Successful treatment of ultra-high-risk refractory multiple myeloma with anti-BCMA CAR-T therapy followed by allogeneic hematopoietic stem cell transplantation: a case report

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Abstract

Recently, chimeric antigen receptor T cell (CAR-T) therapy targeting B cell maturation antigen (BCMA) has produced unprecedented and encouraging results in relapsed and/or refractory multiple myeloma (RRMM) after multiple lines of treatment, especially among high-risk patients; however, most patients inevitably relapse after CAR-T therapy. Exploring therapeutic strategies followed by CAR-T therapy has attracted increasing attention that warrants continued investigation. Herein, we present a young patient with RRMM and ultra-high-risk genetic abnormalities and refractoriness to a proteasome inhibitor (bortezomib), immunomodulatory drugs (lenalidomide and pomalidomide), a cytotoxic drug (liposomal doxorubicin), and anti-CD38 monoclonal antibody. After three lines of treatment, the patient underwent CAR-T therapy targeting BCMA for salvage treatment, then achieved a very good partial response with good tolerability. Subsequently, we performed an allogeneic hematopoietic stem cell transplantation (allo-HSCT) from an HLA-matched unrelated donor as consolidation therapy. The efficacy was evaluated as a stringent complete response 42 days after the allo-HSCT. The patient has achieved progression-free survival for > 9 months after transplantation. The success of our case demonstrated that for carefully selected patients, anti-BCMA CAR-T therapy followed by allo-HSCT is effective and feasible in treating RRMM. A longer duration of follow-up and additional studies are needed to affirm this therapeutic strategy.

Keywords: Multiple myeloma < Blood Disorder, CAR-T < Therapy, Transplantation < Therapy

1. INTRODUCTION

In recent years our understanding of high-risk multiple myeloma (MM) has continued to evolve from static genetics and the microenvironment to dynamic treatment responses [1]. Some researchers have proposed the concept of double-hit and ultra-high-risk MM, which is recognized as at least two adverse genetic abnormalities. Functional high risk (FHR) is defined as patients with primary refractory MM or early progression of MM. The outcomes of patients from these two high-risk subgroups based on various definitions have been dismal. Despite tremendous progress in the treatment of MM in the past two decades, the increasing prevalence of high-risk MM demonstrates resistance to conventional therapy [2], thus the development of new therapeutic strategies is urgently needed.

Immunotherapeutic approaches are changing the current MM landscape [3]. Moreover, due to the impressive clinical efficacy and good tolerability, B cell maturation antigen (BCMA)-specific chimeric antigen receptor T cell (CAR-T) therapy has been approved by
2. PATIENT AND TREATMENT

A 49-year-old male was referred to our hospital in February 2021 with a 2-month history of recurrent lumbar pain. Magnetic resonance imaging showed diffuse multiple abnormal signals in the sternum, thoracic vertebrae, lumbar vertebrae, and pelvis without soft tissue masses. Laboratory investigations revealed anemia with a hemoglobin level of 98 g/L and hyperglobulinemia (65.9 g/L, normal range [NR] < 40.0 g/L). The serum IgG level was 44.8 g/L (NR < 15.6 g/L) and the serum protein electrophoresis showed an elevated monoclonal protein (M protein) level (22.6 g/L, NR < 0.0 g/L). Serum immunofixation electrophoresis (IFE) confirmed a single clone of IgG lambda (λ). A bone marrow biopsy demonstrated λ-restricted clonal plasma cell infiltration (85%) with a CD138+, CD38+, CD56-, and CD20- phenotype. Four-color multiparameter flow cytometric immunophenotypic analysis showed that the tumor cells were positive for CD138, CD38, CD45, CD117, and cLambda, and negative for CD19, CD20, CD28, CD56, CD81, CD200, and cKappa. The albumin level was 8.53 mg/L (NR < 2.53 mg/L), and the lactate dehydrogenase level was 319.3 U/L (NR < 247 U/L). Gain of 1q21, del 17p and del 13q14 were detected by fluorescence in situ hybridization (FISH). The conventional karyotype examination confirmed hypodiploid and complex karyotype as 42-45, XY, +mar1-3[cp10]/46, XY[10]. The patient was diagnosed with IgG-λ MM (Durie-Salmon stage IIIA, ISS stage III, R-ISS stage III) with various high-risk cytogenetics.

Following one cycle of weekly bortezomib, lenalidomide, and dexamethasone (VRd), a fourth agent, daratumumab, was added to induction chemotherapy (DVRd) for a more resounding response. Unfortunately, the patient only achieved a minimal response (MR), according to the International Myeloma Working Group (IMWG) response criteria, after a total of four courses of treatment [6]. Further FiSH examination and targeted next-generation sequencing, as described before [7], were carried out and revealed a new translocation involving the immunoglobulin heavy-chain (IGH) locus on 14q32 and mutations, including DIS3 and FAM46C. Of note, the partner gene of the IGH rearrangement was not FGFR3/MMSET, CCND1, MAF or MAFB. These results reaffirmed the co-existence of multiple high-risk genetic abnormalities and suggested clonal evolution during therapy. The patient was switched to another treatment with pomalidomide, liposomal doxorubicin, and dexamethasone (PAD) for three cycles. Once again, the patient only achieved an MR with the M protein reduced by a maximum of 27%. Given the poor response, he underwent third-line treatment with selinexor, melphalan, and dexamethasone. Despite a modest response, the disease progressed after three courses of treatment, with 80%-90% plasma cells in the bone marrow and 30.6 g/L serum M protein.

In December 2021, the flow cytometry examination of bone marrow aspirate showed 24.7% clonal plasma cells in nucleated cells and the proportion of BCMA-positive plasma cells was 74.8%. Then, the patient was enrolled in a human-derived BCMA-target CAR-T (CT103A) clinical trial (ClinicalTrials.gov number NCT05066646) in our center, but subsequently withdrew due to rapid disease progression. CAR-T cells were prepared and infused for compassionate use. Lymphodepletion preconditioning was started on 14 February 2022; fludarabine (50 mg) and cyclophosphamide (800 mg) were administered once daily for 3 d. On 18 February 2022, anti-BCMA CAR-T cells produced by Nanjing IASO Biotechnology Co., Ltd. (Nanjing, China) were infused at a dose of 1.0×10⁶ cells/kg. Recurrent fevers to a maximum of 39 °C occurred 3 d after the infusion was given and was relieved on the 9th day after symptomatic treatment. The patient developed a grade 1 cytokine release syndrome, according to the ASTCT standard [8]. No central nervous system toxicity was observed. Grade 4 adverse events included neutropenia, thrombocytopenia, leukocytopenia, and lymphopenia. Urinary M protein and minimal residual disease (MRD) in the bone marrow were negative 21 days after the infusion and the serum M protein level significantly decreased (9.1 g/L). The optimal efficacy of the anti-BCMA CAR-T treatment was an MRD-negative very good partial response (VGPR) with a 91.4% decrease in serum M protein (3.0 g/L). Three months after CAR-T therapy (May 2022), the patient received allo-HSCT from an HLA-matched unrelated donor with a myeloablative conditioning regimen consisting of busulfan (3.2 mg/kg on days -6 to -4), melphalan (140 mg/m² on day -3), cyclophosphamide (20 mg/kg on days -2 to -1), and rabbit anti-thymocyte globulin (2.5 mg/kg on days -5 to -2). The allo-HSCT was tolerated with grade 2 atrial fibrillation, grade 2 mucositis, and grade 3 febrile granulocytopenia, and managed with antimicrobials and supportive care. Interestingly, the serum M protein and IFE was negative 42 days after the allo-HSCT and he achieved a stringent complete response (sCR). For approximately 9 months after the allo-HSCT the patient remained in good clinical condition and maintained a sCR. This patient continues to have follow-up evaluations (Table 1 and Figure 1).
3. DISCUSSION

Previous studies have shown that high-risk patients account for 25%–30% of newly diagnosed MM [1]. The prognosis of high-risk MM remains unsatisfactory and the overall survival is < 3 years, even in the era of novel agents [1, 9]. There is significant heterogeneity in the various stratification systems and specific genetic abnormalities are recognized as adverse prognostic factors. Bolli et al. [10] reported that patients with MM enriched for IGH translocations, amp(1q) and del(17p), had the worst median overall survival, as the patient we reported. From another perspective, primary refractory and early relapse, which are defined as FHR, also reflect the biology of a underlying high-risk disease [1]. The patient we presented was initially diagnosed with ultrahigh-risk IgG-λ MM accompanied by a high tumor burden and multiple adverse genetic abnormalities (karyotype, chromosomes, and genes). The patient was also FHR and appeared refractory to one proteasome inhibitor (PI [bortezomib]), immunomodulatory drugs (IMiDs [lenalidomide and pomalidomide]), a cytotoxic drug (liposomal doxorubicin), and an anti-CD38 monoclonal antibody. Because the patient described herein belonged to high-risk patients with respect to genetics and the biology of the disease, his expected survival was extremely poor.

As the disease continued to spiral out of control, reducing the tumor burden as quickly as possible using other potent therapies seemed to be the best strategy. Recently, CAR-T cell therapy has shown great promise in RRMM, and BCMA has been one of the most promising target antigens. Previous studies showed that patients resistant to various new drugs, such as PIs, IMiDs, and anti-CD38 monoclonal antibody, also achieve rapid and good remission after anti-BCMA CAR-T therapy with an objective response rate of 64%–100% [11-13]. It has been reported that CT103A is highly active and induces a rapid response in RRMM with a complete response rate of 72.2% and an undetected MRD rate of 100% [13]. The patient met the absolute indication for CAR-T therapy. Indeed, this patient achieved a VGPR after anti-BCMA CAR-T treatment.

However, the lack of a durable response in the majority of patients is one of the main challenges in current CAR-T treatment management. Among patients with MM, data clearly showed that achieving deep remission (CR/sCR and MRD-negative) could trump high-risk biological features and is associated with prolonged survival [14]. A pooled analysis of the PETHEMA/GEM
Clinical trials revealed that MRD status should be one of the most relevant endpoints for high-risk patients [15]. The ultra-high-risk patient we discussed did not achieve CR/sCR after anti-BCMA CAR-T therapy, which strongly suggested a short duration of response.

At present, allo-HSCT is the only potentially curative strategy for patients with MM; however, the high mortality and treatment-related morbidity rates limit its use. For carefully selected patients, Greil et al. [16] reported that the median overall survival was 39.2 months and the cumulative incidence of non-relapse mortality for 10 years after allo-HSCT was 12.4%. Considering that our patient was very young, extraordinarily high-risk, and refractory to multiple lines of therapy, he finally underwent allo-HSCT after a marked reduction in tumor burden with CAR-T cell treatment. Our patient achieved and maintained a sCR for several months after an HLA-matched HSCT. CART therapy, as bridging therapy before HSCT, was a valiant attempt for our young patient with ultra-high-risk RRMM.

In summary, the present case study highlights the unfavorable outcome for ultra-high-risk patients with MM. The successful attempt to eliminate refractory tumor clones by CAR-T therapy, followed by sequential allo-HSCT, demonstrated the path to cure for certain patients. However, more studies are needed to carefully evaluate the benefit of CAR-T combined with an allo-HSCT in suitable patients with RRMM in the future.

DATA AVAILABILITY STATEMENT
The detailed data of the patient in this case study are available on request from the corresponding author by e-mail.

ETHICS STATEMENT
This case study has been authorized by the Institutional Ethics Committees of Institute of Hematology and Blood Disease Hospital. The procedures in this case adhere to the tenets of the Declaration of Helsinki.

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CONFLICTS OF INTEREST
The authors declare no financial interests in relation to this work.

REFERENCES