

William H.D. Hallett

The Proteasome Inhibitor, Bortezomib, Sensitizes Tumors to Adherent Lymphokine Activated Killer (ALAK)-Cell Mediated Attack

William H.D. Hallett, Isabel Barao, Thomas J. Sayers, William J. Murphy

The proteasome inhibitor, bortezomib (formerly PS-341), has shown direct anti-tumor effects to a variety of human cancers, particularly myelomas. Clinical approval for the treatment of bortezomib in multiple myeloma has been given. We have recently demonstrated that bortezomib can sensitize murine leukemia and renal cell carcinoma cells to TRAIL-mediated killing. This was demonstrated to be in part through the reduction of c-FLIP in the tumor cells by bortezomib pre-treatment. ALAK cells have been demonstrated to mediate numerous anti-tumor effects both in vitro and in vivo and are attractive as a potential adoptive immunotherapy. We reasoned that as c-FLIP is an important mediator in preventing apoptosis and it is reduced by bortezomib that treatment of tumor cells with bortezomib would render those cells more susceptible to ALAK-cell mediated attack. We found that preincubation of tumor cells with bortezomib resulted in increased expression of DR5, the receptor for TRAIL ligand, presenting another means by which tumor killing can be increased. Co-culture of murine tumor cells with bortezomib and ALAK cells resulted in increased killing of the tumors demonstrating that increased susceptibility to immune cell mediated attack did indeed result with bortezomib exposure. Use of mice genetically deficient in certain killing pathways (i.e. perforin or Fas ligand) demonstrated that the majority of NK cell-mediated killing was by the perforin pathway. However, bortezomib incubation resulted in increased tumor cell killing even using perforin- deficient ALAK cells demonstrating that increased susceptibility to killing by bortezomib was affecting multiple killing pathways. We have demonstrated that TRAIL mediated killing is one of the other pathways by which ALAK cells eliminate tumor cells after bortezomib treatment, in this model. Thus, the combination of NK cells with bortezomib may be of clinical use in the treatment of cancer.