From myeloma to POEMS: extending the potential of T-cell redirecting therapies

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In this issue of Haematologica, Talbot and co-authors describe the case of a 73-year-old man with multiply relapsed POEMS syndrome achieving a prompt and sustained remission with teclistamab,[1] a bispecific antibody which engages both CD3 on T cells and B-cell maturation antigen (BCMA) on plasma cells.

POEMS syndrome is a paraneoplastic process related to an underlying plasma cell disorder. Its presentation is protean, and the diagnosis is not infrequently delayed until disabling polyneuropathy, constitutional symptoms, and worsening volume overload warrant hospital admission.[2] Once identified, outcomes are typically excellent with high-dose chemotherapy and stem cell transplantation forming the cornerstone of treatment.[2] Alkylators and corticosteroids have also been a mainstay of therapy but are joined by immunomodulatory agents, proteosome inhibitor and anti-CD38 antibodies.[2] For relapsed and refractory POEMS patients who have exhausted these options, a pressing question remains: what comes next?

The rapid and durable response induced by teclistamab in a POEMS syndrome patient, 20 years into his diagnosis and after 5 prior lines of therapy,[1] is not unexpected given its efficacy (and that of other anti-BCMA bispecific antibodies) in patients with other plasma cell disorders. It is notable, however, that in Talbot's case with teclistamab, not only were there complete hematologic and VEGF responses by cycle 2, but by 6 months, the Castleman's disease adenopathy had resolved by positron emission tomography/computed tomography as well.

As compared to the plasma cells of patients with multiple myeloma (MM), the plasma cells of patients with POEMS syndrome (and other monoclonal gammopathies of clinical significance including light chain [AL] amyloidosis) have both a lower frequency of BCMA positivity (89% *vs*. 56%) and a lower mean fluorescent intensity (1281 *vs*. 553).[3] Although BCMA expression is lower in these other conditions than in MM, it is substantial enough to serve as a therapeutic target.

In heavily pre-treated MM patients, teclistamab has produced an overall response rate of 63%.[4] In five retrospective reports including 32 relapsed, refractory AL amyloidosis patients treated with teclistamab, 87% of patients achieved a very good partial response or better;[5] however, safety remains a central concern in these rare disorders. Patients with POEMS may have debilitating multisystemic involvement - neuropathy, hemodynamic instability, multiple endocrinopathies and volume overload - raising questions about the tolerability of immune-redirecting strategies. The risks of cytokine release syndrome (CRS), cardiorespiratory compromise, immune-effector-cell-associated neurotoxicity, and exacerbation of the existing polyneuropathy must be carefully weighed. Fortuitously, in the case report of Talbot *et al*. using bispecific T-cell engager and in a case report of BCMA chimeric antigen receptor T-cell (CAR T) therapy used in a patient with POEMS, only mild CRS has been seen.[1,6]

The potential for cytokine-mediated toxicity cannot be completely assuaged by a couple of case reports. An interesting concept for pre-emptive CRS mitigation for patients with POEMS syndrome could be the administration of tocilizumab before T-cell directed therapy. This strategy theoretically could deliver a dual benefit in those patients with POEMS syndrome who carry the adverse prognostic biomarker of elevated interleukin 6 (IL-6)[7] by blunting the IL-6 driven biology of both the disease and the T-cell directed therapy induced CRS (Figure 1).

Although, the cytokine milieu of patients with AL amyloidosis is quite different from that of patients with POEMS, one may extrapolate from the limited experience of BCMA T-cell redirecting therapy in AL amyloidosis patients, who share features of frailty and disease associated volume overload. In one series of seven AL amyloidosis patients, five with cardiac involvement, grade 1 CRS occurred in four of seven patients, and one patient died due to cardiac deterioration.[8] In a multinational cohort of 17 teclistamab-treated AL amyloidosis patients, 53% experienced grade 1 CRS,

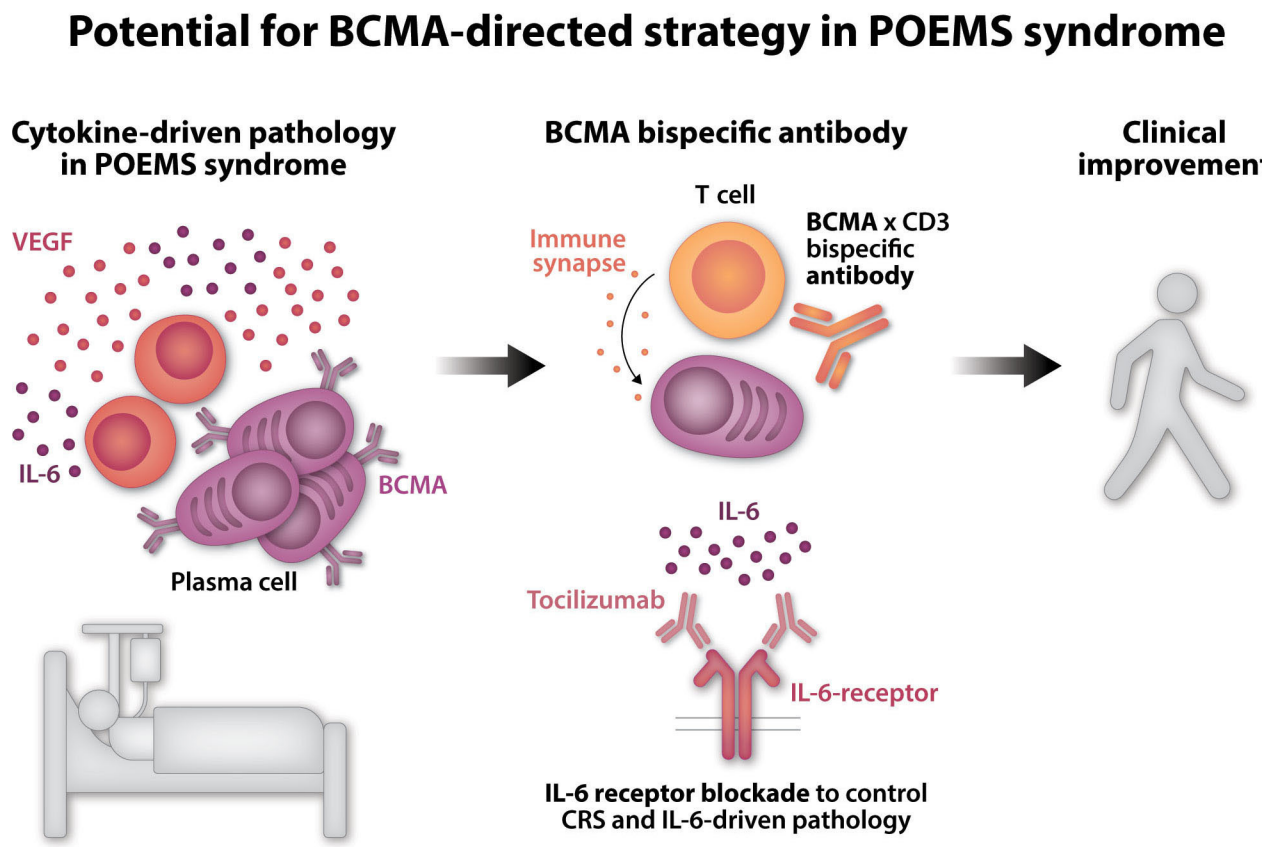

Figure 1. Potential for BCMA-directed strategy in POEMS syndrome. B-cell maturation antigen (BCMA) × CD3 bispecific antibodies target clonal plasma cells to reduce pathogenic cytokine production, while interleukin 6 (IL-6) receptor blockade with tocilizumab may limit both cytokine release syndrome (CRS) and the IL-6–driven pathology, leading to clinical improvement. VEGF: vascular endothelial growth factor.

one patient with a pre-existing auto-inflammatory disease developed grade 3 ICANS (and survived), one patient died of early infection, and another died about a month after discontinuing therapy.[9]

Looking ahead, multicenter registries and collaborative trials will be essential to define the safety and efficacy of BCMA-targeted T-cell–redirecting strategies in rare disorders like POEMS syndrome. Of note, there is an on-going bispecific antibody study for POEMS syndrome in China (*clinicaltrials gov. Identifier: NCT07115654*). Not only will teclistamab need to be studied in these rare disorders, but other BCMA bispecific antibodies with alternative epitope specificities (such as linvoseltamab or elrantamab), BCMA CAR T, and other targets such as GPRC5D and FcRH5 will deserve exploration. An equally important question for bispecific antibody use in POEMS syndrome will be the duration of therapy. The authors successfully tapered the teclistamab to every other month dosing after 6 months, monthly dosing after the 1-year mark and then discontinued after 20 months of therapy. Given the low clonal burden characteristic of POEMS syndrome, it is reasonable to ask whether shorter treatment durations could maintain efficacy while minimizing time on therapy. Such trials using bispecific antibodies for AL amyloidosis - another low plasma cell burden disease - are underway. As safety, efficacy, and duration of therapy are sorted out in patients with POEMS syndrome, timing of such therapies will also need to be examined: first line, second line, etc. While prospective trials will provide the most robust answers, given the rarity of POEMS, well-documented case reports help define the parameters for appropriate use of T-cell and other novel therapies. With this report, Talbot *et al*. give proof-of-concept that BCMA bispecific therapy in POEMS is feasible.[1]

Disclosures

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Contributions

JC and AD wrote and reviewed the article.

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