CAR T cell therapy for myeloma

The impressive success of CD19-targeted chimeric antigen receptor (CAR) T cell therapy for both pediatric acute lymphoblastic leukemia (ALL) and adult diffuse large cell lymphoma (DLBCL) (1, 2) has heightened the enthusiasm to broaden the applicability of this tumor-targeted T cell approach to other malignancies. As a more terminally differentiated lymphoid malignancy with no known uniformly curative option, multiple myeloma (MM) is an obvious choice for exploring CAR T cell therapy. Initial work to identify the optimal target in myeloma implicated a range of targets, including CD19 based on its putative expression on the postgerminal B cell and clonalogenic precursor to the mature plasma cell (PC) (3), markers present on the surface of the malignant myeloma cell, such as CD138 and CD38, and secreted molecules such as the kappa and lambda light chains. B cell maturation antigen (BCMA) is one of three transmembrane proteins important in the development of B cell immunity and maintenance of B cell homeostasis. Moreover, BCMA is expressed on a subset of B cells and virtually all mature healthy and myeloma PCs (4). Experiments in Bcma–/– mice demonstrated impaired long-term survival of PCs compared with their WT counterparts, thereby underscoring a role for BCMA in PC persistence (5). Lastly, BCMA was established as a putative tumor-associated antigen in patients responding to donor lymphocyte infusions (DLIs) upon relapse from an allogeneic transplantation. SEREX (serological analysis of expression cDNA libraries) antibodies of the post-DLI serum in patients who achieved remissions revealed the generation of BCMA-specific antibodies (6). Taken together, the uniform expression, the role in PC signaling and survival, and the ability to generate immunity to this protein make BCMA a desirable target for immune-based approaches such as CAR T cell therapy in MM.

As CAR T cells move from investigator-initiated studies to FDA-approved therapies, many questions remain regarding how to increase the clinical benefit of this labor-intensive therapeutic intervention. Cytokine release syndrome (CRS) appears to be directly related to not just the disease burden but also the amount of circulating disease, as the overall incidence of CRS appears to be higher in ALL than in lymphoma (1, 2). In ALL, CRS has been relatively controlled with early use of the IL6-R antibody tocilizumab (7), and as such, the incidence of CRS in myeloma appears to be lower and less severe.

BCMA is currently the prime target under clinical development for myeloma CAR T cell therapy by several groups. In this issue, Cohen et al. employ a BCMA 4-1BB lentiviral construct in a heavily pretreated myeloma patient population (8). Importantly, in addition to examining the standard toxicity and response criteria, the study offers insight into the critical questions to be addressed regarding adoptive cell therapy (ACT). These questions extend well beyond myeloma, as cell therapy establishes its foothold within oncology.

The first issue involved with the success of CAR T cell therapy is one of space and cell dose. The total lymphocyte number is well defined and tightly maintained through homeostatic proliferation (9). Lymphodepletion has been used to usurp the mechanisms that regulate homeostatic expansion to increase the frequency of adoptively transferred T cells and enhance the therapeutic efficacy of ACT (10). Clinically, the depth of lymphodepletion has been shown to correlate directly with response rates, and total body irradiation further augmented the response in a dose-dependent manner in at least one other study (11). However, in a separate study, the same group compared fludarabine/cyclophosphamide nonmyeloablative regimens with and without radiation and found that radiation added toxicity with no additional therapeutic benefit (12). It should be noted that patients in both these studies were treated with non–gene modified autologous tumor-infiltrating lymphocytes (TILs). If host conditioning needs to be optimized to guarantee maximal homeostatic proliferation in the non–gene modified T cell arena, gene modification of T cells with either a CD28 or 4-1BB intracellular signaling domain (capable of inducing a robust proliferation and growth

Conflict of interest: IB declares ownership and intellectual property in WindMIL Therapeutics. IB receives income and research support from WindMIL Therapeutics, Bristol-Myers Squibb, and Celgene.

Copyright: © 2019, American Society for Clinical Investigation.

advantage for modified T cells) represents an opportunity to examine not only the issue of the dose-intensity of lymphodepletion but also of establishing a dose-response curve. Cohen and colleagues evaluated three cohorts of patients with myeloma (8). Cohort 1 received CAR T cells alone, cohort 2 received a lower dose of CAR T cells with cyclophosphamide, and cohort 3 received the same dose of CAR T cells as cohort 1, along with cyclophosphamide. While the small sample size of the study limits the ability to draw any definitive conclusions, the objective response rate trended with both cell dose and conditioning regimen, with the highest overall response in cohort 3. These data would thus appear to confirm two tenets of ACT, even in the setting of CAR T cells—space and dose matter! Other groups have shown the superiority of fludarabine/cyclophosphamide compared with cyclophosphamide alone, even in the setting of CAR T cell ACT (13). Cumulatively, these studies indicate that cell dose and lymphodepletion of ACT increase the therapeutic efficacy. One question remains in regard to treating myeloma. Would a fludarabine/cyclophosphamide regimen in the Cohen et al. study have further increased the therapeutic efficacy?

Conclusions and future considerations
Is the degree of antigen expression important? An initial study required BCMA expression by either immuno-histochemistry or flow cytometry for enrollment (14). The follow-up Bluebird study initially required patients to have more than 50% BCMA expression in the dose-escalation phase of the study, but subsequently opened the study to patients with low antigen expression (<50%) (15). There was no observed difference in response rates based on BCMA expression level. Moreover, BCMA expression did not correlate with clinical outcomes. The Cohen study had no requirements for BCMA expression and also saw no differences in responses. Taken together, it does not appear that efficacy is dependent upon the degree of antigen expression, which can broaden the pool of potentially eligible patients.

CAR T cell expansion and persistence are also important criteria that contribute to efficacy. The three-arm study design of Cohen et al. (8) also sheds light on the role of these factors. Interestingly, peak CAR T cell counts were highest in the cohorts receiving the higher CAR T cell dose. Persistence was also the greatest in cohort 3, which combined chemotherapy with the higher CAR T cell dose. In contrast to other reported studies, few patients in any group had detectable levels of CAR T cells past 60 days. Cell dose and the conditioning regimen can clearly affect persistence; however, the intrinsic biologic properties of both the gene-modified CAR T cells and the endogenous T cell population also influence CAR T cell longevity. Insight into these properties has been provided recently by a study that examined the polyfunctionality of the immune programs within T cells that ultimately regulate their fate and correlate with the development of CRS and antitumor efficacy (16). The manuscript by Cohen et al. (8) offers important insight into the biologic properties of BCMA CAR T cells and solidifies fundamental attributes to ACT that need to be considered in designing clinical trials. However, the clinical efficacy seen by Cohen and colleagues is lower than that observed in other BCMA CAR T cell studies, which have recently reported overall response rates in excess of 80% and complete response rates ranging from 27% to 74% (17). Several clinical factors that could explain the lower response rate in the Cohen et al. study need to be considered. The study enrolled a heavily pretreated patient population that had received a median of 7 prior therapies, substantially more than the participants of Chinese studies that reported significantly higher response rates (18, 19). Another factor that could play a role in the efficacy of BCMA CAR T cells is a patient’s disease burden and cytogenetics. In the Cohen et al. study, the average percentage of PCs at the time of BCMA CAR T cell infusion was 68% and almost all patients had high-risk cytogenetics (96%), with a deletion in 17p or a p53 mutation present in 68% of patients. In contrast, only 40% of the patients in the bb2121 BCMA CAR T cell study were high risk by these criteria (20). Lastly, the absence of fludarabine as part of the lymphodepletion regimen may underscore the clinical relevance of this agent for subsequent clinical trials.

What is emerging from clinical trials and confirmed by Cohen et al. is that the clinical efficacy of BCMA CAR T cells for MM remains considerably lower that what has been observed for CD19 CAR T cells in ALL and DLBCL. Whether the reduced effectiveness is a reflection of the target or the intrinsic biology of attempting to kill a cell programmed by its very nature to persist for decades in its unmutated form remains to be determined. BCMA is clearly a viable target, and CAR T cells will play an increasing role in the treatment of myeloma.

Address correspondence to: Ivan Borrello, 1650 Orleans Street, CRB-I, Rm 453, Baltimore, Maryland 21231, USA. Phone: 410.955.4967; Email: iborrell@jhmi.edu.