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Slashing the picture of Dorian Gray

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In this issue of *Blood*, Flowers and colleagues report on the risk factors for acute and for chronic graft-versus-host disease (GVHD) in a sizable cohort of 2941 first allogeneic transplantation recipients.[1] Many factors were similar; some were not shared. In risk factors associated with chronic GVHD, point estimates and confidence intervals were not significantly changed after adjustment for prior acute GVHD. These results strongly support the concept that chronic GVHD is not simply the end stage of acute GVHD.

Chronic GVHD has remained an elusive disorder to characterize. Many patients with a history of acute GVHD later develop chronic GVHD. If acute GVHD is totally prevented by rigorous T-cell depletion of the donor graft, the risk of chronic GVHD is reduced to essentially zero. These observations led to the supposition that acute GVHD and chronic GVHD were the same disorder, with distinctive manifestations at different times after transplantation. Thus, as in the novel by Oscar Wilde, the excesses and insults suffered by the recovering immune system during acute GVHD became manifest in the portrait of chronic GVHD. How the portrait looked was dependent on the point in time when you looked at it—but Dorian Gray and his portrait were really one and the same.

The paper by Flowers et al continues many lines of work that now are painting a different, more complex picture of chronic GVHD.[1] Some risk factors had a greater impact on acute GVHD (human leukocyte antigen mismatch recipient, unrelated donor) while other factors were more significant for chronic GVHD (female donor for male recipient). Other risk factors were associated only with acute (total body irradiation) or only chronic (use of mobilized peripheral blood cells, older patient age). Critically, even when the risk factors for chronic GVHD were adjusted for prior acute GVHD, the analysis did not significantly change. This strongly supports the idea that although acute and chronic GVHD may share some common immunologic insults in their pathogenesis, they are different disorders.

Given the advances in our understanding of acute GVHD, as elegantly reviewed recently in this journal by Coghill et al,[2] why has progress in chronic GVHD been so slow? One major issue has been the lack of animal models that fully reproduce the manifestations of chronic GVHD.[3] The Flowers study reported here identifies an additional issue. Older age was identified as a significant risk factor for only chronic GVHD.[1] Yet most studies are conducted in juvenile animals, a far different immunologic host than the typical adult developing chronic GVHD. Another limitation of application of these models to human chronic GVHD is that patients have received pharmacologic agents for prophylaxis and potentially treatment of acute GVHD (predominantly mediated by Th1 cytokines), which alter the T-cell repertoire and cytokines present as clinical chronic GVHD (Th2 cytokine dominated) develops. Despite these concerns, as recently summarized by Martin, these models suggest 4 mechanisms to explain the genesis of chronic GVHD. These include (1) thymic damage and defective negative selection of T cells, (2) abnormal production of transforming growth factor-β, (3) auto-antibody production, and (4) deficiency of T-regulatory cells.[4] It is likely that in humans, chronic GVHD results from a combination of mechanisms, with each patient-donor pair a variable amalgamation, which may account for the wide variety of manifestations of this disorder.

Clinical studies of the pathogenesis have been hampered by the late onset of disease, when most patients have returned home, making obtaining samples at presentation before treatment difficult. Another major issue for chronic GVHD has been the lack consistent diagnostic, staging, and response criteria. This study used the recommendations of the National Institutes of Health (NIH) Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD, which have been embraced by most transplantation centers and are currently being validated and refined in an NIH-sponsored multicenter collaborative study.[5,6] The use of these recommendations ensures a common language, a key step forward in all aspects of this disease.

As slashing of the picture results in the end of the picture and Dorian Gray, is this good for chronic GVHD? In one word: yes. The only way that this disease is ever going to cease causing a metamorphosis, in its worse manifestations leaving patients unrecognizable from their pretransplantation state, is that the basic mechanisms of the disorder are understood. With that knowledge, we can finally begin to paint a brighter picture of the future with rational, immunologically directed treatment for our patients suffering from chronic GVHD.

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REFERENCES

1. Flowers ME, Inamoto Y, Carpenter PA, et al. Comparative analysis of risk factors for acute and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood*. 2011;117(11):3214-3219.

2. Coghill JM, Sarantopoulos S, Moran TP, Murphy WJ, Blazar BR, Serody JS. Effector CD4+ T cells, the cytokines they generate, and graft-versus-host disease: something old and something new [published online ahead of print January 18, 2011]. *Blood*. doi:10.1182/blood-2010-12-290403.

3. Chu YW, Gress RE. Murine models of chronic graft-versus-host disease: insights and unresolved issues. *Biol Blood Marrow Transplant*. 2008;14(4):365-378.

4. Martin PJ. Biology of chronic graft-versus-host disease: implications for a future therapeutic approach. *Keio J Med*. 2008;57(4):177-183.

5. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11(12):945-956.

6. Shulman HM, Kleiner D, Lee SJ, et al. Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II. Pathology Working Group Report. *Biol Blood Marrow Transplant*. 2006;12(1):31-47.

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