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Beyond bortezomib alone: combination therapy and new strategies in targeting the proteasome

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Bortezomib is a selective proteasome inhibitor that has exhibited anti-proliferative, pro-apoptotic, and anti-angiogenic properties in myeloma models.¹⁻⁴ These effects result from activation or inactivation of multiple signaling pathways. In multiple myeloma (MM) cell lines, bortezomib induced downregulation of growth and survival signals as well as upregulation of apoptotic pathways, including mitochondrial release of cytochrome c and activation of JNK, caspase-3 and -8.3 Bortezomib also inhibited activation of nuclear factor- κ B, through stabilization of inhibitor- κ B, resulting in decreased interleukin-6 secretion, apoptosis, and chemosensitization of MM cells.¹⁴ Importantly, MM cells were 170 times more sensitive than normal cells to bortezomib-induced apoptosis.¹

Sensitization of MM cells to several other antineoplastic agents has also been observed with bortezomib. The antimyeloma activities of bortezomib were enhanced several-fold by simultaneous exposure to agents such as dexamethasone, doxorubicin, mitoxantrone, melphalan, histone deacetylase inhibitors (HDAC) or lenalidomide.^{1,5-9} The transcriptional profile of bortezomib-treated cells involved downregulation of growth and survival pathways as well as upregulation of stress response signals, including heat-shock proteins (HSP).³ Furthermore, the anti-tumor activity of bortezomib was enhanced by the addition of a specific heat shock protein inhibitor, 17-AAG.¹⁰ Microarray and proteomic studies of MM cells have started to further uncover the molecular mechanisms of drug sensitivity and resistance and will eventually help to identify the patients that will most likely benefit from these therapies.

Based on these preclinical observations, bortezomib-based combination regimens have been investigated in clinical multiple myeloma trials (Table 1). In the SUMMIT and CREST phase 2 trials, a number of patients benefited from the addition of dexamethasone.^{11,12} In a phase 1 study, bortezomib plus pegylated liposomal doxorubicin produced complete, near complete, or partial responses

in 16 of 22 (73%) evaluable patients with multiple myeloma, including 8 of 13 (62%) patients who had failed prior anthracycline treatment.¹³ Bortezomib with dexamethasone,¹⁴ melphalan,¹⁵ thalidomide,¹⁶ and lenalidomide¹⁷ have also produced high response rates in patients with relapsed and/or refractory disease. The combination with lenalidomide, an important new thalidomide analog, has produced high response rates with excellent tolerability, even in patients previously resistant to either as a single agent.¹⁷

Recently, bortezomib-based combination regimens have demonstrated encouraging activity in newly diagnosed MM patients. In a phase 2 trial, bortezomib with dexamethasone yielded a complete or partial response rate of 88%.¹⁸ In another phase 2 trial, bortezomib plus doxorubicin plus dexamethasone produced a complete response of 24% and a partial response of 71% (95% overall response) before stem cell transplantation with 43% complete responses after transplantation.¹⁹ Bortezomib plus dexamethasone also yielded a complete plus partial response rate of 73% including 21% complete responses prior to transplantation, and a complete plus partial response rate of 90% including 33% complete responses after transplantation.²⁰ Ninety-one percent of patients receiving the combination of bortezomib with melphalan and prednisone,²¹ and 80% of patients receiving bortezomib with thalidomide and dexamethasone also achieved a complete or partial response.²² These findings suggest that combination regimens which include bortezomib with melphalan and prednisone, dexamethasone, doxorubicin, and/or thalidomide are active, and that stem cell transplantation is feasible following bortezomib as induction therapy in patients with newly diagnosed MM.

Evaluation of the efficacy and safety of bortezomib-based combination regimens in randomized trials are now ongoing and will ultimately reveal the optimal treatment strategies for patients with this otherwise deadly disease. The future now holds the promise of a new generation of proteasome

Table. Bortezomib-based regimens in multiple myeloma.

Disease	Regimen	Patients*, n	CR + PR, %	Reference
Relapsed and/or refractory	Bortezomib±dexamethasone	193	27	Richardson et al. ¹²
	Bortezomib±dexamethasone	53	37 [†] , 50 [‡]	Jagannath et al. ¹¹
	Bortezomib+pegylated liposomal doxorubicin	22	73	Orlowski et al. ¹³
	Bortezomib+melfalphan	30	50	Berenson et al. ¹⁵
	Bortezomib+thalidomide	79	25–40	Zangari et al. ¹⁶
Newly diagnosed	Bortezomib+lenalidomide	11	55	Richardson et al. ¹⁷
	Bortezomib±dexamethasone [†]	32	88	Jagannath et al. ¹⁸
	Bortezomib + dexamethasone+doxorubicin [‡]	21	95	Cavenagh et al. ¹⁹
	Bortezomib+dexamethasone	48	67	Harousseau et al. ²⁰
	Bortezomib+melfalphan+prednisone [‡]	35	91	Mateos et al. ²¹
	Bortezomib+thalidomide+dexamethasone [‡]	30	80	Alexanian et al. ²²

*Evaluable patients. [†]At bortezomib 1.0 mg/m² dose level. [‡]At bortezomib 1.3 mg/m² dose level. [‡]Trial enrolled patients with newly diagnosed multiple myeloma. CR = complete response; PR = partial response

inhibitors and the integration of novel agents as combinations, including HSP-90 inhibitors, HDAC inhibitors and other targeted therapies with a backbone of estab-

lished agents such as bortezomib to overcome MM resistance and improve patient outcome.

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