LETTER TO THE EDITOR

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Defying the Odds: Successful Rescue with Teclistamab in a Case of Ultra-High-Risk Relapsed/Refractory Multiple Myeloma Transforming to Secondary Plasma Cell Leukemia Following BCMA CAR T Failure

Tüm Zorluklara Rağmen: BCMA CAR T Tedavisi Başarısızlığını Takiben Sekonder Plazma Hücreli Lösemiye Dönüşen, Ultra Yüksek Riskli Nüks/Refrakter Multipl Miyelom Olgusunda Teclistamab ile Başarılı Kurtarma Tedavisi

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To the Editor,

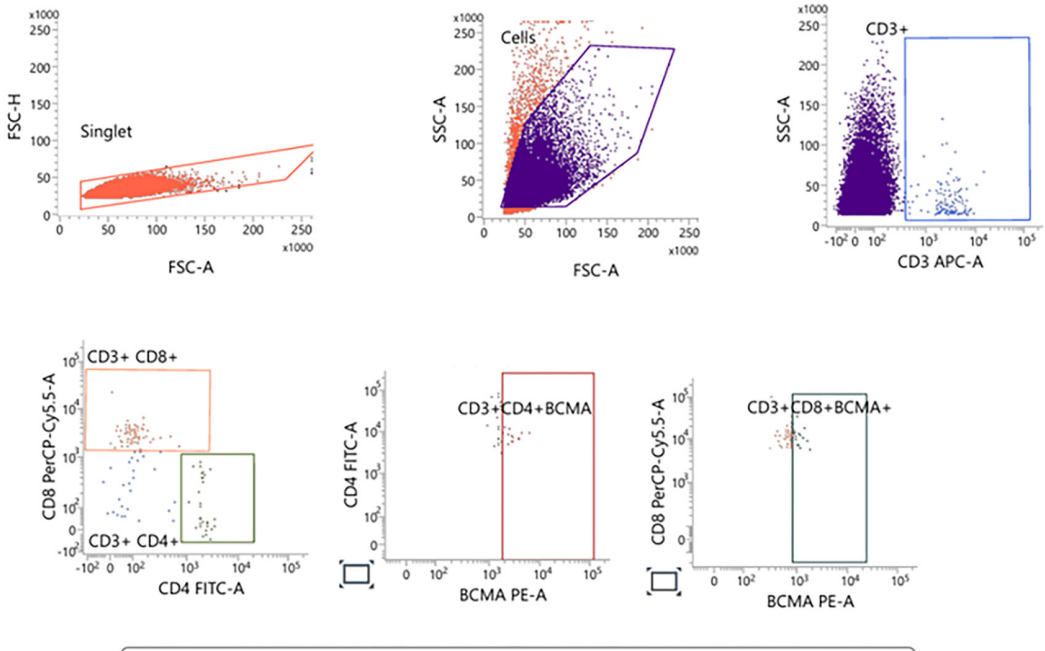
A 67-year-old man with a known diagnosis of immunoglobulin G kappa multiple myeloma (MM) and high-risk cytogenetic abnormalities including deletion of 17p and gain of 1q presented with biochemical and clinical relapse. The patient was initially diagnosed with MM in February 2017. He received induction chemotherapy comprising four cycles of bortezomib, cyclophosphamide, and dexamethasone (VCd regimen). The post-induction response assessment demonstrated complete remission (CR). Subsequently, he underwent consolidation with autologous hematopoietic stem cell transplantation (ASCT) in July 2017. Following ASCT, the patient commenced lenalidomide maintenance therapy.

He remained in sustained CR until March 2022, when he experienced his first relapse. At that time, treatment was initiated with a regimen of bortezomib, pomalidomide, and dexamethasone (VPd regimen), resulting in re-establishment of CR, which was maintained until August 2023. The patient then experienced a second relapse and commenced daratumumab, carfilzomib, and dexamethasone (DKd regimen). He again achieved CR, which was sustained for 1 year.

In August 2024, he had a third relapse and was subsequently referred to our institute for consideration of B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR T-cell) therapy.

Prior to CAR T-cell infusion, the patient received one cycle of bridging chemotherapy with the oral melphalan, thalidomide, and prednisolone regimen. He was subsequently administered BCMA-directed CAR T-cell therapy, manufactured by Abgentil Biomedical (Subang Jaya, Malaysia) in collaboration with ProMab Biotechnologies Inc. (Richmond, CA, USA), at a dose of 5.87 million CAR T-cells per kilogram of body weight. Vein-to-vein time, defined as the duration from apheresis to CAR T-cell infusion, was 21 days. On day +30 after the infusion, biochemical progression was noted with M protein of 0.38 g/dL, serum kappa light chains of 1593 mg/L, lambda of 1.37 mg/L, and an abnormal kappa:lambda ratio of 1171:1. Flow cytometry revealed CAR T-cell expansion (Figure 1), indicating adequate cellular proliferation. Despite the absence of clinical deterioration, the progression of the disease markers warranted continued observation.

By day +45, further biochemical progression was evident with worsening myeloma markers (M protein of 0.36 g/dL, kappa of 2696 mg/L, lambda of 1.74 mg/L, kappa:lambda ratio of 1549:1). The patient reported new-onset myalgia and back pain. Bone marrow aspiration and biopsy confirmed 95% plasma



PBMC Dr.Anil BCMA RunPointerStatistics

Name	CD3+	CD3+ CD4+	CD3+ CD8+	CD3+CD4+BCMA+	CD3+CD8+BCMA+	Cells
Events	140	31	73	3	15	90,237
% Parent	0.16	22.14	52.14	9.68	20.55	90.25

Figure 1. B-cell maturation antigen (BCMA) chimeric antigen receptor T-cell (CAR T) expansion evaluated by flow cytometry.

cell infiltration. Fluorescence in situ hybridization analysis confirmed the persistence of del(17p) and gain(1q). A peripheral blood smear showed 9% circulating plasma cells (Figure 2), and cytopenia was notable with hemoglobin of 80 g/L, total leukocyte count of $3.4x10^9$/L, and platelet count of $53x10^9$/L, findings consistent with transformation to secondary plasma cell leukemia (sPCL).

To investigate CAR T refractoriness, BCMA expression was evaluated via immunophenotyping, which revealed sustained expression (64.79%) in plasma cells (Figure 3), ruling out antigen escape/downregulation.

Given the aggressive disease phenotype and refractoriness to CAR T, the patient commenced teclistamab monotherapy, a BCMAxCD3 bispecific T-cell engager. A step-up dosing regimen was followed, starting at 0.06 mg/kg (day 1), progressing to 0.3 mg/kg (day 4), and culminating in the initial full treatment dose of 1.5 mg/kg on day 7. Within 48 hours of receiving the full dose, the patient developed a high-grade fever (maximum temperature of 38.9 °C), which was unresponsive to broad-spectrum antimicrobials. An extensive infectious workup returned negative results, and a clinical diagnosis of grade 1 cytokine release syndrome (CRS) was established. CRS persisted for a total of 4 days and was effectively managed with a single intravenous dose of tocilizumab at 8 mg/kg, resulting in complete resolution of symptoms. Importantly, the patient did not develop any features of immune effector cell-associated neurotoxicity syndrome during the post-infusion course.

The second treatment dose (1.5 mg/kg) was administered on day 14 without CRS recurrence. The patient continued to receive weekly maintenance therapy with teclistamab.

Following six weekly doses of teclistamab, the patient achieved a significant hematological response and CR. His hemoglobin level improved to 120 g/L, total leukocyte count rose to $4x10^9$/L, and platelet count normalized to $190x10^9$/L. Peripheral blood analysis showed complete clearance of plasma cells. Serum immunofixation electrophoresis revealed no detectable M protein. Bone marrow aspiration and biopsy demonstrated fewer than 5% plasma cells. Additionally, the serum free light chain assay showed a marked reduction, with kappa at 11.6 mg/L, lambda at 0.506 mg/L, and a kappa:lambda ratio of 23:1. At the 4-month follow-up, after receiving 16 weekly doses of teclistamab, the patient continued to maintain CR.

CAR T-cell therapy has reshaped the treatment approach for relapsed and refractory MM. With its broader use, CAR T-cell treatment failure has become evident, as approximately 50% of patients relapse within 1 year of infusion [1,2]. In a pivotal phase 1 trial evaluating the BCMA-targeted CAR T-cell therapy bb2121, over half of the patients experienced disease progression within 1 year after the infusion, even among those who initially responded, including patients who achieved

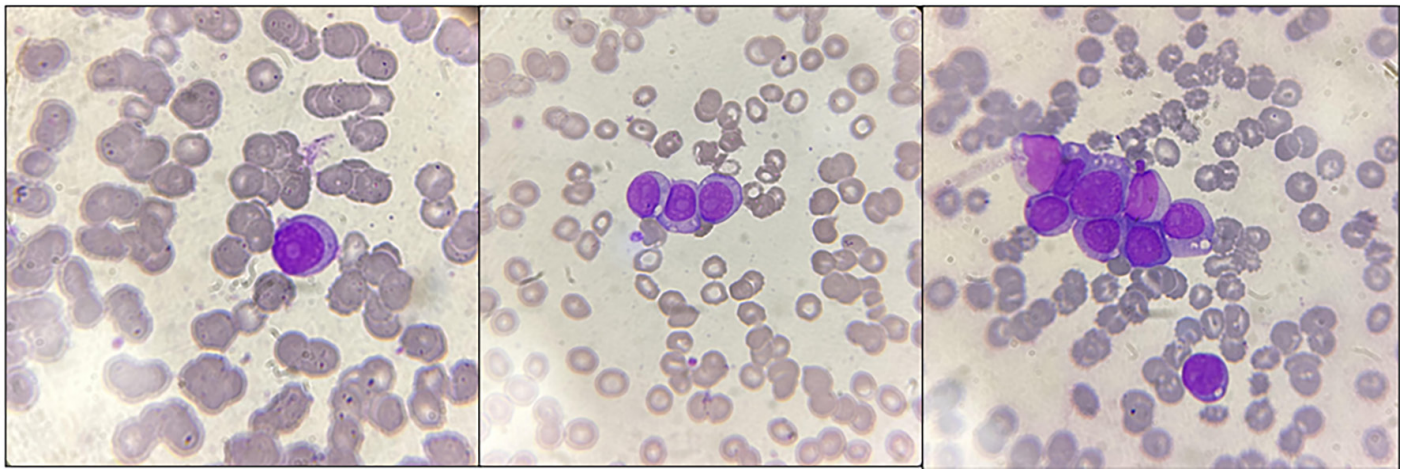


Figure 2. Plasma cells in peripheral blood.

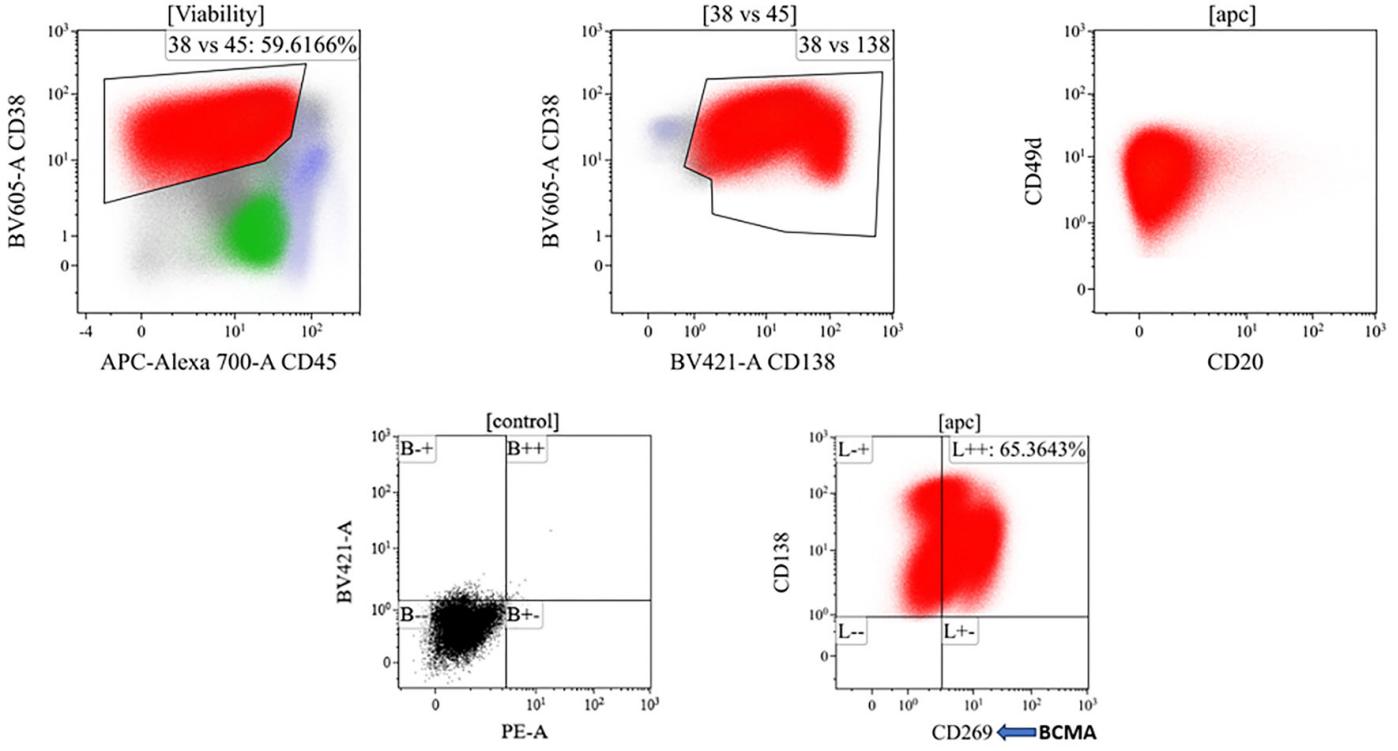


Figure 3. B-cell maturation antigen (BCMA) expression testing of plasma cells by flow cytometry.

undetectable minimal residual disease. Outcomes after BCMA CAR T relapse are significantly influenced by both the timing and nature of the relapse. In particular, early relapse (within 3 months after the infusion) and relapse involving extramedullary disease (EMD) are associated with poor overall survival (OS). Currently, there is no universally accepted standard of care for patients who relapse after CAR T-cell therapy.

One study reported an overall response rate (ORR) of 43% among 76 patients who received post-CAR T-cell salvage therapy, with a notably higher ORR of 91% observed in patients treated with T-cell-engaging agents [3]. Among these agents, bispecific antibodies (e.g., teclistamab) have shown the most promise, demonstrating improved response rates and survival outcomes compared to other treatment modalities. They appear especially capable of overcoming the poor prognosis associated with early relapse and EMD [4].

A key area of ongoing debate is the optimal timing for introducing bispecific antibodies following CAR T-cell therapy. Two major hypotheses are central to this discussion: antigen loss and immune cell exhaustion. The former is supported by findings

of heterogeneous BCMA expression within tumor populations, suggesting that relapse may be driven by the emergence of BCMA-negative clones [5]. T-cell exhaustion, a major barrier to sustained responses, has also emerged as a critical factor, particularly in patients whose T cells were harvested after multiple lines of prior treatment [6]. Consequently, administering additional immunotherapies soon after a CAR T-cell infusion may be suboptimal. However, emerging data have identified teclistamab as a particularly effective post-relapse option, delivering excellent median OS even in patients who relapsed early, or within 3 months of CAR T-cell therapy [4].

In our case, the patient was refractory to BCMA CAR T-cell therapy and experienced early progression to sPCL. To investigate the etiology of this resistance, BCMA expression was assessed using flow cytometry, which demonstrated persistently high expression (64.79%) in plasma cells. Subsequently, the patient was treated with teclistamab using a standard step-up dosing regimen. Initial grade 1 CRS promptly resolved with a single dose of tocilizumab. Importantly, no further CRS episodes occurred after the subsequent administration.

The hematological and biochemical responses to teclistamab were both rapid and profound. Within 6 weeks, peripheral blood plasma cells were cleared, cytopenia was resolved, and free light chain levels showed a marked reduction. This striking response despite prior BCMA-targeted CAR T-cell therapy highlights the continued efficacy of teclistamab in this setting. These findings support its use as sequential or salvage therapy for relapsed/refractory disease following BCMA treatment.

Treatment in the presence of EMD continues to constitute a significant unmet clinical need as conventional therapies have yielded disappointing results in terms of both response and survival. Although CAR T-cell therapy has generated impressive clinical responses overall, patients with EMD at the time of infusion consistently fare worse than those without [7]. Until recently, data on the outcomes of patients who relapsed with EMD after CAR T-cell therapy were limited. Our latest findings suggest that EMD at the time of relapse is a strong predictor of poor prognosis; however, bispecific antibodies may offer a path forward, producing comparable efficacy and survival irrespective of EMD status.

This case highlights the potential of teclistamab as an effective salvage therapy following BCMA CAR T-cell failure, even in cases of aggressive disease with sPCL and high-risk cytogenetics. Despite early progression, our patient achieved a rapid and deep response, with normalization of hematological parameters and clearance of circulating plasma cells. The efficacy of teclistamab in this setting supports its role as a viable option following CAR T-cell infusion, particularly for patients with early relapse or EMD. These findings reinforce the emerging paradigm of sequential immunotherapy in relapsed/refractory MM.

Keywords: Multiple myeloma, Secondary plasma cell leukemia, BCMA CAR T, Teclistamab

Anahtar Sözcükler: Multipl miyelom, Sekonder plazma hücreli lösemi, BCMA CAR T, Teclistamab

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A-O.A.A., B.K., V.P., P.T., I.R.; Concept: A-O.A.A., B.K., V.P., P.T., I.R.; Design: A-O.A.A., B.K., V.P., I.R., M.N.C.K.; Data Collection or Processing: A-O.A.A., B.K., V.P., I.R., M.N.C.K.; Analysis or Interpretation: B.K., V.P., P.T.; Literature Search: B.K., I.R., R.I., M.N.C.K.; Writing: A-O.A.A., B.K., I.R., M.N.C.K.

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References

1. Gagelmann N, Ayuk F, Atanackovic D, Kroger N. B cell maturation antigen-specific chimeric antigen receptor T cells for relapsed or refractory multiple myeloma: a meta-analysis. Eur J Haematol. 2020;104:318-327.
2. St Martin Y, Franz JK, Agha ME, Lazarus HM. Failure of CAR-T cell therapy in relapsed and refractory large cell lymphoma and multiple myeloma: an urgent unmet need. Blood Rev. 2023;60:101095.
3. Van Oekelen O, Nath K, Mouhieddine TH, Farzana T, Aleman A, Melnekoff DT, Ghodke-Puranik Y, Shah GL, Lesokhin A, Giralt S, Thibaud S, Rossi A, Rodriguez C, Sanchez L, Richter J, Richard S, Cho HJ, Chari A, Usmani SZ, Jagannath S, Shah UA, Mailankody S, Parekh S. Interventions and outcomes of patients with multiple myeloma receiving salvage therapy after BCMA-directed CAR T therapy. Blood. 2023;141:756-765.
4. Merz M, Dima D, Hashmi H, Ahmed N, Stölzel F, Holderried TAW, Fenk R, Müller F, Tovar N, Oliver-Cáldes A, Rathje K, Davis JA, Fandrei D, Vucinic V, Kharboutli S, Baermann BN, Ayuk F, Platzbecker U, Albici AM, Schub N, Schmitz F, Shune L, Khouri J, Anwer F, Raza S, McGuirk J, Mahmoudjafari Z, Green K, Khandanpour C, Teichert M, Jeker B, Hoffmann M, Kröger N, von Tresckow B, de Larrea CF, Pabst T, Abdallah AO, Gagelmann N. Bispecific antibodies targeting BCMA or GPRC5D are highly effective in relapsed myeloma after CAR T-cell therapy. Blood Cancer J. 2024;14:214.
5. Samur MK, Fulciniti M, Aktas Samur A, Bazarbachi AH, Tai YT, Prabhala R, Alonso A, Sperling AS, Campbell T, Petrocca F, Hege K, Kaiser S, Loiseau HA, Anderson KC, Munshi NC. Biallelic loss of BCMA as a resistance mechanism to CAR T cell therapy in a patient with multiple myeloma. Nat Commun. 2021;12:868.
6. Fischer L, Grieb N, Born P, Weiss R, Seiffert S, Boldt A, Fricke S, Franz P, Heyn S, Kubasch AS, Baber R, Weidner H, Wang SY, Bach E, Hoffmann S,

Ussmann J, Kirchberg J, Hell S, Schwind S, Metzeler KH, Herling M, Jentzsch M, Franke GN, Sack U, Reiche K, Köhl U, Platzbecker U, Vucinic V, Merz M. Cellular dynamics following CAR T cell therapy are associated with response and toxicity in relapsed/refractory myeloma. Leukemia. 2024;38:372-382.

7. Zanwar S, Sidana S, Shune L, Puglianini OC, Pasvolsky O, Gonzalez R, Dima D, Afrough A, Kaur G, Davis JA, Herr M, Hashmi H, Forsberg P, Sborov D, Anderson LD Jr, McGuirk JP, Wagner C, Lieberman-Cribbin A, Rossi A, Freeman CL, Locke FL, Richard S, Khouri J, Lin Y, Patel KK, Kumar SK, Hansen DK. Impact of extramedullary multiple myeloma on outcomes with idecabtagene vicleucel. J Hematol Oncol. 2024;17:42.

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