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Bortezomib in lymphomas



An increasing number of novel therapies are changing the landscape in oncology – the majority of which are novel biologicals with distinct mechanism from conventional cytotoxics. In the last decades, the discovery of the ubiquitin-proteasome pathway in eukaryotic organisms has revolutionized the understanding of cellular processes indispensable for protein-homeostasis through proteolysis, until then solely attributed to the lysosomal complex. The central 700 kDa protein complex, the 20S proteasome, represents its proteolytically active part.¹ Substrates include abnormal or misfolded proteins (more abundant in cancer cells) and proteins with short half-life (1/3 of proteins made at any given time have a half-life <10 mn most of which are involved in key functions (cell division, apoptosis, DNA repair). Protein degradation initially felt to be a non-specific dead-end process is actually a very complex and regulated process critical for cell survival and adaptation. Almost all intracellular protein degradation occurs within the proteasome, a large multi unit catalytic enzyme, which degrades from 0.5 million proteins per minute in resting cells up to 2 million proteins per minute in dividing cells. Due to its control function in protein oscillation, regulation of cell

cycle progression, signal transduction, transcription and apoptosis, the ubiquitin-proteasome system plays a considerable role in tumorigenesis and represents a very obvious target in cancer therapy. In addition, slightly structurally different inducible (by TNF or IFN for ex) proteasomes are involved in the processing of antigens (generating immunogenic peptides), hence they are called immunoproteasomes.

Inhibitors of the proteasome represent a novel type of anti cancer agents with now proven activity in a variety of tumors. The first of this new class of agents is bortezomib, now FDA approved in multiple myeloma (MM) both in frontline and relapse as well as in relapsed or refractory mantle cell lymphoma (MCL). The single agent activity of bortezomib observed initially in MCL^{2,3,4,5} has remarkably been confirmed with similar response rates in a large multicenter international study including in patients who had failed prior high dose therapy or were refractory to their last chemotherapy as often seen in relapsed MCL patients.⁶ The median duration of response was in excess of 9 ms and not reached at 27 ms follow-up for the patients who had achieved a CR or CRu.⁷ Ongoing studies are looking at biomarkers

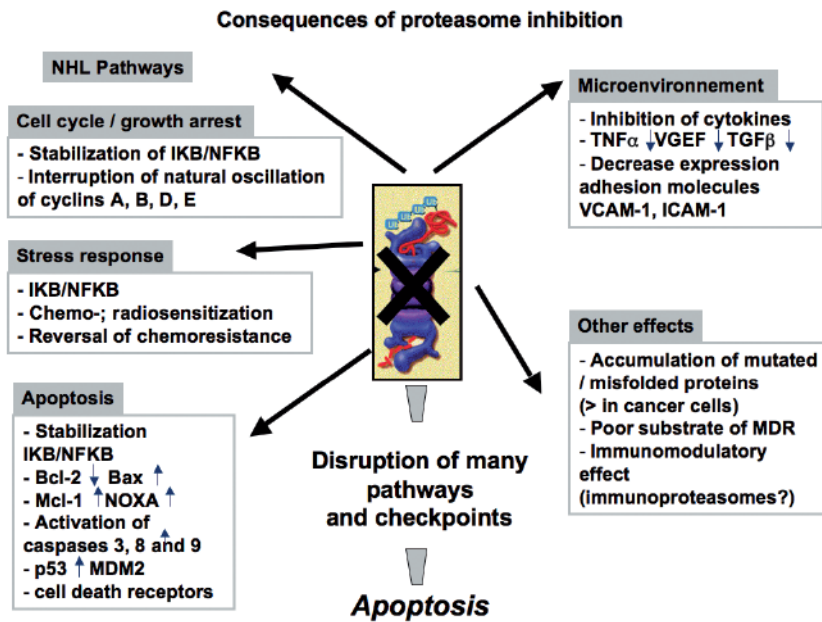


Figure 1. Consequences of proteasome inhibition.

predictive of response to bortezomib in MCL patients.⁸ The toxicity profile in lymphoma patients was similar to what had been observed in MM expect for a more frequent rash which might be a surrogate marker of response to bortezomib in patients with MCL.⁹ Bortezomib was also found active in other subtypes of lymphomas including marginal zone, follicular and Waldenstrom's Macroglobulinemia^{2,3,4,5} and CTCL all being tested further in ongoing or just completed trials. Preclinical studies also suggest that bortezomib can help overcome chemoresistance partly through additive or synergistic effect with a variety of other anticancer agents including cytotoxics, monoclonal antibodies and radiation-induced cell damages, providing a rationale for an impressive number of ongoing combination studies. A phase II of bortezomib plus rituximab was completed in relapsed FL or MZL¹⁰ and served as basis for a recently completed international randomized phase III using bortezomib with or without Rituximab in relapsed follicular

lymphoma only. A growing number of other combinations with chemotherapy which include R-CHOP^{11,12} R-CBzP,¹³ R-fludarabine, R-HyperCVAD or R-modified HyperCVAD¹⁴ as well as combination with radioimmunotherapy or thalidomide¹⁵ are still ongoing or underway in MCL. Second generation proteasome inhibitors (Carfilzomib and NIP-0053) as well as new formulations of bortezomib are being developed while preclinical studies suggest a schedule-dependence in some of the bortezomib based combinations^{16,17,18} which might impact the design of future trials. Combination studies of bortezomib with other new biologicals especially Bcl-2 inhibitors is supported by strong preclinical rationale especially in MCL. The protein degradation/proteasome pathway also includes potential future promising targets with immunoproteasomes inhibitors (lymphocytes specific inhibition) as well as ligase-specific inhibitors which will add to our armamentarium and help improve our patients' outcome.

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