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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Frigault et al, page 860

The CNS can be a safe space for CARs

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In this issue of *Blood*, Frigault et al report that tisagenlecleucel, a CD19-specific chimeric antigen receptor (CAR) T-cell product, has a safety profile in a small series of patients with aggressive B-cell non-Hodgkin lymphomas (B-NHLs) and secondary central nervous system (CNS) involvement similar to that seen in patients without active CNS disease.[1] The Frigault et al study suggests that this product may benefit this previously excluded group of patients without an increased risk of neurotoxicity.

CARs combine the antigen-recognizing moiety of a monoclonal antibody with elements of the T-cell signaling machinery, most frequently a portion of the T-cell receptor–associated ζ chain and part of a costimulatory molecule such as CD28 or CD137 (4-1BB).[2] T cells genetically engineered to express CARs targeting CD19 (CD19-CARTs) have demonstrated remarkable activity in patients with relapsed or chemotherapy refractory B-cell malignancies. In aggressive B-NHL, complete response rates ranged from 40% to 54% in the 2 largest published trials to date.[3,4] On the basis of this activity, 2 CD19-CART products, axicabtagene ciloleucel and tisagenlecleucel, have been approved by the US Food and Drug Administration (FDA).

Frequently complicating administration of CD19-CARTs, however, is the development of significant (black-box worthy) complications, including cytokine release syndrome (CRS) and neurotoxicity (recently named immune effector cell–associated neurotoxicity syndrome [ICANS] by a consensus panel).[5] ICANS is a constellation of manifestations of CNS dysfunctions that include aphasia, altered levels of consciousness, impaired cognitive skills, motor weakness, seizures, and potentially cerebral edema, which has been fatal in patients who were treated in early-phase trials of other CD19-CART products.[6]

The underlying pathophysiology of ICANS has been difficult to elucidate. Expression of CD19 in the brain, which could lead to "on-target, off-tumor" effects, has not been clearly demonstrated. Recent human and animal data suggest that endothelial activation in the CNS and increased permeability of the blood-brain barrier after CAR T-cell treatment may expose pericytes to a high concentration of cytokines, triggering local inflammation.[7] In contrast to CRS, however, interleukin-6 (IL-6) receptor antagonists, such as the monoclonal antibody tocilizumab, are not effective at reversing the manifestations of neurotoxicity. An IL-1 receptor antagonist, anakinra, may have therapeutic activity in this setting,[8,9] but experience with this agent is limited, and clinicians often must resort to using steroids, which have potential deleterious effects on CARTs and are not entirely effective at mitigating neurotoxicity.

In pivotal trials in B-NHL, the reported incidence of neurotoxicity ranges from 21% to 64% (12% to 28% grade 3 or 4).[3,4] However, the rate depends on the specific product and toxicity grading system used, which makes direct comparisons difficult. Nevertheless, patients with active CNS disease have been excluded from trials of CD19-CARTs for B-NHL because of concerns regarding the increased risk of neurotoxicity. Because CD19-CARTs are known to be able to traffic to the CNS,[10] where they could potentially exert a therapeutic effect, these patients are possibly being denied a potentially beneficial treatment.

Frigault et al present a retrospective analysis of 8 patients with relapsed aggressive B-NHL with secondary CNS disease who were treated with lymphodepletion followed by tisagenlecleucel. Their data suggest that this approach has limited toxicity, because no patient required treatment of ICANS. In addition, these patients may benefit from CART therapy, since 4 of the 8 patients had partial responses. Although CART levels were not measured directly, an increase in circulating T cells and a rise in inflammatory markers were consistent with CART expansion, even in the absence of systemic disease. Two patients died with signs of increased intracranial pressure, but autopsy data, which the authors should be commended for obtaining, evidenced disease progression rather than CART-driven toxicity in the CNS.

Although this work describes a limited number of cases, it addresses a management issue for which there was only anecdotal evidence but that frequently arises in patients with relapsed or refractory aggressive B-NHL. These patients often have CNS disease and otherwise would be candidates for CD19-CART therapy. This series suggests that, with careful management (all patients received prophylactic anticonvulsants) and monitoring, at least some CD19-CARTs are a safe and potentially effective option for patients with secondary CNS B-NHL. Moreover, this report raises the possibility of using these cell products for primary CNS lymphoma, a diagnosis with far worse outcomes than its solely systemic counterparts that is not currently included

in the indications for the FDA-approved products. Further studies in these settings are eagerly awaited.

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MYELOID NEOPLASIA

Comment on Zhang et al, page 867

Illuminating neutrophilic myeloid neoplasms

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In this issue of *Blood*, Zhang et al[1] have performed a genetic interrogation of neutrophilic myeloid neoplasms, revealing a distinct combination of genetic events and suggesting that the current use of clinicopathologic features to distinguish some individual entities may not be biologically relevant.

Myeloid neoplasms presenting predominantly with neutrophilia include the myeloproliferative neoplasms (MPN) chronic myeloid leukemia (CML) and chronic neutrophilic leukemia (CNL) as well as diseases considered within World Health Organization (WHO)-defined group of myelodysplastic/myeloproliferative neoplasms (MDS/MPN). Aside from the common feature of leukocytosis and presence or absence of *BCR-ABL1* rearrangement (which defines CML), these diseases traditionally have been distinguished from one another by a host of clinicopathologic features, such as monocytosis, left-shifted granulocytes in the peripheral blood, and morphologic dysplasia of hematopoietic elements. These diseases can be challenging to treat, because the patient's symptoms may be related to marked leukocytosis and splenomegaly, ineffective hematopoiesis with anemia and/or thrombocytopenia, or a combination of both. Moreover, determining the optimal treatment has been difficult: aside from CML, these rare diseases have been subjected to few clinical trials or have been included in clinical trials for myelodysplastic syndromes (MDS).

Zhang et al perform a detailed genetic analysis of a large number of CNL and MDS/MPN in order to determine their genomic landscape and relationship to other myeloid neoplasms, such as MDS. These neoplasms usually display mutations in 3 or 4 major pathways: *ASXL1/ASXL2*, *TET2*, or *GATA2*, and a signaling and/or splicing pathway mutation. This pattern of comutation had been recognized for chronic myelomonocytic leukemia (CMML),[2] but until now its prevalence among other MDS/MPN and CNL had not been clearly delineated. Importantly, this comutation pattern is uncommon in age-related hematopoiesis, MDS, and the *JAK2/MPL/CALR*-associated MPN. It is also rare in another MDS/MPN, juvenile myelomonocytic leukemia (JMML), which typically bears only *RAS* pathway mutations. These data raise the question as to the clinical relevance of separating neutrophilic myeloid neoplasms into subtypes distinguished by their morphology (see figure). Once CML, JMML, and the *JAK2/MPL/CALR*-associated MPN are excluded, these diseases appear to have common genetic features and may be best considered together in terms of prognostic modeling, optimal clinical approach, and inclusion in clinical trials.

What does determine biologic heterogeneity within this disease group? Not surprisingly, the authors find complex mutation associations, including comutations of genes in the same pathway. Certain mutation patterns are associated with clinicopathologic parameters, such as monocyte percentage, degree of leukocytosis, and degree of dysplasia. In addition, certain mutation patterns are overrepresented in particular disease subtypes, such as comutation of *SRSF2* and *TET2* in CMML, as has been shown in prior studies.[2,3] However, the mutation patterns do not clearly segregate with the specific disease types recognized by the WHO classification. Gene expression profiling identifies 3 major clusters with variable representations of mutation frequencies and also does not segregate specific disease subtypes. Presumably, the varied clinical presentations among these diseases are influenced by the specific portfolio of mutations and their interactions, variant allele frequencies and mutational hierarchies of individual genes, and epigenetic factors influencing gene expression. The pattern of mutation hierarchy suggests sequential linear mutation acquisition, which differs from the more complex pattern of mutation acquisition in acute myeloid leukemia. The predicted order of mutation acquisition is heterogeneous, a factor that may also influence the clinical disease presentation, as has also been shown for other myeloid neoplasms such as polycythemia vera.[4]

This study also challenges the important tenet in the WHO classification that in