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detection sequencing (PhasED-seq), a newer methodology with improved detection capacity compared with CAPP-Seq.[10] The investigators showed that baseline ctDNA correlated with disease stage and total metabolic tumor volume, and ctDNA cleared quickly in the large majority of patients treated with APVD. When assessed at cycle 3 day 1 and again at end of treatment, 81% and 92% of patients, respectively, had undetectable ctDNA. The only patient with disease relapse had detectable ctDNA at both time points. Although the numbers are small, the results are provocative and suggest a potential role for ctDNA in response assessment and possibly therapeutic adaptation for patients with cHL treated with frontline PD-1 blockade + chemotherapy.

Lynch and colleagues have made an important contribution to the growing body of evidence supporting the efficacy of incorporating PD-1 blockade into frontline treatment of cHL. Since PD-1 blockade when given as monotherapy for cHL is associated with prolonged responses, yet is rarely curative, longer follow-up of this and other similar trials will be important to ensure that remissions are truly durable. Also, further work needs to be done to establish the best way to monitor disease response with these novel regimens given the suboptimal predictive value of PET/CT scans during and following treatment. The use of ctDNA to monitor disease response will need validation in a larger cohort, and the optimal timing of ctDNA sampling also still remains to be determined. Finally, if the striking efficacy results with APVD and other novel anti-PD1-based regimens are maintained in long-term follow-up, then studies of de-escalation of therapy, potentially driven by dynamic ctDNA results, could be considered.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Biondi et al, page 2587

CXCR4 to improve both T cell homing and function

Miriam Y. Kim | Washington University School of Medicine

In this issue of *Blood*, Biondi et al[1] show that enforcing CXCR4 expression on CD33-targeting chimeric antigen receptor (CAR) cytokine-induced killer (CIK) cells enhances their homing to the bone marrow (BM) and improves their activity against acute myeloid leukemia (AML).

CXCR4 is a chemokine receptor that binds to CXCL12, also known as SDF-1, which is produced by BM stromal cells. Binding of CXCR4 to CXCL12 plays an important role in retention of hematopoietic stem and progenitor cells (HSPCs) in the BM. This is most evident by the use of plerixafor, a CXCR4 receptor antagonist, in clinical practice for HSPC mobilization.

AML is a malignancy that is derived from HSPCs, and CXCR4 expression is also observed on AML and is associated with poor prognosis.[2] One can presume that the mechanisms used to support HSPCs in their BM niche can also support AML, particularly the leukemic stem cells (LSCs) that serve as a nidus for disease relapse. Therefore, expressing CXCR4 on immune effector cells can bring them into close proximity with LSCs and increase the probability of achieving durable remissions in AML.

Initially, the authors examined CXCR4 expression on CD33-targeting CAR-CIK cells. Of note, the CIK cells used by the authors refer to a particular composition of effector lymphocytes that harbor a mixed T and natural killer (NK) cell phenotype and so are somewhat

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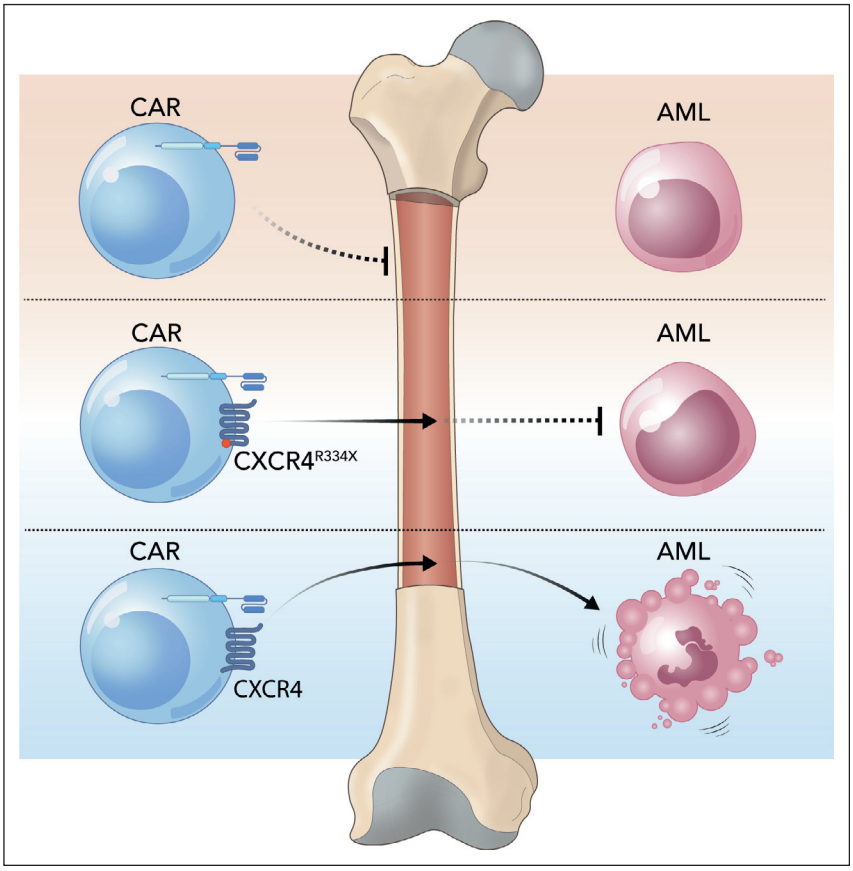

CXCR4 helps CAR-CIK cells reach the BM and eliminate AML. Adding CXCR4, a chemokine receptor, to CAR-CIK cells increases their homing to the BM and also improves cytotoxic activity against AML. Mutant $CXCR4^{R334X}$ improves BM homing but does not increase CAR-CIK cell cytotoxicity. Professional illustration by Somersault18:24.

different from the T cells or NK cells that are commonly used for adoptive cell therapy.[3] The authors show that CD33.CAR-CIK cells have reduced expression of CXCR4 compared with normal T cells and so may be impaired in their ability to migrate to the BM.

To address this concern, the authors investigated coexpressing CXCR4 with the CAR, either in its native format or a mutant $CXCR4^{R334X}$. The mutant $CXCR4^{R334X}$ was discovered in patients with warts, hypogammaglobulinemia, recurrent bacterial infection, and myelokathexis (WHIM) syndrome and has been shown to increase HSPC retention in the BM.[4] The authors hypothesized that the mutant CXCR4 would further improve BM homing of CIK cells and thus their antileukemic effect.

The first part of this hypothesis proved to be correct. CD33.CAR-CIK cells expressing native CXCR4 showed increased migration toward CXCL12 in vitro, which was further increased with expression of mutant CXCR4. Additionally, the authors took advantage of the cross-reactivity of the human CXCR4 receptor toward murine CXCL12 to show that native CXCR4-expressing human CD33.CAR-CIK cells have enhanced homing into mouse BM in vivo, and this is again more pronounced with the mutant CXCR4.

However, the mutant CXCR4 receptor, despite its superior BM homing capabilities, did not enhance CAR-CIK cell antileukemic activity (see figure). In mice engrafted with KG-1, a $CD33^+$ AML cell line, only CD33.CAR-CIK cells expressing the native CXCR4 led to better clearance of leukemia and survival. This suggests that the presence of native CXCR4 not only affects CAR-CIK cell homing but also enhances their cytolytic function, and it is the latter that is more important for disease clearance in this model. Indeed CAR-CIK cells with the native CXCR4, but not the mutant, showed improved tumor-cell killing in vitro. This seems to be due to the ability of the native CXCR4 to stabilize the immunological synapse, which is lacking in the mutant CXCR4.

It will be interesting to see whether these findings are broadly applicable to different types of immune effector cells or are limited to the specific CIK cells used in this study. The initial premise of using CXCR4 to target LSCs also remains to be validated, as the model used in this study was not designed to assess the activity of CAR-CIK cells against LSCs. Nevertheless, the authors' serendipitous finding uncovers an added and unexpected benefit to using CXCR4 as a therapeutic tool that may enhance T cell immunotherapy.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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