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Introduction

Proteasome inhibition as a major advance in oncology

In the last several years, proteasome inhibition has emerged with remarkable rapidity as an exciting new strategy for the treatment of cancer. The expanding understanding of the vital role played by the ubiquitin–proteasome pathway in the regulation of cancer cell growth and replication has led to the development of new therapeutic approaches that have already achieved success in the treatment of patients with multiple myeloma and that appear to hold promise for the treatment of other haematological malignancies and solid tumours as well.

The proteasome is a large multisubunit enzyme complex that is present in large amounts in the nucleus and cytoplasm of all eukaryotic cells. The primary function of the proteasome is to eliminate proteins that have been tagged for degradation through addition of a polyubiquitin chain. The process of polyubiquitination is carried out by a cascade of ubiquitiating enzymes that activate free ubiquitin and add it in a sequential fashion to the target protein [1].

The ubiquitin–proteasome pathway thus controls the level of numerous cellular proteins, many of which are involved in the regulation of critical cellular processes. In particular, proteasome-mediated proteolysis has been shown to play an important role in the regulation of cell-cycle progression, genomic transcription, apoptosis, chemotaxis, cell adhesion, and angiogenesis [1–3]. Disruption of proteasome function is associated with a broad array of effects, particularly in rapidly dividing cancer cells that depend on high levels of growth-promoting proteins to sustain the accelerated cell migration, growth, and proliferation characteristic of the neoplastic phenotype [1]. Specific consequences of proteasome inhibition include the stabilisation of cell-cycle regulatory proteins, tumour suppressors, and inhibitory proteins such as IκB. Increased levels of IκB result in inhibition of NF-κB activation, thereby blocking NF-κB initiated transcriptional events that normally lead to cell adhesion, cytokine production, and inhibition of apoptosis [4].

Proteasome inhibition is part of the larger paradigm shift that has taken place in oncology, from empirical to molecular-based cancer treatment. Rather than utilising non-specific targets such as DNA, therapy can now be directed at specific cancer-associated proteins, signal transduction pathways, and processes such as apoptosis, angiogenesis, and proteasome-mediated protein degradation. In the future, genomics holds the promise of identifying genetic markers in individual patients, which will make it possible to apply targeted therapy even more selectively.

What is the special significance of proteasome inhibition in the new paradigm? First, proteasome inhibition targets a novel mechanism, the ubiquitin–proteasome pathway. In preclinical models, proteasome inhibition has been shown to have a selective effect against tumour cells, most likely due to the presence of higher levels of ubiquitinated proteins in cancer cells and the critical role played by NF-κB in the oncogenesis of many tumours [4]. Importantly, proteasome inhibition has been shown to overcome drug resistance mechanisms [5]. In addition to inhibition of NF-κB, proteasome inhibition acts through multiple mechanisms including direct effects on tumour cells and indirect effects involving suppression of cytokines that promote tumour cell adhesion, growth, and drug resistance. In multiple myeloma, proteasome inhibition affects both the myeloma cell and the bone marrow microenvironment essential to myeloma cell survival [4,6].

Bortezomib is a novel dipeptide boronic acid molecule that potently and reversibly inhibits the 26S proteasome [1–3]. It was the first proteasome inhibitor to enter clinical testing and in June 2003 received accelerated approval in the United States for treatment of patients with multiple myeloma who have failed at least two prior lines of treatment. In Europe, bortezomib received a positive recommendation for marketing approval in January 2004. In 193 patients with heavily pre-treated multiple myeloma, most of whom were refractory to virtually all available anti-myeloma therapy, treatment with bortezomib produced an overall response rate of 35%, including a complete or near-complete response in 10%, with a median duration of response of 12 months and a median overall survival of 16 months [3]. Bortezomib has also demonstrated activity in the treatment of patients with refractory lymphoma [7] and is now being actively tested in patients with a variety of solid tumours.

This supplement presents the proceedings of a symposium held in conjunction with ECCO 12 in Copenhagen, Denmark, on 21 September 2003. Over the course of five sessions, a distinguished group of researchers who have contributed actively to the

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burgeoning field of proteasome research presented data addressing (1) the importance of the proteasome as a novel therapeutic target, (2) the biological effects and anti-tumour mechanism of action of the proteasome inhibitor bortezomib, (3) the therapeutic effects of bortezomib in multiple myeloma, (4) the clinical profile of bortezomib in other haematological malignancies, and (5) the clinical potential of proteasome inhibition in solid tumours. Proteasome inhibition has moved from the laboratory to the clinic in an unusually short period of time. The reports contained in this symposium summarise what we know today. Questions for future clinical development will include how best to use proteasome inhibition at various stages of disease and how best to combine proteasome inhibitors with cytotoxic agents and other novel anti-cancer therapies.

Conflict of interest statement

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