

## Progress Report for the GVHD Clinical Trial Endpoints Workshop

The Open Public Workshop on Clinical Trial Endpoints for Acute Graft-vs-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation was held May 19, 2009 in Rockville, MD. The overall objective of the workshop was to provide a venue for an in-depth discussion of potential endpoints for trials intended to support the approval of new drugs or biologics to prevent or treat AGVHD. This was to be accomplished by obtaining expert insight, reviewing actual data and data analyses, and identify challenges associated with the potential endpoints in order to provide significant input to FDA as well as the investigators to facilitate clinical development programs for products for AGVHD indications.

The first morning session was on GVHD prevention trials. Dr. Farrell from the FDA reviewed the regulatory requirement for drug approval and outlined the issues specific to acute GVHD prevention that confounded study conduct and analysis. These issues were addressed by the speakers who followed. Dr. Martin discussed the diagnostic principles, highlighting the newly established criteria for engraftment syndrome in cord blood transplant recipients. He also described the grading systems for acute GVHD and reviewed the data showing reproducibility and utility for prognostic purposes. Dr. Horowitz reviewed the sources of heterogeneity that confounded analyses and provided quantitative estimates on how these altered study outcomes, identifying which endpoints best described a clinical benefit and how analyses must be adjusted.

The second morning session was on statistical considerations. The first scheduled speaker developed a medical emergency the weekend before the workshop and was quickly replaced by Dr. Eric Leifer from NHLBI. Dr. Leifer reviewed some innovative statistical methods that could be applied for Phase I trials of GVHD therapeutic even in the face of the confounding factors noted by Dr. Horowitz. This was followed by a discussion from Dr. Logan on methods for analysis in the face of competing risks in pivotal Phase III trials.

The majority of the afternoon session was devoted to GVHD treatment trials. Dr. Przepiorka from the FDA reviewed the issues specific to acute GVHD treatment that confounded study conduct and analysis, especially the lack of any validated endpoint associated with a clinical benefit. This was followed by presentations from Drs. Alousi, Weisdorf and Carpenter which in analyses of three independent data sets demonstrated that achievement of complete or partial response by assessment on treatment day 28 or 56 was predictive of nonrelapse mortality and survival.

Two additional speakers addressed potential surrogates. Dr. Hansen talked about use of biomarkers to improve the accuracy of diagnosis, prognosis, monitoring therapy and assessing response. Several candidates, including a biomarker panel, are ready for clinical validation. Dr. Lee reviewed the methodological challenges of patient reported outcomes and other measures of quality of life as clinical trial endpoints, and described the on-going and recently completed studies validating the tools that can be used for GVHD trials.

Dr. Pavletic closed the workshop with a summary of the findings which showed that the stated objectives were met. Speaker presentations remained posted on the internet at [http://www.cibmtr.org/MEETINGS/Meeting\\_Materials\\_Archive/index.html](http://www.cibmtr.org/MEETINGS/Meeting_Materials_Archive/index.html). The current status of completed publications is provided below. Two additional papers on treatment trial endpoints and one on statistical methods are pending.

Publications of information presented at the workshop:

Alousi AM, Rondon G, Okoroji GJ, Popat U, De Padua Silva L, Hymes S, Neumann J, Brunelle NM, Kebriaei P, Hosing C, Khouri IF, Shpall EJ, Qazilbash MH, Giralt S, Champlin RE and Saliba RM.. Co-morbidity Score at the Time of Transplant Determines Prognosis in Older Patients who Develop Acute Graft-vs.-Host Disease (GVHD). *Blood* (submitted).

Carnevale-Schianca F, Leisenring W, Martin PJ, Furlong T, Schoch G, Anasetti C, Appelbaum FR, Carpenter PA, Deeg HJ, Kiem HP, Storb R, McDonald GB, Nash RA. Longitudinal assessment of morbidity and acute graft-versus-host disease after allogeneic hematopoietic cell transplantation: retrospective analysis of a multicenter phase III study. *Biol Blood Marrow Transplant*. 2009;15:749-56.

Hansen JA. Genomic and Proteomic Analysis of Allogeneic Hematopoietic Cell Transplant Outcome. Seeking Greater Understanding the Pathogenesis of GVHD and Mortality. *Biol Blood Marrow Transplant* 2009;15:1-7.

Lee SJ, Williams LA. Patient-Reported Outcomes for Acute Graft-versus-Host Disease Prevention and Treatment Trials. *Biol Blood Marrow Transplant* (In press)

MacMillan ML, DeFor TE, Weisdorf DJ. The Best Endpoint for Acute GVHD Treatment Trials. *Blood* (In press).

Martin PJ. Study design and endpoints in graft-versus-host disease. *Best Practice Res Clin Haematol*. 2008;21:357-372.