The CAR DNA copy numbers peaked 5 to 10 days after CAR T-cell infusion in both groups, with a peak copy number of up to 10^5. In addition, BCMA CAR T-cells persisted ($> 1*10^3$ copies/μg DNA) for 3 to 4 months in vivo. At one month after CAR T-cell infusion, there was no significant difference in copy numbers of CAR DNA between the two groups ($p = 0.7491$). Notably, without pomalidomide treatment, CAR DNA became undetectable within 100 days (Fig. 4). However, data from studies with larger sample sizes are required to draw valid conclusions.

Pomalidomide-mediated direct antimyeloma activity, inhibition of CAR T-cell apoptosis, and enhanced cytotoxicity of BCMA CAR T-cells increase the efficacy of the combination regimen

Pomalidomide has been verified to promote the antitumor efficacy of BCMA CAR T-cells, and the OS and TTP of R/R MM patients, who received oral pomalidomide treatment following CAR T-cell infusion, were remarkably prolonged. However, the underlying mechanism remains unclear. Pomalidomide is a third-generation immunomodulatory drug (IMiD) that has a significant antimyeloma effect by inducing cell apoptosis, interrupting cytokine production, and inducing immunomodulation [30]. To investigate the mechanisms by which pomalidomide synergistically promotes the antimyeloma activity of CAR T-cell therapy, BCMA CAR T-cells were cultured in vitro with or without pomalidomide for 4 days. Apoptosis of BCMA CAR T-cells was significantly suppressed by sustained pomalidomide treatment in a concentration-dependent manner (Fig. 5a–c). Notably, a high concentration (10 μg/mL) of pomalidomide did not benefit CAR T-cell survival (Fig. 5c). A large number of

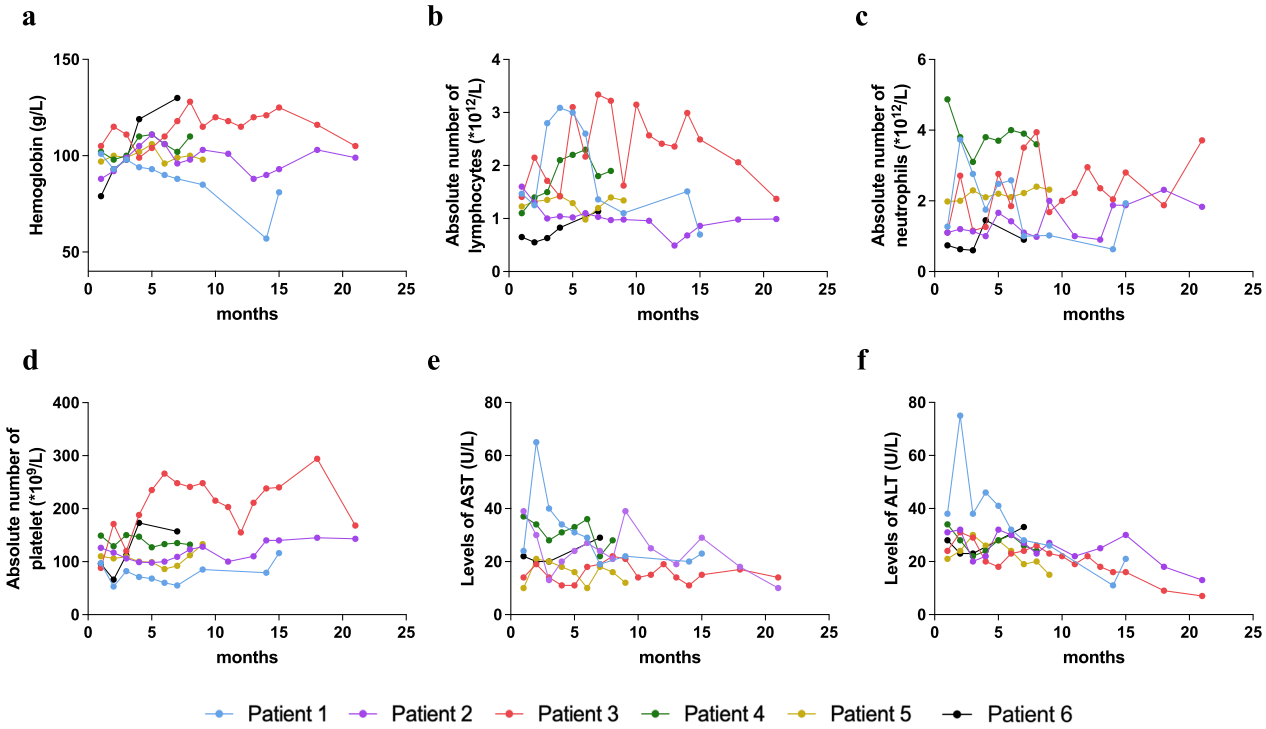


Fig. 3 Levels of circulating hematopoietic cells and transaminase were monitored following BCMA CAR-T infusion. Peripheral blood from R/R MM patients, who received oral pomalidomide administration following BCMA CAR-T cells infusion, were collected at the indicated timepoints. Levels of hemoglobin (**a**), and absolute number of lymphocytes (**b**), neutrophils (**c**), and platelet (**d**), and transaminases (**e**, **f**) were documented and shown as a trend chart

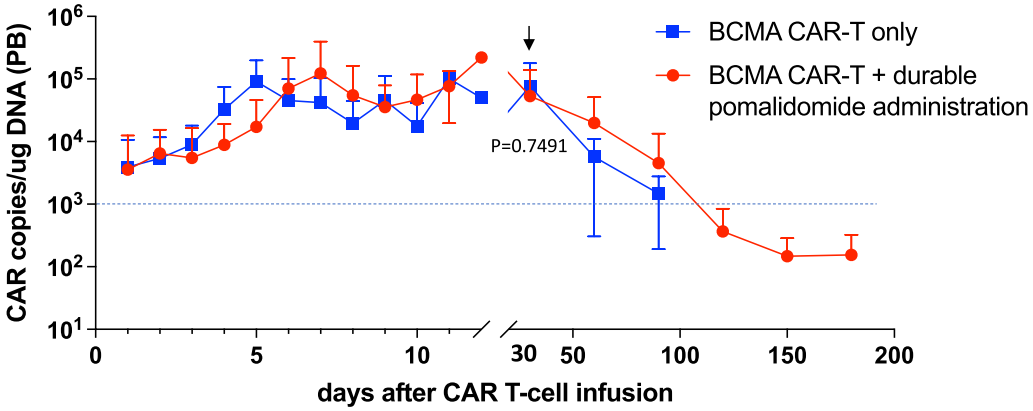


Fig. 4 Monitoring of Chimeric antigen receptor (CAR) transgene copy numbers after BCMA CAR-T infusion. Circulating CAR transgene copy numbers from R/R MM patients after BCMA CAR T-cell infusion, were quanlified by qPCR at the indicated timepoints. A copy number less than 10^3/ug DNA, was considered that CAR T-cell does not exist in vivo (detection threshold)

clinical reports have shown that continuous proliferation of CAR T-cells in vivo is key for ensuring therapeutic effects [31, 32]. However, upon TCR-mediated stimulation, the proliferation rates were comparable between the in-vitro cultured BCMA CAR T-cells treated with or without exogenous pomalidomide, since the MFI of CFSE (a dye that dilutes as cells divide) was similar in every group (Fig. 5d). To evaluate the effect of pomalidomide on the cytotoxicity of BCMA CAR T-cells, we performed a cytotoxicity assay. Preliminary experiments have shown that pomalidomide does not directly impair cell expansion or induce apoptosis of BCMA-expressing K562 cells

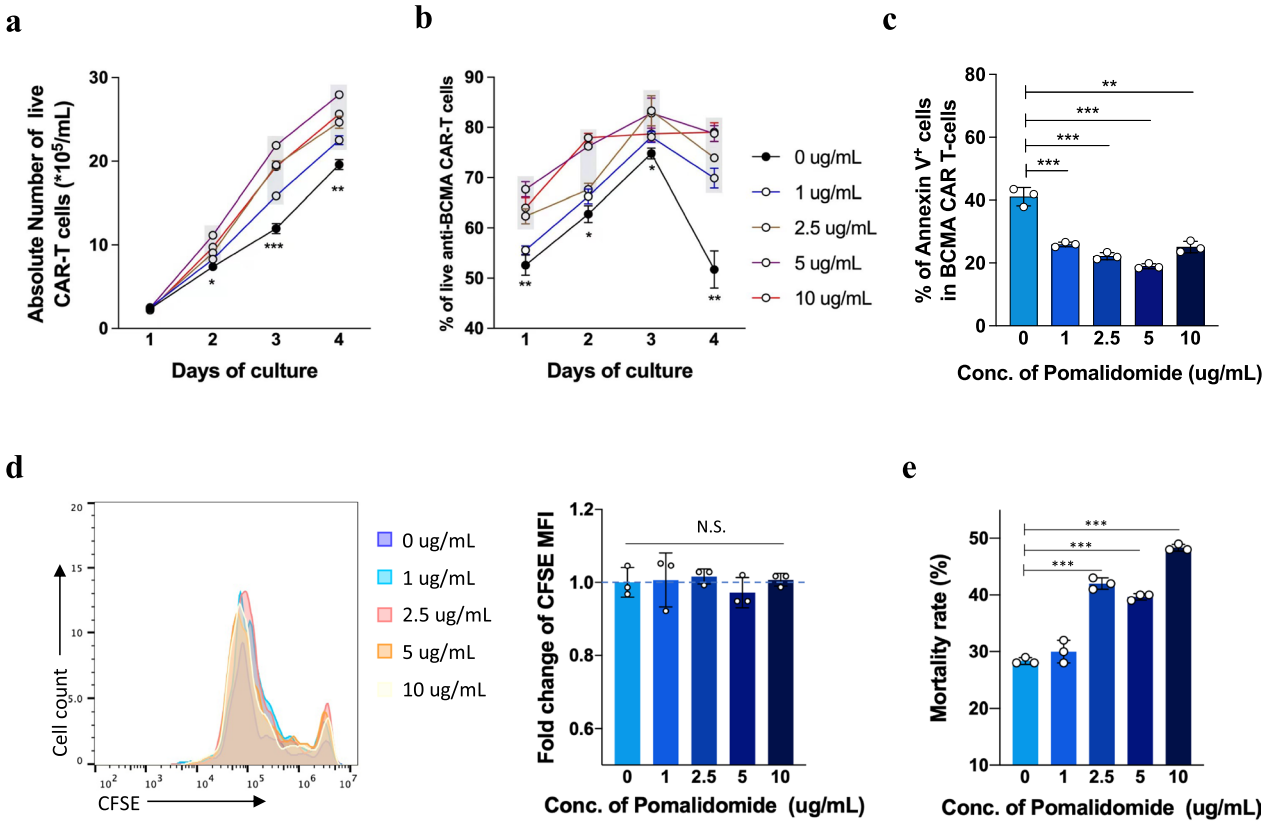


Fig. 5 Pomalidomide promotes the cell survival and killing efficiency of BCMA CAR T-cells, but not proliferative capability. **a**-**c** BCMA CAR T-cell products provided from Yucardi bio-pharmaceuticals company were cultured and continuously activated by anti-CD3 and anti-CD28 monoclonal antibodies in vitro for 4 days, treated with pomalidomide at different gradient concentrations. The absolute numbers (**a**) and percentages (**b**) of live BCMA CAR T-cells at the indicated timepoints were determined by trypan-blue staining. **c** After 4 days of continuous pomalidomide treatment with indicated gradient concentrations, apoptosis of BCMA CAR T-cells were assessed by FACS. **d** BCMA CAR T-cells were labeled with CFSE and stimulated by anti-CD3 and anti-CD28 monoclonal antibodies and treated with pomalidomide at the indicated concentrations simultaneously. Four days after anti-CD3/CD28 stimulation, CFSE intensities of CAR T-cells were assessed by FACS. The fold changes of CFSE MFI (Mean fluorescence intensity) were calculated and further analyzed. **e** After 3 h of co-cultivation, the killing efficiencies were determined with the LDH-release assay. The cytotoxicity (cell lysis, %) for each well was calculated as follow: [(OD-value of samples to be tested – OD-value of Control group) / (OD-value of Maximum LDH release group – OD-value of Control group)] × 100%. Experiments above were performed three times and similar results were obtained in each. Results shown are mean ± S.D. of triplicates from one experiment

(Supplementary Fig. 2). Pomalidomide enhanced the antigen-specific killing efficiency of BCMA CAR T-cells (Fig. 5e) at a low concentration (1 μg/mL). In summary, in addition to the direct antimyeloma activity of pomalidomide, pomalidomide administration following BCMA CAR T-cell therapy produces synergistic effects in the treatment of R/R multiple myeloma by promoting cell survival and enhancing the killing capability of BCMA CAR T-cells.

Discussion

Several clinical studies have demonstrated encouraging efficacy of BCMA CAR T-cells in R/R MM, with response rates of 73.4% and 94.8% for the idel-cel and cilta-cel BCMA CAR T-cell products, respectively [33]. However, the long-term efficacy is poor, and the progression-free survival (PFS) reported for R/R MM patients who received BCMA CAR T-cell therapy was 6 to 17.4 months; the PFS is closely related to the quality of CAR T-cell products and high-risk prognostic factors of MM patients [34]. Enhancing the antitumor efficacy or prolonging the maintenance of BCMA CAR T-cells by optimizing the design of the CAR structure and combining CAR T-cell therapy with other drugs is the key to achieving long-term inhibition or killing of myeloma cells [9]. This single-center prospective clinical study is the first to focus on the efficacy and safety of BCMA CAR T-cell therapy combined with a long-term pomalidomide (a third generation IMiD) maintenance regimen in patients with relapsed or refractory multiple myeloma

with or without extramedullary lesion. This combination regimen effectively deepened disease remission and prolonged progression-free survival in R/R MM patients.

Extramedullary involvement of multiple myeloma is an independent risk factor related to poor prognosis [35, 36]. A previous study found that the progression-free survival of patients with EMD who received BCMA CAR T-cell therapy was significantly shorter than that of MM patients without EMD (121 vs. 361 days) [37]. Notably, pomalidomide-based regimens have been reported to have a high ORR in MM patients with extramedullary involvement who are resistant to multiline therapies [38]. Encouragingly, a MM patient with central nervous system (CNS) involvement who received pomalidomide-based regimens as a bridge to BCMA CAR T-cell therapy achieved stringent complete response (sCR) [39]. In this study, long-term pomalidomide administration after BCMA CAR T-cell therapy benefited R/R MM patients who were resistant to frontline drugs and even those who developed new extramedullary lesions (patients 1 and 3). Moreover, high-risk genetic alterations acquired during treatment are closely related to poor prognosis for R/R MM patients [40]. Among them, *TP53* mutation is generally considered an independent risk factor [41]. In this study, a drug-resistant MM patient (patient 2) who acquired high-risk genetic alterations during rapid disease progression, including abnormal amplification of 1q21, deletion of TP53, RB1 and D13S319, and a complex karyotype, regained a normal karyotype after receiving BCMA CAR T-cell infusion combined with pomalidomide maintenance therapy for 3 months. The patient eventually achieved CR, and up to the end of follow-up, no disease progression or relapse was observed. Moreover, in this study, patients with R/R MM who received BCMA CAR T-cell infusion without any combined therapy had poorer clinical outcomes than published data from BCMA CAR T-products, that the median time to disease progression was 5.85 months. This could be partially explained by the unpublished data from Yucardi, that the median PFS of R/R MM patients was limited to 6 months. More importantly, the patients enrolled in this study carried a series of high-risk prognostic factors and showed minimal response to previous multiline treatment regimens, leading to poor outcomes after BCMA CAR T-cell infusion. In summary, the R/R MM patients included in this study had high-risk factors and poor prognosis and remarkably benefited from long-term pomalidomide administration after BCMA CAR T-cell infusion, providing a feasible option for the treatment of R/R MM patients with high-risk factors.

The serious hematological toxicity of lenalidomide is a major limitation of its clinical application [16, 17]. CAR T-cell infusion related cytokine release syndrome and transient reductions in hematological cell numbers were common; thus, the combination treatment should not be applied during the acute phase of BCMA CAR T-cell infusion to avoid amplification of treatment-related toxicities. In a previous case report, oral lenalidomide administration was started the day before BCMA CAR T-cell infusion, and the treatment needed to be discontinued due to severe cytopenia [16]. Low-dose pomalidomide exerts sufficient antitumor activity and has a lower incidence of drug-related toxicities. Although some studies have shown that pomalidomide promotes the efficacy of CAR T cells, there is no consensus on the specification of combination therapy. Jie Zhao et.al emphasized pomalidomide improves the CAR-T treatment by enhancing tumor microenvironment (TME) and preserving T cell functionality, that the administration of pomalidomide at a dosage of 1 to 2 mg started from the same day as the infusion of CAR T-cells[42]. Moreover, considering the direct anti-meyloma effect of pomalidomide, oral pomalidomide treatment at a adequate dosage was applied from 1 month after BCMA CAR T-cell infusion in this study, at which time the abnormalities in hematological cell numbers had resolved, and the dosage of pomalidomide was adjusted according to the tolerance of patients. The safety of this combination regimen was demonstrated by the long-term follow-up.

As high-risk MM patients significantly benefit from BCMA CAR T-cell therapy in combination with long-term pomalidomide treatment in this study, the underlying mechanisms were further explored, including the direct antimyeloma activity, inhibition of CAR T-cell apoptosis, and enhanced killing efficacy of BCMA CAR T-cells mediated by pomalidomide, which are consistent with the pharmacological properties of IMiDs shown in previous studies [12, 30]. Lenalidomide, the second-generation IMiD, relies on the presence of circulating BCMA CAR T-cells to exert synergistic effect by promoting CAR T-cells proliferation [14, 16, 43]. However, in this study, pomalidomide administration did not increase the abundance of CAR T-cells, but prolonged the maintenance of CAR T-cells by inhibition of CAR T-cells apoptosis. Remarkably, consistent with the enhanced antimyeloma activity of BCMA CAR T-cells mediated by pomalidomide, there were more patients in the "pomalidomide" group achieved deeper remission (VGPR or better) within 2 months after CAR T-cell infusion. In addition, the direct antitumor effect of pomalidomide in combination regimens cannot be ignored. As pomalidomide is a third-generation IMiD, the antimyeloma effect of pomalidomide is stronger than that of thalidomide and lenalidomide [18]. Moreover, pomalidomide can penetrate the blood–brain barrier and is clinically applied in the treatment of patients with MM with central nervous system

involvement [39, 44]. Therefore, it is necessary to maintain oral administration of pomalidomide even if CAR T-cells are gradually depleted and eventually become undetectable in peripheral blood.

This is the first study to explore the feasibility of BCMA CAR T-cell therapy combined with a long-term pomalidomide maintenance regimen in patients with R/R MM. This study provided an additional strategy for improving the efficacy of BCMA CAR T-cell therapy. However, there were various limitations in the current study. Due to the limited sample size and missing data, it is hard to draw generalizable conclusion. Secondly, because of the growing perception that IMiDs contribute to the efficacy of CAR T-therapy, MM patients who received BCMA CAR T-cell infusion at a recent time were more likely accepted pomalidomide administration as a maintenance therapy, which led to selection bias. Furthermore, there are certain differences in the choice of front-line treatment regimens, resulting in differences in the sensitivity of different R/R MM patients to pomalidomide, which might have influenced the outcomes. A large-scale completely randomized clinical study with subgroup analyses is required to support the conclusion and to standardize the clinical application of this combination regimen in patients with R/R MM. Our innovative clinical combination strategy can improve the efficacy of established CAR T-cell products and further prolong the survival of high-risk MM patients. In the future, the development of new chemotherapeutic or immunomodulatory drugs and new combination regimens will benefit more patients with R/R MM.

Conclusions

BCMA CAR T-cell therapy combined with long-term pomalidomide had a low recurrence rate and manageable therapy-related side effects, providing a promising option for treating R/R MM.

Abbreviations

BCMA	B-cell mature antigen
CAR T-cells	Chimeric antigen receptor T-cells
R/R MM	Refractory or relapsed multiple myeloma
ORR	Objective response rate
sCR	Stringent complete response
CR	Complete response
VGPR	Very good partial response
PR	Partial response
TTP	Time to progression
OS	Overall survival
PFS	Progression-free survival
PI	Proteasome inhibitor
IMiDs	Immunomodulatory drugs
BTK	Bruton's tyrosine kinase
EMD	Extramedullary disease
ASCT	Autologous hematopoietic stem cell transplantation
CRS	Cytokine release syndromes
ICANS	Immune effector cell-associated neurotoxicity syndrome
CNS	Central nervous system
IMWG	International Myeloma Working Group
BM	Bone marrow
MRD	Minimal residual disease
SPEP	Serum protein electrophoresis
UPEP	Urine protein electrophoresis
MRI	Magnetic resonance imaging
CT	Computed tomography
IL-6	Interleukin-6
CRP	C-reactive protein

Supplementary Information

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Additional file 1.

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Author contributions

Y.H.Y. and Y.X.T. conducted the research and summarized the data. Q.C., J.Z., and E.H.W. provided the clinical cases included in this study. L.Q.K. provided the BCMA CAR-T-cell products and BCMA-expressing K-562 cells used in this study. L.C. provided technical assistance for the immunohistochemistry staining of involved extramedullary tissue. Q.C., Z.Q.D., Y.Y., L.W.W., and R.L. provided critical advice and discussed the work. X.L. and J.L. designed and directed the entire study. Y.H.Y., Y.X.T., and X.L. wrote the manuscript with input from the other authors.

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Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board of the Third Xiangya Hospital of Central South University. All patients included in this study provided written informed consent.

Consent for publication

Informed consent was obtained from all individual participants included in the study.

Competing interests

The authors declare that they have no competing interests.

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