Leukemia Research 38 (2014) 1–9

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Review

New orally active proteasome inhibitors in multiple myeloma

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ARTICLE INFO

Article history:
Received 19 August 2013
Received in revised form 17 October 2013
Accepted 20 October 2013
Available online 29 October 2013

Keywords:
Multiple myeloma
Proteasome inhibitor
Therapy
Oral administration
Bortezomib
Carfilzomib
Marizomib
Ixazomib
Delanzomib

ABSTRACT

Bortezomib is the first proteasome inhibitor approved for the therapy of multiple myeloma (MM). Although Bortezomib has renovated the treatment of MM, a considerable proportion of subjects fail to respond to Bortezomib treatment and almost all patients relapse from this drug either alone or when used in combination therapies. However, the good clinical outcome of Bortezomib treatment in MM patients gave impulsion for the development of second generation proteasome inhibitors with the ambition of improving efficacy of proteasome inhibition, enhancing antitumor activity, and decreasing toxicity, as well as providing flexible dosing schedules and patient convenience.

This review provides an overview of the role of oral proteasome inhibitors including Marizomib, Oprozomib, Delanzomib, chemical proteasome inhibitors, and cinnabaramides, in the therapy of MM, focusing on developments over the past five years.

These emerging drugs with different mechanisms of action have exhibited promising antitumor activity in patients with relapsed/refractory MM, and they are creating chances to target multiple pathways, overcome resistance, and improve clinical outcomes, mainly for those subjects who are refractory to approved agents.

Future steps in the clinical development of oral inhibitors include the optimization of the schedule and the definition of their antitumor activity in MM.

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Contents

1. Introduction

The ubiquitination and proteasome degradation pathway is a multistep enzymatic cascade in which ubiquitin is conjugated via a lysine residue at position 48 to target proteins for destruction. Proteins tagged with lysine 48-linked chains of ubiquitin are marked for degradation in the proteasome enzyme complex [1].

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0145-2126/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.leukres.2013.10.018

Table 1
Summary of the most relevant oral proteasome inhibitors in multiple myeloma.

	Type	Administr.	Development status	Structure	MTD	Resp.
Marizomib (NPI-0052)	Irreversible	i.v.; oral	Phase I	Salinosporamide	0.4 mg/m^2 over 1 h	>PR19%
Ixazomib (MLN9708/MLN2238)	Reversible	i.v.; oral	Phase I/II	Boronic acid	2 mg/m^2	>PR 11–13%
Oprozomib (ONX0912)	Irreversible	Oral	Phase I	Epoxiketone		
Delanzomib (CEP-18770)	Reversible	i.v.; oral	Phase I/II	Boronic acid	2 mg/m^2	No response

Ligation with ubiquitin initiates the ATP-driven process, which is achieved within the cylindrical core of the 20S proteasome [2]. In fact, the 26S proteasome consists of a barrel-shaped 20S proteolytic core, made of 2 identical α-subunit rings and 2 identical β-subunit rings, plus 2 19S regulatory complexes that cap the 20S barrel. Proteins destined for degradation are first polyubiquitinated; the 19S cap distinguishes and binds ubiquitinated proteins, and directs them to the 20S core, where proteolytic cleavage is mediated by 3 β-subunits: β1 (caspase-like activity), β2 (trypsin-like activity), and β5 (chymotrypsin-like activity). Disruption of proteasome activity results in growth arrest and cell death because of induction of an apoptotic cascade, as a result of the rapid amassing of incompatible regulatory proteins within the cell [3,4].

The ubiquitin-proteasome pathway is responsible for degradation of the majority of regulatory proteins in eukaryotic cells, including proteins that control apoptosis, cell-cycle progression, and DNA repair, and for that reason plays a critical role in preserving normal cellular homeostasis. Inhibition of the proteasome leads to stabilization and accumulation of these proteasome substrates, resulting in concomitant activation of pro- and anti-proliferative signals, disruption of cell-cycle regulation, and, ultimately, activation of apoptotic pathways and cell death [5,6].

Neoplastic cells usually have higher levels of proteasome activity compared with normal cells and, in addition, are more sensitive to the proapoptotic effects of proteasome inhibition than normal cells, making the proteasome a rational therapeutic target in multiple myeloma. Based on promising preclinical results, proteasome inhibition has been widely explored as a therapeutic strategy in MM, and proteasome inhibitors (PIs) now form a keystone of antimyeloma treatment [7,8].

MM is in fact a neoplastic proliferation of plasma cells, which normally serve as engines for the synthesis of immunoglobulins. It is perhaps paradoxical, therefore, that one of the most successful therapeutics against this disease disrupts normal protein homeostasis, by targeting the proteasome [9].

Bortezomib is the first PI approved by the US Food and Drug Administration for the treatment of relapsed MM [10]. Bortezomib-induced cell death is related with induction of endoplasmic reticulum stress and activation of the unfolded protein response, inhibition of the nuclear factor kappa B inflammatory pathway, activation of caspase-8 and apoptosis, and augmented generation of reactive oxygen species [11].

Even if the approval of Bortezomib has modified treatment of MM, a large amount of patients fail to respond to Bortezomib therapy, and almost all patients relapse from this drug, either when it is used alone or as combination therapies.

Carfilzomib is a highly interesting compound, which can provide responses in cases of MM in which Bortezomib is inactive. Carfilzomib (previously known as PR-171) is a tetrapeptide epoxyketone-based, irreversible proteasome inhibitor. As an irreversible inhibitor, Carfilzomib produces more sustained inhibition of the proteasome, compared with Bortezomib, because synthesis of new proteasome complexes is required to reverse the effects of Carfilzomib. Compared with Bortezomib, Carfilzomib is a more potent and more selective inhibitor of the chymotrypsin-like activity of the proteasome and the immunoproteasome. Carfilzomib remains cytotoxic to some cells that are resistant to Bortezomib. For example, Carfilzomib induced cell death in CD138-positive multiple myeloma cells from Bortezomib-refractory patients [12].

It was granted approval in 2012 in the United States for Relapsed or Resistent MM, based on efficacy results from the single-arm trial PX-171-003-A17, 8 and combined safety data from 4 phase 2 studies (PX-171-003-A0 [003-A0], PX-171-003-A1 [003-A1], PX-171-004 [004], and PX-171-005 [005]) [13].

Notably, the incidence of peripheral neuropathy was low overall (13.9%), including in patients with baseline peripheral neuropathy (12.7%). Additionally, the incidence of discontinuations or dose reductions attributable to adverse events was low.

Other PIs with diverse mechanisms of action have been developed, in an effort to overcome resistance to Bortezomib and develop proteasome inhibitors with different toxicity profiles. These additional PIs include drugs that bind irreversibly to the active sites of the proteasome, as well as molecules that allosterically inhibit the function of the proteasome by binding the complex outside of the active site [14].

Nevertheless, "second generation" PIs representing distinct structural classes (peptidyl epoxyketones, beta-lactones, peptidyl boronic acids, and salinosporamides), affinities for the different catalytic sites within the proteasome core, pharmacological and pharmacodynamic activity profiles, mechanisms of action and therapeutic indices have now entered clinical development (Table 1). These agents may expand the clinical utility of PIs inhibitors for the treatment of MM, and solid tumors [15–17].

This review provides an overview of the role of oral PIs including Marizomib, Ixazomib, Oprozomib, Delanzomib, chemical proteasome inhibitors and cinnabaramides, in the treatment of MM, focusing on developments over the past five years.

2. Marizomib (NPI-0052)

Because of their peptidic composition, PIs such as Carfilzomib and ONX0192 can be degraded by endogenous proteases and peptidases in the plasma, which reduces their efficiency. Thus, there is interest in developing nonpeptidic PIs, which should have better bioavailability than the peptidic PIs. A series of such compounds are the omuralide derivatives, which include Marizomib.

The genus *Salinispora* represents a group of diverse actinomycetes that is widely distributed in ocean sediments [18,19].

Salinispora tropica was first isolated from a heat-treated marine sediment sample collected in the Bahamas. The potent biological activity of crude extracts obtained from shake-flask culture and solid phase extraction, led to the isolation of the major secondary metabolite *salinosporamide A*.

In 2003, Feling et al. reported that *S. tropica* produced the effective and structurally novel proteasome inhibitor *salinosporamide A* (Marizomib; NPI-0052) [20].

Structure elucidation revealed its dense functionality, including the fused bicyclic β-lactone-γ-lactam core reminiscent of omuralide and 5 contiguous stereocenters (2R, 3S, 4R, 5S, and 6S).

The crystal structure of Marizomib, in complex with yeast 20S CPs, reveals that it is covalently bound to all proteolytic subunits

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