Clinical Cases in Medicine

ISSN: 2770-2359

Case Report

CAR-T Cell Therapy after Treatment with Bispecific Monoclonal Antibody: Case Report

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Abstract

We report successful clinical experience in a patient treated with B-Cell Maturation Antigen (BCMA) Chimeric Antigen Receptor (CAR) T-cell manufactured before the treatment with a GPRC5D-bispecific monoclonal antibody. The patient was a 51-year-old man diagnosed with light chain kappa Multiple Myeloma (MM) on January 2018. After 6 prior lines of treatment, including proteasome inhibitors, immune modulatory drugs, anti CD38 monoclonal antibodies, selinexor, chemotherapy and even treatment with GPRC5d-bispecific monoclonal antibody, the patient was treated with BCMA-CAR-T cells that had been frozen 31 months ago because of his inclusion in other clinical trial. Three months after the infusion, maintenance with lenalidomide 10 mg daily was initiated. Patient achieved undetectable measurable residual disease and complete remission 3 months after the CAR-T infusion and this response lasted for 9 months. This case represents how it is feasible to collect and manufacture T-cells before treatment with bi specific antibodies trying to preserve the T-cell function.

Keywords: Multiple Myeloma; Bispecific monoclonal antibody; CAR-T Cell therapy

Background

Multiple Myeloma (MM) is the second most frequent hematologic cancer. The approval of new drugs has improved survival and helped control disease. However, relapse is common, and most patients become as triple-class exposed and refractory. In this setting, responses to standard therapies are suboptimal, with median progression-free survival of 3-5 months, and overall survival less than 1 year [1-4]. Moreover, a standard of care in these patients had not been established [5] until the arrival of the new immune therapies' strategies, basically based on T-cell redirecting therapies.

B-Cell Maturation Antigen (BCMA) and G-protein-coupled receptor family C group 5-member D (GPRC5D) are antigens expressed on the plasma cell surface at a much higher level compared to other types of cells. Both CAR-T cells and bi specific monoclonal antibodies targeting both antigens have shown to be effective in MM patients heavily pretreated and Idecabtagene vicleucel (also known as ide-cel) and Ciltacabtagene autoleucel (also known a cilta-cel) are BCMA-CAR-T cells approved for RRMM patients triple class exposed [6-10]. In addition, the bi specific monoclonal antibodies, teclistamab and elranatamab targeting BCMA and talquetamab targeting GPRC5D, are also approved in the same setting [11-13].

One of the main challenges in the clinic is to know what the appropriate sequencing of these options is. Further research is required to know the mechanisms of resistance to these novel approaches including both target as well as T-cell exhaustion, what it is more relevant for bi specific antibodies delivered as continuous treatment [14-16].

We report here a clinical case treated with Idecabtagene vicleucel after treatment with GPRC5D-bispecific monoclonal antibody but the CAR-T cells were manufactured and frozen before the treatment with the bi specific antibody.

Case Presentation

This is a 51 years-old male patient diagnosed with a light chain kappa multiple myeloma on January 2018, ISS-I, with no FISH available at diagnosis. He received at his referral center induction with bortezomib-lenalidomide-dexamethasone (VRD) for 6 cycles. After fourth cycle, the patient achieved Complete Remission (CR) and peripheral blood stem cells were collected in order to proceed to autologous stem cell transplantation. However, the patient relapsed after the sixth cycle with Spinal Cord Compression (SCC) at thoracic vertebrae 8th. He was treated with radiotherapy and chemotherapy (VBCMP/VBAD) for 4 cycles, such as second line. He achieved Partial Response (PR) but new progression occurred before proceeding to autologous transplant. The patient was included in a Clinical Trial (CT) (GEM-Selibordara Study; NCT03589222) with Selinexor-bortezomib-dexamethasone-daratumumab. He received only three cycles, and after the achievement of only stable disease, he had a new progression with new paraskeletal plasmacytoma. In this situation, the patient was referred to our unit to be included in the KarMMa-3 clinical trial on October 2019, a phase 3 CT which compared different standards of care *vs.* CAR-T cell therapy (NCT03651128). The patient was assigned to the control arm and he received Daratumumab-Pomalidomide-Dexamethasone (DaraPd). He achieved PR and after six cycles, he progressed again with a new lytic lesion and associated soft tissue mass.

The KarMMa-3 trial allowed crossover, and therefore, we proceeded with the leukapheresis, performed on June 2020, followed by ixazomib-lenalidomide-dexamethasone for one cycle as bridging therapy. At the moment of starting the lymph depletion in our center (July 2020), the patient reported diplopia. Work-up

Citation: Rey-Búa B, Alejo E, Puertas B, González-Calle V, Puig N, Gutiérrez-Gutiérrez NC, et al. CAR-T Cell Therapy after Treatment with Bi Specific Monoclonal Antibody: Case Report. Clin Cases Med. 2024;4(1):1024.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Apr 04th, 2024

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was done to exclude the Central Nervous System involvement and a new plasmacytoma in the cranial calotte with soft parts as well as a mass in the left petroclival area extending to Meckel's cavum and left cavernous sinus were identified. In spite of the fact that SNC involvement was discarded it was not allowed to proceed with the CAR-T administration.

The patient received local radiotherapy but he presented another new plasmacytoma in his left leg. Patient was referred to his center and was treated with chemotherapy (VDT-PACE) for four cycles waiting for a new clinical trial or other better option, because he was a very young patient. Tolerability was good and he achieved partial remission.

On March, 2021 the patient experienced new progression and the patient was included in a clinical trial (TRIMM-2: NCT04108195) based on the combination of daratumumab plus talquetamab, a bispecific monoclonal antibody anti-GPRC5d, such as six lines of therapy. The patient achieved complete response after third cycle, together with undetectable measurable disease in the bone marrow and complete metabolic response. He received up to 21 cycles with good tolerability. Of note, patient developed dysarthria without any lesion detected in serial magnetic resonances that were performed. After 21 cycles, the patient presented with a new plasmacytoma in sternal bone and elevation the free light chain kappa up to 214 mg/L on December 2022.

In this situation, the patient was not only triple refractory but refractory to the bispecific monoclonal antibody anti-GPRC5D (talquetamab) plus daratumumab. In this challenging scenario we had his CAR-T cells against BCMA frozen, and we got the approval for their use in this setting from the Spanish Medicine Agency through compassionate use.

As the relapse was basically asymptomatic, bridging therapy was not prescribed and proceeded on January 2023 with the lymphodepletion (fludarabine (30 mg per square meter of body-surface area per day) and cyclophosphamide (300 mg per square meter per day) for 3 consecutive days), followed by the administration of a single infusion of bb2121 (ide-cel) at dose of 150-450 × 108 CAR-T cells.

Tolerability was good: patient developed CRS grade 124 hours after ide-cel administration without no other complications and was managed with symptomatic treatment. The first response evaluation, done one month after infusion, the patient was in CR with negative Minimal Residual Disease (MRD) in Bone Marrow Aspiration (BMA). Three months after infusion, MRD was confirmed as negative in the BM and the PET-CT showed no uptake indicating the patient was in complete metabolic response. Maintenance with lenalidomide single agent at dose of 10 mg was prescribed at months 3 in order to maintain the response and tolerability was good.

Absence of disease inside and outside of the bone marrow was confirmed in subsequent determinations until the month 9 after infusion in which new plasmacytomas were observed in the PET-CT together with escape of the free light chains in serum. The patient now is receiving a new line of therapy with carfilzomib plus isatuximab with the idea of proceeding to autologous stem cell transplantation if it possible.

Discussion

This MM patient does represent, firstly, the group of patient's triple class exposed and refractory after the first three lines of therapy for who there was an unmet need. This population, treated with at least 3 prior therapies who are triple refractory have very short overall survivals, less than 1 year, according to the LocoMMotion or MaMMoth studies [1,2]. These observational studies stated the lack of standard of care for these patients and the incorporation of new therapies, especially T-cell redirecting therapies have led to an improvement in the survival of these patients.

B-Cell Maturation Antigen (BCMA) [17] which is highly selectively expressed on the surface of plasma cells has proved to be an ideal target for the development of treatments directed against this target [18-20]. Nowadays, BCMA-targeted therapies include anti-BCMA monoclonal antibodies, Antibody-Drug Conjugates (ADCs), Bispecific T-cell antibodies (BiABs), and therapies based on adoptive cell therapy with chimeric antigen receptor T cells directed against BCMA. Their efficacy has been proven in multiple clinical trials, and in particular CAR-T therapy with ide-cel has demonstrated its efficacy in the main phase II trial (BB2121-MM-001 (MM-001, KarMMa-1) [15]. In addition, the results have been consolidated with other clinical trials such as KarMMa-2 and a phase 3, KarMMa-3 conducted in a less pretreated population [21-23]. The median PFS was 8.8 months in KarMMa-2 and 13.3 months in KarMMa-3 in the intent-to-treat patient population [15-23] (Table 1).

Moreover, anti-BCMA BiABs results are promising. MajesTEC-1 results shown Overall Response Rates (ORR) 63% and median PFS 11.3 months in patients with TCR disease [24].

There is also other new target BiABs, such as the G-protein-coupled receptor family C group 5-member D (GPRC5D). Talquetamab has been evaluated in a phase 1/2 in TCE or TCR patients and approved because of the efficacy data with 63% of ORR and median PFS of 11.9 months with the administration every two weeks [25].

Concerning sequencing strategies, patients who have received previous BCMA therapy (ADCs, AcBi or CAR-T) could be re-treated with another BCMA therapy. In a real-life study, the efficacy of this treatment sequence was evaluated and the response of patients receiving CAR-T therapy with ide-cel after other BCMA treatment showed suboptimal responses with short progression-free survivals. In this US study, the median PFS was 3.2 months in those patients who had received prior BCMA [13]. This could be due to several reasons. First, because of the loss of BCMA expression, since in this study both therapies target BCMA [26]. However, another theory that could be even more important is the T-cell exhaustion because as it is well known, bispecific drugs redirect patient's T lymphocytes into the tumor niche. Therefore, the rescue with T-cell redirecting therapies for patient's refractory to bispecific therapies is a challenging situation [27-30]. However, a possibility would be to collect and/or manufacture the T-lymphocytes before the treatment with bispecific antibodies to preserve the T-cell fitness.

This was the situation for our patient, as T cells were collected prior to bispecific therapy and administered after relapse following bispecific treatment. The patient achieved complete remission and its durability was of approximately 9 months, similar to the progression-free survival reported in the pivotal KarMMa-2 CT. As the patient had achieved complete remission, we expected a bit longer durability of the complete remission, but this patient was a heavily pretreated patient with very short duration of the responses to the previous lines with the exception of the bispecific monoclonal antibody (BiABs). But

Table 1: Subsequence of treatments and duration of the response.

Line	Start - End	Cycles	Best response - Duration	Progression
1st: VRD	Mar/2018 Sept/2018	4	CR 6 months	Progression with medular compression
2nd: radiotherapy + VBCMP/VBAD	Sep/2018 Mar/2019	4	PR 6 months	Progression
3rd: CT GEM SeliVd-Dara	Apr/2019 Sep/2019	3	SD 5 months	Progression
4th: EC KARMMA-3 Control arm (DaraPd) Crossover to experimental arm	Nov/2019 Apr/2020	6	PR 5 months	Progression after 6 cycles not candidate to CAR-T infusion because CNS disease
5th: chemotherapy (VDT-PACE)	Nov/2020 Mar/2021	4	PR4 months	Progression
6th: TRIMM-2 Dara-talquetamab	Mar/2021 Nov/2022	21	CR –veMRD 21 months	Progression
7th: ide-cel infusion (CAR-T anti-BCMA) Lymphodepletion with CyFlu	Jan/2023	6	CR –veMRD 10 months	Progression
Lenalidomide*	April/2023 Nov/2023	6	CR –veMRD 10 months	Progression

Abbreviations: VRD: Bortezomib lenalidomide dexamethasone; VBCMP/VBAD: Vincristine carmustine Melphalan cyclophosphamide and Prednisone alternating with vincristine, Carmustine, Doxorubicin, Dexamethasone, Doxorubicin, Dexamethasone; SeliVd-Dara: Selinexor, bortezomib, dexamethasone, daratumumab; DaraPd: daratumumab, Pomalidomide, dexamethasone; CR: complete remission; PR: Partial response; SD: Stable disease; -veMRD: Minimal residual disease negative; CAR-T: Chimeric antigen receptor T; VDT-PACE: bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide; BCMA: B-cell maturation antigen: CyFlu: Cyclophosphamide-fludarabine. *Maintenance

overall, the durability of the response achieved has been longer than that reported in the previous studies with BCMA- CAR-T cells after treatment with bispecific monoclonal antibodies (BiABs) [16].

In order to complement the potential ideal sequencing of T-cell redirecting therapies, in this case, we had the opportunity for switching the target from GPRC5D to BCMA, what we believe it is important to highlight not only the fact that we moved from bispecific to CAR-T with T-cells previously manufactured to preserve their function but we switched from GPRC5D to BCMA, what it is also relevant because the loss of expression of the target is another mechanism of resistance and in the case of GPRC5D, seems to be very frequent [31].

The ideal situation for what we planned for this patient would be the use of allogeneic CART cell therapies and some clinical trials are ongoing. Although more studies and research are needed to clarify the optimal sequencing of T-cell redirecting therapies, it seems that immune profiling and evaluation of the target in the plasma cells could be something relevant to be implemented in the clinical practice.

Conclusion

This patient is, in our knowledge, the first-one treated with BCMA-CAR-T cell therapy manufactured prior to treatment with bispecific monoclonal antibodies targeting GPRC5D. This approach seems to be feasible and the use of frozen CAR-T cells is safe and it could be an option in the future.

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