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Innovative treatments: bortezomib

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 far the disease remains. For example, there are few effective treatment options for patients with mantle celI 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 alI 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 welI 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 malignandes. 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-κB, the stabilization of celI 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-κB. Many investigators have demonstrated that inhibitors of the proteasome can block the activation of the transactivating transcription factor NF-κB by inhibiting the degradation of its natural inhibitor, IkB. In normalIy quiescent celIs, NF-κB exists in an inactivated form bound to IkB. In malignant celIs, and in celIs stimulated or stressed through exposure to various cytokines, cyto-

toxic 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-κB. The inhibition of NF-κB through proteasome inhibition is thought to result in the downregulation of cytokines, celI adhesion molecules and anti-apoptotic factors, eventualIy 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.[1-3] The demonstrated efficacy in the treatment of MM has led to the recent approvaI 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.[4-7]

Some authors have reported that a key role may be played by NF-κB in the cutaneous T-cell lymphoma (CTCL) resistance to apoptosis, which supports a potential therapeutic role for bortezomib in the treatment of patients with CTCL.[6-9] Recently, our report suggested activity for the proteasome inhibitor bortezomib 1.3 mg/m^2 on day 1, 4, 8, and 11 with a 67% response rate among 15 patients, 10 of whom had CTCL[8] without any significant toxicity. On the basis of these preliminary data, several phase I-II trials are ongoing for testing bortezomib as a single agent and in combination with other drugs in CTCL and peripheral T-cell lymphoma patients.

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