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CLINICAL TRIALS AND OBSERVATIONS

Comment on Frigault et al, page 2306

No CNS sanctuary for lymphoma from CAR T

Elise A. Chong and Stephen J. Schuster | University of Pennsylvania

In this issue of *Blood*, Frigault et al[1] report that anti-CD19 chimeric antigen receptor–modified T cells (CAR T cells) can proliferate in the blood, traffic to the central nervous system (CNS), and successfully target primary central nervous system lymphoma (PCNSL). Complete remissions were observed in this patient group with historically poor outcomes.

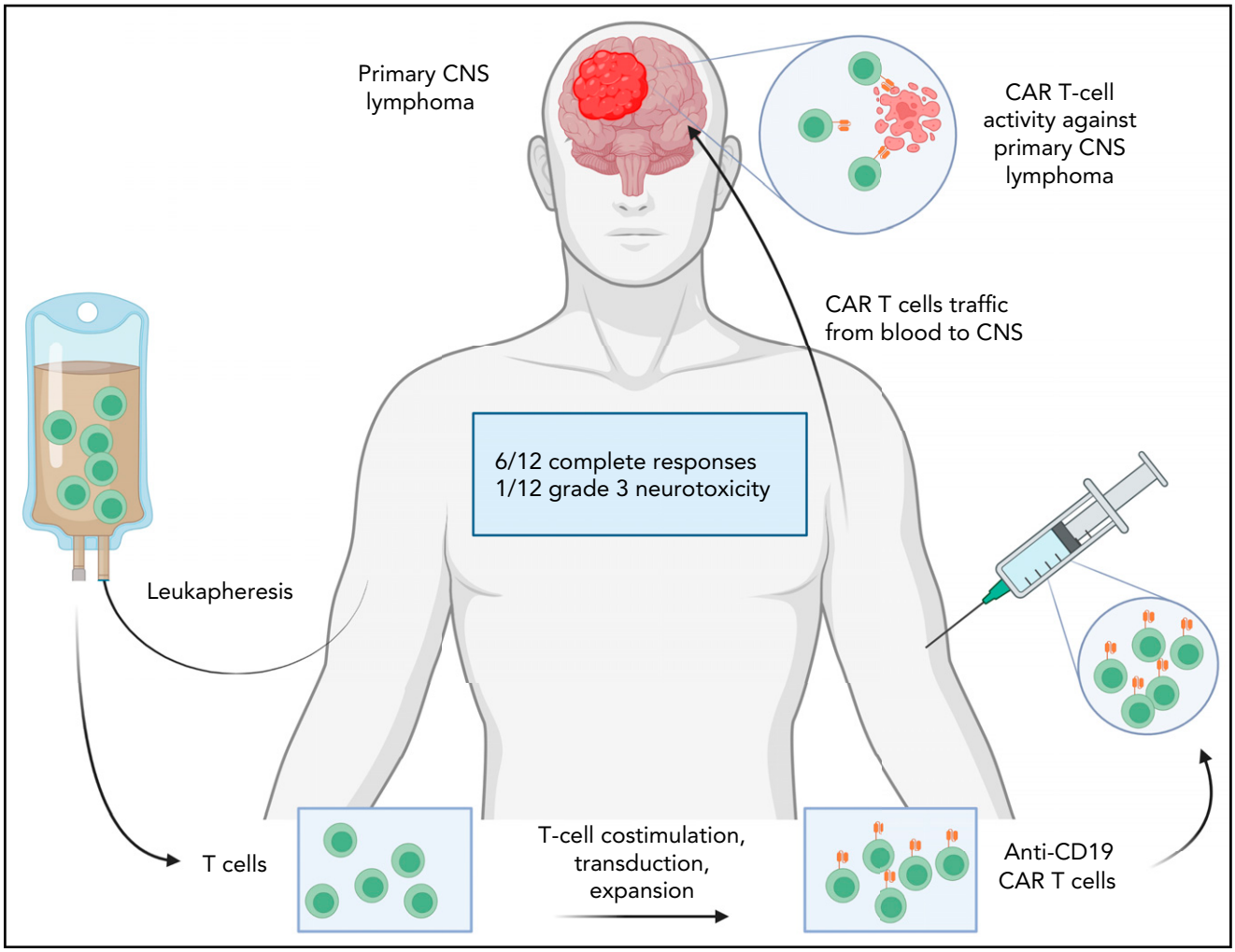
PCNSL is a rare disease, comprising 3% of primary brain tumors in the United States. Unfortunately, only about 50% of patients with PCNSL will remain disease free after first-line methotrexate-based therapy.[2] For those patients with relapsed/refractory PCNSL, there is no standard curative approach. In a significant number of patients, with multiply relapsed or refractory systemic B-cell lymphomas,[3] CAR T-cell therapies targeting CD19 can achieve durable remissions and are commercially available.[4,5] A unique toxicity of CAR T cells is neurologic, termed immune effector cell–associated neurotoxicity syndrome or ICANS.[4,5] Even in the absence of CNS involvement by lymphoma, CAR T cells are known to traffic into the CNS, and ICANS has been observed.[6] Although CD19 is traditionally considered a lineage-specific B-cell marker, pericytes, which surround endothelial cells along the walls of capillaries as part of the blood-brain barrier, may also express the isoform of CD19 targeted by CAR T cells; this is thought to possibly contribute to the neurologic toxicity of CAR T cells.[7] For these reasons, patients with PCNSL were specifically excluded from registrational CAR-T trials owing to concerns for precipitation or exacerbation of ICANS. Although 7 patients with secondary CNS involvement were included in 1 registrational trial,[5] data to support CAR T cell use in PCNSL are limited to small retrospective case series and post hoc analyses of prospective clinical trials.[8,9]

In this study, Frigault et al present results of a single-center, prospective study of tisagenlecleucel (anti-CD19, 4-1BB, CD3ζ CAR T cells) in patients with PCNSL relapsed after, refractory to, or ineligible for standard first-line high-dose methotrexate-based therapy. This is the first report of a prospective clinical trial examining commercially available CD19-directed CAR T cells in patients with PCNSL. Corticosteroids, up to dexamethasone 4 mg daily or equivalent, were permitted during leukapheresis, as well as prior to, during, and after CAR T-cell infusion. The primary endpoint was safety. Secondary endpoints included overall and complete response rates. Twelve patients received tisagenlecleucel, which was generally well tolerated. One of 12 (8%) patients had grade 3 ICANS; severe cytokine release syndrome was not observed. The authors observed that CAR T cells infused IV expanded in blood and trafficked to the CNS, with responders having higher levels of CAR T cells in cerebrospinal fluid. At 12 months' median follow-up, overall response rate is 7/12 (58%) with a continuing response in 3/12 (25%) patients at the time of reporting (see figure).

The number of patients treated on this study is small; however, PCNSL is a rare disease. Thus, a small sample size is expected. Although the rate of severe neurologic toxicity in this study is comparable to the historical rate for tisagenlecleucel in systemic lymphoma, it is noteworthy that 50% (6/12) of patients developed some degree of mild to moderate neurologic toxicity.[1] From a historical perspective, fewer (21%) patients in the registrational trial of tisagenlecleucel, JULIET, for systemic large B-cell lymphomas had any grade neurologic toxicity.[4] The concurrent use of corticosteroids in 25% of patients on this trial would be expected to bias toward lower rates of neurotoxicity. The timing of neurologic toxicity reported in this study appears comparable to JULIET (4 vs 6 days after CAR T-cell infusion, respectively); however, the median duration of neurologic toxicity was shorter (5 vs 14 days, respectively). This study's shorter duration of neurotoxicity may reflect the evolving practice of early initiation of corticosteroids at onset of neurologic toxicity.

This study confirms CAR T-cell expansion in peripheral blood in the absence of systemic lymphoma, an observation previously reported in patients with systemic lymphoma who received CAR T cells while in complete remission.[10] It also allays the theoretical concern that CAR T cells might not expand adequately in B-cell–depleted patients with isolated CNS tumors. Similar to some prior studies of CAR T-cell therapy in systemic lymphoma that described an association between higher CAR T-cell levels in peripheral blood and efficacy,[5] the authors observed higher CAR transgene levels in the cerebrospinal fluid of patients who achieved complete remission.

The patients enrolled on this study were a poor-prognosis group, including 5 of 12 (42%) with an Eastern Cooperative Oncology Group performance status of 2 or greater, a median of 4 prior lines of therapy (range: 2-9), and all had lymphoma progression after a Bruton tyrosine kinase inhibitor (BTKi), an active



Tisagenlecleucel for PCNSL (N = 12 infused patients). Created with Biorender.com

therapeutic class for PCNSL. Despite these unfavorable characteristics, 6 of 12 (50%) patients achieved complete responses with 3 of 12 (25%) still in remission at 1 year. These results are particularly encouraging for a group of patients with previously described response durations of 2 to 3 months.[2] It is also noteworthy that concurrent dexamethasone did not appear to abrogate the expansion or efficacy of CAR T cells, which is a theoretical concern among physicians administering CAR T.

These results are significant and suggest a path forward for treatment of relapsed/refractory PCNSL, a disease that often has a poor outcome and represents an unmet medical need. In addition, this study provides a signal that CAR T cells may become a compelling backbone with which to pair other agents that are active in PCNSL and compatible with T-cell–based therapy, such as BTKi, immunomodulatory drugs (IMiDs), and programmed cell death protein 1 (PD-1) blockade. We look forward to future studies of earlier application of CAR T cells for treatment of PCNSL, optimization of bridging therapy to control CNS lymphoma before CAR T-cell infusion, novel approaches to monitoring neurologic toxicity in patients with preexisting focal neurologic deficits, and CAR T cells in combination with other active therapies for PCNSL.

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LYMPHOID NEOPLASIA

Comment on Bachy et al, page 2338

Chemotherapy-free regimens in frontline follicular lymphoma

Connie Lee Batlevi | Memorial Sloan Kettering Cancer Center

Lenalidomide and anti-CD20-based combinations have validated efficacy in treatment of follicular lymphoma in both the frontline and the relapsed settings. In this issue of *Blood*, Bachy et al[1] report the tolerability and efficacy of obinutuzumab and lenalidomide in the frontline therapy of follicular lymphoma.

Patients with follicular lymphoma display a wide spectrum of clinical presentations. While some patients are suitable for observation with low-volume advanced-stage disease, most patients will eventually require treatment.[2] In just the last 10 years, frontline therapy for follicular lymphoma has evolved from anti-CD20 antibody with chemotherapy-based regimens to multiple options, including immunomodulatory treatment with therapies like lenalidomide with rituximab or obinutuzumab.[3] Regimens without chemotherapy holds promise as the majority of patients with follicular lymphoma are older with a variety of comorbidities and benefit from treatments with reduced long-term toxicities.

Obinutuzumab is an engineered humanized IgG1k antibody with more effective anti-lymphoma activity in both in vitro and animal models than other anti-CD20 antibodies (see figure).[4] Glycoengineering reduced fucosylation in the Fc domain, which generated greater antibody dependent cellular toxicity through enhanced binding to FcγRIII receptor on immune effector cells. A modified elbow hinge binding site to CD20 facilitates a type II antibody effect by decreasing complement dependent cytotoxicity and inducing less lipid rafting and internalization of CD20.[4] While clinical efficacy of obinutuzumab in diffuse large B-cell lymphoma has been disappointing, obinutuzumab with chemotherapy has demonstrable improved progression-free survival (PFS) compared with rituximab in follicular lymphoma.[5]

Lenalidomide is an immunomodulatory therapy that binds the cereblon E3 ligase complex and triggers ubiquination and degradation of Ikaros and Aiolos, which are key transcription factors in B and T cells (see figure).[6] As a result, lenalidomide results in cell cycle arrest at G_1, and reduced proliferation. Lenalidomide upregulates immune responses by increasing anti-inflammatory cytokines, enhancing immune synapse formation, and increasing T-cell effector activity.[7]

The Lysa group study by Bachy et al is a phase 2 clinical trial from 21 centers in France and Belgium that evaluated the combination of obinutuzumab and lenalidomide in the frontline treatment of follicular in patients meeting Groupe d'Etude des Lymphomes Folliculaires criteria. Treatment consisted of obinutuzumab and lenalidomide induction for 6 months followed by maintenance for 2 years, the first year with the obinutuzumab every 8 weeks and reduced dose lenalidomide, and a second year with only obinutuzumab every 8 weeks. The population included 43% of patients with high follicular lymphoma international prognostic index, and >30% with a bulky lymph node >7 cm. The current combination produced an overall response rate (ORR) of 92% and complete response (CR) of 47% at the end of induction, and ORR 79%, CR 63% at the end of therapy based on International Working Group 1999 criteria. Understanding the challenges and appropriateness of cross trial comparison, this represents a 15% absolute increase of patients achieving a complete remission compared with the rituximab-lenalidomide arm of the frontline RELEVANCE trial.[3] The results with the obinutuzumab-lenalidomide combination using metabolic responses from Lugano 2014 criteria are more impressive with 80% achieving a metabolic complete remission at the end of induction. At nearly 4 years of follow-up, the median PFS is 82%. Another study of obinutuzumab and lenalidomide in untreated follicular lymphoma has reported similar efficacy using the Lugano 2014 criteria.[8] Furthermore, the 6-year follow-up data from the frontline study of rituximab and lenalidomide compared with chemotherapy demonstrated similar PFS of 60% and overall survival of 89% in the 2 groups, suggesting that an anti-CD20 antibody and lenalidomide combination resulted in sustained clinical responses.[9] Although the mechanism of action of obinutuzumab favors it as a more effective anti-CD20 antibody, it remains uncertain as to whether rituximab or obinutuzumab is the more effective anti-CD20 antibody when combined with lenalidomide in follicular lymphoma.

As with all treatments, clinicians must also balance treatment risks with benefits.