MEETING SUMMARY

Chronic Graft-versus-Host Disease—Implementation of the National Institutes of Health Consensus Criteria for Clinical Trials

Based on collaborative discussions of the community of hematopoietic cell transplant (HCT) physicians, the National Institutes of Health (NIH) Consensus Criteria for Clinical Trials in Chronic Graft-versus-Host Disease (GVHD) established for the first time comprehensive diagnostic, staging, and response criteria for chronic GVHD (cGVHD). The recommendations from this group were published in a series of articles in this journal [1-6]. Implementation of the criteria and follow-up research are needed to ensure continued progress. Therefore, representatives of the national and international cGVHD community met in Bethesda, MD, on March 8 and 9, 2007, to report on continuing studies, identify unmet needs, and consider future options. Here, we summarize findings of the 2-day meeting and the present spectrum of activities in the field of cGVHD.

DIAGNOSIS, STAGING, AND RESPONSE CRITERIA

There is considerable need to evaluate the diagnosis, staging, and response criteria prospectively in clinical trials and retrospectively using existing databases. It is highly likely that refinements will be needed, because such criteria should always be considered a “work in progress,” as clinical practice and treatments evolve over time. Challenges to completion of validation studies include the large number of patients from multiple centers required for an adequate statistical evaluation, the protracted time frame needed for adequate observation, and funding needed to support the effort. Jagasia et al. [7] and Arora et al. [8] have recently completed the first single-site retrospective validation studies of the diagnosis and staging criteria. These studies showed a correlation of GVHD subtype (late acute versus classic chronic) and severity with overall survival (OS). At the workshop, Jacobsohn et al [9] presented a comparison of the Johns Hopkins Hospital skin response criteria as used in the recently published pentostatin trial with the NIH consensus response criteria. Their data showed that the 2 scales had similar and complementary, although not identical, properties. Mitchell et al. [10] have performed a small assessment of feasibility and reproducibility of the NIH response criteria in a prospective study conducted at multiple sites in the United States. A large prospective cohort investigation has recently received NIH funding and is led by S. Lee of the Fred Hutchinson Cancer Research Center (FHCRC). A validation project is currently underway led by D. Wolff and the German/European Union (EU) collaborative group [11].

ORGAN-SPECIFIC RESEARCH AND ANCILLARY AND SUPPORTIVE CARE

Because the multiple-organ clinical manifestations of cGVHD can persist for prolonged periods of time, supportive care is critical in long-term management. Because there is a profound lack of data in these areas, most of the NIH consensus recommendations are based on extrapolation of clinical results from other fields of medicine. To conduct trials in this area it will be essential to develop organ-specific severity scales, which will require long-term data. Research addressing organ dysfunction includes skin, pulmonary, and oral mucosal complications and conjunctival therapeutic intervention studies. The bronchiolitis obliterans syndrome (BOS) is a rare, but devastating, complication in need of improved diagnostic criteria and therapy [12]. Studies of oral mucosa suggest that immunologic features of cGVHD might be quantified by immunohistochemistry. This type of research represents an opportunity to study the immunologic processes of cGVHD directly at the anatomic site of the disease [13].

BIOLOGY, BIOMARKERS, AND NEW TARGETS

Chronic GVHD is remarkable for lack of insight into the basic biology of the disease. Because of this, there are no validated biomarkers. Targeted drug therapy has been impaired by this absence of specific immunologic targets. Preclinical mouse models that approximate the full spectrum of human cGVHD are lacking, although there are several useful models that demonstrate selected aspects of the disease process (reviewed by Shlomchik et al. [14] and Chu and Gress [15]). The long duration of follow-up required to assess murine cGVHD has inhibited both the development and utilization of these models. Prior studies using patient samples have focused mainly on
peripheral blood, which likely misses mechanisms that function within tissues affected by cGVHD. Studies to characterize new biomarkers and confirm or refute those suggested by smaller studies in cGVHD will require large numbers of samples linked to detailed information on the clinical course. Small studies have suggested a role for diverse immunologic cells/soluble factors including T cells and T cell subsets, thymic-dependent and -independent pathways of T cell recovery, B cells, and B cell subsets, and B cell activating factor (BAFF) [16-19]. For example, 4 inflammatory ery, B cells, and B cell subsets, and B cell activating independent and -independent pathways of T cell recovery. Biologic markers that could be used as short-term predictors of therapeutic benefit would be especially helpful for early drug development trials in cGVHD. Results from recent relatively small phase II studies suggestive of benefit from extracorporeal photopheresis (ECP) and Rituximab (humanized anti-CD20) for the treatment of cGVHD were presented [28,29]. Multi-center studies of mycophenolate mofetil (MMF) and its enteric coated formulation as an adjunct to standard front line cGVHD therapy are currently underway in the United States led by P. Martin at FHICRC (see also #NCT00089141 at www.ClinicalTrials.gov) and in Europe led by G. Socie (#NCT00298324 at www.ClinicalTrials.gov), respectively.

RESOURCES—TRANSPLANT NETWORKS AND CLINICAL TRIALS CONSORTIA

The total number of patients with cGVHD is small, so that cGVHD qualifies as a “rare disease,” even though as many as half of all patients undergoing allogeneic HSCT experience this complication. Cooperative clinical studies in cGVHD will be needed to accomplish progress in the field. There is a corresponding need to identify the type of infrastructure that will best facilitate such multicenter projects. Both national and international clinical collaborations should be strongly encouraged. In the United States, 1 or more existing networks, for example, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), may be well positioned to provide the type of infrastructure needed. In the recent “BMT CTN State of the Science Symposium” [30], cGVHD was identified as an area of immediate need for both intensive studies of disease mechanisms as well as therapeutic clinical trials. A proposal for a prospective multicenter clinical trial in cGVHD that would be coupled with immunologic ancillary studies is currently in development by the consortium. The Pediatric Blood and Marrow Transplant Consortium (PBMTC), which is a member of the BMT CTN, is an important resource for study of aspects of cGVHD. The database of the Center for International Blood and Marrow Transplant Research (CIBMTR), which contains information on over 240,000 HCT procedures performed worldwide, serves as a unique and perhaps insufficiently utilized resource available for retrospective analyses in HCT including cGVHD. Practical aspects of International collaborations were discussed at the workshop by representatives of the European Group for Blood and Marrow Transplantation (EBMT), the BMT CTN, and the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP).

RESOURCES—INVESTIGATOR INITIATED RESEARCH

Availability of funding support for studies in cGVHD has been extremely limited. The standard NIH Research Project (R01) format may not be...
a good fit for applications in cGVHD that need a multicenter or interdisciplinary clinical trials design. For cGVHD in particular, the relatively small number of cases, with lack of clear assignment of responsibility to a single NIH Institute/Center (IC) presents an additional challenge in applying for and successfully obtaining NIH funding. However, even in this era of relative fiscal constraint for the NIH, using the National Institute of Allergy and Infectious Diseases (NIAID) as an example, over half of the annual budget of the Division of Allergy, Immunology and Transplantation (DAIT) remains available for investigator-initiated research, representing a significant opportunity [31]. It may be reasonable to consider cooperation of NIH ICs having a direct or partial interest in cGVHD studies, or support through existing networks or other consortia, when developing a funding plan for large cooperative clinical trials. A Program Project (P01) approach may be appropriate. Interactive discussions with U.S. Government funding agencies should be pursued, to promote intramural and extramural NIH and government-wide collaborations where feasible. Investigators should approach NIH ICs with their proposals for joint ventures. It is likely that the NIH would view collaborative efforts that result in elimination of redundant funding or cost saving as advantageous. Opportunities for funding other than NIH should be considered, including other U.S. Government agencies, such as, for example, the Food and Drug Administration (FDA) Office of Orphan Products Development, as well as private foundations such as the Biomarkers Consortium of the Foundation for the NIH, and others.

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REFERENCES

17. She K, Gilman AL, Aslanian S, et al. Altered Toll-like receptor 9 responses in circulating B cells at the onset of extensive chronic


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