We have also observed priapism in the Berkeley transgenic sickle-cell mice, as well as the same biochemical phenotype of nitric oxide resistance and phosphodiesterase 5A dysregulation as in priapic mice with knockout of nitric oxide synthases.[6] These functional abnormalities of vasoregulation are present despite very subtle histologic changes in the penis.

Both gallstones and priapism contribute significantly to the complications of sickle-cell disease. These 2 functional manifestations in this transgenic mouse model of severe sickle-cell disease highlight the possible links between hemolysis and low nitric oxide bioavailability. Some disease similarities may accumulate as the mice age. While we acknowledge that there are differences in the physiology of mice compared with humans, the animal model has potential utility for functional studies relevant to sickle-cell disease pathophysiology.

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To the editor:

Remarkable activity of novel agents bortezomib and thalidomide in patients not responding to donor lymphocyte infusions following nonmyeloablative allogeneic 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)[3] occurred in 24 (38.1%) patients, and chronic GVHD[4] 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[5] 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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Table 1. Efficacy of bortezomib and thalidomide in DLI-refractory patients

Patient	Stem cell source	No. DLIs (maximum T-cell dose, T cells/kg)	Interval DLI next therapy, mo	Reason to add treatment	Next therapy	Response	Response, mo	Toxicity
1	Sibling	2 (1×10^8)	5	NR to DLI	Bort 6	PR	6	No
2	Sibling	3 (1×10^8)	4	NR to DLI	Bort 8	VGPR	8+	PNP grade 2
3	Sibling	2 (1×10^7)	5	NR to DLI	Bort 3	PR	3	PNP grade 3; reason to stop therapy
4	MUD	2 (1×10^7)	5	NR to DLI	Bort 8	VGPR	9	PNP grade 2
5	Sibling	1 (1×10^7)	4	NR to DLI	Thal 100	PR	9+	GVHD grade I; death from lung embolus
6	Sibling	1 (1×10^7)	4	NR to DLI	Thal 200	PR	6+	GVHD grade I
15	Sibling	1 (1×10^6)	5	NR to DLI	Bort 8	PR	9+	PNP grade 2, dose reduction after cycle 3
28	Sibling	1 (1×10^7)	15	Relapse from CR	Thal 100 + bort 4	CR	19+	No
29	Sibling	1 (1×10^7)	21	Relapse from CR	Thal 100 + bort 4	CR	8+	No
32	MUD	1 (1.3×10^7)	6	NR to DLI	Thal 100	PR	8	No
35	MUD	2 (1×10^6)	2	NR to DLI	Thal 300	PD	NA	No
37	Sibling	1 (1×10^6)	4	NR to DLI	Thal 100-300	PD	NA	No
39	Sibling	2 (5×10^6)	3	NR to DLI	Thal 100-200	PR	7	No
39	Sibling	2 (5×10^6)	10	PD after thal	Bort 4	CR	6	No
41	MUD	1 (5×10^6)	5	NR to DLI	Thal 100	PR	24+	No
49	Sibling	1 (1×10^6)	2	NR to DLI	Thal 200	PR	14	No
54	MUD	1 (1×10^7)	4	NR to DLI	Bort 6	PR	6	No
59	Sibling	2 (1×10^8)	1	NR to DLI	Thal 100	NR	NA	No
59	Sibling	2 (1×10^8)	3	PD after thal	Bort 3	PD	NA	PNP grade 2
63	Sibling	3 (1×10^8)	14	NR to DLI	Bort 8	MR	10	No
63	Sibling	3 (1×10^8)	40	PD after bort	Thal 100	PR	15+	PNP grade 2

Bort n indicates that patients received an intravenous bolus of bortezomib (1.3 mg/m^2) on days 1, 4, 8, and 11 for n 3-week cycles; MUD, matched unrelated donor; Thal, thalidomide; PNP, polyneuropathy; GVHD, graft-versus-host disease; NR, no response; MR, minor response; PR, partial response; VGPR, very good partial response; CR, complete response; PD, progressive disease; NA, not applicable; and No, no WHO toxicity > 1.

Response to salvage therapy was assessed according to the criteria of the European Group for Blood and Marrow Transplantation (EBMT).[3]

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