Bortezomib: Understanding the Mechanism of Action

Bilal Piperdi1, Yi-He Ling1, Leonard Liebes2, Franco Muggia2, and Roman Perez-Soler1

Commentary on:

This pivotal article by Ling et al. in the August 2002 issue of Molecular Cancer Therapeutics addressed the mechanism by which a novel proteasome inhibitor, PS341 (bortezomib), caused G2–M cell cycle arrest and apoptosis (1). Bortezomib is the first in-class novel dipeptide boronate proteasome inhibitor and is now approved for treatment of multiple myeloma and mantle cell non-Hodgkin’s lymphoma (NHL).

In 1984, the ubiquitin-proteasome pathway was originally identified as the principal cellular pathway responsible for the degradation of intracellular dysfunctional proteins and a rapid turnover of key regulatory proteins (2). The immediate downstream effect of inhibiting 20S proteasome, in particular the unique proapoptotic effects of bortezomib, was not completely understood at the time of this publication. Using an H460 lung cancer cell line, the Ling et al. article eloquently described how bortezomib induced G2–M cell cycle arrest and apoptosis by causing Bcl-2 phosphorylation and cleavage. The molecular aspects that the article addressed was the mechanism by which bortezomib regulates the bcl-2 family of proteins. In H460 cell lines, bortezomib induced bcl-2 phosphorylation and a unique cleavage product and this was associated with G2–M phase cell cycle arrest and the induction of apoptosis.

Since the publication of this landmark paper, the clinical development of bortezomib has been intriguing. Bortezomib has been very effective in the treatment of hematological malignancies, including multiple myeloma and NHL (5). However, the results in solid tumors, including lung cancer, has been somewhat disappointing. Despite initial single agent activity against non-small cell lung cancer (NSCLC) patients in phase I studies (6), the standard dose of bortezomib at 1.3 mg/m² twice a week has limited single agent activity in patients with advanced NSCLC (7). In a multicenter phase II study, the addition of bortezomib to gemcitabine and carboplatin has shown interesting activity and survival (8). However, in other randomized phase II studies, the addition of bortezomib to single agent docetaxel, pemetrexed, or erlotinib offered no statistically significant response or survival advantage (9–12). One of the key issues may be the very narrow therapeutic index. Because the peripheral neuropathy was the dose-limiting toxicity of bortezomib, the combination of bortezomib at meaningful dosages with other active chemotherapies like cisplatin and paclitaxel was difficult. At the approved dosages of 1.3 mg/m² twice daily, there is a concern as to whether there is enough tissue concentration of bortezomib in solid tumors to cause the effect on cell cycle and apoptosis as seen in vitro.

Despite the clinical success of bortezomib in myeloma and mantle cell lymphoma, resistance to this drug remains a clinically significant problem. Inherent and acquired resistance to bortezomib has been noted in clinical studies. It has been hypothesized that either the defect at the level of bortezomib and proteasome interaction or the defects downstream of proteasome inhibition, including the proapoptotic effects, may lead to the mechanism of resistance. Nevertheless, the mechanism is poorly understood and more research is needed. (17). As we develop new drugs targeting this unique pathway, understanding the downstream effects of proteasome inhibition on apoptosis, cell survival, and other cellular mechanisms will play an important role in developing more effective therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References


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