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The earlier the better: timely mitigation of CRS

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In this issue of *Blood*, Gardner et al demonstrate that early pharmacologic mitigation of cytokine release syndrome (CRS) can reduce the severity of this commonly encountered syndrome without diminishing responses to CD19 chimeric antigen receptor (CAR) T cells.[1]

As the use of CD19 CAR T cells has transitioned from early trials to commercial use, the number of patients experiencing CRS is now estimated at >2000 in total.[2-5] Practitioners and patients alike often refer to the syndrome as a "necessary evil," because its symptoms coincide with expansion/activation of CAR T cells as they come into contact with $CD19^+$ targets. Although it is the most commonly encountered adverse event following infusion of autologous CD19 CAR T cells preceded by lymphodepleting chemotherapy, strategies for curtailing CRS have remained largely reactive, rather than proactive.[2-8]

Early morbidity and mortality related to CRS led to substantial research, uncovering the key cytokines mediating this inflammatory storm and leading to widespread use of targeted cytokine therapy.[2-6] Although tocilizumab (IL6-R antagonist) is able to eradicate the majority of cases, corticosteroids are often required in refractory cases. Still, the question of whether to intervene early (before symptom escalation) with cytokine-directed therapy or corticosteroid remains largely unanswered, namely due to a lack of prospective well-controlled trials.[6,7]

Addressing this critical gap in knowledge, the authors provide evidence that early intervention (EI) with tocilizumab and corticosteroids in patients with mild CRS following treatment with SCRI-CAR19v1 CAR T cells did not adversely affect outcomes. The authors compare the first 23 patients treated in their dose escalation cohort and in whom CRS was graded using CTCAEv4 (hereafter the "dose-limiting toxicity [DLT] cohort") to an "early intervention cohort" of 20 patients, treated after completion of dose escalation.

The DLT cohort only received tocilizumab ± corticosteroids in the event of uncontrolled or persistent grade 4 toxicity or DLT. As expected, the CTCAEv4 criteria overestimated the number of patients with grade 4 CRS, resulting in 9 patients graded as grade 4 vs 0 using the more conventional Lee or UPENN criteria. The protocol was subsequently modified to incorporate earlier intervention based on contemporary symptom-based grading strategies and emerging evidence that intervention with tocilizumab and limited corticosteroids once CRS was underway did not appear to abrogate antitumor response or CAR T expansion/persistence.[4,8] Therefore, the EI cohort received tocilizumab and a defined dose of dexamethasone for persistent symptoms of mild CRS.

The most noteworthy differences in the EI strategy were that interventions were made on fever alone, with fever ≥39°C for >10 hours, prompting tocilizumab. Persistence after tocilizumab prompted dexamethasone. Furthermore, interventions with tocilizumab and dexamethasone using the EI strategy were based on individual symptoms/interventions, relying less on extent of support required to stabilize the patient and more on the presence (and duration) of the symptom.

The authors achieved their goal: As expected, EI resulted in nearly twice as many patients receiving tocilizumab/corticosteroids, but also appeared to reduce the frequency of transitioning from mild to severe CRS (sCRS). Not surprisingly, the predominant symptom that contributed to severity of CRS was hypotension requiring vasopressor support, which occurred in 9 of 10 cases of sCRS.

The data provided here challenge the previously accepted concept that steroids have deleterious effects on adoptively transferred T cells,[9] while underscoring the notion that not all CARs are created equal. Most importantly, EI with tocilizumab/corticosteroids did not affect the rate of minimal residual disease–negative remissions nor did it appear to adversely affect expansion/persistence of functional CAR T cells. Last, EI did not increase the rate of neurotoxic events nor infectious sequelae.

Several important questions remain, perhaps most obviously, to what extent these findings translate to different CAR constructs? Do the results apply to other investigational/commercial CD19 CARs or those directed at other antigens? The differences in onset in various investigational and commercialized CD19 CAR products signal that the kinetics of CRS (onset, duration, and severity) differ based on intrinsic CAR features.[2-5] The construct used in this protocol contains a defined 1:1 ratio of CD4:CD8 T cells transduced with a second-generation (4-1BB) CAR and incorporates additional culture modifications to retard terminal differentiation in an effort to prevent T-cell exhaustion. Although the distinct mechanism of how CAR structure and manufacture impact onset and severity of CRS is yet to be determined, these features almost certainly play a role.

The average onset of CRS in this study was 8 days, vs 1 to 3 days, with recently

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commercialized CD19 CAR T-cell products. Thus, the definition of "early" intervention differs based on study, as it relates to intervention after the start of CRS symptoms. For example, although intervention occurred earlier than in the DLT cohort, the timing of intervention in relation to CAR T-cell infusion was not dissimilar to published reports of CD19 CAR T cells.[2-5] Interestingly, there was no significant difference between the timing of intervention with tocilizumab or corticosteroid in the DLT and EI cohorts, although it is certainly worth pointing out that patients who were treated in the EI cohort received corticosteroid courses that were, on average, 5 days shorter than those in the DLT cohort. This indicates that earlier intervention with steroids in patients with persistent mild CRS symptoms, although increasing exposure to steroids, may limit the overall duration of steroid course, especially in those whose symptoms persist despite tocilizumab.

Furthermore, this is one of the only published CD19 CAR T-cell studies that found no correlation between sCRS and disease/CD19 antigen burden (with CAR T-cell dose emerging as the only predictor of CRS). However, because CRS was graded using different scales in the DLT and EI cohort, it raises the question of whether the reduction in sCRS can be attributed solely to EI, or if the inadequacy of CTCAEv4 in delineating mild vs sCRS was also a factor.[7] It is also important to point out that the incidence of neurotoxicity was similar between the groups, which is not surprising, but underscores the premise that neither tocilizumab nor steroids prevent neurotoxicity.

The promising results reported here represent a major step forward for the field, and future controlled studies should address whether corticosteroid can be used as prophylaxis prior to onset of CRS, as has been shown with tocilizumab.[10]

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LYMPHOID NEOPLASIA

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Subclassifying peripheral T-cell lymphoma NOS

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In this issue of *Blood*, Amador et al identified 2 distinct subtypes of peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS) using gene expression profiling (GEP) and an immunohistochemistry (IHC) algorithm. The authors also showed that these lymphomas display distinct prognostic and morphologic features (see figure).[1]

Previous GEP studies have defined 2 major molecular subtypes within the group of PTCL-NOS diseases.[2,3] One subtype was identified by the expression of GATA3 and its target genes and was designated as the PTCL-GATA3 subtype; the other was identified by the expression of T-box 21 (TBX21) and its target genes and was designated as the PTCL-TBX21 subtype.[2,3] GATA3 is the transcriptional regulator in T_H2 cell differentiation, whereas TBX21 is the regulator in T_H1 and cytotoxic T-cell differentiation. Therefore, it has been hypothesized that PTCL-GATA3 and PTCL-TBX21 could originate from T_H2 or T_H1, respectively. Very recently, genetic studies have highlighted the role of distinct genetic pathways and enrichment of oncogenic pathways in the development of these lymphomas[4] (see figure).

Starting from these GEP results, Amador et al have successfully generated an IHC algorithm with proven interobserver reproducibility and easy applicability to clinical practice for PTCL-NOS subclassification. Once the PTCL-NOS diagnosis has been made, 4 additional stains using commercially available antibodies for GATA3, CCR4, TBX21, and CXCR3 on formalin-fixed-paraffin-embedded tissue sections were recommended to recognize the 2 molecular subtypes. The PTCL-GATA3 and the PTCL-TBX21 subtypes identified by the IHC algorithm strongly matched those identified by the GEP results. Therefore, the IHC algorithm was suitable as a valid surrogate for GEP to subclassify PTCL-NOS. The study also showed that the PTCL-GATA3 and the PTCL-TBX21 subtypes exhibited distinct morphologic patterns and distinct tumor microenvironment (TME) compositions. However, the morphologic pattern was not integrated within the IHC algorithm. Furthermore, according to the conclusions of the study, the IHC algorithm

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