Bortezomib: Understanding the Mechanism of Action

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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 proteosome 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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