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The Bottom Line

# Can Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Predict Chimeric Antigen Receptor T Cell Adverse Effects?

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CD19 directed chimeric antigen receptor (CAR) T cells have shown remarkable successes in the treatment of relapsed/refractory B cell malignancies. In the initial clinical trials for B acute lymphoblastic leukemia (ALL), which saw outstanding complete remission rates, severe cytokine release syndrome (CRS) was observed in up to one third of patients [1-5]. Since that time, efforts have been made to define and grade CRS, as well as to establish treatment guidelines [3,6-9]. We note, however, that the majority of the published experience with CRS pertains to the B ALL patient population. Since the US Food and Drug Administration approval of commercial CAR T cells for the treatment of relapsed/refractory large cell lymphoma in 2017 to 2018, more clinicians need to recognize and manage CRS complications in this patient population. Risk factors for CRS in B cell non-Hodgkin lymphoma (NHL) are currently not well defined. In this issue of *Biology of Blood and Marrow Transplantation*, Jiasheng Wang et al. [10] retrospectively analyzed pretreatment positron emission tomography/computed tomography (PET/CT) characteristics of 19 patients with B cell NHL who were treated in a clinical trial with a CD19-directed second-generation CAR using 41BB as the costimulatory domain. They compared the metabolic tumor volume (MTV) and total lesion glycolysis between those patients who had cytokine release syndrome and those who did not. They found that patients who had higher grade CRS had a statistically significantly higher median MTV compared with those who did not experience CRS. The median MTV also differed significantly between those who received tocilizumab and those who did not. There were no statistically significant differences between CRS groups with respect to total lesion glycolysis. Within this study, the authors also demonstrate the utility of PET/CT in helping to recognize CAR T-related pseudoprogression and highlight the importance of recognizing pseudoprogression in the management of these patients. Given the growing use of CAR T in B cell NHLs, this article is timely in trying to understand if PET/CT measurement of tumor burden may predict severe CRS. Cytokine release syndrome has now become a well-recognized toxicity of T cell engaging immunotherapies, including CAR T cells. CRS results from elevated inflammatory cytokine levels produced by T cell engagement and proliferation [6]. Given the antigenic dependence of T cell proliferation, it is not surprising that the severity of CRS corresponds with T cell dose, T cell expansion, and initial disease burden [7,11]. As most previous publications on CRS pertain to patients with B-ALL, determination of pretreatment tumor burden by cross-sectional imaging has not been shown to correlate with occurrence of CRS. In this study, PET/CT was used to determine tumor burden in patients with B cell NHL, and the median MTV was found to be significantly higher in those patients who experienced CRS, indicating that a higher metabolically active tumor burden may have contributed to CRS. We note, however, that many patients who had severe CRS did not have a high pretreatment MTV, and these differences may be reflective of the heterogeneity of the patients included in this analysis. For example, T cell dose, bone marrow disease burden, thrombocytopenia, and choice of lymphodepleting regimen have all been shown to influence the propensity for CRS [12]. Although the patients included in this study received the same lymphodepleting regimen, they were otherwise heterogeneous. They received differing doses of T cells, had different types of B cell lymphoma, and were of varied clinical stages, indicating heterogeneity in the level of bone marrow involvement. Therefore, in clinical practice, it would be difficult to accurately predict the occurrence or severity of CRS in any patient receiving CAR T cells based on a single metric, such as the MTV. Finally, it is important to underscore that CAR T cells themselves are highly variable products, and their toxicities therefore are not as predictable as that for a traditional biochemical pharmaceutical. In this retrospective study, the patients were treated in the study with a CD19-directed second-generation CAR T cell. This study product is distinct from the commercially available CAR T products tisagenlecleucel and axicabtagene ciloleucel but shares the 41BB costimulatory domain of tisagenlecleucel. CD28-containing CAR T cells may elicit earlier cytokine responses compared with the 41BB-containing construct, most likely because of differential kinetics of expansion, with CD28 contributing to a more rapid T cell expansion [3]. Therefore, detailed analyses of predictors of toxicities may not be entirely generalizable to a different CAR T

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product. In the absence of a larger prospective study examining CRS occurrence in patients with B cell lymphoma using a specific CAR T product of interest, this study is a valuable contribution to the literature. The general findings are that increased metabolic disease burden likely heightens the risk of severe CRS in NHL treated with CAR T cells, and PET/CT is a useful tool in capturing cases of pseudoprogression, which is of significant importance in NHL owing to clinical consequences of mass effect. These findings contribute to our understanding of CAR T-related toxicities in the treatment of NHL and adds to the growing evidence of the relationship between disease burden and risk of CRS.

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