



Letter to the editor

Pomalidomide-based regimens bridging CAR-T therapy in multiple myeloma with central nervous system involvement

Dear editors,

Central nervous system involvement in multiple myeloma (CNS-MM) is a rare complication which indicates an extremely poor prognosis [1]. Conventional interventions for this condition include systemic chemotherapy, local radiotherapy, intrathecal injection and autologous hematopoietic stem cell transplantation (auto-HSCT), but none of them could induce satisfactory complete response (CR) rate, resulting in a poor median overall survival (OS) shorter than 6–7 months [2]. The situation has been changed since Raje et al. demonstrated the promising efficacy of B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T (CAR-T)-cells in patients with relapsed/refractory (R/R) MM with an objective response rate of 85% [3]. Although BCMA CAR-T therapy has shed light on CNS-MM patients, its clinical application is hindered by the time-consuming manufacture of CAR-T cells. Hence, a prompt and individualized bridging therapy is necessary to stabilize the aggressive disease. Pomalidomide, a new generation IMiD, has been proved safe and effective for MM patients [4]. Mussetti et al. observed the clearance of plasma cells in cerebral spinal fluid (CSF) induced by pomalidomide-based regimen in a patient with CNS MM and other extramedullary diseases [5]. In this report, we will discuss an encouraging case of a CNS-MM patient who achieved stringent complete response (sCR) with pomalidomide-based regimens bridging BCMA CAR-T therapy.

A 48-year-old male was diagnosed with IgD λ MM in 2016. The flow chart of his treatment history and CAR-T therapy were shown in Fig. 1A. He was assessed as international staging system (ISS) stage III, Durie-Salmon Staging (DS) stage IIIB, and presented high-risk cytogenetic features including IgH gene rearrangement, 1q21 amplification, and P53 mutation and RB-1 mutation, along with complex karyotype. He received induction chemotherapy with 2 cycles of bortezomib, cyclophosphamide, and dexamethasone (BCD) and 1 cycle of bortezomib and dexamethasone (BD) and was assessed as stable disease (SD) according to International Myeloma Working Group (IMWG) response criteria. Subsequently, he was given 2 cycles of bortezomib, dexamethasone, etoposide, cyclophosphamide, and cisplatin (VDECP) and remained SD. Given his poor response, he received 5 more cycles of bortezomib, lenalidomide, and dexamethasone (VRD) and eventually achieved CR. Lenalidomide and dexamethasone was continued for 6 more months as maintenance therapy. 31 months later, he presented impaired vision and strabismus, which were considered to result from CNS infiltration of

relapsed MM. CNS lesions located in sella turcica, sphenoid sinus, clivus, the petrous part of temporal bone and the base of occipital bone were identified by enhanced cranial magnetic resonance imaging (MRI), while clonal plasma cells in CSF, which accounts for 55.446% of the nucleated cells, were revealed by FCM. Although MRI had reported no significant abnormality after systemic chemotherapy (ixazomib, rituximab, and dexamethasone, IRD), intrathecal injection, and local radiotherapy, the symptoms of impaired vision and strabismus didn't resolve. Unsurprisingly, later cranial MRI revealed, again, lesions in skull, along with new lesions in dura mater and cervical vertebrae (Fig. 1B). At the same time, bone marrow (BM) aspiration and FCM confirmed the recurrence of abnormal plasma cells (14% and 29.41%, respectively). While immunofixation electrophoresis (IFE) and serum protein electrophoresis were unable to identify M protein, elevated free light chain (FLC)- λ (203 mg/mL) was reported with a FLC- κ /FLC- λ ratio of 0.109.

Considering the poor prognosis with conventional treatments in patient with CNS-MM, he was therefore enrolled in a clinical trial of BCMA CAR-T cell therapy (ChiCTR.org.cn, ChiCTR1800017404) after the approval by the ethics committee of the First Affiliated Hospital of Zhejiang University School of Medicine. The design and manufacture of CAR-T cells were performed as previously described [6]. For the high burden and aggressive nature of the disease, a cycle of pomalidomide, cyclophosphamide, and dexamethasone (PCD) and a cycle of pomalidomide and dexamethasone (PD) were administered as bridging therapy during the evaluation of his eligibility for CAR-T therapy and the manufacture of CAR-T cells. Abnormal plasma cells in CSF decreased to 17.842% after these pomalidomide-based therapies, with a percentage of 17.04% in BM.

Following the Fludarabine- (30 mg/m², day –4 to –2) and Cyclophosphamide- (500 mg/m², day –3 to –2) based lymphodepletion regimen, he received autologous anti-BCMA CAR-T cells at a dose of 2.04×10^6 /kg on day 0. As a result, significant expansion of CAR-T cells was observed, the absolute count and percentage of CAR-T cells in peripheral blood (PB) peaked at 7658.02×10^6 /L on day 13. It is notable that CAR-T cells, although accounted for only a tiny fraction, sustained in PB at day 151, while CAR-T cells were also detected at a relatively low level in CSF by FCM with the clearance of BCMA⁺/CD138⁺ cells. Accompanied with the expansion of CAR-T cells, inflammatory biomarkers including interleukin (IL)-6, IL-10, interferon (IFN)- γ , and ferritin increased rapidly, peaked between day 13 and day 15 (IL-6 2369.07 pg/mL; IL-10 361.53 pg/mL; IFN- γ 685.37 pg/mL; ferritin 11182.5 ng/mL), and returned to base lines within 15 more days.

The patient had a high fever (>39 °C) since day 8, which was subsequently diagnosed as a Grade 1 cytokine release syndrome

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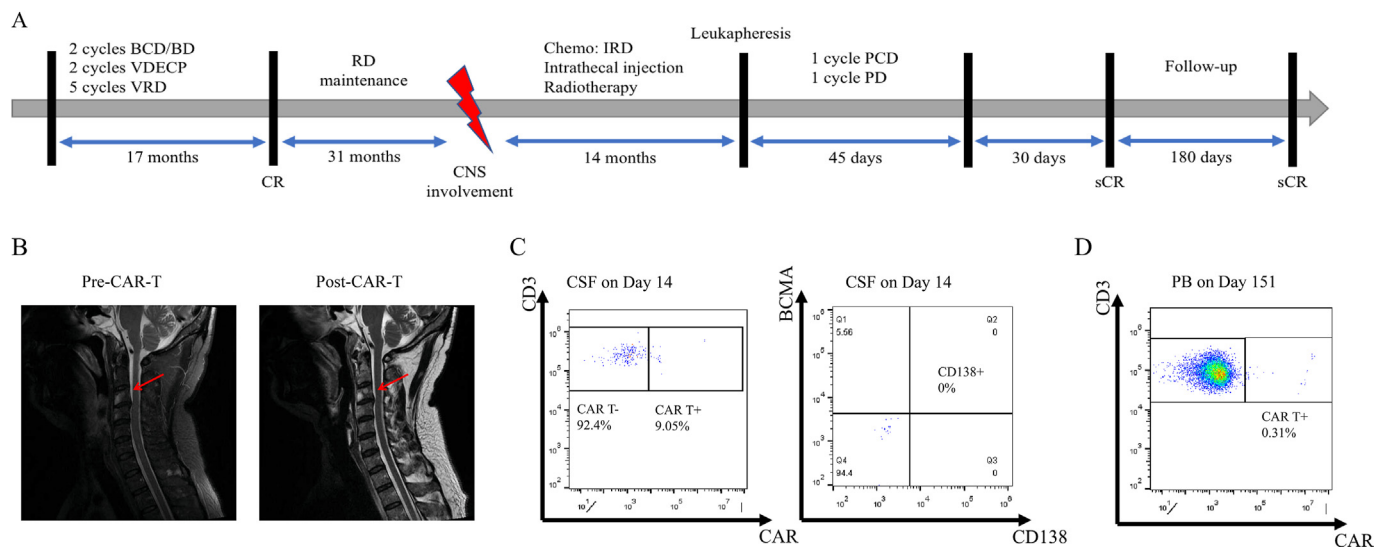


Fig. 1. A. The flow chart of patient's treatment and efficacy of CAR-T therapy. B. Pre-CAR-T MRI showed lesions in upper cervical vertebrae, and post-CAR-T MRI showed reduction in the size of lesions. C. Flow cytometry of CSF 14 days after CAR-T infusion. D. CAR-T cells were still detectable at day 151 in PB.

(CRS). While CAR-T cells were found in CSF, no evidence of neurotoxicity was observed. During CRS, the patient developed enterocolitis caused by *Clostridium difficile*, which was successfully managed with vancomycin. Regarding the response, after transient elevation in FLC- λ (564 mg/mL) and positivity for monoclonal IgD and FLC- λ in serum (day 7), IFE and serum light chain quantitation reported no abnormality on day 35, exhibiting the extraordinary efficacy of BCMA CAR-T cells. MRI also reported a regression of the lesion in cervical vertebrae (Fig. 1B). In addition, FCM showed <0.01% plasma cells in both CSF and BM, while CAR-T cells were detectable in CSF (Fig. 1C). He was thus assessed as sCR as per IMWG criteria with the disappearance of neurologic symptoms. With the negativity of M proteins in the latest IFE performed on day 184 and the normal levels of serum FLC on day 212, the patient presented a prolonged and ongoing remission, which is consistent with the long-term persistence of CAR-T cells for at least 151 days (Fig. 1D).

CNS involvement of MM represents a dismal prognosis, while neither conventional intervention nor novel agents could induce a satisfactory response. In most trials of CAR-T therapy, CNS-infiltrated patients have been excluded for the potential fatal neurotoxicity. Zhang et al. were confronted with rather severe but reversible immune effector cell-associated neurotoxicity syndrome (ICANS), manifesting as headache, lethargy, chemosis, stiff neck, aphasia, pupil asymmetry with loss of light reflex, and obtundation which further developed into stupor, after the infusion of BCMA CAR-T [7]. Interestingly, patients with higher tumor burden have been reported to incline toward higher rate of inflammation-driven serious adverse events (i.e., CRS and ICANS) [8]. Thus, it is rational to reduce disease burden with a proper bridging therapy whilst CAR-T cells are under manufacture.

Pomalidomide is the third IMiD to have significant activity in MM, which exerts anti-myeloma effect by inducing cell cycle arrest and apoptosis, impeding cytokine production, and immunomodulation [9]. While earlier-generation IMiDs exhibited poor CNS penetration, pomalidomide has been reported to surpass its predecessors [10]. The administration of pomalidomide alone resulted in an overall response rate (ORR) of 48% in a phase 1 study treating patients with primary CNS lymphoma [11]. In addition, pomalidomide, in combination with other agents, showed efficacy for myelomatous meningitis [5].

Regarding our patient, abnormal plasma cells were reported to be dominant in CSF (55.446% of the nucleated cells) and neither

radiotherapy nor conventional chemotherapy could eliminate the malignant cells. Given such a high disease burden, we started pomalidomide-based regimens once the peripheral blood mononuclear cells (PBMCs) required for CAR-T manufacture were obtained. As we expected, one cycle of PD and one cycle of PCD achieved a satisfactory reduction of tumor burden (17.842% in CSF, 17.04% in BM), and neurotoxicity was not observed in the following CAR-T therapy. Although this is not decisive evidence to prove the benefit of bridging therapy before CAR-T administration, such an inference is reasonable and deserves future exploration.

Recently, lenalidomide has been reported to enhance the function of CAR-T cells when administered *in vitro* and *in vivo* [12]. Given the extremely long-term persistence of CAR-T cells in our patient (151 days and ongoing), one couldn't help thinking whether pomalidomide may have the similar potential. Although CAR-T cells might not be directly exposed to pomalidomide in this case, the effects of pomalidomide, especially the modulation of immune microenvironment, may last long enough to impact CAR-T cells behavior. Therefore, preliminary *in vitro* validation of this assumption is in progress. In addition, this letter only reports one IgD MM patient with CNS infiltration, larger clinical trial is necessary to evaluate the efficacy and safety of CAR-T therapy following bridging therapy in CNS-MM.

Authorship contributions

Q.Z., C.Z., Y.H. and H.H. designed the study; Q.Z. and Z.Y. analyzed and interpreted the data; Q.Z. and C. Z drafted the article; M.Z., Z.Z., Y.H. and H.H. provided CAR-T cell treatment and care to patient.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Qiqi Zhang¹, Cheng Zu¹, Fang Ni

Bone Marrow Transplantation Center, The First Affiliated Hospital, Zhejiang University School of Medicine, China

Liangzhu Laboratory, Zhejiang University Medical Center, China

Institute of Hematology, Zhejiang University, China

Zhejiang Province Engineering Laboratory for Stem Cell and Immunity Therapy, China

Zhe Yang

Department of Radiology, The First Affiliated Hospital, Zhejiang University School of Medicine, China

Zhiye Zhang

Fuyang Hospital Affiliated to Anhui Medical University, China

Mingming Zhang, He Huang^{**}, Yongxian Hu^{*}

Bone Marrow Transplantation Center, The First Affiliated Hospital, Zhejiang University School of Medicine, China

Liangzhu Laboratory, Zhejiang University Medical Center, China

Institute of Hematology, Zhejiang University, China

Zhejiang Province Engineering Laboratory for Stem Cell and Immunity Therapy, China

* Corresponding author.

** Corresponding author.

E-mail addresses: huanghe@zju.edu.cn (H. Huang), 1313016@zju.edu.cn (Y. Hu)

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¹ These authors contributed equally to this work.