CARTs on the Road for Myeloma

Marcela V. Maus\textsuperscript{1,2} and Carl H. June\textsuperscript{1,3}

Chimeric antigen receptors redirect T cells to surface antigens. Discovery and validation of appropriate target antigens expands the possible indications for chimeric-antigen receptor (CAR) T cells. CS1 is expressed at high levels by multiple myeloma cells, but also to some extent on other lymphocytes. CS1 may be a viable target for CAR T cells in multiple myeloma. Clin Cancer Res; 20(15); 1–3. ©2014 AACR.

In this issue of Clinical Cancer Research, Chu and colleagues (1) explore the potential of targeting the CS1 glycoprotein antigen with chimeric-antigen receptor (CAR)–transduced T cells, with the goal of developing a clinical T-cell therapy to treat multiple myeloma.

The early and impressive success of CAR-transduced T cells targeting the CD19 antigen in B-cell malignancies has spurred a great deal of interest in broadening this type of technology to other malignancies. Briefly, CARs are engineered proteins that fuse the antigen-binding domains of antibodies to T-cell signaling molecules such as CD3\textsubscript{z} with or without additional signaling domains derived from costimulatory molecules such as CD27, CD28, or 4-1BB (2). The technology to molecularly engineer the constructs is readily available, and producing retroviral vectors and transducing T cells with the construct of interest is rapid and reliable. Obtaining or generating an antibody sequence on which to base the antigen-binding moiety can take time, but the greatest challenge in developing a new CAR remains finding a suitable antigen to target.

CS1 is a glycoprotein expressed on the cell surface of nearly all myeloma cells. However, it is also expressed at lower levels on the majority of lymphocytes, including natural killer (NK) cells and subsets of T cells and B cells, but not hematopoietic stem cells (3). Although testing is performed and published as part of the development of the CS1-directed antibody elotuzumab (3), the function of CS1 is not completely understood, and most of its signaling function has been described in lymphocytes. Elotuzumab is known to inhibit myeloma cell adhesion to marrow stromal cells (7), but its principal mechanism of action is to induce NK-mediated antibody-dependent cell-mediated cytotoxicity (ADCC; ref. 8). Given its nearly universal expression on myeloma cells, it is tempting to speculate that CS1 performs an essential function for the maintenance of the tumor.

The authors show that a second-generation CAR based on a single chain variable fragment of an antibody related to elotuzumab effectively redirects T cells to secrete cytokines, degranulate, and exhibit cytotoxic activity in response to myeloma cell lines and primary human myeloma cells in vitro (Fig. 1). CS1-directed T cells also inhibited tumor growth and prolonged survival in orthotopic xenograft mouse models of myeloma. However, at issue is whether the mice were actually cured by the CS1 CART cells, because follow-up of the mice was short in the reported experiment (1). The authors demonstrate that CS1-directed T-cell activity correlates with the expression level of CS1 on myeloma cells. One clinical question that will emerge is whether previous treatment with CS1-specific antibodies (i.e., elotuzumab), binding the same target as the CAR T cells, will select for escape variants that may or may not be visible to CART cells. Interestingly, CS1 is detectable as a soluble form in the serum of patients with multiple myeloma, and the serum level of CS1 correlates with disease stage (7). We would predict that CAR T cells may be inhibited by soluble versions of the same target if the binding epitope is preserved in the soluble form compared with the membrane-bound form; experiments to address this question could be performed in vitro, and correlative studies to address this question could be included in the first trials.

An interesting question is why T cells, which also express CS1, do not seem to commit suicide or "fratricide." Elotuzumab cytotoxicity occurs via antibody-dependent, NK-cell–mediated cytotoxicity, and is specifically directed to CS1-bearing myeloma tumor cells. There is no apparent
cytotoxicity directed to fraternal CS1-bearing NK cells, as demonstrated both \( \text{in vitro} \) and \( \text{in vivo} \) (8, 9). In the findings described in this article, CS1-directed T cells did not seem to degranulate in the absence of myeloma target cells, although there was increased expression of the activation marker CD69, suggesting some low-level recognition of fraternal CS1-bearing T cells. Significant fratricide could impair CAR T-cell expansion, and therefore reduce the feasibility of manufacturing the target cell dose. Moreover, immune deficiencies could occur \( \text{in vivo} \) if a specific subset of T cells, such as CMV-specific T cells, were subject to CS1-directed elimination. Although some of these safety questions could be addressed in the preclinical setting, the ultimate determination of safety and efficacy can only occur in clinical trials. In this article, the authors report on their transduction of T cells; the same group previously transduced the same type of CAR into NK cells (10). Recent studies have shown that NK and T cells can exert cytotoxic activity with remarkably different contact dynamics (11). Therefore, it would be interesting to evaluate the two CAR cell types side by side \( \text{in vitro} \), and even perhaps \( \text{in vivo} \) in a competitive repopulation trial design.

Finally, the CS1-directed antibody elotuzumab is safe, and although it has almost no single-agent activity, it does improve response rates when administered in combination with agents commonly used in the treatment of myeloma. Elotuzumab in combination with the immunomodulatory drug lenalidomide and low-dose dexamethasone yielded an 82% objective response rate (12); elotuzumab in combination with the proteasome inhibitor bortezomib yielded a 48% objective response rate (13). The mechanism of these drugs is thought to be synergistic with the postulated mechanisms of elotuzumab. Although investigators often use lymphodepleting drugs with CAR T cells, it would be interesting to integrate this new platform more closely with standard myeloma therapies.

Given the knowledge that antibody targeting of CS1 is safe, and that CS1-directed CAR T cells effectively eliminate myeloma \( \text{in vitro} \) and in xenogeneic mouse models, CS1-CAR T cells have significant potential to change the landscape of myeloma treatment.

Disclosure of Potential Conflicts of Interest
C.H. June has ownership interest in a patent in the field of CAR T cells. No potential conflicts of interest were disclosed by the other author.

Authors’ Contributions
Conception and design: M.V. Maus
Writing, review, and/or revision of the manuscript: M.V. Maus, C.H. June

Received April 24, 2014; accepted April 27, 2014; published OnlineFirst June 11, 2014.

References


Clinical Cancer Research

CARTs on the Road for Myeloma
Marcela V. Maus and Carl H. June

Clin Cancer Res  Published OnlineFirst June 11, 2014.

Updated version  Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-14-0721

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pub@aacr.org.
Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.