blood advances

CARs for Hodgkin: engine fine-tuning is in order

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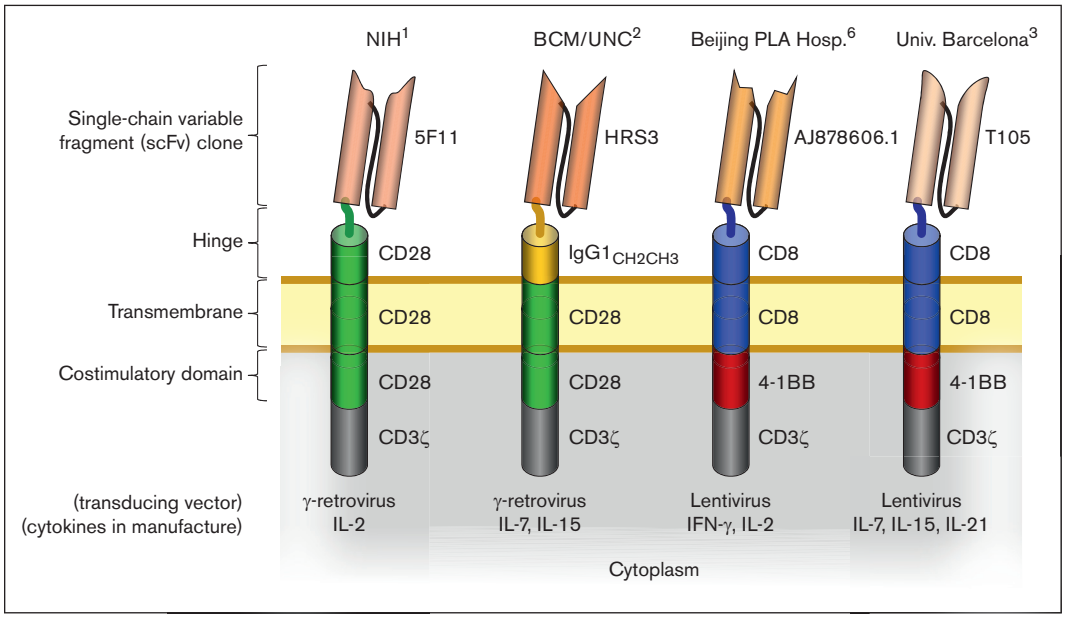
Comment on Brudno et al, page 802

In this issue of *Blood Advances*, Brudno et al[1] present the results of a phase 1 clinical trial using a second-generation CD30-specific chimeric antigen receptor (CAR) in which 21 patients, primarily with relapsed or refractory classical Hodgkin lymphoma (cHL), were treated. Patients received lymphodepleting chemotherapy (cyclophosphamide and fludarabine) followed by infusion of 0.3 to 9 million autologous CAR^+ T cells per kg. Clinical responses were limited in degree and duration, with an overall response rate (ORR) of 43%, corresponding to a single complete response (CR) and 8 partial responses (PRs), and a median duration of response of 8.9 weeks; toxicities included those expected with CAR T-cell (CART) therapy, such as cytokine release syndrome (CRS) and cytopenias, but some of the cytopenias, either by themselves or because of their treatment, were associated with significant infectious complications (sepsis in 2 patients). No neurotoxicity (NT) clearly attributable to CARTs was observed. Similar to other reports of CD30-specific CARTs (CD30-CARTs),[2,3] a nonspecific rash was seen in approximately half the patients, but, distinct from those accounts, 2 patients required immunosuppressive therapy. The limited clinical activity and excess toxicities led to early study closure. As noted by the authors, these results contrast with the higher response rates and lower toxicities reported by other groups investigating CD30-CARTs. Nevertheless, the authors should be commended on their thoughtful analysis of their study, which illustrates potential limitations of CD30-CARTs.

CARTs targeting CD19 and B-cell maturation antigen have demonstrated impressive efficacy in B-cell non-Hodgkin lymphomas (NHLs) and multiple myeloma, respectively, but alternative viable CAR targets for other disorders have been more challenging to define. Because CD30 has been validated as a target for cHL and T-cell lymphomas,[4,5] several groups have been interested in developing CD30-CART platforms. The first published phase 1 trial of CD30-CARTs, from Chinese PLA General Hospital in Beijing, also included mostly patients with cHL and reported an ORR (39%) comparable with that in the trial by Brudno et al, with 7 of 18 patients achieving a PR and having a slightly longer median progression-free survival (PFS) of 6 months.[6] A larger study, treating only patients with cHL and combining efforts from the University of North Carolina (UNC) and Baylor College of Medicine (BCM), showed a higher ORR (62%), with 19 of 37 patients (51%) who had active disease at the time of CART infusion achieving CR.[2] The 1-year PFS was 36%, and patients who achieved a CR had a median PFS of 14.6 months, with the longest ongoing CR reported being 25 months. Of note, the type of lymphodepleting chemotherapy appeared to be associated with efficacy, with no responses noted in the 5 patients who received bendamustine alone as lymphodepletion, compared with an ORR of 72% for patients who received fludarabine as part of their lymphodepleting regimen. Initial results of a multicenter phase 2 trial using a CD30-CART product similar to that in the UNC/BCM study corroborated the findings, with an ORR of 73% in 15 patients with cHL and a median PFS of 6.5 months.[7] A phase 1 study from the University of Barcelona, Spain, treating 10 patients reported a best ORR of 100%, including 5 CRs (CR rate, 50%) and a mean PFS of 7.8 months.[3] Overall, these studies showed higher response rates and more durable responses in patients with cHL treated with CD30-CART.

Additionally, in the previous CD30-CART trials, there was more limited toxicity, with the majority of patients having mostly grade 1 to 2 adverse events.[2,3,6,7] The incidence of CRS across trials was variable, but the events were generally low grade and did not usually require any anticytokine therapy. Brudno et al also reported lower grade CRS than what is seen in patients with B-cell NHL treated with CD19-CART, although more patients had grade ≥2 CRS than those in other CD30-CART trials. Similarly, although NT was reported in this trial, it was not clearly consistent with immune effector cell–associated NT syndrome, which has also not been reported in other CD30-CART clinical trials to date.



A CAR combines the binding portions of a monoclonal antibody (scFv) with segments of proteins involved in the signaling machinery of T cells, including CD3ζ, and usually 1 or more additional costimulatory domains, such as CD28 and 4-1BB. When expressed on the surface of T cells, a CAR allows for the direct binding of the immune cells to tumors expressing an antigen of interest on their surface, such as CD30. This recognition bypasses the native requirement for antigen processing and HLA restriction, making a CAR a universal receptor for a particular tumor antigen, thus greatly simplifying the production of cellular immune therapies. The CD30-CARs that have been used in clinical trials conducted at different centers have distinct structures, as illustrated in the figure, and are introduced into autologous T cells using variable methodologies.

Similar to Brudno et al, 2 of the trials reported a maculopapular skin rash developing in approximately half of the treated patients and more frequently in those who received cyclophosphamide, but in contrast to this report, these rashes resolved without specific therapy. As in the trial by Brudno et al, biopsy samples of the affected skin showed a nonspecific spongiotic dermatitis. In the UNC/BCM trial, grade 3 to 4 cytopenias were reported and were mostly attributed to lymphodepleting chemotherapy, because these were not seen in a previous trial using the same CART product that did not include lymphodepleting chemotherapy.[8] Some patients in the UNC/BCM trial had prolonged cytopenias, including 24% with grade 3 to 4 thrombocytopenia and 10% with grade 3 to 4 neutropenia. However, distinct from this study, these did not require additional interventions. Finally, there was no evidence of excess infectious complications.

The reasons for the differences in efficacy and toxicity seen among trials of CD30-CARTs are not immediately obvious. Nonetheless, this is not the first instance in which distinct CART products targeting the same antigen demonstrate different efficacy and toxicity profiles.[9] CD30-CART trials have treated a limited number of patients, the characteristics of whom are likely to be quite heterogeneous, especially, as pointed out by the authors, in a heavily pretreated population. The patients in the current trial seem to be overall similar to those in prior trials, although tumor burden, as calculated based on metabolic tumor volume, which has previously been associated with worse outcomes with both CD19-CARTs and CD30-CARTs, may be higher in the trial by Brudno et al than in the UNC cohort.[10] On the contrary, subtle differences in cellular products (see figure), whose effects are impossible to ascertain in preclinical studies, may influence outcomes, even when comparable amounts of CARTs are infused among trials. For example, unlike the commercially available CD19-CARTs (which share the same scFv, FMC63), each CD30-CAR in clinical use is derived from different monoclonal antibodies and likely has distinct affinities for the corresponding epitopes. Moreover, although the costimulatory domain used by Brudno et al (CD28) is the same as that used by UNC and BCM, the overall structure of the artificial receptor differs by other possibly important components, such as the hinge segment. In addition, manufacturing conditions are variable between centers, with different vectors and growth factors used, which may preferentially transduce or expand certain subpopulations of T cells with distinct potential efficacy and toxicity.

In light of all these studies, what is the future for CD30-CARTs? Despite the lower toxicity and higher efficacy seen with other constructs, long-term data suggest a shorter duration of responses compared, for example, with CD19-CART in aggressive lymphomas. Hence, new strategies are still needed. One approach enhances CD30-CART traffic to tumors by coexpressing CCR4 (the receptor for CCL17, which is secreted in abundance by tumor cells and ordinarily has immunosuppressive activity).[11] Moreover, autologous products may not be optimal, because patients have often been exposed to multiple rounds of lymphotoxic chemotherapy. Therefore, allogeneic products, such as virus-specific T cells (which may mitigate product alloreactivity) expressing a CD30-CAR are an attractive alternative.[12] Long-term results from these and other ongoing studies will be welcome additions to our knowledge in the field.

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