Settling the (Risk) Score for CGVHD Patients

February 16, 2015

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Chronic graft-versus-host disease (CGVHD) is a complication that may arise in patients who have received bone marrow or stem cell transplants from another person (allogeneic transplants), in which the transplanted immune cells attack the host's own cells. Compared with acute GVHD, the chronic form usually occurs later, normally after 100 days post-transplant, and lasts longer, and it is the leading cause of late morbidity and mortality among recipients of allogeneic hematopoietic cell transplantation (HCT).

In 2011, a risk score was developed for patients with CGVHD in a study from the Center for International Bone Marrow Transplant Research (CIBMTR) that included a number of Fred Hutch investigators. CIBMTR is a voluntary research organization that involves more than 500 transplantation centers that have agreed to share patient data and collaborate in scientific studies. Using multivariate analysis of a cohort of 5343 CGVHD patients, ten significant variables were successfully identified for predicting the overall survival and non-relapse mortality; the latter defined as death in continuous remission (Arora *et al*., 2011). The variables were age, prior acute GVHD, time from HCT to CGVHD, donor type, disease status at transplantation, GVHD prophylaxis, gender mismatch, serum total bilirubin, Karnofsky performance status (the ability to perform ordinary, daily activities on a scale from 0 to 100) and platelet count at the time of CGVHD diagnosis. The study concluded that patients could be categorized into six well-defined risk groups that adequately reflected the assessed outcomes, but to advance from "promising" to clinically useful the score needed to be validated in an independent dataset.

To determine the reproducibility of the risk scores developed in the earlier study, the researchers followed up by identifying a new set of 1128 CGVHD patients that received HCT between 2005 and 2007, and applied the same inclusion criteria and risk-score calculations. In both studies, all patients were registered with CIBMTR. Some discrepancies were seen between the validation cohort and the training cohort; most importantly, the proportion of patients assigned to the various risk groups differed considerably. The proportion of patients in risk groups 1 and 2 (lowest risk) were significantly higher in the validation study, and no patients qualified for groups 5 or 6 (highest risk). Only 12% of all patients in the validation cohort were assigned risk group 3 or 4, and the two groups were therefore combined; the final comparison was consequently carried out in three separate risk groups

(RG1 = lowest risk, RG2 = intermediate, RG3 = highest). The disparity between the two patient cohorts was likely due to uniquely different baseline characteristics; nevertheless, good discriminatory ability was demonstrated for the CIBMTR CGVHD risk score in predicting overall survival and non-relapse mortality in patients with CGVHD. Simply put, better survival was seen in patients with a lower risk score (< RG3) than in those with a higher risk score.

The results of this validation study were recently published in *Biology of Blood and Marrow Transplantation*, with Dr. Mary Flowers as the senior and corresponding author. Dr. Flowers is the director of the Adult Clinical Service Long-Term Follow-Up Program (LTFU) at Fred Hutch and Seattle Cancer Care Alliance. Although the lower rate of patients assigned to the highest risk groups (RG4 to RG6) has yet to be fully explained, another study by Dr. Flowers and colleagues described comparable findings when evaluating the score in patients diagnosed using the National Institutes of Health (NIH) consensus criteria for GVHD (Inamoto *et al*., 2014).

"The CIBMTR risk score performed well in predicting differences in overall survival also when applied in other cohorts treated for NIH chronic GVHD in two individual centers," Dr. Flowers said, adding that, "Of interest, lower non-relapse mortality was observed in patients with more risk factors (> group 3) at the Fred Hutch cohort compared to the Princess Margaret Hospital (Toronto, ON, Canada) and the CIBMTR cohort. The dedicated long-term follow up program at Fred Hutch may have contributed to the superior outcome noted in this high-risk group."

And there is more good news for the transplantation community; according to Dr. Flowers, the validated risk score can be readily introduced in the clinic: "The CIBMTR CGVHD score is easy to apply and can be used for prediction of major outcomes, treatment planning and enrollment in clinical trials." Another handy tool for improving the care of cancer patients.

Arora M, Hemmer MT, Ahn KW, Klein JP, Cutler CS, Urbano-Ispizua A, Couriel DR, Alousi AM, Gale RP, Inamoto Y, Weisdorf DJ, Li P, Antin JH, Bolwell BJ, Boyiadzis M, Cahn J-Y, Cairo MS, Isola LM, Jacobsohn DA, Jagasia M, Klumpp TR, Petersdorf EW, Santarone S, Schouten HC, Wingard JR, Spellman SR, Pavletic SZ, Lee SJ, Horowitz MM, Flowers MED. 2014. CIBMTR Chronic GVHD Risk Score Predicts Mortality in an Independent Validation Cohort. *Biol Blood Marrow Transplant*. [Epub ahead of print]

See also: Arora M, Klein JP, Weisdorf DJ, Hassebroek A, Flowers ME, Cutler CS, Urbano-Ispizua A, Antin JH, Bolwell BJ, Boyiadzis M, Cahn JY, Cairo MS, Isola L, Jacobsohn DA, Jagasia M, Klumpp TR, Lee SJ, Petersdorf EW, Santarone S, Gale RP, Schouten HC, Spellman S, Wingard JR,

Horowitz MM, Pavletic SZ. 2011. Chronic GVHD risk score: a Center for International Blood and Marrow Transplant Research analysis. *Blood*. 117(24):6714-20

Inamoto Y, Kim DD, Storer BE, Moon JH, Lipton JH, Kuruvilla J, Martin PJ, Flowers ME. 2014. Application of CIBMTR risk score to NIH chronic GVHD at individual centers. *Blood*. 123(3):453-5

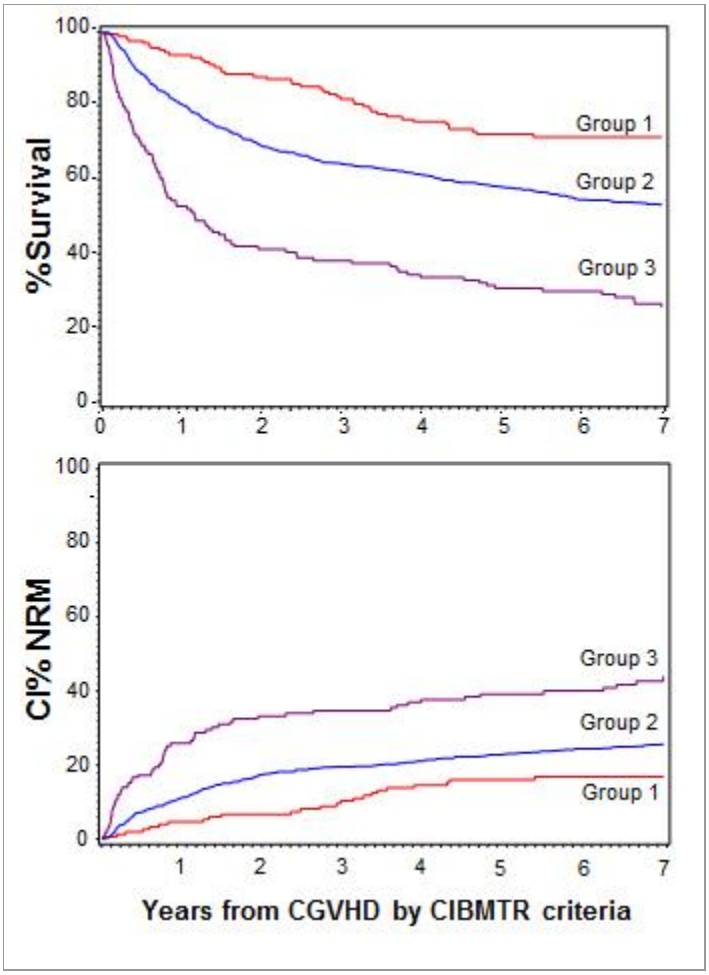

Image provided by Dr. Mary Flowers

Kaplan-Meier curves showing overall survival and non-relapse mortality (NRM) among patients with chronic graft-versus-host disease (CGVHD) according to CIBMTR risk score (n = 1128).