Commentary on "Proteasome Inhibitors: A Novel Class of Potent and Effective Antitumor Agents"

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Abstract

The relatively recent clinical success of bortezomib, particularly in multiple myeloma, has established the validity of the proteasome as a viable target for anticancer drug development. This highly cited 1999 *Cancer Research* article from Adams and colleagues was published during the period when this drug was transitioning from preclinical studies to phase I clinical trial status. Their results detail structure–activity analyses using a series of boronic acid proteasome inhibitors and correlate cytotoxicity with inhibition of proteasome activity. In and of itself, the recognition that interference with proteasome functions represented a novel therapeutic approach likely underlies the popularity of this article. In addition, the provision of *in vitro* (at that time using the NCI 60 cell line panel) and *in vivo* antitumor activity, toxicology, and mouse pharmacokinetic and pharmacodynamic data provided a solid basis for establishing the future credentials for bortezomib to gain initial FDA approval in 2003. *Cancer Res; 76(17); 4916–7. ©2016 AACR.*

See related article by Adams et al., Cancer Res 1999;59:2615–22.

Bortezomib: Then and Now

In 1995, scientists at Myogenics Inc. synthesized bortezomib and originally designated it as PS-341, the name used in this 1999 article (1). The drug is an N-protected dipeptide with a boron atom, and subsequent to the 1999 article, it has been characterized as binding with high affinity and specificity to the catalytic site of the 26S proteasome (2). In the 1990s, ubiquitin-oriented proteasomal pathways were considered both unusual and novel targets, and as pointed out by the authors, the results of their structure–activity studies supported the interpretation that selective proteasome inhibitors killed cells by blocking ordered protein degradation. They linked this effect with tumor cell growth inhibition and provided support that the inhibition of the biochemical target, the proteasome, was related directly to the biological effects of PS-341 and related analogues. Their overall conclusions made tangible the now widely held tenets that the proteasome is a novel drug target and that PS-341 represented a unique class of antitumor agent. It is interesting to reflect that in 2004, the Nobel Prize in Chemistry was awarded to Rose, Ciechanover, and Hershko in recognition of their earlier work carried out at the Fox Chase Cancer Center in Philadelphia, PA, describing ubiquitin-mediated protein degradation pathways (3, 4). Arguably, the availability of the types of drugs discussed in this article (able to target protein breakdown/turnover) could have aided their cause by adding translational relevance to important biochemical pathways described by Rose and colleagues.

The high proliferation indexes found in tumors interpolate with commensurately high protein-folding requirements. In turn, this predisposes cancer cells to a need for disproportionately active endoplasmic reticulum functions. Indeed, these are found in cancers, such as multiple myelomas, where such cells have the highest rate of secretion of proteins with disulfide bonds (5). Precision in protein folding is a crucial process, and multiple signaling pathways have evolved to ensure quality control. The unfolded protein response (UPR) is a stress response pathway that leads to a cascade of transcriptional/translational events that are designed to preserve accurate protein-folding capacity by three interrelated mechanisms. In 1999, there was a beginning to the understanding of how UPR-associated pathways might be critical in controlling cell survival. Subsequent analyses have determined that the UPR has three phases. First, to restore normal function of the cell by halting protein translation; second, degradation of misfolded proteins; and third, activation of signaling pathways that lead to increased production of molecular chaperones involved in protein folding. When the accumulation of unfolded proteins is sustained and the stress becomes too severe, the UPR will be insufficient to regain homeostasis, and cells will be pushed towards apoptosis (6). The veracity of such principles has evolved since the original publication of this 1999 article (indeed, the term UPR was not used in this article) but now conceptualize both the preclinical and clinical basis for the therapeutic utility of bortezomib.

NCI Antitumor Panels

The 60-cell line panel was adopted by the NCI (Rockville, MD) to identify tumor-specific drug selectivity patterns. Despite the fact that it was not universally popular, in this 1999 study, it was used to show that the proteasome inhibitors possessed potent and wide-ranging antitumor activities with a unique pattern of tumor inhibition, as judged by the COMPARE program (7). Compound efficacy was also evidenced by the

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use of another NCI screening tool, the hollow fiber assay. Thus, the authors exemplified how NCI screens could be adapted to identify candidate agents with antitumor activity, without the prerequisite for extensive metabolism and pharmacokinetic studies. As a consequence, the authors concluded that their results facilitated a more rapid development of the class of drugs exemplified by PS-341 and also supported the conclusion that drug-induced arrest of cell-cycle progression caused apoptosis. Moreover, there is little doubt that the reported murine pharmacokinetics and pharmacodynamics were useful in moving the development of this drug class forward. Even in 1999, the authors were able to imply that dose-limiting toxicities (DLT) were likely to be mild.

Clinical Utility

At the time of publication, phase I clinical trials had been started. Subsequent results revealed that the DLTs of bortezomib were reasonably mild (as suggested from the mouse data) and included peripheral neuropathy (30% of patients), myelosuppression causing neutropenia and thrombocytopenia. Gastrointestinal effects, asthenia, increased risk of herpetic infections, and acute interstitial nephritis were less common adverse events. However, in general terms compared with bone marrow transplantation or other existing treatment options for patients with advanced cancers, these adverse effects were considered eminently manageable (8). Two ensuing open-label, phase II trials (SUMMIT and CREST) established the efficacy of bortezomib (with or without dexamethasone) administered by intravenous bolus in heavily pretreated patients with relapsed/refractory multiple myeloma (9). A phase III APEX trial demonstrated the superiority of bortezomib over high-dose dexamethasone regimens (1-year survival 80% vs. 66%). In 2003, based on the results from the SUMMIT phase II trial, bortezomib (marketed as Velcade by Millennium Pharmaceuticals Inc.) was approved in the United States by the FDA for use in multiple myeloma. Bortezomib was later approved (2008) for front-line therapy for initial treatment of multiple myeloma and in 2014 for the retreatment of this same disease in adult patients previously responsive, but relapsed at least 6 months following the completion of prior treatment. Early success rates with subsets of patients have been tempered by the discovery that many patient relapses are associated with the development of drug resistance. Nevertheless, in 1999, such concerns were consigned to the future and did not detract from the importance of the drug class or the timeliness of this contribution to *Cancer Research* by Adams and colleagues.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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