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PREDICTING RISK FOR NEUROTOXICITY IN RESPONSE TO CAR-T CELL IMMUNOTHERAPY

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BACKGROUND: CD19 chimeric antigen receptor (CAR)-modified T cell therapy has produced impressive results in patients with CD19+ B cell malignancies. However, treatment with CAR-T cell therapy can be complicated by severe cytokine release syndrome (CRS) and severe neurotoxicity, ranging from delirium, incoherence, seizures, to cerebral edema and death. Corticosteroids and other drugs that are regularly administered for neurotoxicity & CRS reduce/negate the efficacy of CAR-T cell therapy.

INNOVATION SUMMARY: In partnership with the Fred Hutch Cancer Research Center and the University of Washington, Bloodworks has identified a clinically-relevant biomarker panel for use as a diagnostic tool of vascular dysregulation that is relevant to CAR-T cell therapy. This diagnostic test may effectively identify patients at the highest risk of developing severe cytokine release syndrome and/or neurotoxicity after CAR-T cell immunotherapy.

STUDY SUMMARY*: We reported a detailed clinical, radiologic, and pathologic characterization of neurotoxicity after CD19 CAR-T cells, and identify risk factors for neurotoxicity. We observed endothelial dysfunction and increased BBB permeability in neurotoxicity and found that patients with evidence of endothelial activation before lymphodepletion may be at increased risk of neurotoxicity.

In 133 adults treated with CD19 CAR-T cells, we found that acute lymphoblastic leukemia, high CD19 + cells in bone marrow, high CAR-T cell dose, cytokine release syndrome, and preexisting neurologic comorbidities were associated with increased risk of neurologic adverse events. Patients with severe neurotoxicity demonstrated evidence of endothelial activation, including disseminated intravascular coagulation, capillary leak, and increased blood–brain barrier (BBB) permeability. The permeable BBB failed to protect the cerebrospinal fluid from high concentrations of systemic cytokines, including IFN-alpha, which induced brain vascular pericyte stress and their secretion of endothelium-activating cytokines. Endothelial activation and multifocal vascular disruption were found in the brain of a patient with fatal neurotoxicity. Biomarkers of endothelial activation were higher before treatment in patients who subsequently developed grade ≥4 neurotoxicity.

We investigated strategies to reduce the risk of severe neurotoxicity during CAR-T cell immunotherapy. We demonstrated that reduction in CAR-T cell doses to reduce the peak in vivo CAR-T cell blood counts were associated with reduced risk of neurotoxicity, but that the narrow therapeutic index of this approach would lead to loss of anti-tumor efficacy. To maintain CAR-T cell peak counts in blood, we developed a strategy to identify patients early after CAR-T cell infusion who might be at risk of subsequent severe neurotoxicity and could be candidates for early intervention studies. Using classification tree modeling, we demonstrated that in the first 36 hours after CAR-T cell infusion, we could effectively identify patients at high risk of subsequent grade 4 or greater neurotoxicity (sensitivity 100%; specificity 94%). We also demonstrated that endothelial activation before lymphodepletion or CAR-T cell infusion may be a risk factor for neurotoxicity that identifies patients who would benefit from a modified treatment regime.

*Gust J et al. (2017). Endothelial activation and blood-brain barrier disruption in neurotoxicity after adoptive immunotherapy with CD19 CAR-T Cells. *Cancer Discov* 7(12):1404-1419.

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