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CLINICAL TRIALS AND OBSERVATIONS

Comment on Hill et al, page 1231

T-cell lymphoma: the CAR-T revolution is coming

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In this issue of *Blood*, Hill et al demonstrate the safety and feasibility of chimeric antigen receptor T (CAR T) cells targeting CD5 in treating patients with relapsed and refractory mature T-cell lymphoma.[1]

The prognosis for patients with relapsed or refractory T-cell lymphoma is poor, with few effective therapies, so novel treatment approaches for this patient population are desperately needed.[2] Unfortunately, although CAR T cells have transformed the care for patients with B-cell lymphomas, the CAR-T revolution has not yet had similar success in the treatment of T-cell lymphomas.[3]

The effective design and use of CAR T cells for T-cell lymphoma face several unique challenges. First, most potential target antigens are expressed on normal T cells in addition to malignant T cells. Thus, using pan–T-cell markers could lead to T-cell fratricide with CAR T cells killing other CAR T cells, thereby preventing successful manufacturing of the CAR T product.[4] Similarly, T-cell aplasia and resultant infectious complications could occur as CAR T cells target the normal immune system.[5]

Several potential mechanisms to overcome these issues are under investigation. One method is to target antigens, such as CD30, with limited expression on normal T cells but that are expressed on a handful of $CD30^+$ T-cell lymphomas.[6] However, most T-cell lymphomas do not express CD30, thus limiting its widespread use. An alternative approach is to use gene editing (eg, with CRISPR/Cas9) to disrupt the target on CAR T cells before CAR transduction to avoid fratricide.[7] A final risk that is particular to using CAR T therapy to treat T-cell malignancies is the possibility of contamination leading to the transduction of malignant cells, especially if there are high numbers of lymphoma cells in circulation.[4]

Despite expression of the CD5 antigen on normal T cells as well as T-cell malignancies, the potential pitfalls described above did not occur in this study of autologous CD5.CAR T cells. A possible explanation can be found in the results of prior work conducted by these authors. They demonstrated that CD5 appears to be downregulated when it binds to its target, and their preclinical studies confirmed that there was not significant fratricide observed with CD5.CAR T cells.[8] Further steps were taken in trial design to minimize other potential risks of targeting T-cell lymphoma. For example, to minimize the infection risk in the setting of T-cell aplasia, the CAR T was meant to be a bridge to allogeneic stem cell transplant (alloSCT) in responding patients, thereby allowing donor cells to expand the normal T-cell population. Finally, before release of manufactured product, analyses were performed to ensure there were <0.5% CAR-transduced malignant T cells. One patient, who had adult T-cell leukemia/lymphoma, had malignant cell contamination, and the patient's CAR T product was not infused.

CD5.CAR T therapy demonstrated activity and safety in patients with heavily pretreated T-cell lymphoma with a median of 5 prior lines of therapy. Responses were seen in 4 of the 9 patients (44%) who actually received the CAR T cells. Two patients achieved a complete response (CR) after their first infusion but declined to proceed to alloSCT and ultimately relapsed 6.4 and 7.2 months later. A third patient achieved a partial response, but had progressive disease shortly after receiving a second CAR T infusion. A fourth patient initially had a mixed response but achieved a partial response after a second CAR T cell infusion and is in an ongoing CR 41 months after alloSCT.

CD5.CAR T therapy was well tolerated in the short-term; however, as one-third of patients died within 2 months of treatment, data on long-term complications are limited. The main toxicities seen were cytopenias, as would be expected with the lymphodepletion regimen. However, 1 patient had severe pancytopenia lasting >8 weeks and ultimately received a stem cell boost from a prior alloSCT donor. It is unclear at this point whether this is related to lymphodepletion in a patient who is heavily pretreated, but prolonged cytopenias have been reported with CD19 and B-cell maturation antigen–directed CAR T cells as well.[9] Cytokine release syndrome (CRS) was seen in 4 patients, although this was all grade 1 to 2. One patient had neurotoxicity, which occurred concurrently with CRS, and it is difficult to state whether this was consistent with immune-effector cell–associated neurotoxicity syndrome. Interestingly, the anticipated prolonged T-cell aplasia was not seen, suggesting a mechanism that leads to resistance of normal T cells to CD5-directed killing. Overall, there were low rates of infections, with 2 episodes of catheter-associated bacteremia and 1 patient with viral reactivation (cytomegalovirus and BK virus). No

deaths occurred secondary to treatment toxicity.

These results provide hope for treating patients with T-cell lymphoma with CAR T cells and the ability to overcome some of the challenges and concerns related to manufacturing and infectious complications. However, follow-up is still short, and only 2 of the 9 patients were still alive at time of publication: 1 after alloSCT and 1 after progression; and in this small cohort, durable remissions without transplant were not seen. Future studies will show whether CD5.CAR T therapy can be curative on its own or whether it will serve only as a bridge to alloSCT. In addition, these results underscore the challenges of treating patients with T-cell lymphoma with autologous CAR T cell products given how aggressive their disease is. Almost half (8/17) of enrolled patients were unable to be treated, and in half (n = 4) of these patients, it was due to death and/or progressive lymphoma. These patients often have rapid progression that cannot be effectively controlled with bridging therapy while awaiting CAR T manufacturing. The median time from consent to infusion was 8 weeks; if this could be shortened, more patients might be able to be treated. Finally, allogeneic CAR T cells may be an ideal approach for being able to successfully treat patients as this might be the fastest way to get CAR T cells to patients. We eagerly await more studies that tackle this challenging disease.

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LYMPHOID NEOPLASIA

Comment on Durand et al, page 1242

TP53 function over forms in multiple myeloma

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In this issue of *Blood*, Durand et al describe a functional score that identifies cells with loss of *TP53* and demonstrate a role for *TP53* function in the response to BH3 mimetics in multiple myeloma (MM).[1]

MM is a disease that is defined in part by structural variations that occur during the germinal center reaction, consistent with dysfunctional class switch recombination. Approximately 50% of patients with MM harbor translocations that result in the juxtaposition of oncogenes to the strong enhancers of the *IGH* locus.[2] However, these truncal events are soon followed by additional alterations that help drive disease progression and can influence disease outcome. These secondary events include copy number variations, non-*IGH* translocations, and single-nucleotide variations (SNVs). Independently, few of these have a significant impact on outcome, with the notable exceptions of gains/amplifications of chromosome 1q ($1q^+$ or amp) and loss of chromosome 17p (del17p).[3] The latter is where the tumor suppressor *TP53* is found and is the only gene where SNVs have been shown to be a predictor of outcome,[4] likely due to the fact that most *TP53* SNVs occur in patients who harbor del17p and reflect biallelic loss of function.[5,6] Therefore, identifying patients with biallelic loss of *TP53* to be able to consider alternative treatment options, given their poor response to standard therapies, is necessary.

To address these issues, Durand et al aimed to identify a gene expression signature that could be used to functionally identify biallelic loss of *TP53*. Previous work on *RAS*/*RAF* mutations in MM has demonstrated that a functional output, in that case gene expression associated with mitogen-activated protein kinase pathway activation, can be more accurate in predicting outcome than just determining if there are mutations in *NRAS*, *KRAS*, or *BRAF*.[7] For the current studies, a *TP53* gene signature was derived by comparing expression of cells where *TP53* expression was inhibited by gene editing in 2 human myeloma cell lines with wild-type *TP53*. The authors found downregulation of 16 genes (including *TP53*). To derive a functional readout of p53 activity, they focused on 13 genes that have been previously shown to be early targets in the pathway (see figure panel A). More important, when similar editing was performed in cells that lacked a functional p53 due to mutations and deletions, no change in the expression of these genes was observed. In addition, MDM2 inhibition with nutlin3a only increased the p53 score in cell lines that had wild-type *TP53*, and a low score also accurately predicted biallelic loss of