



Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org



Letters-to-the-Editor

Comments Regarding “ASBMT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells”

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Article history:

Received 25 February 2019

Accepted 28 February 2019

To the Editor:

We read with interest the article by Lee et al. [1] presenting the updated consensus grading for the management of cytokine release syndrome (CRS) and neurologic toxicity associated with immune effector cells. We applaud experts for gathering to develop consensus grading and welcome unanimity in this new and emerging field given the plethora of published CRS grading systems that emerged with the approval of both tisagenlecleucel and axicabtagene ciloleucel. Authors have noted the importance of streamlining and simplifying toxicity grading to ease implementation across a wide variety of centers [2-5]. New definitions and grading for CRS were reported, namely the elimination of constitutional symptoms (organ toxicity) from grading of CRS.

Although the consensus goal was to streamline and simplify the grading system, we believe special attention should be brought to hypotension and vasopressor requirements with grades 3 and 4 CRS. Earlier grading, although more specific, was complicated by the need to calculate vasopressor equivalents, something that brought some difficulty when assessing patients at the bedside [1,3]. Lee et al. have defined grade 3 hypotension as “requiring a vasopressor with or without vasopressin,” which eases bedside evaluation and grading. However, we believe there are limitations of not making a differentiation between a patient on a low-dose vasopressor and a patient on maximum doses of 2 vasopressors (both grade 3). Critical care data in patients with septic shock suggest that patients requiring a second vasopressor have increased mortality [6-8]. Subgroup analysis has shown a reduction in

mortality when vasopressin is applied to patients on norepinephrine to reduce its dosing to less than 15 $\mu\text{g}/\text{min}$ [8]. This suggests that a “high versus low” dose of norepinephrine can have an effect on mortality, and the severity of shock and dose of vasopressor may directly correlate to severity of illness. Although these data are obtained from patients with septic shock, hypotension secondary to CRS is also a vasodilatory response to inflammation, and such interventions could be extrapolated. With this in mind, however, future studies evaluating the effectiveness of interventions used in the general critically ill population and their effects on the immune effector cells population are necessary.

We recognize the authors' earlier statement noting that “patients who are easily managed with minimal vasopressors are decidedly distinct in terms of CRS severity from those who require high-dose or multiple vasopressors, a key difference accounted for by the grading criteria”; however, concerns could arise that such an observation is not delineated in the grading criteria. Therefore, future efforts in treatment guidelines will hopefully focus on different approaches in treatment on patients on low- versus high-dose vasopressors. Future treatment guidelines should consider increasing corticosteroid dosing on patients with increasing doses of norepinephrine (or first vasopressor of choice at each institution) in an effort to avoid delayed interventions when patients are on high doses of two vasopressors (grade 3) or more than 2 vasopressors (grade 4). Moreover, clinical considerations such as signs of hypoperfusion, organ failure, and increasing lactate levels should also be considered when assessing patient's response to ongoing treatment.

In conclusion, the consensus grading is necessary and has simplified significantly the evaluation of these patients at bedside. We do, however, caution the oversimplification of CRS assessment in patients with shock. The omission of vasopressor dose in the grading may lead to under-recognized worsening clinical response. Prompt treatment with global suppression of inflammatory response is imperative in these patients to prevent untimely death, particularly when CRS is usually reversible when treated aggressively and early. Hopefully future treatment guidelines will take this into consideration when managing patients with CRS.

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<https://doi.org/10.1016/j.bbmt.2019.02.027>

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