Biol Blood Marrow Transplant 25 (2019) e121–e122

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Editorial

Harmonizing Immune Effector Toxicity Reporting

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Article history:
Received 2 January 2019
Accepted 2 January 2019

Keywords:
Immune effector cells
Toxicity
Guidelines

A B S T R A C T

In this issue of *BBMT*, a multicenter group of investigators convened by the American Society of Blood and Marrow Transplantation outlines new consensus definitions and grading systems for the most common toxicities associated with immune effector cell therapies, including cytokine release syndrome and the newly named immune cell-associated neurotoxicity syndrome.

In this issue of *BBMT*, a multicenter group of investigators convened by the American Society of Blood and Marrow Transplantation (ASBMT) outlines new consensus definitions and grading systems for the most common toxicities associated with immune effector cell (IEC) therapies: cytokine release syndrome (CRS) and the newly named immune cell-associated neurotoxicity syndrome (ICANS) [1].

IEC therapies are an area of intense investigation, and more than 100 trials are currently evaluating chimeric antigen receptor (CAR) T cell therapies. Two CD19 CAR T cell products have already been approved by the US Food and Drug Administration (FDA), and many more strategies are under early- and late-phase investigation [2]. However, although the clinical responses of these agents in hematologic malignancies have been very encouraging, they have also produced significant morbidity and occasionally mortality due to toxicity. The FDA has therefore required a Risk Evaluation and Mitigation Strategy program for the 2 approved products, and the Foundation for Accreditation of Cell Therapy has published standards for the clinical and quality infrastructure needed for safe administration of IEC therapy, as well as monitoring and reporting of patient outcomes [3]. One limitation in such monitoring has been the lack of a consistent grading system for the specific toxicities observed with these therapies.

In the initial studies of CD19 CAR T cells, it became apparent that patients could develop profound immune activation, resulting in CRS and neurotoxicity [4,5]. With greater experience, the toxicity profile became better defined, and it did not mesh well with the Common Terminology Criteria for Adverse Events scale that the National Cancer Institute developed to define toxicity. Thus, several groups developed alternate grading systems to both grade toxicity and guide intervention. The multicenter criteria developed by Lee et al [6] are perhaps the most widely used, but additional criteria have been reported by the Penn, MSKCC, and CARTOX groups [4,5,7]. The major differences were in the scoring of grade 2-3 toxicities, making comparisons between different IEC therapy products and trials challenging. Moreover, with the FDA requirements for long-term follow up data on the commercial products there was a major need for harmonization of definitions and grading systems for both CRS and neurotoxicity that could be broadly applied to all IEC products, given that CRS has also been reported with T cell products that are not genetically engineered [8].

To this end, ASBMT convened a group of experts that included the authors of the existing guidelines with the goal of clarifying the definition of CRS and neurotoxicity and harmonizing the grading criteria. After obtaining input from multiple stakeholders, this group has now published the final ASBMT consensus guidelines [1]. They define CRS as "a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells." Of note, this is a simple grading system in which fever is a prerequisite for diagnosis and hypotension and hypoxia are the principle determinants of the consensus grading scale. The major change from the Lee criteria is that any requirement for vasopressor support now moves the grade to 3, as opposed to the previous definition, in which low-dose versus high-dose vasopressor use was split between grade 2 and grade 3. Similarly, the oxygen requirements for grading have been simplified. Low-flow oxygen requirement is now grade 2, high-flow oxygen requirement is grade 3, and positive-pressure, including intubation, requirement is grade 4. These logical changes have markedly simplified the CRS grading process.

Financial disclosure: See Acknowledgments on page e122.

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https://doi.org/10.1016/j.bbmt.2019.01.001
1083-8791/

Neurotoxicity was initially considered part of the CRS syndrome, but it became clear that it has a distinct pathogenesis [9,10] and does not respond to treatments, such as tocilizumab, that have proven effective for CRS. The CARTOX group proposed the term "CAR-related encephalopathy syndrome" to describe the syndrome in their report on neurotoxicity grading [7]. The ASBMT guidelines propose renaming this syndrome ICANS to include other symptoms beyond encephalopathy and in recognition that other immune effectors may cause neurotoxicity as well. They define ICANS as "a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other IECs. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, and impairment of cognitive skills, motor weakness, seizures, and cerebral edema." They reiterate the experience of the CARTOX and MSKCC groups [7,10] that expressive aphasia is a very specific and early symptom and propose a simple 10-point examination tool, termed the Immune Cell Encephalopathy (ICE) score, to grade neurologic manifestations seen after IEC administration. For children age <2 years, they recommend using the Cornell Assessment of Pediatric Delirium.

We applaud the authors for developing a much simpler grading system than its predecessors that takes advantage of increasing knowledge about the pathogenesis of both CRS and ICANs and it should be broadly applicable, although it will need to be validated. In addition, this grading system should facilitate reporting to the Center for International Blood and Marrow Transplant Research Registry to serve as the required follow-up for the REMS programs and will allow centers to evaluate the toxicity profile of IEC products in a consistent manner to meet the audit requirements of the Foundation for the Accreditation of Cellular Therapy's IEC standards. Although the ASBMT guidelines are focused on grading and do not recommend management, strategies, the availability of a consensus grading system will also likely facilitate the refinement of optimal strategies for prevention and/or management of these toxicities. There will also be substantial benefits if CRS and ICANS associated with IEC therapies across all clinical trials as well as in the postapproval standard of care setting are reported with the same grading system.

ACKNOWLEDGMENTS

Financial disclosure:

Conflict of interest statement: H.E.H. is a cofounder with equity in Marker Therapeutics and ViraCyte, has received research support from Cell Medica and Tessa Therapeutics, and has served on advisory boards for Novartis, Gilead Biosciences, and Cytosen. E.J.S. has received research support from Mesoblast and Celgene and has served on advisory boards for Novartis, Magenta, and Adaptimmune.

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