

# Bortezomib: a promising treatment for inflammatory diseases

*“If the efficacy seen in mice translates to humans, the current results may provide new insights and therapeutic approaches for treating inflammatory and autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus and psoriasis.”*

**KEYWORDS:** autoimmunity ■ bortezomib ■ contact hypersensitivity ■ immunotherapy ■ inflammation ■ skin ■ T lymphocyte

A drug already available for treating cancer could be successful in treating a range of autoimmune and inflammatory diseases: bortezomib, currently used to treat cancers that affect leukocytes, induces cell death only in active and proliferating T cells, leaving the remainder unharmed. This offers hope that bortezomib or similar drugs might be effective in treating inflammatory diseases without the side effects seen with current drugs that affect all T cells equally.

The major intracellular pathway for protein degradation is the ubiquitin–proteasome pathway [1]. Proteasomes are large multimeric protease complexes located in both the cytoplasm and nucleus [2,3]. Proteasomes selectively and rapidly degrade most cellular proteins. The ubiquitination of target proteins is an important mechanism for ensuring selectivity in protein degradation by proteasomes [3]. Proteasome inhibitors have recently received much attention because of their potent anti-tumor activity [4]. In particular, bortezomib, a boronic acid dipeptide derivative, is a specific proteasome inhibitor that has recently been approved for the treatment of relapsed multiple myeloma (a plasma cell neoplasia) owing to its direct growth-inhibitory and apoptotic effects on this cancer [4,5].

Over the past several years, bortezomib has been shown to attenuate excessive inflammation. Sun *et al.* have reported that bortezomib treatment provided significant protection from acute graft-versus-host disease in a murine allogeneic bone marrow transplantation model by inhibiting allogeneic T-cell proliferation [6]. Neubert *et al.* have also shown that bortezomib treatment of mice with lupus-like disease significantly reduced disease severity [7]. Proteasome inhibitors induce apoptosis in activated and proliferating, but not in resting, T cells [8,9],

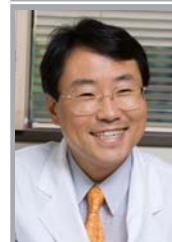
which suggests a possible mechanism for the suppression of T-cell-mediated immune responses by bortezomib. Recently, we reported that bortezomib suppresses T-cell-dependent inflammatory responses in a murine contact hypersensitivity (CHS) model [10]. CHS is an inflammatory immune reaction that is mediated by T cells in sensitized individuals following contact with a sensitizing hapten. Haptens are low-molecular-weight chemicals that covalently bind to discrete amino acid residues on self or exogenous proteins. During CHS sensitization, hapten-presenting Langerhans cells migrate from the sensitized skin to the draining lymph nodes and prime hapten-specific T cells [11]. These T-cell populations develop into cells that produce the cytokines that mediate and regulate CHS responses. Subsequent challenge with the same hapten at a separate skin site directs the hapten-primed T cells to the challenge site where they mediate local inflammation, resulting in edema or spongiosis that peaks 24–48 h after challenge and thereafter decreases [12]. To assess the therapeutic effect of bortezomib during CHS responses, we treated oxazolone-sensitized mice twice a week with bortezomib. Remarkably, oxazolone-induced ear swelling was significantly diminished in mice treated with bortezomib compared with vehicle-treated mice. These findings suggest that bortezomib treatment suppressed T-cell-mediated inflammatory responses. Furthermore, bortezomib treatment reduced both CD4<sup>+</sup> and CD8<sup>+</sup> T-cell infiltration in the inflamed ear and draining lymph nodes.

Then, how does bortezomib reduce the number of T cells and suppress CHS responses? We hypothesized that bortezomib treatment induced T-cell apoptosis, thereby suppressing CHS responses. We therefore assessed the



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number of apoptotic T cells in the draining lymph nodes after oxazolone challenge. In line with our hypothesis, the number of apoptotic T cells was significantly increased in mice treated with bortezomib compared with vehicle-treated mice. It has been reported that proteasome inhibitors prevent nuclear factor (NF)- $\kappa$ B activation by reducing the proteasomal degradation of inhibitory I $\kappa$ B proteins. NF- $\kappa$ B is a transcription factor that plays a pivotal role in cytokine signaling and the generation of cell-mediated immune responses. Therefore, we next examined the transcriptional activity of NF- $\kappa$ B by real-time PCR of the NF- $\kappa$ B-induced I $\kappa$ B $\alpha$  mRNA. Remarkably, the levels of I $\kappa$ B mRNA in CD4<sup>+</sup> and CD8<sup>+</sup> T cells in the draining lymph nodes from bortezomib-treated mice were significantly enhanced compared with those in the vehicle-treated mice. Thus, bortezomib treatment enhanced T-cell death by inhibiting NF- $\kappa$ B activation. The results of our study showed that bortezomib treatment significantly enhanced the apoptosis, and suppressed the activation by NF- $\kappa$ B of CD4<sup>+</sup> and CD8<sup>+</sup> T cells during CHS responses. Furthermore, bortezomib treatment decreased T-cell IFN- $\gamma$  production during CHS responses. IFN- $\gamma$  is considered to play an important role in the development of CHS. Taken together, NF- $\kappa$ B inhibition is likely to contribute to bortezomib-induced cell death in T cells, thereby suppressing CHS responses by reducing IFN- $\gamma$  production.

In conclusion, bortezomib treatment in mice resulted in attenuated CHS responses, suggesting that such treatment may also be effective for T-cell-mediated inflammatory and autoimmune diseases. Further studies are needed to determine the precise mechanisms by which bortezomib treatment attenuates T-cell-dependent inflammatory responses. As bortezomib is already on the market, it could be comparatively simple to begin clinical trials for other indications. If the efficacy seen in mice translates to humans, the current results may provide new insights and therapeutic approaches for treating inflammatory and autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus and psoriasis. Even in the event that bortezomib is not effective in humans, there is a strong likelihood that other proteasome inhibitors could be promising for the treatment of autoimmune and inflammatory diseases.

#### Financial & competing interests disclosure

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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▪▪ of considerable interest

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