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

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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. 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 chronic GVHD 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 two day meeting and the present spectrum of activities in the field of chronic GVHD.

I. 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, since 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

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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. At the workshop, Jacobsohn and Vogelsang presented a comparison of the Johns Hopkins Hospital skin response criteria as used in the recently published pentostatin trial[9] with the NIH consensus response criteria. Their data showed that the two 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 (US). A large prospective cohort investigation has recently received NIH funding and is led by S. Lee of 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].

II. Organ-specific research and ancillary and supportive care

Because the multiple-organ clinical manifestations of chronic GVHD can persist for prolonged periods of time, supportive care is critical in long-term management. Since 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 chronic GVHD might be quantified by immunohistochemistry. This type of research represents an opportunity to study the immunologic processes of chronic GVHD directly at the anatomic site of the disease[13].

III. 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 chronic GVHD are lacking, although there are several useful models that demonstrate selected aspects of the disease process (reviewed by Shlomchik et al[14]; Chu and Gress[15]). The long duration of follow-up required to assess murine chronic GVHD 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 chronic GVHD. Studies to characterize new biomarkers and confirm or refute those suggested by smaller studies in chronic GVHD 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, four inflammatory plasma markers and an activated B cell population identified as potential biomarkers in chronic GVHD in a study performed by the Children's Oncology Group (COG) will require validation in a larger population that includes adults[16,17]. Larger cooperative studies, in particular those conducted by the EU, have included examination of gene polymorphisms in chronic GVHD[20, 21], and proteomics studies[22].

IV. Graft-versus-leukemia (GVL) effects

Growing clinical evidence suggests a major contribution of chronic GVHD in mediating allogeneic GVL effects. Research in this important area is lacking and efforts to investigate the pathophysiologic basis of the GVL effect as compared to the GVHD effect should be

pursued. Representative presentations at the workshop addressed preclinical models and their limitations, T cell and B cell aspects of the GVL effect, and the role of hematopoietic chimerism. The possibility of a humoral component in the GVL effect, in addition to the documented T cell contribution, was discussed[23-27]. The relation of chronic GVHD biomarkers to the GVL effect will be investigated in the COG study of GVHD prophylaxis for children receiving allogeneic HCT for acute lymphoblastic leukemia (see also #NCT00382109 at www.ClinicalTrials.gov).

V. Therapeutic clinical trials

Regarding design of clinical trials in chronic GVHD in general, the selection of short term endpoints was emphasized as key, including consideration of composite endpoints. Challenges to endpoint design include lack of validated short-term predictors (less than 6 months) of the more long-term outcomes (years) of the natural history of chronic GVHD, as well as the obvious need for validation studies of response criteria in chronic GVHD. The trajectory of disease progression should be given more attention when patients are enrolled in a clinical trial. For example, stabilization of disease manifestations could be considered a benefit in a patient with rapidly progressive chronic GVHD manifestations but not in those with improving or stable manifestations before an intervention. Biological markers that could be used as short term predictors of therapeutic benefit would be especially helpful for early drug development trials in chronic GVHD. Results from recent relatively small phase II studies suggestive of benefit from extracorporeal photopheresis (ECP) and Rituximab (humanized anti-CD20) for the treatment chronic GVHD were presented[28,29]. Multi-center studies of mycophenolate mofetil (MMF) and its enteric coated formulation as an adjunct to standard front line chronic GVHD therapy are currently underway in the US led by P. Martin at FHCRC (see also #NCT00089141 at www.ClinicalTrials.gov) and in Europe led by G. Socie (#NCT00298324 at www.ClinicalTrials.gov) respectively.

VI. Resources - transplant networks and clinical trials consortia

The total number of patients with chronic GVHD is small, so that chronic GVHD qualifies as a “rare disease”, even though as many as half of all patients undergoing allogeneic HSCT experience this complication. Cooperative clinical studies in chronic GVHD 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 multi-center projects. Both national and international clinical collaborations should be strongly encouraged. In the US, one 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], chronic GVHD 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 multi-center clinical trial in chronic GVHD 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 chronic GVHD. 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 chronic GVHD. 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).

VII. Resources – investigator initiated research

Availability of funding support for studies in chronic GVHD has been extremely limited. The standard NIH Research Project (R01) format may not be a good fit for applications in chronic GVHD which need a multi-center or inter-disciplinary clinical trials design. For chronic GVHD 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 chronic GVHD 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 US 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's likely that the NIH would view collaborative efforts which result in elimination of redundant funding or cost saving as advantageous. Opportunities for funding other than NIH should be considered, including other US 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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