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ICANS prophylaxis: potentially transformative but elusive

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Comment on Strati et al, page 6785, and Jacobson et al, page 6790

In this issue of *Blood Advances*, Strati et al[1] and Jacobson et al[2] report on 2 interventional trials of prophylactic strategies to prevent immune effector cell–associated neurotoxicity syndrome (ICANS) after anti-CD19 chimeric antigen receptor (CAR) T-cell therapy for large B-cell lymphoma (LBCL). Both trials enrolled patients planned to receive axicabtagene ciloleucel (axi-cel), the product that has been most associated with ICANS in clinical trials and real-world data.[3,4]

ICANS is the most feared and clinically challenging complication of CAR T-cell therapy. Acute manifestations range from those that are relatively mild, including tremor, inattention, and disorientation to more severe disturbances, including alterations in conscious state, focal neurological deficits, seizures, and acute cerebral edema. Severe cases may be fatal. Delayed manifestations of ICANS, more commonly reported with anti–B-cell maturation antigen CAR T-cell therapy, include neuroimmunological syndromes and movement disorders. The pathophysiological basis remains incompletely understood. Acute ICANS typically follows cytokine release syndrome (CRS), and an inflammatory cascade initiated by CAR T-cell activation and amplified by myeloid lineage cells likely contributes.[5,6] Cytokines temporally associated with the development of ICANS include interleukin-1 (IL-1), granulocyte-macrophage colony-stimulating factor, IL-6, interferon-gamma, IL-15, and tumor necrosis factor–α, among others. Cytokine-mediated endothelial injury leading to disruption of the blood-brain barrier may provide some or all of these cytokines and/or inflammatory cells with increased access into the central nervous system.[7,8] The trials reported in this issue of *Blood Advances* pursue 2 possible contributing components: IL-1 and endothelial activation.

The evidence base for the optimal management of established ICANS is limited. The current accepted backbones of treatment are corticosteroids and supportive care, with the precise role of anticytokine therapy yet to be defined. There remain lingering concerns regarding the potential impact of corticosteroids on CAR T-cell proliferation and effector function and other adverse consequences of prolonged steroid exposure.[9] In the ZUMA-1 study, alternative management or prophylaxis strategies for CRS/ICANS were explored in several safety cohorts and compared with those in the pivotal cohorts. Earlier[10] or prophylactic[11] use of corticosteroids, respectively, appeared to reduce the incidence and severity of ICANS without an apparent impact on efficacy. Some centers have adopted 1 or both of these strategies, at least for patients considered at high-risk of severe ICANS. By contrast, the use of prophylactic tocilizumab was associated with a slight increase in severe ICANS despite a reduction in CRS.[12] Although the data were nonrandomized, concomitant increases in systemic and cerebrospinal fluid IL-6 after prophylactic tocilizumab administration led to the hypothesis that IL-6R blockade was detrimental, and, therefore, inhibition of the IL-6 axis as a prophylactic strategy has fallen out of favor.

A new lead appears to be the inhibition of IL-1 signaling using the IL-1 receptor antagonist anakinra based on preclinical studies[13,14] and emerging data reporting the use of anakinra for the treatment of steroid-refractory ICANS.[15-17] Park et al recently reported an interim analysis of their prophylactic study across a range of histological subtypes of lymphoma and CAR T-cell products, demonstrating a lower-than-expected rate of severe ICANS.[18] It should be noted that other studies of anakinra prophylaxis are ongoing (NCT04150913 and NCT04359784).

Here, Strati et al report the results of a phase 1 study in which anakinra was administered to patients receiving axi-cel for LBCL, commencing before infusion and continuing for 7 days. Two dose levels were explored, 100 mg daily and 100 mg twice daily, and 10 patients were treated at each dose level.

The primary objective was to evaluate the safety, tolerability, and recommended phase 2 dose (RP2D) of prophylactic anakinra, with secondary objectives including the efficacy of the prophylactic strategy (CRS and ICANS incidence, severity, and duration) and the CAR T-cell therapy (response, progression-free survival, and overall survival rates). All patients completed the intended course of anakinra, and no dose-limiting toxicities were observed. Results were compared with those of a contemporaneous cohort matched for total metabolic tumor volume and treated with axi-cel off study without prophylactic anakinra. The comparisons, therefore, come with the caveat that the data are nonrandomized. Somewhat surprisingly, the rate, severity, and duration of CRS appeared similar in the anakinra cohort (both dose levels combined) compared with those in the matched cohort and with the pivotal cohorts of ZUMA-1. The incidence and severity of ICANS was numerically lower in the anakinra cohort than in the matched cohort, with 35% any grade ICANS compared with 60%, and 20% grade 3 to 4 ICANS compared with 30%, although the numbers were small, and statistical comparisons were not meaningful because the cohorts were not randomized. In the pivotal cohorts of ZUMA-1, a total of 64% of patients experienced neurological adverse events, 28% of which were grade ≥3 (this study predates the definition and grading of ICANS). Corticosteroid use was also lower in the anakinra cohort (35% of patients) than in the matched cohort (55% of patients), suggesting that prophylaxis may indeed allow for reduced corticosteroid exposure. Analogous to the treatment setting,[17] the authors observe that the optimal dose of anakinra for prophylaxis remains undefined; higher doses and combinations with other therapies are worthy of exploration. There was no evidence of an impact on early response to CAR T-cell therapy (overall and complete response rates were 90% and 60%, respectively, on day +90).

Jacobson et al took the approach of targeting endothelial dysfunction directly. Defibrotide protects the endothelial lining of blood vessels from clotting and activation through mechanisms that are not well understood and is used to treat hepatic, renal, and pulmonary veno-occlusive disease/sinusoidal obstructive syndrome after allogeneic hematopoietic stem cell transplantation. It was, therefore, hypothesized that prophylactic defibrotide may abrogate the early endothelial injury thought to be important in the pathophysiology of ICANS. Defibrotide was administered on 11 days in total, including before each dose of lymphodepleting chemotherapy and then 4 times a day, commencing before the CAR T-cell infusion and ending on day +7. After a safety lead-in, 20 patients in total received the RP2D dose of 6.25 mg/kg of defibrotide. This prophylactic strategy was also well tolerated, with no dose-limiting toxicities. The rate of any grade ICANS was 50%, and the rate of severe (grade 3/4) ICANS was 25%. Although these results represented a modest reduction compared with those of historical controls, the study was terminated early because it was considered unlikely to meet its primary end point. Again, early responses to CAR T-cell therapy were within expectations, with 95% and 52% overall and complete response rates, respectively, up to day +60.

Both studies are important and timely and represent well-reasoned attempts to improve the safety of CAR T-cell therapy based on the current understanding of the pathophysiology of ICANS. Both studies, along with the study by Park et al, come with the caveats of the data being nonrandomized. Furthermore, rates of severe ICANS in some real-world studies are lower than those in the pivotal trials,[3,4] potentially because of changes in toxicity-management practice over time. Randomized studies may be needed to assess the true magnitude of impact of promising prophylactic strategies before widespread adoption in clinical practice.

The consequences of significantly reducing the incidence and severity of both CRS and ICANS are potentially transformative. CAR T-cell therapy is currently extremely resource intensive, requiring inpatient delivery and/or close outpatient follow-up owing to the potential for severe toxicities. A more detailed understanding of the mechanisms and pathophysiology of these toxicities is needed. An effective prophylactic strategy could potentially allow for safe outpatient administration and delivery of these curative-intent therapies at higher doses to a broader group of patients for whom the risks are currently considered to outweigh the benefits because of age or comorbidities. The studies of Strati et al and Jacobson et al demonstrate early steps toward this goal.

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