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GVHD in Allogeneic Transplant Recipients Treated with BCMA CAR-T: Case Series

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Introduction

B Cell Maturation Antigen (BCMA) targeting Chimeric Antigen Receptor T Cell (CAR-T) therapy in Relapsed Refractory Multiple Myeloma (RRMM) has improved the dismal outcomes in heavily pre-treated patients [1]. Currently approved anti-BCMA CAR-T include idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) [2-6]. CAR-T clinical trials in RRMM have thus far excluded allogeneic Stem Cell Transplant (allo-SCT) recipients, and there are no available real-world safety or efficacy reports on CAR-T therapy in alloSCT recipients [3-5]. The administration of autologous CAR-T therapy in patients who have previously undergone allo-SCT may result in "pseudo-allogeneic" CAR-T, where the engineered cells are derived from the original allo-SCT donor cells [7,8]. While there are reports on the safety of anti-CD19 CAR-T for acute lymphoblastic leukemia allo-SCT recipients, limited literature exists on the safety profile and potential risk of GVHD after anti-BCMA CAR-T administration in allo-SCT recipients in RRMM [9,10]. GVHD can lead to significant morbidity in the post-CAR-T setting, and treatment for GVHD, which may include steroid and immunosuppressive therapy, could limit the CAR-T efficacy, and increase infectious complications [11,12]. BCMA CAR-T therapy, ide-cel generated after the patients had undergone prior allo-SCT and subsequently had a recurrence of RRMM.

Patients and Methods

Patient records were reviewed retrospectively. CRS and ICANS were graded according to the American Society for Transplantation and Cellular Therapy grading criteria [13]. GVHD severity was graded according to Glucksberg and Center for International Blood and Marrow Transplant Registry criteria [14]. Revised international Prognostic Scoring System staging for MM, and International Myeloma Working Group response criteria were used [15].

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Case 1 was a 60-year-old male with high-risk (17p deleted) IgA Kappa MM and concurrent mantle cell lymphoma, who achieved a Complete Response (CR) prior to allo-SCT for both MM and mantle cell lymphoma. He underwent Fludarabine/Melphalan (Flu/Mel) Reduced Intensity Conditioning (RIC) allo-SCT using a Matched Sibling Donor (MSD). GVHD prophylaxis was Tacrolimus and Methotrexate (Tac/MTX). Around 3 months post-allo-SCT, he progressed and was treated with salvage daratumumab-based therapy. He did not respond and subsequently received standard-of-care ide-cel infusion 9.8 months post-allo-SCT. Prior to CAR-T infusion, he did not experience any aGVHD or cGVHD symptoms. On Day 2 of CAR-T, he developed grade 1 CRS, which resolved with tocilizumab. He did not experience ICANS. Around days 2-7, he experienced diarrhea, oral ulcers, a rash affecting 75% of body surface area **(Figure 1)**, and transaminitis. Gastrointestinal (GI) tract and skin biopsies proved new onset aGVHD **(Figure 2)**. High-dose steroid therapy (prednisone 2mg/kg) was initiated by Day 7, and symptoms improved; however, he did not tolerate steroid taper. Ruxolitinib was started on Day 46, which he did not tolerate due to cytopenia. Three months post-CAR-T, belumosudil was started, and finally, prednisone was tapered off at 7 months post-CAR-T. A month later (8 months post-CAR-T), he started developing symptoms of "mild" cGVHD, with rash and scleroderma skin changes, oral mucosa, GI, and eye involvement, which responded to high-dose steroid treatment. Ruxolitinib was trialed again, and he was successfully tapered to low-dose steroid maintenance.

He had achieved CR with CAR-T, but a year after CAR-T (three months after starting ruxolitinib), he had systemic and Central Nervous System (CNS) MM relapse. Ruxolitinib was held, and he was started on salvage chemoimmunotherapy. While his disease responded, within a month, he again had an exacerbation of his scleroderma rash, affecting his lower extremities, head, face, stomach, and arms, requiring steroids. The GVHD responded to high-dose steroids. However, his disease progressed shortly after, and he was started on cyclophosphamide-pomalidomide-dexamethasone (14 months post-CAR-T). Again, while he achieved CR, therapy was interrupted due to a flare of skin GVHD, which was treated with high-dose steroids. He developed complications of long-term steroid use including frequent infections and fungal keratopathy. He progressed again and passed 18 months after ide-cel infusion.

Case 2 was a 56-year-old female with standard risk stage III IgG kappa MM. She received a Flu/Mel RIC MSD allo-SCT for RRMM with Tac/MTX for GVHD prophylaxis. Her early post-allo-SCT was complicated with mild aGVHD affecting the liver and GI tract. She later experienced mild chronic cGVHD involving the oral cavity. She was treated with several lines of therapy after allo-SCT for RRMM. Around 12 years after her allo-SCT, she received ide-cel for progressive disease. She had mild chronic GVHD involving the oral cavity at the time of CAR-T infusion.

On day 2 post-ide-cel, the patient developed CRS, max grade 1, which resolved with tocilizumab. She did not experience ICANS. No changes in cGVHD symptoms were reported, and no new symptoms developed post-ide-cel. She achieved a very good partial response but progressed 10.5 months post-CAR-T.

Case 3 was a 45-year-old male with standard risk stage II IgA kappa MM. Two years after initial therapy with induction, auto-SCT, and maintenance, he developed myelodysplastic syndrome (MDS) for which he received a Flu/Mel RIC MSD allo-SCT, and Tac/MTX for GVHD prophylaxis. His post-transplant course was complicated by mild cGVHD involving his GI tract and oral cavity, requiring local therapies. This later progressed to involve the lungs 18 months post-allo-SCT, requiring escalation of therapy to systemic steroids. The lung cGVHD was refractory to steroids. He was initiated on extracorporeal photopheresis and rituximab, with the improvement of symptoms to mild extensive GVHD. While his MDS was treated, the RRMM progressed on several therapies, and he received ide-cel around 6.9 years after allo-SCT. At the time of infusion, his lung cGVHD had resolved, and he had mild eye cGVHD, controlled with local therapies.

Post-ide-cel, the patient developed CRS max grade 1 throughout Days 1 and 2, which resolved after two doses of tocilizumab. He did not experience ICANS. There was no change or flare of GVHD noted as of 21 months post CAR-T. He continues to be in remission at 21 months post-CAR-T.

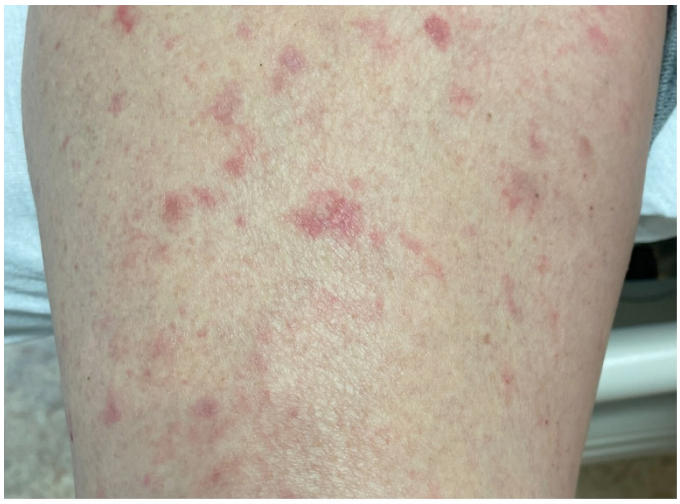

Figure 1: Skin rash after CAR T (Case 1).

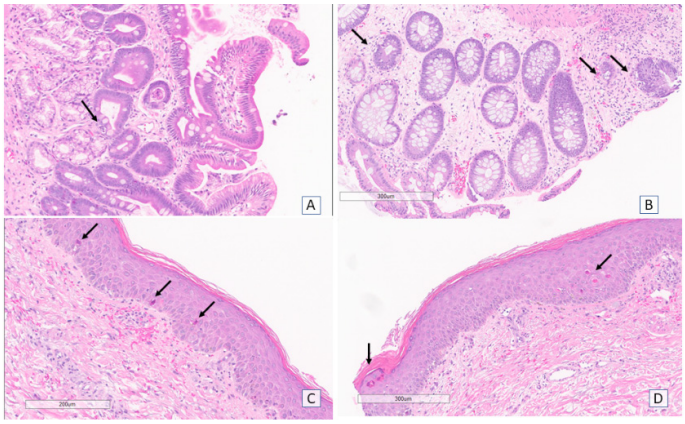

Figure 2: 2A. Duodenal mucosa: Mildly increased epithelial apoptosis, compatible with graft-vs-host disease in the appropriate clinical setting. **2B.** Colonic mucosa: Prominent epithelial apoptosis, compatible with graft-vs-host disease (GVHD). **2C and D.** Skin: Scattered dyskeratosis suggestive of GVHD.

Discussion

This series is the first, to our knowledge, to describe debilitating steroid-dependent acute and chronic GVHD flare post-BCMA CAR-T. We did not observe an increase in the severity of immune mediated toxicities such as CRS and ICANS. We did observe a case of steroid-dependent GVHD, where the patient succumbed to complications of long-term immunosuppression and inability to tolerate further immunochemotherapy.

However, we also observed that two of the three cases did not experience a GVHD flare and had reasonable efficacy outcomes with CAR-T. It is important to note that a prior history

of GVHD may not predict the likelihood of a GVHD flare following CAR-T therapy. Our series describes two allo-SCT recipients who had mild persistent cGVHD, without flare after CAR-T. The interval between allo-SCT to CAR-T may impact the likelihood of developing GVHD. The patient with the GVHD flare had a shorter interval between allo-SCT to CAR-T therapy, compared to the others.

In conclusion, based on our series, BCMA-directed CAR-T (ide-cel) after a prior allo-SCT did not increase the severity of CRS or ICANS. There is a risk of GVHD flare, but this was not universally observed. Allo-SCT recipients should be counseled on potential risks and not be precluded from CAR-T consideration.

Statement of equal author Contribution: NA was responsible for creating the idea for this manuscript. WW was responsible for the data collection and initial revisions. KL was responsible for the initial drafting. All authors provided critical review for content and revisions and provided approval for the final manuscript.

Abbreviations

BCMA: B Cell Maturation Antigen; CAR-T: Chimeric Antigen Receptor T Cell Therapy; RRMM: Relapsed Refractory Multiple Myeloma; CRS: Cytokine Release Syndrome; ICANS: Immune Effector Cell-Associated Neurotoxicity Syndrome; Ide-Cel: Idecabtagene Vicleucel; Cilta-Cel: Ciltacabtagene Autoleucel; Complete Response (CR); Flu/Mel: Fludarabine/ Melphalan; RIC: Reduced Intensity Conditioning; Tac/MTX: Tacrolimus And Methotrexate; Agvhd: Acute Graft-Versus-Host Disease; Cgvhd: Chronic Graft Versus Host Disease; GI: Gastrointestinal; MDS: Myelodysplastic Syndrome.

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