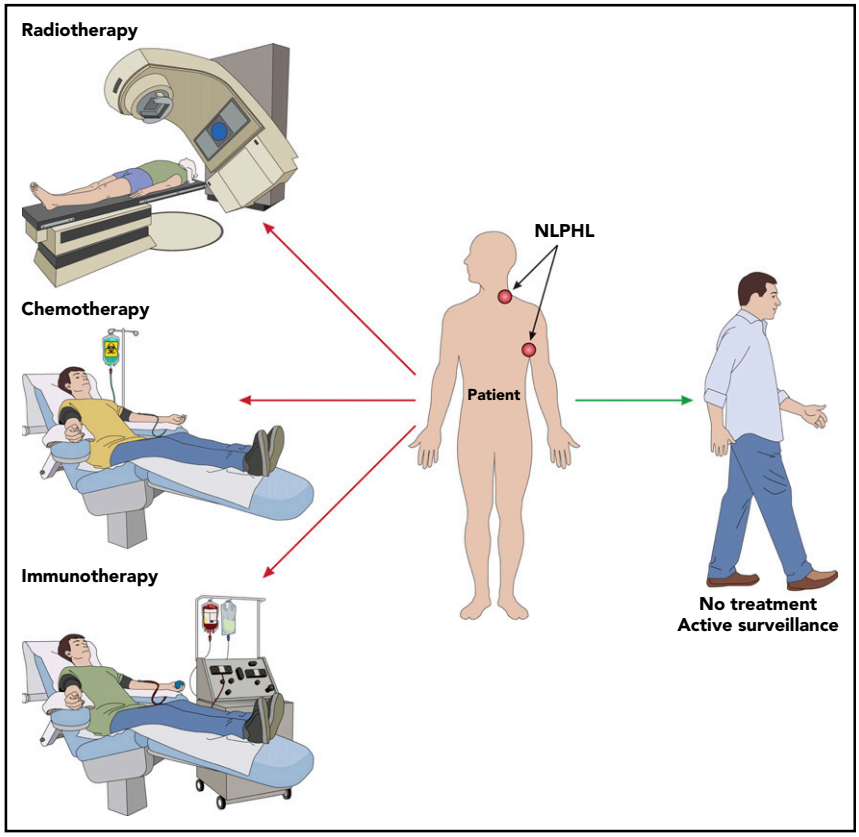

Nodular lymphocyte predominant Hodgkin lymphoma: therapeutic choices. Professional illustration by Patrick Lane, ScEYEnce Studios.

chemoimmunotherapy in 3 patients. Transformation developed in the active surveillance group no more frequently than in the active intervention group.

Recommending deferral of intervention when a patient is found to have a potentially fatal but straightforwardly treatable disease must be done very carefully. We must be reassured that eventual outcomes are not inferior compared with those seen after immediate intervention both in terms of survival and in the quality of that survival. Borchmann et al's observations suggest that patients on active surveillance of asymptomatic, low tumor burden NLPHL do not suffer any disadvantage compared with those receiving intervention at diagnosis in terms of long-term disease control, responsiveness to subsequent treatment, overall survival, or freedom from transformation to large B-cell lymphoma. Indeed, almost three-fourths of their observed patients avoided the cost, inconvenience, and long-term toxicity of cancer treatment. However, such patients must be chosen very carefully. They should have no disease-related symptoms or mass lesions threatening organ compromise. They should be psychologically comfortable with treatment deferral, and they must be committed to long-term follow-up with clinicians experienced in the management of lymphoid cancer. Finally, this approach, reliance on active surveillance for NLPHL, should be regarded as provisional, and only continued if validated by other groups adopting a similar approach.

Conflict-of-interest disclosure: J.M.C. has received honoraria from Seattle Genetics and Takeda Pharmaceuticals. ■

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

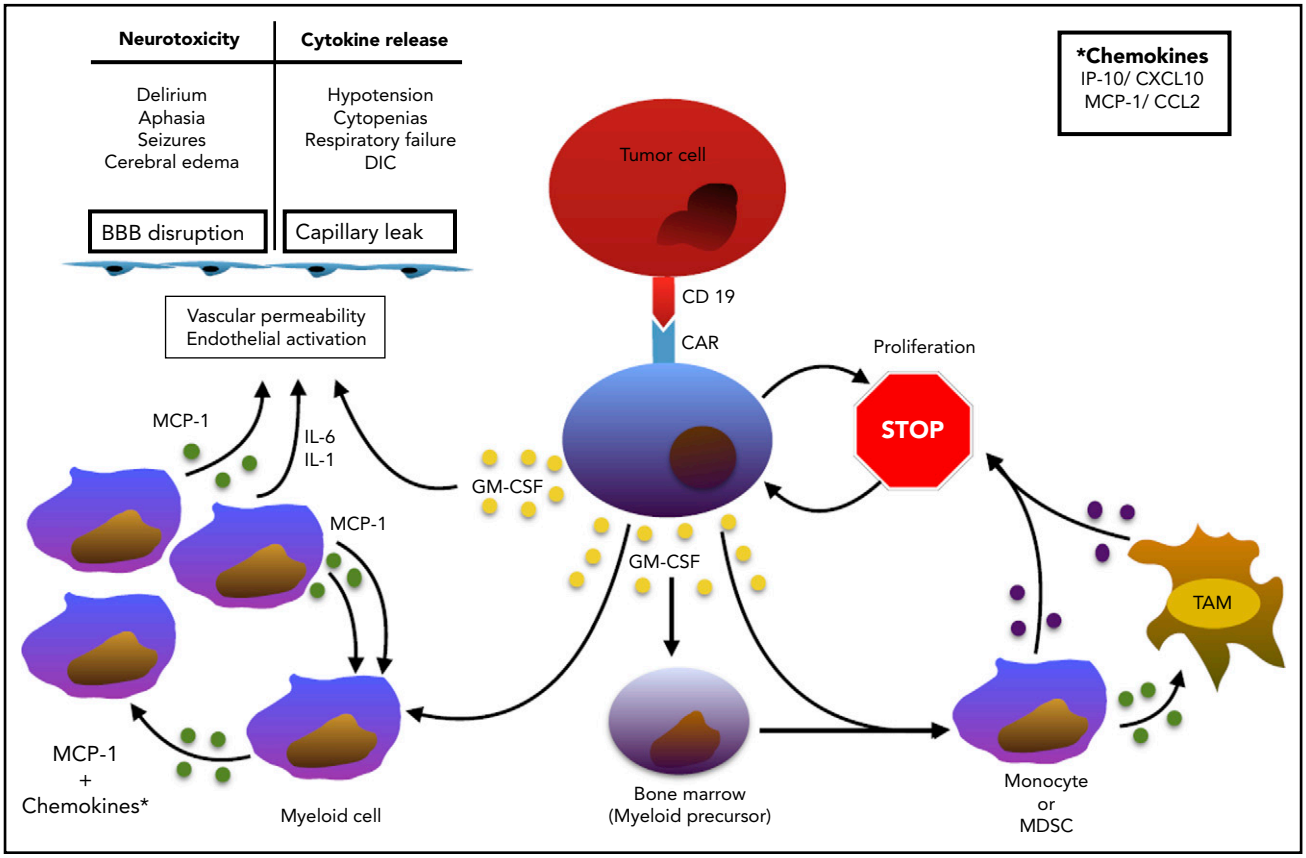
Comment on Karschnia et al, page 2212

CAR-T–cell neurotoxicity: hope is on the horizon

Omar Ahmed | Humanigen

In this issue of *Blood*, Karschnia et al spotlight the "Achilles heel" of chimeric antigen receptor (CAR) T-cell therapy and call for prospective clinical trials to evaluate strategies to manage and potentially prevent CAR T cell–induced neurotoxicity (NT).[1]

Although the emergence of CAR T-cell therapy has dramatically improved response rates for patients with relapsed or refractory B-cell hematologic malignancies, its utility is hampered by the potential for significant side effects, including severe



Pathophysiologic mechanism of neurotoxicity and CRS. GM-CSF is produced by CAR T cells upon contact with tumor and serves as a communication conduit between the specific immune response of the CAR T cells and the off-target inflammatory cascade produced by myeloid lineage cells. GM-CSF acts directly on myeloid cells to expand, activate, and promote the production of other chemokines, including MCP-1/CCL2, IP-10/CXCL10, and cytokines IL-6 and IL-1. Once initiated, the inflammatory cascade can become self-perpetuating as the production of chemokines results in further expansion and trafficking of myeloid cells to the tumor bed. The positive feedback loop can result in abnormally high levels of inflammatory cytokines, endothelial activation, vascular permeability, and ultimately, NT and CRS. GM-CSF also acts directly on myeloid lineage cells to promote the expansion and trafficking of myeloid derived suppressor cells (MDSC) and tumor-associated macrophages (TAM), which have been demonstrated to inhibit T-cell proliferation and effector functions.

NT, which as reported by Karschnia et al is a negative prognostic factor for overall survival. Corticosteroids are currently the recommended treatment of NT, but prolonged exposure of >10 days in patients with severe NT may negatively influence overall survival. The potential impact of NT on overall survival is a significant finding as >50% of CAR T cell–treated patients with NT in this study had developed severe NT. In addition, NT is associated with cytokine release syndrome (CRS), and the anti–interleukin-6 (IL-6) receptor antagonist, tocilizumab (Actemra), currently the only Food and Drug Administration (FDA)-approved therapy for the treatment of severe CRS, has been shown to increase both the overall rate of NT and the rate of severe NT when used prophylactically.[2] Moreover, the majority of patients treated with CAR T cell are treated as in-patients, and admission to the intensive care unit (ICU) for the management of these toxicities is often required, creating an added health economic burden and less favorable reimbursement for hospitals and institutions, which inevitably results in restricted access. Analyses of health resource utilization point to length of hospitalization and length of stay in the ICU as the primary drivers of non-drug–related costs for CAR T cell–treated patients, which are projected to be at least twice as high for those who develop these severe toxicities.[3,4] Strategies to improve the safety profile of CAR T-cell therapy without negatively impacting efficacy are needed to improve its benefit-to-risk profile and cost-effectiveness and to enable CAR T-cell therapy to move beyond use solely in relapsed/refractory patients to earlier lines of therapy.

There are no FDA-approved therapies available for the prevention, nor for the treatment, of NT. Much has been learned regarding the possible mechanisms and pathophysiology of CAR T cell–induced NT, including the role of myeloid cells, endothelial cells, and proinflammatory cytokines. In addition to ferritin, a biomarker that has been shown by Karschnia et al and others to correlate with severe NT, an analysis by Rossi et al evaluating axicabtagene ciloleucel (axi-cel, Yescarta), the first CAR T cell therapy approved for the treatment of relapsed/refractory diffuse large B-cell lymphoma, showed that levels of IL-15 and granulocyte-macrophage colony-stimulating factor (GM-CSF) are elevated 1 day following CAR T-cell administration, and the early elevation of these cytokines are correlated with severe NT.[5] No other proinflammatory cytokines were directly or indirectly associated with severe NT. It is proposed that upon contact with the tumor, CAR T cells produce GM-CSF,[6] which serves as a communication conduit between the specific immune response of the CAR T cells and the off-target inflammatory cascade produced by myeloid lineage cells, causing myeloid cells to expand and promote the production of other proinflammatory chemokines and cytokines, including monocyte chemoattractant protein-1 (MCP-1), IL-1, and IL-6, among others (see figure). Fever and

elevated levels of MCP-1 36 hours after CAR T-cell administration have been demonstrated to be the best predictors of severe NT and CRS with high levels of specificity and sensitivity.[7] Moreover, IL-6 is only released by the antigen-presenting cells, or tumor cells, in a contact-independent manner, which helps explain why the prophylactic administration of tocilizumab is not effective in reducing the overall incidence of CRS or NT, as this cytokine is downstream in the inflammatory cascade.[2,6] Once initiated, this inflammatory cascade can become a self-perpetuating "storm," resulting in further expansion and trafficking of myeloid cells to the tumor bed, abnormally high levels of inflammatory cytokines, endothelial activation, vascular permeability, and ultimately, CRS and NT.

Blood-brain barrier (BBB) disruption and infiltration of myeloid cells and proinflammatory cytokines into the central nervous system (CNS) are other important factors in the pathogenesis of NT. In the study by Karschnia et al, low platelet counts, a biomarker for BBB disruption, prior to CAR T-cell infusion were associated with severe NT. The integrity of the BBB can be noninvasively monitored by magnetic resonance imaging (MRI). Conventional contrast agents containing gadolinium are used in association with MRI to detect and quantify BBB leakage. Preclinical in vivo studies have shown diffuse neuroinflammation and BBB impairment following CAR T-cell therapy, enabling a massive influx of proinflammatory cytokines into the CNS, which is thought to propagate neuroinflammation.[8] This is consistent with data reported in CAR T cell clinical trials, where disruption of the BBB and a significant increase in levels of proinflammatory cytokines and $CD14^+$ myeloid cells in the cerebrospinal fluid were seen in patients who developed severe NT, suggesting the potential for local CNS-specific production.[2,9]

Considering the high rates of NT, including severe cases, after CAR T-cell therapy, strategies to manage or prevent the onset of NT need to be evaluated in prospective clinical trials as proposed by Karschnia et al. One such strategy that has shown significant promise is GM-CSF neutralization, which for the first time has demonstrated that the toxicities associated with CAR T-cell therapy can be effectively prevented in vivo.[8] Preclinical in vivo studies have shown that neutralizing GM-CSF prevents CAR T cell–induced CRS and significantly reduces NT.[8,10] Quantification of MRI via gadolinium-enhanced T1 hyperintensity showed a 75% decrease in neuroinflammation and BBB impairment. Enhanced antitumor activity, improved overall survival, and improved durability of response with a reduced rate of relapse were also observed with GM-CSF neutralization in this xenograft model.[8] Prospective clinical trials evaluating GM-CSF neutralization in combination with CAR T-cell therapy are expected to be initiated this year. Other approaches to improve the safety of CAR T-cell therapy include the use of debulking chemotherapy, and high-dose corticosteroids; however, the extent of improvement in rates of NT and CRS and whether this comes at the expense of efficacy remain to be determined.

Conflict-of-interest disclosure: O.A. is employed by Humanigen. ■

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LYMPHOID NEOPLASIA

Comment on Lee et al, page 2222

HAP1 loss in L-asparaginase resistance

Maristella Maggi and Claudia Scotti | University of Pavia

In this issue of *Blood*, Lee et al identify huntingtin associated protein 1 (HAP1) loss as a new marker of L-asparaginase resistance in acute lymphoblastic leukemia (ALL) and provide evidence for the pathway involved. They discovered that HAP1 is essential for the formation of the ternary complex with huntingtin (Htt) and inositol 1,4,5-triphosphate receptor ($InsP_3R$) and that its loss impairs the L-asparaginase–mediated increase of cytosolic Ca^{2+} needed for triggering apoptosis (see figure). Their data were confirmed by specific knockdown of HAP1 in SEM cells and by measurement of both endoplasmic reticulum–released Ca^{2+} and external Ca^{2+} influx.[1]

ALL is a tumor of lymphoblasts and is characterized by great heterogeneity at the molecular level.[2] ALL mostly affects children (more than 50% of total cases) with an overall 5-year survival rate of 68%. The rate increases to 80% if only pediatric