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Bortezomib

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The incidence of non-Hodgkin's lymphoma (NHL) has markedly increased in the US and Western Europe in recent years and presents a considerable clinical challenge. Despite many advances in the treatment of NHL, the challenge to develop treatments for the disease remains. For example, there are few effective treatment options for patients with mantle cell lymphoma (MCL) and, while there are a number of therapies that can induce remission in patients with follicular lymphoma (FL), the disease remains incurable. Recently, preclinical and clinical studies have shown the potential for proteasome inhibition in the treatment of NHL.

The proteasome is one component of a larger intracellular pathway responsible for the degradation of more than 90% of all cytoplasmic protein, a pathway commonly referred to as the ubiquitin-proteasome pathway. It is responsible for the degradation of unassembled, damaged or misfolded proteins, as well as the prompt degradation of proteins that require short half-lives. In addition, it degrades proteins for antigen presentation. The first step involves the poly-ubiquitination of the proteins targeted for degradation. The second major component of the pathway is the proteasome itself which is responsible for the degradation of the tagged proteins. The proteasome consists of two parts, the 20S proteasome and the 19S regulatory subunit. They combine to form the active 26S proteasome.

Protein degradation mediated by the ubiquitin-proteasome pathway is crucial to many important cellular functions and presents a target for therapy of hematological malignancies. Bortezomib is the first proteasome inhibitor to reach the clinical arena. It is a very potent and selective inhibitor the chymotryptic like enzymatic function residing in the 26S proteasome. Inhibition of this particular enzymatic activity has been associated with a variety of different biological effects, including the regulation of NF-kB, the stabilization of cell cycle regulatory proteins and the induction of apoptosis through the up-regulation of specific proapoptotic proteins. To date, the most extensively studied mechanism revolves around the inhibition of NF-kB. Many investigators have demonstrated that inhibitors of the proteasome can block the activation of the transactivating transcription factor NF-kB by inhibiting the degradation of its natural inhibitor, IkB. In normally quiescent cells, NF-kB exists in an inactivated form bound to IkB. In malignant cells, and in cells stimulated or stressed through exposure to various cytokines, cytotoxic drugs, viruses, oxidative triggers, or other mitogenic factors, IkB is phosphorylated by IkB kinase and then ubiquitinated, leading to its eventual degradation and liberation of active free NF-kB. The inhibition of NF-kB through proteasome inhibition is thought to result in the downregulation of cytokines, cell adhesion molecules and anti-apoptotic factors, eventually leading to the induction of apoptosis.

Inhibition of the proteasome has been associated with clinical effects in a variety of hematologic malignancies, including multiple myeloma (MM) and NHL. The demonstrated efficacy in the treatment of MM has led to the recent approval of bortezomib for the treatment of MM at first relapse by the EMEA and the US Food and Drug Administration (FDA). In addition, preclinical and clinical studies have demonstrated the activity of the proteasome inhibitor bortezomib in subtypes of NHL, in particular MCL and FL.

In a phase I study of bortezomib in patients with advanced hematologic

malignancies, bortezomib demonstrated significant antitumor activity in patients with refractory MM, with one patient achieving a durable complete remission (CR). Two patients with NHL also had partial responses, including one each with FL and MCL. The study demonstrated that bortezomib had a tolerable safety profile. Dose-limiting toxicities included malaise, fatigue, thrombocytopenia, and electrolyte abnormalities. Based on the activity seen in the Phase I studies, single agent Phase II trials of bortezomib in indolent lymphoma and MCL were initiated. In one study, an overall response rate of 58% was seen, with durable responses, including CRs in patients with relapsed and/or refractory FL, marginal zone lymphomas and MCL. Another study reported a slightly lower ORR of 41% in patients with relapsed and/or refractory MCL and CRs were again documented in patients with small lymphocytic lymphoma, FL and MCL.

Studies to date have demonstrated promising results of bortezomib for the treatment of NHL, and additional studies are underway to further define the role of bortezomib in this setting. Of particular interest are studies investigating the addition of bortezomib to other MCL and FL treatments, such as chemotherapy and immunotherapy.

The mechanisms by which bortezomib elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. The aim of this study was to determine the efficacy and toxicity of bortezomib in previously pretreated patients with peripheral T-cell lymphoma unspecified (PTCLU) with only skin involvement and cutaneous T-cell lymphomas (CTCL). Eligibility criteria included PTCLU or CTCL (according to REAL/WHO classification) with measurable disease; any stage, any IPI, any bone marrow status; second or more relapse or refractory disease; age ≥ 18; ECOG performance status ≤ 2; Hb ≥ 10 g/dL, ANC ≥ 1.5×10^9/L and platelets ≥ 100×10^9/L; normal hepatic, renal and cardiac functions; and voluntary written informed consent. Bortezomib was given at 1.3 mg/m^2 IV push on days 1, 4, 8 and 11 every 21 days. Restaging was done every 2 cycles. Patients were treated for up to a total of 6 cycles unless removed from study for failure to respond or toxicity. The response criteria were those recommended by NCI sponsored Working Group. At data reporting for this abstract, 15 patients were enrolled. Final efficacy and safety data will be presented.

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