those with underlying organ dysfunction. It is hypothesized that this strategy will make allotransplantation feasible for patients in this latter category who would not be candidates for myeloablative regimens.

This issue contains a report by Hogan and colleagues (page 78) that studied the impact of one reduced-intensity regimen, low-dose total body irradiation (TBI), with or without fludarabine, on hepatic toxicity, the most common cause of fatal regimen-related toxicity after ablative transplant preparation. Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is characterized by fluid retention, painful hepatomegaly, and jaundice. VOD/SOS is more common in patients with active liver inflammation who undergo transplantation, in those who receive more intensive conditioning, and in the setting of active infection during the peritransplantation period.

In their article, Hogan et al describe the incidence, severity, and outcome of hepatic toxicity in 193 consecutive patients prepared for allogeneic transplantation using 200 cGy total body irradiation, with or without fludarabine, and who received cyclosporine and mycophenolate mofetil for postgrafting immunosuppression. Of the patients, 26% developed hyperbilirubinemia (bilirubin levels of 68.4 μM [4 mg/dL] or higher) by day 200 (compared with 48% in a historical group of 1149 patients who underwent transplantation using an ablative regimen), but in none was this due to VOD/SOS. Graft-versus-host disease (GVHD), or cholangitis lenta, was the most common cause of jaundice in these patients. Survival was superior in patients with normal or minimally elevated bilirubin levels and in those whose bilirubin level exceeded 68.4 μM (4 mg/dL) within the first 28 days compared with patients whose bilirubin level reached 68.4 μM (4 mg/dL) after day 28. Among patients with bilirubin levels of 68.4 μM (4 mg/dL) or higher, those with aggressive histologies were more likely to die than those with more indolent disease. Patients who received fludarabine with their preparative regimen were more likely to develop hyperbilirubinemia, although fludarabine was not an independent risk factor for death. There were 3 patients, all with chronic liver disease at the time of transplantation, who died of liver failure.

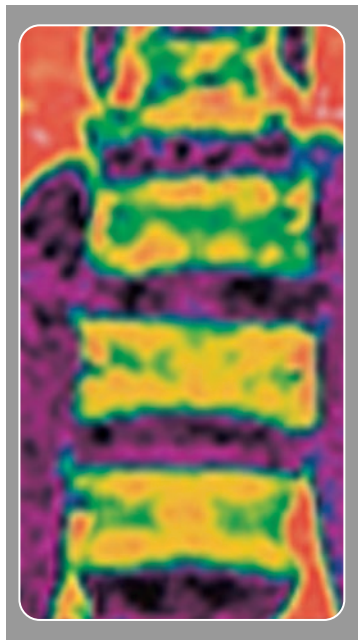
What does this report show us? First, it shows that allotransplantations can be performed without patients developing VOD/SOS. We must remember, however, that 200 cGy TBI (± fludarabine) is only one of many nonmyeloablative regimens and that VOD/SOS has been reported after conditioning using other reduced-intensity programs. Second, it demonstrates that patients with chronic and pre-existing liver disease remain at high risk for early death and that reduced-intensity preparation does not protect them. It also makes clear that hyperbilirubinemia beyond day 28 is associated with an adverse outcome even in the absence of VOD/SOS and independent of the relative intensity of the regimen. The utility of this marker in predicting overall survival was sufficiently strong to make it both important to look for and discouraging to find in any patient undergoing a reduced intensity allograft. Finally, while Hogan and colleagues have provided important data indicating that this approach significantly reduces regimen-related hepatic toxicity, assessing the effect of nonablative transplantations on long-term outcome will require longer follow-up as well as improved treatment or prevention of other complications such a relapse, GVHD, and infection.

—Thomas C. Shea and Scott I. Bearman
University of North Carolina at Chapel Hill and University of Colorado Health Science Center

Surrogate markers for lysosomal storage

Enzyme replacement therapy (ERT) for lysosomal storage disorders (LSDs) is safe and effective treatment. It was first developed for Gaucher disease (GD), a disorder in which the bone marrow and the tissue macrophages derived from it play a central role in its pathogenesis. Currently, ERT is being developed for other LSDs following the blueprint developed for GD. This approach uses receptor-mediated endocytosis of glycoprotein lysosomes/enzymes by naturally occurring lectins.[1] Successful clinical trials resulted in new enzyme therapies becoming available a few months ago for patients with Fabry disease and mucopolysaccharidoses I.

The development of enzyme replacement therapy for GD prompted several research groups to identify biochemical markers to allow the clinician to monitor the disease



and make the appropriate dosing decisions. Currently, chitotriosidase, angiotensin-converting enzyme, and tartrate-resistant acid phosphatase are the most commonly used surrogate markers to monitor disease progression and response to ERT in GD patients. Chitotriosidase is a good marker for this purpose because it is specific for GD and shows a dramatic response after initiation of therapy, decreasing an average of 50% after the first 3 months of treatment and by 80% after one year. The usefulness of chitotriosidase is limited to a small degree by a recessively inherited 24-bp deletion that is present in 5% to 6% of the population.[2] Treating physicians would

welcome surrogate markers that could confirm the value of chitotriosidase and be universally applicable in the evaluation of the disease severity and the monitoring of treatment.

Boot and colleagues (page 33) have found that CCL18 is an interesting marker that can be very useful in this regard.

The use of surface-enhanced laser desorption/ionization–time of flight (SELDI-TOF) mass spectrometry is important in identifying potential previously unknown factors related to GD, regardless of its severity. The technique is currently used with success to identify biomarkers of disease activity in several research fields, including cancer biology. It was applied to GD to uncover the chemokine CCL18 as a marker. The correlation between the reductions of plasma CCL18 and the other markers studied in the report demonstrates CCL18 to be a reliable marker to monitor responses to treatment. What makes this marker a particularly promising approach for monitoring GD therapy is that, besides presenting similar response patterns to ERT to those observed with chitotriosidase, it is closely correlated with experiments in the lumbar bone marrow fat fraction. This provides an important adjunct in documenting the skeletal response to ERT.

This interesting report raises many questions regarding possible interferences with the utility of CCL18 as a biomarker. Pathologic entities such as rheumatoid arthritis and other inflammatory conditions that affect bones and joints can be concurrent with GD.[3] CCL18 has not yet been studied in these. Although CCL18 has been noted to be increased in unrelated pathologic conditions,[4] the clinical manifestations of these diseases make it easy to distinguish between them and not diminish the value of CCL18.

This study provides new insight into the pathophysiology of GD and to the association of CCL18 with the phenotypic expression of the disease. This advance is a first step in further research on this chemokine. The fact that commercially available products can be used to determine the levels of this chemokine facilitates experimental and clinical applications. The report also demonstrates the feasibility of using SELDI-TOF mass spectrometry to identify surrogate markers in other lysosomal storage diseases that allow the follow-up of patients for whom enzyme therapy has been made available in the last few months.

—Mario A. Cabrera-Salazar and John A. Barranger
University of Pittsburgh

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Hard time for anergic cytotoxic T cells

T lymphocytes require at least 2 signals to be activated and to differentiate into antigen-specific effector cells: signal 1 results from T-cell receptor (TCR)–dependent antigen recognition, while signal 2 is provided by cognate interactions between costimulatory receptors on T cells (such as CD28) and their corresponding ligands on antigen-presenting cells (such as CD80 and CD86). In the absence of signal 2, T cells cannot respond to the antigen that they recognize via their TCR and thus become anergic.[1] Anergy is a fundamental process in T-cell biology that contributes to the functional phenotype of T-cell tolerance, with both beneficial and detrimental consequences for the organism. Consider organ transplantation as an example: here, the induction of donor-specific T-cell anergy in the transplant recipient is the ultimate goal of transplantation immunologists, and numerous approaches based on the interference with costimulatory signalling pathways have been explored.[2] On the other hand, T-cell ignorance of tumor cells may allow tumors to escape immune attack. In this scenario, it would be desirable to prevent the induction of anergy, or even to reverse established tumor-induced T-cell anergy, in order to turn ignorant T cells into furious tumor-attacking cytolytic T lymphocytes (CTLs). By providing interleukin-2 or CD28 costimulation, anergy in $CD4^+$ T cells can be prevented or reversed in vitro, and signalling through OX40 (CD134) or CD40 molecules together with TCR engagement breaks $CD4^+$ T-cell anergy even in vivo.[3] So far, however, it has not been possible to reverse established anergy in $CD8^+$ CTLs in vivo.

Wilcox and colleagues (page 177) have now identified a novel approach to prevent, and even reverse, established anergy in $CD8^+$ T cells by using an agonistic anti-CD137 monoclonal antibody (mAb). CD137 (4-1BB) is a member of the tumor necrosis factor–receptor (TNFR) superfamily with well-known costimulatory and cell death–preventing activity on $CD8^+$ T cells. In their studies, Wilcox et al investigated the effect of anti-CD137 mAb in 3 murine model systems of $CD8^+$ T-cell anergy in vivo. In the first system, anergy was induced with a tumor antigen–derived peptide, with the consequence of progressive growth of an otherwise nonprogressive regressor P815R tumor cell in the immunized mice. In the second system, anergy was induced by soluble ovalbumin peptide in mice carrying a transgenic TCR specific for the $H\text{-}2K^b$–restricted ovalbumin peptide. Finally, they also explored the induction of $CD8^+$ T-cell anergy to cell-associated (as opposed to soluble) antigens in bone marrow chimeras using the bone marrow from 2C TCR transgenic mice with an $H\text{-}2L^d$–reactive TCR transplanted into lethally irradiated C57BL/6 × DBA/2 F1 mice. Remarkably, the infusion of the agonistic anti-CD137 mAb not only prevented the induction of anergy in the $CD8^+$ CTLs, but, more importantly, even reversed the established anergy in all 3 instances. These impressive results suggest that triggering of the CD137 receptor by agonistic mAb might