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Response to: Correspondence on "Hyperleukocytosis in a neuroblastoma patient after treatment with natural killer T cells expressing a GD2-specific chimeric antigen receptor and IL-15" by Ataca Atilla and Atilla

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We would like to thank the authors of the letter for bringing attention to our case report describing a fatal hyperleukocytosis event in a patient with neuroblastoma treated with natural killer T cells (NKTs) expressing a GD2-specific chimeric antigen receptor and interleukin (IL)-15.[1] We appreciate their recognition that 'the report provides a valuable account…' and that our findings '…significantly contribute to the ongoing discourse on cell-based immunotherapy'. We also welcome the opportunity to address some critiques raised in the letter.[2]

First, the authors expressed concern about our root-cause analysis. The study PI and co-investigators, in consultation with the IND holders (Center for Cell and Gene Therapy, Baylor College of Medicine), developed a plan for root-cause analysis that was reviewed by the FDA and the External Data and Safety Monitoring Board of the Dan L. Duncan Comprehensive Cancer Center, who both provided helpful input.

The primary concern raised in the letter is that our patient was treated for cytokine release syndrome (CRS) with tocilizumab and anakinra rather than with infliximab, which the authors suggest should have been used based on their findings in a xenogeneic acute myeloid leukemia (AML) model. We respectfully disagree with their suggestion for the reasons listed below.

The Standard Operating Procedure we used followed recommendations from the American Society for Transplantation and Cellular Therapy (ASTCT) for consensus grading of CRS and neurologic toxicity associated with immune effector cells outlined by Lee *et al*.[3] To treat CRS and emerging neurotoxicity symptoms, we used tocilizumab and anakinra followed by corticosteroids and supportive care in accordance with clinical practice standards outlined in the most recent version of National Comprehensive Cancer Network (NCCN) guidelines available at that time.[4] Multiple cytokines including tumor necrosis factor (TNF)-α have been implicated in the pathogenesis of CRS. However, IL-6 is considered a central mediator of CRS,[3] and tocilizumab (a humanized IgG1κ anti-IL-6R antibody) was approved by the FDA in 2017 to treat severe or life-threatening CAR T cell-induced CRS in adults and pediatric patients.[4] The NCCN guidelines also discuss the use of anakinra (an IL-1Ra antagonist) and corticosteroids as important alternatives or adjuncts to tocilizumab in managing CRS. Despite acknowledging preclinical studies on the role of TNF-α in CRS, the guidelines do not mention infliximab or other TNF-α inhibitors as a treatment option.

A careful analysis of the data presented in Ataca Atilla *et al*[5] reveals no evidence supporting the use of infliximab to treat CRS or hyperleukocytosis in patients with neuroblastoma on our trial. The study reported rapid onset of lethal toxicity in a xenogeneic AML mouse model following treatment with IL-15-expressing C-type lectin like molecule-1-specific CAR T cells.[5] In contrast, preclinical studies evaluating IL-15-expressing GD2-specific CAR T cells[6] and CAR NKT cells[7] did not show evidence of significant toxicity in a xenogeneic neuroblastoma model, with no detectable levels of human cytokines, including TNF-α, in the serum of

treated mice. Differences in tumor type, target antigen, vector design, and other factors could explain the stark contrast in toxicity levels between AML and neuroblastoma models.

Moreover, in the Atilla paper, mice treated with CAR/IL-15 T cells and anti-TNF-α survived only marginally longer than those treated with CAR/IL-15 T cells alone, and the anti-TNF-α treatment had no effect on CAR T expansion. To further modulate toxicity and extend survival, the authors activated an inducible caspase-9 (iC9) safety switch as part of their IL-15-expressing construct. While we recognize the value of iC9 in controlling excessive expansion and related toxicity of CAR T cells, the GD2-CAR construct in our neuroblastoma trial does not contain iC9, making this approach inapplicable to our study. Nevertheless, we agree with the authors that the use of safety switches, including iC9, should be considered in the development of cytokine-armed CAR T or NKT products, as discussed in our case report.[1] Moreover, we further validated the clinical utility of iC9 in modulating CRS in a recently published clinical study evaluating GPC3-specific CAR T cells co-expressing IL-15 and iC9 in patients with GPC3+ solid cancers.[8]

We believe that this response addresses the concerns raised in the letter and contributes to the ongoing dialogue about approaches to control the toxicity of immune effector cell-based immunotherapies.

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