Comment on Wang et al, page 2890

BCMA CARs in multiple myeloma: room for more?

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In this issue of *Blood*, Wang et al report their phase 1 trial of CT103, a fully human 4-1BBζ chimeric antigen receptor (CAR) targeting the B-cell maturation antigen (BCMA), in 18 patients with relapsed or refractory multiple myeloma (MM).[1]

With the dose escalation, patients received 1, 3, or 6 × 10^6 CAR T cells per kg and an expansion group received 1 × 10^6 CAR T cells per kg. The overall response rate was 100%, and 72% achieved a complete response or stringent complete response. With a median follow-up of 13 months, median progression-free survival (PFS) was not reached, but 58% of all patients were progression free at 1 year. Cytokine release syndrome (CRS) was experienced by 94% of the patients, and there was a comparatively high rate of severe CRS (28% grade ≥3; 13% would have had grade ≥3 if the highest dose had been excluded).

Wang et al describe clinical outcomes that we have come to expect in the field today and include sufficient details on their trial protocol and patient cohort to allow considered comparison with other trials globally. The authors are candid in their assessment of the trial, and they discuss the possible impact of their comparatively treatment-naïve cohort and their lymphodepletion regimen (combining fludarabine with high-dose cyclophosphamide) on response, toxicity, and CAR persistence. Even so, the study is noteworthy for the duration of CAR persistence and its inclusion of patients previously treated with a murine BCMA CAR.

Both points are significant because it is well known that CARs targeting CD19 in acute lymphocytic leukemia (ALL) can maintain durable responses in 40% of patients despite therapy being given for refractory disease and multiple relapses.[2] However, even with initial disease regression, durable responses with CAR T cells have not been achieved in MM.[3-5] In the first 2 BCMA CAR trials reported, patients had a median PFS of <1 year.[3,4] Although the outcomes reported in the CARTITUDE-1 trial[5] were better, it is still not clear whether prolonged remissions can be obtained with existing CAR T-cell products in MM.

One feature that casts doubt for any real potential for durable responses in MM is that MM CAR T cells do not persist in patients. The correlation of persistence with duration of response is imperfect and may vary with diagnosis, but it is particularly relevant in ALL in which persistence can be 2 years.[2,6] In trials assessing the earliest BCMA CARs, bb2121 and LCAR-B38M/JNJ-4528, persistence was typically ≤6 months.[3-5] Given this landscape, the reported persistence of CT103 is notable. The maximum concentration of circulating CT103 is lower than has been reported with other CARs,[4] but it has a median persistence of 308 days, which will likely increase with follow-up. Robust expansion was seen in all patients, and at last follow-up (median, 13 months), CAR T cells had fallen below 1 × 10^2 copies per μg of DNA in only 5 patients.

The key drivers of persistence are not clear. The authors propose that the human CT103 binder may reduce the incidence of CAR-directed immune clearance, and they explore this relationship with drug-directed antibodies. Indeed, emergence of these antibodies was associated with reduced levels of CT103 CAR in 1 patient; however, the authors admit that the role of CAR-directed immunity in treatment failure remains uncertain. Consideration of the assays used may be of particular relevance for plasma cell (PC)-directed therapies, especially because BCMA is required for the maintenance of long-lived PCs[7] that are spared with CD19 CAR therapy.[8] Thus, assessment of CAR-directed immunity may have to include cellular immunity before clearer conclusions can be drawn in MM. Furthermore, increased persistence has not been universally observed with human or humanized CAR constructs.

Another unusual feature of CT103 is its relatively low binding affinity (10 nM), which the authors have usefully compared with that of bb2121. CT103 has a slower on-rate, and both binders have similarly fast off-rates compared with the CD19 binder in tisagenlecleucel and axicabtagene ciloleucel (ie, FMC63).[6] The association between binding affinity and clinical outcomes is still uncertain and is likely to be target and context dependent. In CD19, a lower-affinity CAR has been associated with improved persistence in pediatric ALL[6] in which the authors postulated that a faster off-rate may facilitate serial triggering. More work is needed to define the binding kinetics that may influence the efficacy of BCMA CARs.

Unusually, this study enrolled 4 patients who had previously been treated with a murine BCMA CAR. CT103 expanded in all 4 patients, and in 3 of them, there was transient and low-level expansion of the murine BCMA CAR construct after lymphodepletion. This indicates that undetectable levels of CAR T cells can remain at disease relapse with antigen-positive disease, but they are likely to be exhausted or terminally differentiated. This further underlines the importance of defining the drivers of disease control in terms of CAR manufacture or in the tumor niche.

This trial also illustrates the possibility of retreatment with CAR therapy in MM. Greater understanding of the determinants of relapse and treatment failure will afford a rational approach to retreatment. For example, Wang et al did detect CT103 targeting antibodies, and with the global availability of CAR constructs that encode humanized and various xenogeneic tumor binders, we may soon be in a position to offer CAR retreatment selected on the basis of immune response to previous therapy.

More widely, we are witnessing rapid developments in MM CAR T-cell therapy. We await maturity of promising but early data from an increasing number of MM CARs jostling for a spot on the global landscape, some of which may achieve

persistence to rival CT103.[9] A confusing array of augmentation strategies are also under investigation, including enhanced T-cell engineering, coadministration with immune modulators such as immunomodulatory drugs, and checkpoint blockade. Enhancement of bb2121 with PI3K inhibition skews effector T-cell memory phenotype, favoring long-term persistence which may exceed that described for CT103.[10] But before considering augmentation strategies, the recent report of delayed neurotoxicity in the CARTITUDE-1 study[5] reminds us that the ideal BCMA CAR that can provide the platform for such strategies to maximize this treatment of MM has yet to be established. CT103 thus enters a rather crowded field but is a welcome addition for its report of increased persistence and contribution to the discussion surrounding the prospect of retreatment.

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GENE THERAPY

Comment on Nair et al, page 2902

A new "FIX" for hemophilia B gene therapy

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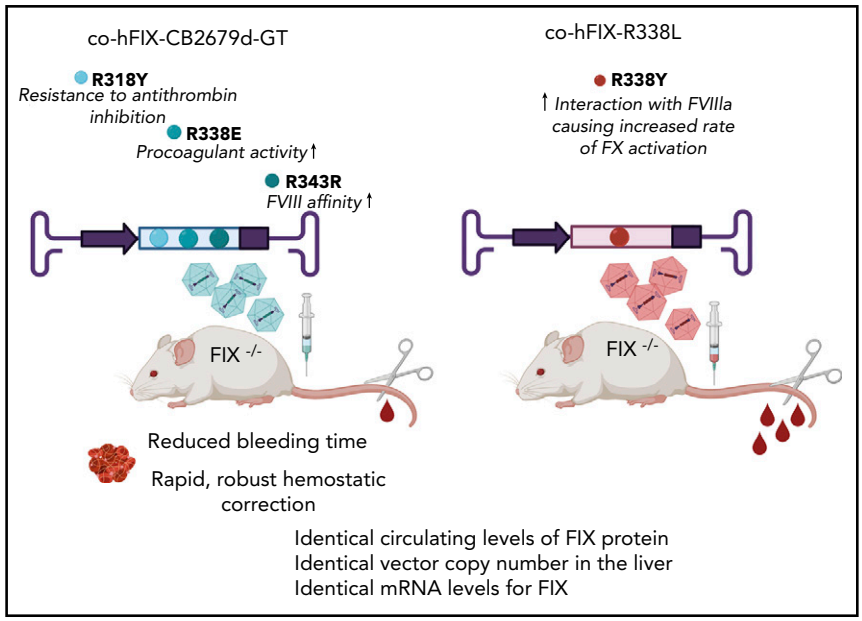
In this issue of *Blood*, Nair et al[1] demonstrate that AAV-directed gene therapy using a new bioengineered FIX transgene provides higher FIX activity and superior hemostatic efficacy than other FIX variants and may allow for lower and potentially safer vector doses in future human clinical trials.

Hemophilia B, a bleeding disorder caused by a deficiency in blood coagulation factor IX (FIX), occurs as a result of *F9* gene mutations. Although prophylactic therapy with FIX protein is effective in preventing bleeding episodes, the requirement for frequent intravenous infusions, development of inhibitors to FIX, and fluctuations



Adult hemophilia B mice were treated with identical AAV vectors, encoding either the FIX CB 2679d-GT or R338L-Padua variants, at the same dose. Evaluation of treated animals demonstrated nearly identical circulating levels of FIX protein, liver vector copy number, and FIX mRNA levels. However, the new CB 2679d/ISU304 transgene, which is designed to have improved FIX functions such as catalytic activity, affinity for activated FVIII, and resistance to antithrombin inhibition, outperformed the R338L-Padua by providing rapid and robust hemostatic correction. Thus, the FIX variant CB 2679d-GT could improve tolerability of the vector in future gene therapy trials.