Chronic graft–versus-host disease (cGVHD) is a major cause of long-term nonrelapse morbidity and mortality in patients who undergo an allogeneic hematopoietic cell transplantation (HCT).1 cGVHD classically arises more than 100 days and rarely later than 500 days after transplantation. It presents as a progressive clinical syndrome that can involve multiple organs. Features of cGVHD resemble certain autoimmune diseases such as progressive systemic sclerosis, systemic lupus erythematosus, and others. Among the target organs commonly involved are the skin, liver, eyes, and/or oral pharynx. cGVHD can be treated with immunosuppression, and the mainstay of therapy is corticosteroids. However, despite immunosuppressive treatment, approximately 20% to 50% of patients who develop cGVHD die from complications associated with this disease.1

The pathophysiology of cGVHD is poorly understood. Donor T cells are thought to be the principal cause of both forms of GVHD—acute and chronic. However, different target antigens and effector pathways seem to mediate these clinical syndromes. Whereas acute GVHD is triggered by alloantigens recognized by T cells that mature in the thymus of the donor, the pathologic process of cGVHD is less certain. It has not yet been determined if donor postthymic or de novo graft–derived T cells predominate in this aberrant immune response. Whether the inciting antigens represent different allelic forms of donor and recipient molecules (alloantigens) or nonallelic endogenous molecules (autoantigens) is also not known. Recent clinical studies have shown that antibody responses against documented allogeneic targets correlate with the development and severity of cGVHD.2 Since alloantibodies are not thought to play a role in acute GVHD, these data further suggest that distinct pathologies underlie these syndromes.

Few animal models exist for the study of cGVHD. Some of the best-studied models use strain combinations that differ at the mouse major histocompatibility complex (MHC) equivalent of the human HLA, called H-2.3,4 In humans, HLA disparities certainly increase the likelihood of developing cGVHD. However, approximately 40% of recipients of HLA-matched sibling grafts develop the syndrome. Thus, in the search for ways to accurately model the cGVHD syndrome, investigators are now more frequently turning to the use of donor/recipient strain combinations that are matched at H-2 but differ at other genetic loci (minor alloantigens).5

In this issue of Blood, Zhang and colleagues report on the development of a new mouse model of cGVHD. The novelty of the model is based on the investigators’ use of a donor/recipient pair that has not been previously reported, and disease is induced in recipients given the equivalent of a mouse nonmyeloablative transplant. DBA/2 and BALB/c mice are matched at H-2 but have multiple minor antigenic differences. When sublethally irradiated BALB/c mice receive transplants of large numbers of DBA/2 spleen cells (which contain progenitor and mature immune cells), the mice develop a syndrome with features resembling human cGVHD within 20 to 50 days after HCT. These features include sclerodermatous skin changes (more pronounced than in an existing model) and lupuslike abnormalities including serum antibodies to double-stranded DNA and glomerulonephritis. Removal of the thymus in some recipients did not change disease outcome, suggesting that donor postthymic T cells cause this syndrome. More importantly, Zhang et al show that mature donor B lymphocytes and not de novo B cells that arise after transplantation are associated with disease development. The investigators also address the role of donor T-cell subsets in mediating disease, including the activities of regulatory CD4+CD25+ cells. Development of cGVHD in this model is dependent upon CD4+ and not CD8+ T cells, and CD4+CD25+ cells are required for cGVHD induction, whereas CD4+CD25+ cells suppress the disease.

This newly established mouse model, which shares important features with the human syndrome, is certainly a welcomed addition to the armamentarium against cGVHD. The work of Zhang et al reinforces the notion...
that it will be possible to unravel the complex pathophysiology of cGVHD with the help of our furry friends.

REFERENCES


Comment on Bennett et al, page 2639

Putting the “Tux” on ITP

Douglas B. Cines

Bennett and colleagues report that approximately one third of children and adolescents with severe or refractory chronic immune thrombocytopenic purpura (ITP) showed a sustained response to treatment with the monoclonal anti-CD20 antibody, rituximab. This prospective study is notable for several reasons and it also serves to highlight several unanswered questions as to the drug’s mechanism of action and place in ITP management.

The benefit of treating children with ITP remains contentious, and the severity of bleeding in the enrolled subjects just prior to enrollment is unstated. Nevertheless, the pre-treatment platelet count (mean of 9-10 x 10^9/L), duration of disease (4 years on average), number of prior treatments (mean of 4), severity of bleeding after therapy (grades 3-4 in 60% of nonresponders), and inclusion of patients with Evans syndrome (which has a worse prognosis) document the severity of the disease in this cohort and the real benefit of ameliorating thrombocytopenia. These demographic help to explain the lower response rate than reported previously, but they also clearly establish that rituximab induces sustained meaningful responses in a subset of severely affected young patients.

That responses occur at a median of one week seems difficult to reconcile with B-cell apoptosis, which is presumed to mediate delayed and durable response. The possibility that the initial effect may be through competition between the clearance of antibody-coated peripheral B cells (which are considerably reduced in contrast to relatively stable total IgG levels) and platelets, analogous to anti-D, has not been established, nor is it obvious why early responses are generally sustained unless the 2 processes are intertwined (see left side of figure).

Hematologists’ use of rituximab differs considerably, ranging from use always before splenectomy to exactly the opposite. This is based on its cost and variable reimbursement, uncertain long-term effects, but largely on the wish of increasing numbers of patients to avoid splenectomy. However, it may be premature to conclude that rituximab might be preferable to splenectomy in younger patients. The high rate of first infusion-related complications such as serum sickness teaches that treatment should be confined to those truly in need of therapy. Even the longest follow-up of rituximab-treated patients is far less than for splenectomy, so the durability of response and incidence of delayed immunologic complications remain to be defined. One is still left wondering if and, if so, how, a nonselective inhibitor of B-cell costimulatory help places a “hole” so selectively in the B-cell antibody repertoire and whether a similar effect on other unusually sensitive or low-prevalence B-cell populations may impair the development of a normal immune repertoire, especially in younger patients.

Last, the authors describe the pharmacokinetics of rituximab in children. This not only serves to highlight that children are not simply small adults but also reminds us that we have adopted a lymphoma-style regimen to treat an autoimmune disease because no phase 2 trials have been performed in ITP. Neither the optimal dose, frequency of administration, nor duration of treatment has been thoroughly delineated. Studies that better define the effect on rituximab on immunoglobulin gene repertoire and expression of platelet antibody-producing B cells may alleviate this glaring gap in our knowledge, alter treatment in ways that increase response rates and lessen concerns about persistent immune paresis, and identify patients whose disease is more amenable to this modality.

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