Achieving stringent complete remission in relapsed/refractory multiple myeloma with liver extramedullary disease after CAR-T cell therapy: A case report

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Abstract. Multiple myeloma (MM) is a clonal plasma cell malignancy characterized by bone marrow infiltration and the presence of monoclonal proteins in the blood and urine. However, despite the advances that have been made in terms of its treatment, relapsed/refractory MM (RRMM) remains a significant challenge. Chimeric antigen receptor (CAR)-T cell therapy, which involves the engineering of T-cells to express CARs targeting specific antigens on tumor cells, has emerged as a promising therapeutic approach for RRMM. The present case report presents a patient with RRMM with liver extramedullary disease (EMD) who achieved stringent complete remission following CAR-T cell therapy. This case report highlights the efficacy of CAR-T cell therapy in treating RRMM, also discussing the patient's clinical course, treatment outcomes and side effects, and moreover, a review of the literature that focuses on the treatment of EMD using CAR-T cell therapy.

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Abbreviations: ASCT, autologous stem cell transplant; BCMA, B cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; EMD, extramedullary disease; FCM, flow cytometry; FISH, fluorescence in situ hybridization; ICANS, immune effector cell-associated neurotoxicity syndrome; IL-6, interleukin-6; ImiDs, immunomodulatory drugs; ISS, International Staging System; MM, multiple myeloma; NMPA, National Medical Products Administration; NPS, non-paraskeletal; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PET/CT, positron emission tomography/computed tomography; PIs, proteasome inhibitors; PR, partial response; sCR, stringent complete response; VGPR, very good partial remission

Key words: multiple myeloma, chimeric antigen receptor T cell therapy, stringent complete remission, relapsed/refractory multiple myeloma, extramedullary disease, cytokine release syndrome

Introduction

Multiple myeloma (MM), the second most common type of hematologic malignancy, accounts for approximately 1% of all cancers and 10% of hematological malignancies globally, with an estimated 176,000 new cases annually (1). Despite therapeutic advancements, including proteasome inhibitors and immunomodulatory drugs, nearly all patients eventually relapse, and relapsed/refractory MM (RRMM) remains a leading cause of cancer-related mortality, responsible for over 117,000 deaths worldwide in 2022 (2). Patients with RRMM face a median overall survival (OS) of 12-18 months, which drops sharply in high-risk subgroups such as those with extramedullary disease (EMD) (3). EMD, characterized by tumor cell infiltration into organs beyond the bone marrow (such as liver, soft tissues), occurs in 10-30% of MM cases and correlates with aggressive biology, chemotherapy resistance, and a median OS of <12 months (4). Chimeric antigen receptor (CAR) T-cell therapy has revolutionized RRMM treatment, with pivotal trials (e.g., CARTITUDE-1) reporting overall response rates of 97-98% and stringent complete remission (sCR) rates of 67-80% in heavily pretreated patients (5). However, data on CAR-T efficacy in EMD-particularly visceral EMD-remain sparse due to its exclusion from many clinical trials (6). Recent studies suggest that CAR-T therapy may overcome the poor prognosis associated with EMD, with early data showing promising response rates in this subgroup (6,7). This case report presents a patient with RRMM and liver EMD who achieved durable sCR post-CAR-T therapy, addressing a critical gap in understanding CAR-T's potential in this high-risk population.

Case report

A 54-year-old male patient presented to the Department of Orthopedics of Shenzhen Luohu People's Hospital (Shenzhen, China) with lower back pain following exercise in December 2019. Lumbar spine MRI revealed a mass, and bone destruction at the L2-3 vertebral bodies. Biopsy results indicated plasma cell myeloma, with positive immunohistochemical staining for the antigens CD138, CD38, MM oncogene 1 and CD56, along with κ light chain restriction, and the Ki-67 index was 60%. A bone marrow smear revealed ~5.5% plasma cells, with flow cytometry (FCM) detecting 3.51% of monoclonal plasma cells restricted to the κ light chain. The serum IgA level of

the patient was 13.32 g/l (reference range, 0.7-3.5 g/l), whereas levels of β2-microglobulin, calcium and free light chain levels remained normal. Serum immunofixation electrophoresis assay yielded a positive IgA-κ result. Cytogenetics and fluorescence *in situ* hybridization assay revealed chromosomal 17p and 13q deletions. Furthermore, a whole-body positron emission tomography/computed tomography (PET/CT) scan revealed generalized osteoporosis and multiple sites of vertebral bone destruction. The patient was subsequently diagnosed with MM (8) of the IgAκ subtype, and classified as stage IA according to the Durie-Salmon staging criteria (9), stage I according to the International Staging System (ISS) (10) and stage II according to the revised-ISS (11). Because the patient had a chromosomal 17p chromosomal deletion, he was also considered at high risk per the Mayo Stratification of Myeloma and Risk-Adapted Therapy criteria (12).

Upon diagnosis, the patient promptly underwent treatment that was in line with the Guidelines for the Diagnosis and Management of MM in China (2017 revision) (8) and the National Comprehensive Cancer Network Guidelines for MM, version 1.2020 (13). The specific treatment progress and response details are presented in Fig. 1. The doctor repeatedly advised the patient to undergo an autologous stem cell transplant (ASCT); however, the patient refused the procedure for fear of complications associated with the transplant. Lenalidomide was discontinued after June 2020 due to the potential harm it may cause to the patient's hematopoietic stem cells when used for an extended period. Despite the patient's persistent opposition to autologous hematopoietic stem cell transplantation, we, as doctors, were reluctant to entirely close off this avenue for the patient. In July 2020, bortezomib was switched to isazomib due to the availability of the drug at that time, as both belong to the same class of medication. Additionally, isazomib is an oral medication, making it more convenient to use, as the patient did not need to frequently visit the hospital. Henceforth, the reason for the numerous changes in the initial treatment is that the disease progressed multiple times (Fig. 1).

In April 2023, a whole-body PET/CT scan revealed multiple novel osteolytic bone lesions, including a newly developed lesion of hypermetabolism in segment S4 of the liver measuring ~25x24 mm compared with the previous results (Fig. 2C and D). The patient declined to undergo percutaneous biopsy of the lesion. Based on these findings, the patient was considered to have an aggressive relapse of MM with concomitant extramedullary involvement in the liver. Between April 2023 and July 2023, the patient underwent four cycles of a Dara + SKd regimen (daratumumab, 16 mg/kg, once a week for the first 8 weeks, once every 2 weeks from the 9th week; carfilzomib, 51 mg on days 1-2, 8-9 and 15-16; and dexamethasone, 10 mg on days 1-2, 8-9 and 15-16, 4 weeks as a treatment cycle) as the therapeutic protocol. Re-evaluation of the results after completing two cycles of the treatment regimen revealed the presence of an IgA-κ type M protein on immunofixation electrophoresis, accompanied by a serum IgA level of 5.84 g/l. The disease status of the patient was therefore considered to be a partial response (PR).

In July 2023, after having completed four cycles of the Dara + SKd regimen, a PET/CT scan revealed an increase in osteolytic bone destruction lesions (Fig. 2A and B). Additionally, a significant increase in the patient's serum IgA concentration to 8.27 g/l was observed, with a slight reduction in the size of the lesion located in hepatic segment S4, now measuring ~17x10 mm. Bone marrow cytological analysis indicated that plasma cells comprised ~1.5% of the total cells, and FCM analysis detected a population of 0.1% monoclonal plasma cells with an aberrant immunophenotype. The patient was considered to have progressive disease. At this point, the doctor again recommended that the patient undergo an ASCT, and the patient continued to refuse. In addition, at this time, the first Chinese anti-BCMA CAR-T cell product (FUCASO®; also known as 'Equecabtagene Autoleucel'; IASO BioTherapeutics, Ltd. and Innovent Biologics, Inc.) was approved by the China National Medical Products Administration (NMPA). After discussion with the care team, the patient selected the anti-BCMA CAR-T cell therapy.

A lymphocyte-depleting chemotherapy protocol consisting of fludarabine (50 mg/m^2 on days 1-3) and cyclophosphamide (500 mg/m^2 on days 1-3; namely, an fludarabine and cyclophosphamide regimen) was administered in August 2023. Subsequently, 5 days afterwards (day 0), the patient received a reinfusion of anti-BCMA CAR-T cell therapy (FUCASO®; Equecabtagene Autoleucel) provided by IASO BioTherapeutics, Ltd.

After CAR-T cell infusion, the patient's vital signs, such as body temperature, blood pressure, oxygen saturation and heart rate, were closely monitored, and calculation, orientation and reading abilities were assessed. On day 1 of treatment, the patient had a fever that peaked at 38.6˚C, although his blood pressure and oxygen saturation remained normal. A preliminary diagnosis of grade 1 cytokine release syndrome (CRS) was made, and tocilizumab, antipyretics, valacyclovir, levofloxacin, entecavir and cefoperazone sodium/sulbactam sodium were prescribed to prevent infection. Subsequently, the patient's temperature gradually returned to normal, and an increasing trend in the level of interleukin-6 (IL-6) was observed. On day 4 of treatment, the patient's temperature increased again to 38.3˚C, and tocilizumab (8 mg/kg) was administered for the second time. On day 5 of treatment, the patient's temperature increased to 39.0˚C, and the IL-6 level rose to a peak of 3,809.06 pg/ml. In response to these observations, treatment with tocilizumab (8 mg/kg) was restarted, and imipenem/cilastatin was also added to the regimen as an adjunctive therapy. As a result, both a significant reduction in the level of IL-6 and a gradual stabilization of the patient's temperature were observed (Fig. 3A). The CRS was therefore resolved following treatment, and there was no evidence of immune effector cell-associated neurotoxicity syndrome (ICANS) by assessing the calculative, orientational and reading abilities of the patient.

Both the proportion of CAR-T cells among CD3$^+$ cells (CAR-T cells/CD3$^+$ T cells) and the concentration of CAR-T cells began to significantly increase beginning on day 4, reaching a plateau on day 10 (62.72 and 813.16 cells/μl, respectively), before gradually decreasing to 1.42% and 61.79 cells/μl, respectively, on day 42 (Fig. 3B and C).

On day 14, the patient's test results indicated that the level of IgA had returned to normal, and the concentration of IgA-κ type M protein was 0.4 g/l. Bone marrow cytology, FCM for

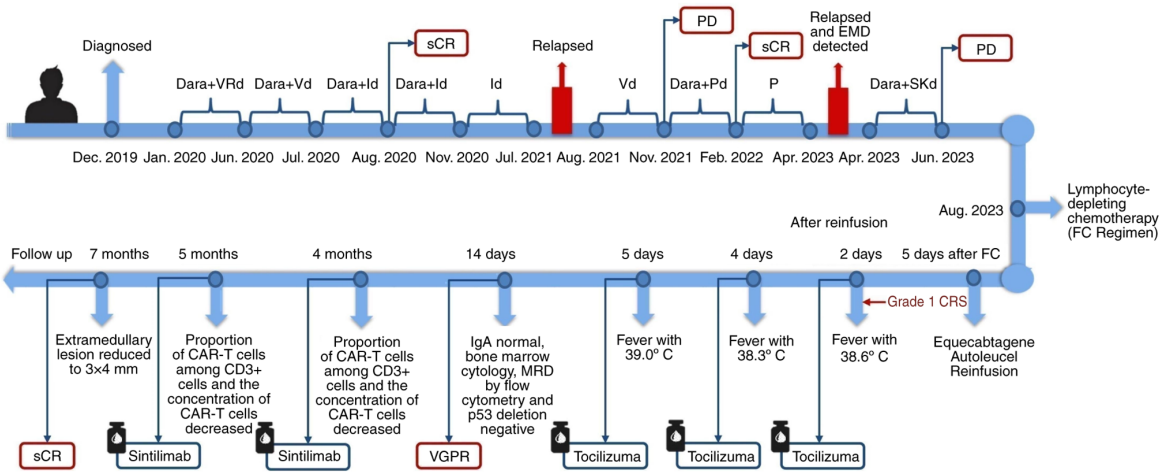

Figure 1. Treatment progress and response details. Dara + VRd=Daratumumab 16 mg/kg, once a week for the first 8 weeks, once every 2 weeks from the 9th week, and once every 4 weeks from the 25th week; bortezomib 1.3 mg/m^2 on days 1, 4, 8 and 11; lenalidomide 25 mg days 1-21; dexamethasone 20 mg on days 1-2, 4-5, 8-9 and 11-12; 4 weeks as a treatment cycle. Id=Ixazomib 4 mg on days 1, 8 and 15; dexamethasone 10 mg on days 1, 8, 15 and 16. Vd=bortezomib 1.3 mg/m^2 on days 1, 8, 15 and 22; dexamethasone 20 mg on days 1, 8, 15 and 22; 4 weeks as a treatment cycle. Dara + Pd=Daratumumab 16 mg/kg, once a week for the first 8 weeks, once every 2 weeks from the 9th week; pomalidomide 4 mg on days 1-21; dexamethasone 40 mg on days 1, 8, 15 and 22; 4 weeks as a treatment cycle. Dara + SKd=Daratumumab 16 mg/kg, once a week for the first 8 weeks, once every 2 weeks from the 9th week; carfilzomib 51 mg on days 1-2, 8-9 and 15-16; dexamethasone 10 mg on days 1-2, 8-9 and 15-16; 4 weeks as a treatment cycle. sCR, stringent complete response; PD, progressive disease; FC, fludarabine and cyclophosphamide; EMD, extramedullary disease; CRS, cytokine release syndrome; MRD, minimal residual disease; VGPR, very good partial remission; CAR-T, chimeric antigen receptor T cell.

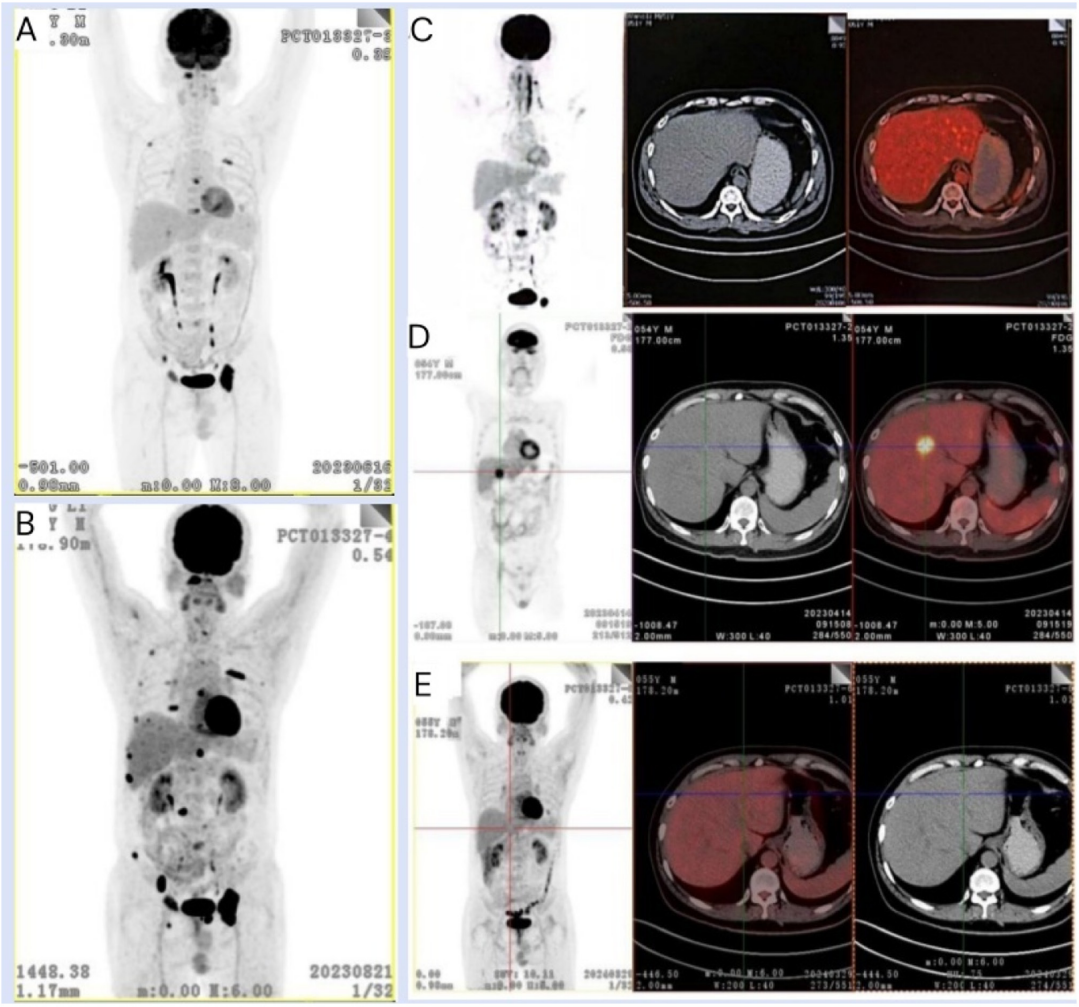

Figure 2. Whole-body PET/CT scans. (A) Osteolytic bone destruction lesions (June 2023). (B) Osteolytic bone destruction lesions increased (August 2023); (C) No lesion change in the S4 segment of the liver on diagnosis (December 2019); (D) Lesion changes in the S4 segment of the liver (April 2023). (E) Lesion changes in the S4 segment of the liver reduced with no hypermetabolism (March 2024). PET/CT, positron emission tomography/computed tomography.

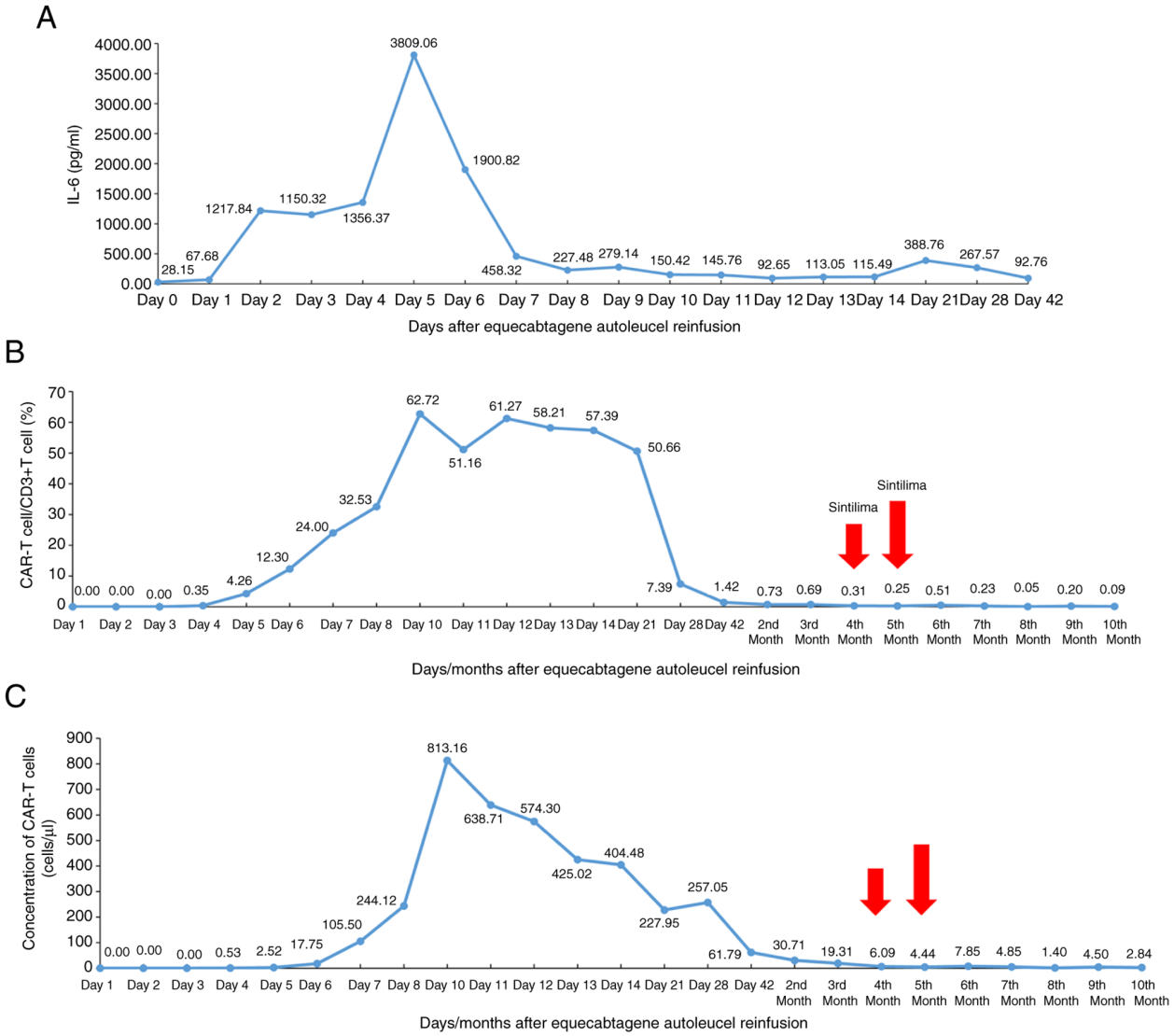

Figure 3. Changes in patient-associated indicators after Equecabtagene Autoleucel reinfusion. (A) Changes in the patient's IL-6 concentration are shown. (B) Changes in the proportion of CAR-T cells among $CD3^+$ cells are shown. (C) Changes in the patient's internal expansion of CAR-T cells are shown. CAR-T: chimeric antigen receptor T cell.

minimal residual disease and p53 deletion all elicited negative results. Furthermore, a significant reduction (>90%) in the liver involvement lesion was observed compared with its previous size by ultrasonogram. The patient's response was considered to be very good partial remission (VGPR). At 1-month post-infusion, no monoclonal protein was detected for the patient, and the normalization of free light chains was observed.

Follow-up examinations at 2 and 3 months following CAR-T cell infusion revealed further decreases in the patient's CAR-T cell/$CD3^+$ T cell ratio, which decreased to 0.73 and 0.69%, respectively, and decreases in the CAR-T cell concentration to 30.71 and 19.31 cells/μl, respectively, were also observed. The patient subsequently received sintilimab (200 mg), which is a PD-1 blocker, once a month to enhance CAR-T cell function from December 2023 (4 months following CAR-T cell infusion) onwards. Subsequently, 5 months following CAR-T cell infusion, both the CAR-T cell/$CD3^+$ T-cell ratio and the concentration of CAR-T cells dropped to 0.25% and 4.44 cells/μl, respectively. The 6-month follow-up data indicated that the percentage ratio of CAR-T cells/$CD3^+$ T cells and the concentration of CAR-T cells increased to 0.51% and 7.85 cells/μl, respectively, before gradually decreasing up to the 10th month (Fig. 3B and C). The decay rate of CAR-T cells was decreasing. The lesion located in the S4 liver segment also showed a significant reduction to ~3x4 mm, and no hypermetabolism was observed in the PET/CT scan results at 7 months following reinfusion (scan taken in March 2024) (Fig. 2E). In addition, bone marrow biopsy confirmed the absence of clonal plasma cells, and the patient was classified as having achieved sCR.

Discussion

The present case report presents a successful case of anti-BCMA CAR-T cell therapy in a patient with penta-refractory MM who also presented with extramedullary involvement. The successful treatment in this case has offered novel therapeutic insights for patients with penta-refractory MM, also providing valuable information for treating patients with extramedullary soft tissue involvement. Furthermore, the prompt and protocolized management of adverse events, in addition to

the innovative strategy of enhancing CAR-T cell functionality with programmed cell death 1 (PD-1) blockade during periods of lymphopenia, has yielded important empirical evidence, which may contribute to advancements in CAR-T cell therapy management and maintenance in clinical settings, highlighting the importance of such strategies in improving treatment safety and efficacy.

The management of MM is becoming more complex due to an increasing array of treatment options, including immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (mAbs), which are now standard for newly diagnosed and relapsed/refractory MM. However, even with these advancements, dealing with triple-class and penta-refractory MM poses ongoing challenges (14-18). The term 'penta-refractory' describes a therapeutically challenging subset of MM characterized by resistance to at least two different IMiDs, two PIs and a single anti-CD38 mAb (19). Patients with penta-refractory MM exhibit poor outcomes, with a median overall survival (OS) time of 5.6 months. This trend of diminishing therapeutic efficacy is further underscored by a decrease in the response rates for stable disease, PR and VGPR with each subsequent treatment line (19). In the present case, the patient underwent a variety of treatment regimens, including Dara + VRd, Dara + Vd, Dara + Id, Id, Vd, Dara + Pd and Dara + SKd (Fig. 1), all of which failed to achieve satisfactory outcomes, and were followed by inevitable relapses; therefore, novel therapeutic interventions are urgently required.

Currently, multiple BCMA CAR-T cell therapies have been approved, including Ciltacabtagene Autoleucel and Idecabtagene Vicleucel, which have been approved by the U.S. Food and Drug Administration (FDA), and Equecabtagene Autoleucel and Zevorcabtagene Autoleucel, which has been approved by the China NMPA, and also by the FDA. Clinical investigations up to this time pertaining to the aforementioned approved therapies have demonstrated that, in the treatment of heavily pretreated MM, BCMA CAR-T cell therapy achieves an overall response rate (ORR) ranging from 75-100%, with a composite endpoint of VGPR or greater [sCR + complete response (CR) + VGPR] reaching 50-100%. The median progression-free survival ranges from 8.8 months to not being reached, the median duration of response extends from 10.7 months to not being reached, and the median OS varies from 19.4 months to not being reached (Table I) (20-26). Furthermore, the majority of cases of CRS and neurotoxicity are of lower than grade 3 toxicities, and grade 5 toxicity (resulting in death) accounts for only 0.8-1.0 and 1.0%, respectively (Table I) (20-26). Therefore, for patients who have been heavily pretreated, BCMA CAR-T cell therapy is indeed an effective and safe treatment option, offering a novel therapeutic strategy for patients with RRMM who have become resistant to multiple prior treatment modalities.

Equecabtagene autoleucel (CT103A) is a novel CAR-T cell therapy that specifically targets BCMA, incorporating a fully human aspect through the utilization of a single-chain variable fragment derived from a human antibody. This humanized approach potentially offers advantages in terms of reduced immunogenicity and potentially improving the persistence of CAR-T cells within the body, thereby enhancing therapeutic efficacy (27). It was approved by the NMPA in China on 30th June 2023 for the treatment of adult patients with RRMM, whose disease has progressed after having received at least three lines of prior therapy (including at least one PI and an IMiD) (28). FUMANBA-1, a phase 1b/2 study, evaluated the therapeutic efficacy and safety profile of Equecabtagene Autoleucel (27). This study revealed a median ORR of 96.1% among the 103 participants, with 91.3% of them achieving a VGPR (or greater) response. In addition, the combined rate of sCR and CR was 77.7%, demonstrating significant clinical benefit to patients, especially patients with MM who had been heavily pretreated (25). The patients described in this study were patients with penta-refractory MM. In the present case report, following anti-BCMA CAR-T cell therapy (FUCASO®; Equecabtagene Autoleucel), at 7 months post-reinfusion, the patient was classified as having achieved sCR.

CAR-T cells, although they are engineered to target specific cancer cells, may have their efficacy compromised within the tumor microenvironment where, for example, programmed cell death ligand 1 (PD-L1) on cancer cells may interact with PD-1 on CAR-T cells, thereby impeding their antitumor activity (29). In fact, the interaction between PD-L1 molecules expressed on cancer cells and PD-1 proteins expressed on CAR-T cells provides a prime example of this. This interaction weakens the ability of CAR-T cells to effectively destroy cancer cells (29). Blocking the PD-1/PDL-1 molecular interaction enables CAR-T cells to maintain their activity, thereby targeting tumor cells more effectively (30). In the present patient, the CAR T-cell ratio and the CAR T-cell concentration were both decreased at 28 days post-reinfusion, which had a negative impact on the efficacy of the treatment. Therefore, a PD-1 blocker (sintilimab) was administered when the number of CAR-T cells had decreased, providing valuable real-world evidence for CAR-T maintenance therapy.

The safety of CAR-T cell treatment requires vigilant monitoring, given the possibility of severe adverse reactions, which may aggravate the condition or even lead to a fatal outcome (31). The incidence of CRS in patients with heavily pretreated MM who receive approved CAR-T cell therapies ranges from 83.6-100.0%, depending on the specific therapy administered (Table I) (20-26). In the FUMANBA-1 study, which featured the CAR-T cell therapeutic agent that was administered to the patient in the current study, a CRS incidence rate of 93.3% (98/105) was reported. The vast majority of patients experienced CRS grades 1-2, with only one patient having a CRS grade ≥3. Additionally, only 1.9% (2/105) of patients developed ICANS, with one case each of grade 1 and grade 2 ICANS, and no cases of grade ≥3 ICANS (Table I) (25). Following the guidelines of the product manual, after CAR-T cell infusion, the patient's vital signs, including body temperature, blood, oxygen saturation and heart rate, were closely monitored. In addition, the patient's calculative, orientational and reading abilities were assessed. Apart from fever, no other adverse events were detected. On this basis, the patient was diagnosed with grade 1 CRS, which was successfully treated with tocilizumab. Notably, the levels of IL-6 closely paralleled the progression of the fever, reaching a plateau on day 5, before subsequently tapering off. Concurrently, the CAR-T cells reached their peak expansion on day 10, and gradually decreased thereafter. During grade 1 CRS, to prevent infection, the patient was prescribed antipyretics, valacyclovir, levofloxacin, entecavir and cefoperazone

Table I. Efficacy and safety data for approved BCMA CAR-T therapies.

Clinical trial (Trial ID)	Site	Therapy	n	Median previous LOT, no. (range)	Triple class refractory, no. (%)	Penta-drug refractory, no. (%)	High-risk cytogenetic profile, no. (%)	ORR, % (95% CI)	CR or greater (sCR + CR), n %	VGPR or greater (sCR + CR + , VGPR) n %	Median PFS, months	Median DOR, months	Median OS, months	CRS, n (%)			Neurotoxicity, n (%)			(Refs.)
														Any grade	Grade 3 or 4	Grade 5	Any grade	Grade 3 or 4	Grade 5	
CARTITUDE-1 (NCT03548207)	USA	Cilta-cel (JNJ-68284528)	97	6 (4-8)	85 (87.6)	41 (42.3)	23 (23.7)	97.9 (92.7-99.7)	65 (67.0)	90 (92.8)	NR	NR	NR	92 (94.8)	4 (4.1)	1 (1.0)	21 (21.6)	11 (11.3)	1 (1.0)	(20)
CARTITUDE-1 (NCT03548207)	Japan	Cilta-cel (JNJ-68284528)	9	5 (3-7)	8 (88.9)	2 (22.2)	5 (55.6)	100.0 (66.4-100.0)	9 (100.0)	7 (87.5)	NR	NR	NR	8 (88.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	(21)
KarMMa (NCT03361748)	/	Ide-cel (bb2121)	128	6 (3-16)	108 (84.4)	33 (25.8)	45 (35.2)	73.4 (66-81)	42 (32.8)	67 (52.3)	8.8 (5.6-11.6)	10.7 (9.0-11.3)	19.4 (18.2-NE)	107 (83.6)	7 (5.5)	1 (0.8)	23 (18.0)	4 (3.1)	0 (0.0)	(22)
KarMMa (NCT03361748)	Japan	Ide-cel (bb2121)	9	4 (3-15)	3 (33.3)	0 (0.0)	2 (2.2)	88.9	5 (55.6)	8 (88.9)	NR (4.9-NR)	NR (3.9-NR)	NR (3.3-NR)	9 (100.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	(23)
	Switzerland	Ide-cel (bb2121)	16	6 (3-12)	16 (100.0)	-	6 (37.5)	75.0	11 (68.8)	8 (50.0)	-	-	-	15 (93.8)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	(24)
FUMA-NBA-1 (CTR20-192510, NCT05-066646)	China	Equecabtagene Autoleucel (CT10-3A)	105	4 (3-23)	-	-	73 (69.5)	96.1	80 (77.7)	94 (91.3)	NR	NR	-	98 (93.3)	1 (0.9)		2 (1.9)	0 (0.0)	0 (0.0)	(25)
LUMMICAR STUDY1 (NCT03975907)	China	Zevorcabtagene autoleucel (CT053)	102	4 (3-15)	23 (22.5)	-	46 (45.1%)	92.8 (84.9-97.3)	43(42.2)	83 (81.4)	NR	NR	-	92 (90.2)	7 (6.9)	0 (0.0)	2 (2.0)	0 (0.0)	0 (0.0)	(26)

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor t-cell; CI, confidence interval; LOT, lines of therapy; ORR, overall response rate; VGPR, very good partial remission; sCR, stringent complete response; CR, complete response; PFS, progression-free survival; DOR, duration of response; OS, overall survival; CRS, cytokine release syndrome; NR, not reached; NE, not estimated. Cilta-cel, Ciltacabtagene Autoleucel; Ide-cel, Idecabtagene Vicleucel.

Table II. Anti-BCMA CAR-T cell products used in clinical trials involving patients with EMD.

			EMD			Non-EMD			
Clinical trial (Trial ID)	Therapy	EMD, n (total patients)	ORR, % (95% CI)	CR or greater (sCR + CR), n %	VGPR or greater (sCR + CR + VGPR), n %	ORR, % (95% CI)	CR or greater (sCR + CR), n %	VGPR or greater (sCR + CR + VGPR), n %	(Refs.)
CRB-401 (NCT02658929)	bb2121	9 (33)	88.9 (51.8-99.7)	4 (44.4)	6 (66.7)	83.3 (62.6-95.3)	11 (45.8)	18 (75.0)	(35)
KarMMa (NCT03361748)	Idecabtagene vicleucel (bb2121)	50 (128)	NAV	NAV	NAV	NAV	NAV	NAV	(22)
LEGEND-2 (NCT03090659)	LCAR-B38M	5 (17)	80.0	3 (60.0)	4 (80.0)	91.7	9 (75.0)	11 (91.7)	(34)
N/A (NCT02546167)	Anti-CART-BCMA cells	7 (25)	57.1	2 (28.6)	4 (57.1)	44.4	0 (0.0)	1 (5.6)	(33)
N/A (ChiCTR1800018137)	CT103A	5 (18)	100.0	2 (40.0)	4 (80.0)	100.0	11 (84.6)	12 (92.3)	(27)
N/A (ChiCTR-OPC-16009113)	Anti-CART-BCMA cells	9 (30)	88.9	6 (66.7)	7 (77.8)	90.5	7 (33.3)	9 (42.9)	(36)
N/A (ChiCTR1800017404)	Anti-CART-BCMA cells	28 (61)	100.0	16 (59.3)	21 (77.8)	96.8	25 (80.6)	26 (83.9)	(37)
N/A (ChiCTR1800017051 and ChiCTR2000033925)	Anti-CART-BCMA cells	12 (21)	100.0	5 (41.7)	8 (66.7)	88.9	4 (44.4)	7 (77.8)	(38)

BCMA, B cell maturation antigen; CAR-T, chimeric antigen receptor t-cell; CI, confidence intervals; EMD, extramedullary disease; ORR, overall response rate; VGPR, very good partial remission; sCR, stringent complete response; CR, complete response; NAV, no accurate values; N/A, not applicable.

sodium/sulbactam sodium. Owing to our timely and standardized adverse event management, our patient experienced only grade 1 CRS within the designated treatment duration, and subsequently, no ICANS was observed following the infusion of Equecabtagene Autoleucel. These findings were consistent with the results of the FUMANBA-1 study (25).

In addition to bone marrow lesions, extramedullary lesions are also an important issue for patients with RRMM. There are two main types of extramedullary disease (EMD) in MM, reflecting the proliferation of malignant plasma cells outside the bone marrow, namely paraskeletal disease and non-paraskeletal (NPS) spread (32). Our patient was a patient with heavily pretreated MM who presented with NPS spread and concomitant liver involvement. This condition, characterized by increased aggressiveness, generally leads to poorer survival outcomes, making patient treatment more challenging. Although the majority of published studies have attested to the safety of anti-BCMA CAR-T cell therapy in the treatment of RRMM, a notable deficiency persists in the research literature concerning its efficacy in patients with extramedullary MM, who are frequently excluded from clinical trials (6,7,33).

Table II presents a compilation of the findings from selected BCMA CAR-T cell clinical trials wherein patients with EMD were enrolled (22,27,33-38). Analysis of the data in Table II revealed an ORR for patients with EMD between 57.1 and 100.0%, with a CR or greater rate ranging from 28.6 to 66.7% and a VGPR or greater rate ranging from 57.1 to 80.0%. For patients without EMD, the ORR ranged from 44.4 to 100.0%, the CR or greater rate ranged from 0.0 to 84.6%, and the VGPR or greater rate ranged from 5.6 to 92.3%. However, these data do not capture the full extent of the impact of this therapy due to the limited number of patients with EMD who were included; moreover, there were inconsistencies in the study designs. Consequently, there is an urgent need for more extensive and methodologically consistent studies to be performed that also include patients with EMD to accurately assess the efficacy and safety profile of BCMA CAR-T cell therapy in this specific patient group. Building upon the discussed research, the present case study has presented a compelling example of the effectiveness of anti-BCMA CAR-T cell therapy. Specifically, our patient, who had a lesion located in the liver, achieved notable control post-treatment, highlighting this as a successful therapeutic option.

In conclusion, CAR-T cell therapy has shown significant promise in the treatment of RRMM, especially in patients who have exhausted other therapeutic options. This case has demonstrated the potential of CAR-T therapy to induce long-lasting responses for a patient with EMD, resulting in only mild adverse effects, thereby underscoring the potential of CAR-T cell therapy to achieve sCR in patients with RRMM. Further studies and clinical trials, however, are required to optimize the efficacy and safety of this therapy, and to improve understanding of the long-term outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LZ, DL, FD, JC, WL, HX and HC were involved in management of the patient and contributed to the preparation of this manuscript. All authors read and approved the final manuscript. LZ, DL, FD, JC, WL, HX and HC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This report was reviewed and approved by the Scientific Ethics Committee of Shenzhen Luohu People's Hospital (approval no. 2024-LHQRMYY-KYLL-088). Data collection and manuscript writing were carried out by following the guidelines of Declaration of Helsinki. The consent letter was signed by the patient.

Patient consent for publication

Written informed consent was obtained from the patient of this case report and accompanying images.

Competing interests

The authors declare they have no competing interests.

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