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To the editor:

Pathology of “Berkeley” sickle-cell mice includes gallstones and priapism

We appreciate the histopathologic survey of “Berkeley” transgenic sickle-cell mice by Manci and colleagues,1 and we have similar results in a larger range of ages (2 to 23 months) in another subcolony of these mice originally from Drs Chris Pastzy and Mohandas Narla. We also concur that the hemizygote mice are poor models for human sickle trait.2 However, we would like to add 2 additional similarities between these mice and human sickle cell disease that may have relevance to pathophysiology of sickle cell disease.

While Manci et al found no gallstones, we consistently see a 20% to 30% incidence of pigmented gallstones in examining nearly 100 of these mice. Photomicrographs (see figure) were visualized using an Olympus BX51 microscope (Olympus, Melville, NY) equipped with UPlan Apo 4 X/0.16 and PlanApo 1.25 X 0.04 objective lenses. Images were captured with an Olympus DP70 camera, and were formatted using Adobe Photoshop software (Adobe Systems, San Jose, CA). Affected mice typically have a dilated gallbladder containing a single large stone and several smaller ones. Some gallbladders with gallstones are hyperplastic (Figure 1B), but none have histologic signs of cholecystitis or biliary duct obstruction, and we conclude that these gallstones are asymptomatic. The youngest mouse with pigmented gallstones was 6 weeks old. All mice exclusively expressing human sickle hemoglobin have elevated serum total bilirubin (13 ± 1 µM/L; mean and SEM, n = 16). This is another manifestation of human sickle-cell disease in the mouse model, and it correlates with the high-grade hemolysis in these mice. The only other mice with pigmented gallstones are those with spherocytosis due to the n/bnb mutation, manifesting gallstones after 6 months of age.3,4 Dogs, prairie dogs, and guinea pigs also form pigmented stones.5

Pigment gallstones in “Berkeley” transgenic sickle cell mice. H&E. (A) Stones in a dilated gallbladder; original magnification, ×12.5. (B) Stones in a hyperplastic gallbladder; original magnification, × 40.
Remarkable activity of novel agents bortezomib and thalidomide in patients not responding to donor lymphocyte infusions following nonmyeloablative allo geneic stem cell transplantation in multiple myeloma

Nonmyeloablative conditioning can establish durable and stable engraftment with acceptable transplantation-related mortality (TRM) and excellent disease control in various hematologic malignancies, including multiple myeloma.1,2 We evaluated donor lymphocyte infusions (DLIs) given in 8 European transplantation centers for relapsed (n = 48) or persistent (n = 15) myeloma following nonmyeloablative allogeneic stem cell transplantation (allo-SCT). Twenty-four (38.1%) of 63 patients responded to DLI: 12 (19.0%) with a partial response (PR) and 12 (19.0%) with a complete response (CR). The median follow-up time after DLI of the 43 (68.3%) patients still alive was 14.0 months (range, 3.0-50.7 months). Nine patients relapsed from DLI, 5 from PR, and 4 from CR. Median progression-free survival after DLI was 27.8 months (range, 1.2-46.2 months) and median overall survival, 23.6 months (range, 1.0-50.7 months). Twenty (31.7%) patients have died, 13 (20.6%) from progressive disease and 7 (11.1%) from TRM. Acute graft-versus-host disease (GVHD) responded in 24 (38.1%) patients, and chronic GVHD occurred in 27 (42.9%) patients.

DLI following nonmyeloablative allo-SCT is a valuable strategy for relapsed or persistent disease, although major drawbacks remain: the graft-versus-myeloma (GVM) effect of DLI seems inextricably bound up with the occurrence of GVHD, and durable remissions are restricted to a minority of patients who achieve CR. Still, survival after DLI in this study was remarkably long, probably due in part to the fact that 15 (83.3%) of 18 patients not responding to (n = 16) or relapsing (n = 2) after DLI were sensitive to additional treatment with bortezomib and thalidomide (Table 1). All 7 patients treated with bortezomib administered according to the Richardson et al scheme responded, including 2 patients with a very good partial response (VGPR). Six of 9 patients achieved a PR after treatment with thalidomide (100-300 mg daily), and 2 of 2 patients receiving both drugs achieved CRs that are still ongoing at 8 and 19 months (Table 1). Two patients received bortezomib after treatment failure to thalidomide; one of these patients achieved CR. One patient received thalidomide after treatment failure to bortezomib and achieved PR (Table 1). In 2 patients treated with thalidomide, a transitory flare up of GVHD was observed (1 skin, 1 skin and liver).

Several studies have shown that the novel agents bortezomib, thalidomide, and thalidomide derivatives may have strong immune-modulating effects resulting in enhancement of graft-versus-tumor reactions without stimulation of GVHD.6,8 The dissociation of GVHD and GVM is of vital importance in improving the efficacy of allo-SCT and DLI. It is therefore questionable whether DLI as a single treatment should be recommended for post-allo-SCT therapy. Our data support the initiation of studies in which novel agents such as bortezomib, thalidomide, and thalidomide derivatives are incorporated into the treatment of relapsed and persistent disease following allo-SCT, alone or in combination with (low-dose) DLI.

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References
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