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Editorial

2014 National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: Preface to the Series

Steven Z. Pavletic [1,*], Georgia B. Vogelsang [2], Stephanie J. Lee [3]

[1] National Cancer Institute, Bethesda, Maryland
[2] Johns Hopkins School of Medicine, Baltimore, Maryland
[3] Fred Hutchinson Cancer Research Center, Seattle, Washington

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The majority of us entered the field of allogeneic hematopoietic cell transplantation (HCT) to cure hematologic cancers—by means of immunotherapy. Although this goal has come closer and, with the expansion of transplantation to more high-risk patients, it often seems a miraculous success, chronic graft-versus-host disease (GVHD) has increasingly become the major barrier preventing patients from resuming their normal lives. Unfavorable trends in incidence and severity of chronic GVHD have been observed overall, despite better supportive care and advances in transplantation practice [1]. In 2004, the National Institutes of Health (NIH) summoned stakeholders in the field and initiated the Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD. The primary impetus for this effort was to establish common terminology and best practices for clinical trials and biomarker studies to advance the chronic GVHD field and development of new therapies. The first consensus conference took place in Bethesda in June 2005. This project produced 6 original publications, which were published in the *Biology of Blood and Marrow Transplantation,* cited in peer-reviewed literature more than 1650 times since, and generated more than 35,000 visits to the journal's web site [2-7]. One half of those citations referred to the article on diagnosis and staging by Filipovich et al. [2] that defined the new conceptual understanding of chronic GVHD as a clinical rather than calendar-driven diagnosis and provided the new scoring system based on number of organs involved, severity, and functional disability.

The following decade passed quickly. What did we accomplish as a community since 2005, and did the NIH chronic GVHD criteria affect clinical research and generate research momentum? Are we any closer today to the goal of eliminating chronic GVHD-related suffering in patients cured by allogeneic HCT? The reality is that we still have no US Food and Drug Administration–approved agent with an indication for chronic GVHD treatment or prevention. Today, the standard initial treatment with steroids is profoundly frustrating because of the 50% failure rate of front-line steroid therapy and the significant toxicity of steroids. Second-line therapy, and beyond, is still a laundry list of possible options without biological or clinical indicators to tailor therapy. Preventive and preemptive strategies to decrease incidence and severity of chronic GVHD are in their infancy. And our understanding of the basic immunobiology that drives this autoimmune transplantation-related complication is profoundly incomplete.

So what has changed? First of all, the field is much better organized. We are speaking the same and more understandable language, which fosters new clinical, translational, and basic collaborations. The newly formed NIH-funded US chronic GVHD consortium, the German-Austrian-Swiss GVHD consortium, and several single centers produced the first prospective cohort studies enrolling more than 2000 patients using the new consensus criteria. These studies provided evidence of the validity of the Consensus-recommended diagnostic and scoring system and measures for patient-reported outcomes. Some studies collected clinical samples for immunobiologic studies. There is also substantial national and international support for use of the Consensus criteria in routine clinical practice [8]. The time has come to reconvene, assess the accomplishments and shortcomings, and use the data generated over the last decade, instead of expert opinion, to refine the recommendations [9].

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* Correspondence and reprint requests: Steven Z. Pavletic, MD, National Cancer Institute, 9000 Rockville Pike, 10/CRC-3-3330, Bethesda, MD 20892-1203.
E-mail address: pavletis@mail.nih.gov (S.Z. Pavletic).

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In the summer of 2013, the second Chronic GVHD Consensus conference was approved, thanks to major funding support provided by the National Cancer Institute, Center for Cancer Research, and the Office of Rare Diseases Research, National Center for Advancing Translational Sciences. The original 6 working groups reconvened with a major influx of new and junior investigators representing all facets of the national and international HCT community, including academia, government, regulatory agencies, industry, professional societies, and advocacy groups. This time, a separate task force was also formed specifically to address the new directions in studying and hopefully decoding chronic GVHD biology. Through the assistance of the Meredith Cowden GVHD Foundation, the first in-person planning meeting was held in November 2013 in Cleveland, Ohio in conjunction with the Fourth National GVHD Symposium. Frequent conference calls of all working groups ensued, and documents were prepared for the 2014 conference, held on June 17 at the new National Cancer Institute facility at Shady Grove, Gaithersburg, Maryland. The conference was attended by 250 participants. All 6 working group drafts were available on the web site for public comments until August 15, 2014. Such productive collaboration was the result of dedicated effort by the chairs and all working group participants. The organizers also wish to thank all participants as well as the funding agencies for their support and dedication to this project.

The first of the 6 2014 working group reports, the diagnosis and staging recommendations, is appearing in this issue of the *Biology of Blood and Marrow Transplantation* [10]. Five others will follow in monthly succession, providing updates in the areas of histopathology, biomarkers, response criteria, ancillary and supportive care, and design of clinical trials. All group documents have been revised and clarifications provided based on the accumulated interim data and questions that emerged through use of the 2005 guidelines [9]. The diagnosis and staging framework has been maintained, though organ scoring scales have been refined. The histopathology document provides important interim updates and expanded discussion on entities such as lung and kidney manifestations. The biomarkers manuscript has been revised, and, although there is still no proven biomarker for clinical use in chronic GVHD, a number of candidates exist. The manuscript is updated with the new Food and Drug Administration nomenclature and provides guidance for biomarkers clinical development. The response criteria manuscript provides a simplified and more practical framework for use in trials based on the studies examining the feasibility, reliability, and validity of the original 2005 criteria. The ancillary and supportive care document is substantially updated. Finally, although the clinical trials document leaves much of the original 2005 paper intact, it expands the definitions of eligibility, selection of endpoints, definition of clinical benefit, and charts potential developmental paths for regulatory agencies' approval as a critical step in new drug development.

In summary, we are convinced that the field of chronic GVHD is now poised to capitalize on the advances made over last 10 years. The momentum generated by the first consensus meeting has resulted in unprecedented progress in chronic GVHD. We believe that the second NIH consensus effort will be remembered as an important endeavor that was the turning point in our understanding and ability to control chronic GVHD, this final major impediment to full recovery from allogeneic transplantation. Credit goes to many, but our patients reap the benefits.

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