The Paradoxical Effect of Bortezomib on Acute GVHD

Kai Sun, Danice E.C. Wilkins, Miriam R. Anver, Thomas J. Sayers, Angela Panoskaltsis- Mortari, Bruce R. Blazar, Lisbeth A. Welniak and William J. Murphy

Graft-versus-host disease (GVHD) is a complicating factor that impairs the efficacy of allogeneic bone marrow transplantation. In our model, GVHD is induced by injecting MHC mismatched spleen and bone marrow cells from (H2d) mice into C57Bl/6 (H2b) mice. GVHD is induced when alloreactive donor T cells respond to alloantigens on host antigen presenting cells (APCs) by producing cytokines, proliferating, and inducing apoptosis in target tissues such as the gut, liver, and skin. Bortezomib is a proteasome inhibitor that has recently been approved for use against multiple myeloma. Our previous studies have shown that administration of bortezomib at the time of allogeneic bone marrow transplantation (BMT) prevents the development of GVHD while retaining crucial graft-versus-tumor (GVT) effects in tumor bearing mice. However, new data shows that delayed administration of bortezomib after the induction of GVHD results in increased gastrointestinal toxicity and accelerated morbidity. Analysis of mRNA from gastrointestinal cells in mice receiving delayed bortezomib treatment showed an increase in the steady state level of TNFR1, the principle pro-inflammatory and pro-apoptotic receptor for TNF-alpha. This increase in TNFR1 was not seen in untreated GVHD control mice, and there was no difference detected in the expression of other apoptosis associated genes such as Fas and FasL. Increased levels of TNF-alpha were also detected in the serum of late treated mice. These results suggest that, in our model, TNFR1 may play a role in the toxicity associated with delayed GVHD treatment with bortezomib, and that this agent may be useful in the protection, but not the treatment of GVHD after BMT.

Danice Wilkins dwilkins@ unr.edu.mailloc