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Jacobs Journal of Cell and Molecular Biology

Review Article

Proteasome Inhibition in Lymphoproliferative Disorder

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Received: 02-26-2015

Accepted: 03-20-2015

Published: 04-02-2015

Abstract

Proteasomes are multi-subunit protein complexes, which present numerous targets for therapeutic interference. The most commonly used proteasome is 26S proteasome, which contains one 20S proteolytic core subunit and two 19S regulatory cap subunits. There are three different types of active sites of 20S proteolytic core and both, natural and synthetic proteasome inhibitors have been developed for this active site. The bortezomib is a Peptide boronate proteasome inhibitor and it targets the vital degradation process of intracellular protein, through proteasome. It is used for the treatment of non-Hodgkin lymphoma (NHL), mantle cell lymphoma, and multiple myeloma. There are newly developed Merizomib, Carfilzomib, ONX-0912, TMC-95A, and Syringolin A proteasome inhibitors, which are being evaluated in clinical trials for the treatment of lymphoma and other cancers. The mechanisms of proteasome inhibitors are very typical because they affect various pathways, which are not completely understood. The mechanism of action of bortezomib is distinct from the other proteasome inhibitors, which are used in NHL treatments. There are various preclinical evidences, which indicate that the proteasome inhibitors have additive or synergistic property, with a bulk quantity of agents, either in vivo or in vitro, from cytotoxic to biological, which support an increasing quantity of combination studies, recently in progress in NHL patients.

Keywords: Proteasome Inhibitor; Bortezomib; Non-Hodgkin Lymphoma; Ubiquitin-Proteasome Pathway

Introduction

Lymphoma is a common hematologic malignancy, which presents itself in two forms: Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL). Lymphoma occurs due to the abnormal proliferation of lymphocytes, a subdivision of white blood cells. Lymphocytes are mainly of two types: T-lymphocyte (T-cells) and B-lymphocytes (B-cells). The NHL is the most common hematologic malignancy, and according to World Health Organization (WHO), NHL has around 61 different types. NHL is classified in to two groups: T-cell lymphomas and B-cell lymphomas. The T-cell lymphomas evolves from abnormal T-lymphocytes, which hold around 15% of all NHL and B-cell lymphomas evolves from abnormal B-lymphocytes, which hold around 85% of NHL. Night sweats, fever, lack of energy, weight loss, and swelling of lymph node are among the common symptoms of NHL [1].

There are more than 70,000 patients suffering from NHL annually, in the United States [2] and one out of three patients dies, within five years, after the diagnosis [3].WHO developed a group, in which malignancies are classified, according to their cell of origin such as T- cells, B-cells, natural killer cells and HL (Table-1).

Mature B-cell neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable
*Splenic diffuse red pulp small B-cell lymphoma**
Hairy cell leukemia-variant*
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Heavy chain diseases
Alpha heavy chain disease
Gamma heavy chain disease
Mu heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
Pediatric follicular lymphoma
Primary cutaneous follicular center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), NOS
T-cell/histiocyte-rich large B-cell lymphoma
EBV+ DLBCL of the elderly
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Large B-cell lymphoma arising in HHV-8–associated multicentric Castleman disease
Primary effusion lymphoma
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma

Mature T-cell and NK-cell neoplasms

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells*
Aggressive NK cell leukemia
Systemic EBV+ T-cell lymphoproliferative disease of childhood
Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
*Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma**
*Primary cutaneous CD4+ small/medium T-cell lymphoma**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK+
*Anaplastic large cell lymphoma, ALK−**

Hodgkin lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma
Classic Hodgkin lymphoma
Nodular sclerosis classic Hodgkin lymphoma
Lymphocyte-rich classIc Hodgkin lymphoma
Mixed cellularity classic Hodgkin lymphoma
Lymphocyte-depleted classic Hodgkin lymphoma

Posttransplantation lymphoproliferative disorders (PTLDs)

Early lesions
Plasmacytic hyperplasia
Infectious mononucleosis-like PTLD
Polymorphic PTLD
Monomorphic PTLD (B and T/NK-cell types)†
Classic Hodgkin lymphoma type PTLD†

***Provisional entities for which the WHO Working Group thought there was insufficient evidence to recognize as distinct diseases at this time.**
†These lesions are classified according to the leukemia or lymphoma to which they correspond. Diseases shown in italics were newly included in the 2008 WHO classification.

Table 1. Major World Health Organization subtypes of B-cell, T-cell, NK-cells, and Hodgkin's lymphoma .[4]

Follicular lymphoma (FL) is a most common and indolent subtype of NHL, which consists of about 22% of all the cases of NHL [5,6], whereas diffuse large B cell lymphoma (DLBCL) is a most common aggressive lymphoma in adults. Mantle cell lymphoma contains around 5% cases, of all the cases of NHL in Europe and North-America [7-11].Even then, lots of the patients finally relapse [12].For relapsed cases of NHL, namely DLBCL, the combination of stem cell transplantation and high dose chemotherapy is very effective [13].

Rituximab has showed enhanced objective response rate (ORR), and complete remission rates (CR), in both aggressive and indolent lymphomas of B cell origin, since its development, along with the combination in the B-cell NHL treatment protocols, in the last three decades. However, overall survival and remission rate in NHL mainly depends on the subtype of disease because NHL in a non-homogenous group of diseases, with different pathophysiology, patient's characteristics and response rates to various treatment protocols. Along with this, there are always a number of patients, showing early relapse or refractoriness with the standard therapies. The combination of autologous stem cell transplantation and high dose chemotherapy is efficient for relapsed NHL, but the final prognosis is generally poor in this group of patients, with primary failures and early relapse [13].These observations emphasize on the requirement of novel therapeutic options for NHL, especially relapsing and primary refractory cases.

Ubiquitin-Proteasome System: Ubiquitin is the developing part of a family of structurally preserved proteins, which controls a host of process in the eukaryotic cells. Ubiquitin and its other relatives achieve their functions via covalent attachment to the other cellular protein, thereby changing the activity of target protein, localization, and stability [14].The ubiquitin is a small 8.5 kD regulatory protein, which is present in all the cells with nuclei (eukaryotes). The ubiquitin proteasome pathway is the mechanism for the catabolism of protein in the mammalian nucleus and cytosol. It affects various cellular processes, defects, and substrates in the system.

Ubiquitin is a marker of protein, which is connected to the protein, in order to mark them for the elimination through the cells. Sometimes ubiquitin pathway is used for the clearance of harmful viral proteins, which infect the cells, or recycle resources. The ubiquitin system plays an important role in various cellular processes, which includes apoptosis, cell cycle and division, antigen processing, differentiation and development, viral infection, biogenesis of organelles, immune response and inflammation, morphogenesis of neural network, ribosome biogenesis, neural and muscular degeneration, modulation of cell surface receptors, ion channels and the secretory pathway, DNA transcription and repair, and response to stress and extracellular modulators [15].

The proteasome is a non-lysosomal endoprotease, which is present in the nucleus and cytoplasm of eukaryotic cells and some bacteria. It is also responsible for quality control of protein, by removal of abnormal and damaged proteins. It is a large hollow cylindrical 26S enzymatic complex of 2.5 MDa, which is comprised of at least 66 proteins, with chaperone proteins [16-18].

It is made up from two 19S or 11S regulatory units and catalytic 20S unit at either ends. The catalytic 20S core is systemized into a bunch of four to seven subunit rings, and seven polypeptides forms the top and bottom rings, known as α-subunits, and two rings of the seven β-subunits. The poly-ubiquitination drags the interaction between 20S particle and 19S (11S) particle, and it needs three enzymes: Ubiquitin activating enzyme (E1), Ubiquitin conjugating enzyme (E2), Ubiquitin protein ligase enzyme (E3) [19].

There are different mechanisms behind the poly-ubiquitination; one mechanism stated that ubiquitin is added continuously to grow the chain, which is known as elongation [20,21]. Other mechanism stated that poly-ubiquitin chain is preformed and after that added to the target protein [22].The 19S particle has an affinity and recognizes the N-terminal ubiquitin like (UBL) domain, which is an integral part of the ubiquitin receptor proteins. When 19S recognize the poly-ubiquitinated protein, then hydrolases unfold the substrate protein, and it enters to 20S particle and gets degraded.

The 20S core proteolytic chamber has three different catalytic activity and that are caspase-like (β1 subunit), trypsin-like (β2 subunit), and chymotrypsin-like (β3 subunit). In immune cells, these subunits are replaced by β1i, β2i, and β3i induced subunits, which compress the immunoproteasome. The immunoproteasome presents, trypsin-like and chymotrypsin

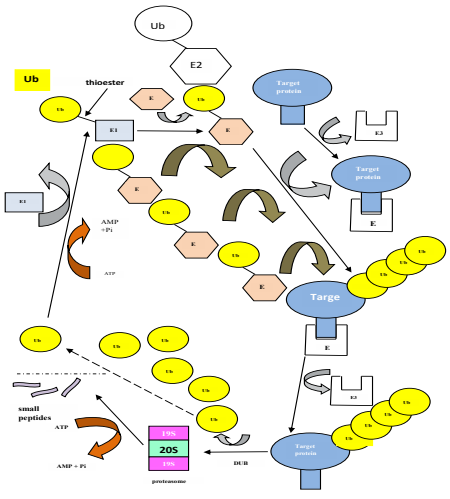

Figure 1. Ubiquitin-proteasome pathway (UPP). E1, which is dependent on ATP,is activated by ubiquitin (Ub), using C-terminal adenyla-

tion. It is followed by high-energy thioester formation. The activated Ub transfers from E1 to E2, with the preservation of thioester bond. E3 is responsible for the Ub transfer to the target protein, from E2. The chain of polyubiquitin can be dissociated using deubiquitinating enzymes (DUBs), for the target proteins. These free Ubs can then involve in next substrate targeting..

like activity, as compared to the normal eukaryotic proteasome, which support in antigen processing [18].The immunoproteasome employ the 11S regulatory particle, on behalf of 19S, which opens the 20S gate and energize the translocation and unfolding of substrate. Same thing happens with 19S because 11S binds to 20S through its C-terminal tails and the proteolytic gate opens, due to the conformational changes of α-ring [23].

Proteasome Inhibitors: This is a special approach, which targets the proteasome function for the treatment of cancer. The different tests and development of proteasome inhibitors are in process, which attach to the active site of the proteasome and inhibit composite, irreversibly. Some other proteasome inhibitors are in preclinical development, which acts in the catalytic center, at the site of proteasome. The proteasome inhibitors are of different types and these inhibitors have different drugs (Table 2).

Chemical Class	Drug	Therapeutic Use
Peptide Boronate	Bortezomib	EMA and FDA approved for the treatment of mantle cell lymphoma, multiple myeloma
	MLN-9708(Ixazomib), MLN-2238	Under clinical examination for the treatment of non-Hodgkin lymphoma, refractory multiple myeloma and non-hematologic malignancy for which treatment is no longer effective (Head-neck cancer, prostate cancer, NSCLC, soft-tissue sarcoma)
	CEP-18770	Under clinical examination for the treatment of non-Hodgkin lymphoma, refractory solid tumors, relapsed multiple myeloma
Peptide aldehydes	MG132, PSI, CEP1612	Block chymotrypsin-like activity, but no potential therapeutic effect in cancer treatment.
β-lactone-γ-lactam inhibitors	Marizomib	Under clinical examination for the treatment of refractory/relapsed multiple myeloma, advanced solid tumors (Malenoma, pancreatic cancer, NSCLC) and refractory lymphoma
	Lactacystin	Preclinical examination only
Peptide epoxyketone inhibitors	Carfilzomib	Under clinical examination for the treatment of advanced solid tumors (NSCLC, SCLC, ovarian and renal cancer), primary, refractory or relapsed multiple myeloma
	ONX-0912 (Oprozomib)	Under clinical examination for the treatment of advanced refractory or recurrent solid tumors
	Eponemycin	Preclinical examination only
	Epoxomicin	Preclinical examination only
Peptide Amide	Fellutamide-B	Preclinical examination only
	TMC-95A	Preclinical examination only

Table 2. Different Proteasome inhibitors with its therapeutic uses [24].

There are following proteasome inhibitors:

Peptide boronates inhibitors:

These types of inhibitors are great in their potency and target the proteasome. The hydroxyl group of N-terminal threonine residue binds these inhibitors, through a non-covalent bond in the proteasome. A strong tetrahedral intermediate is formed because boron atom can gain loan pair of oxygen molecule of N-terminal threonine residue [19].These inhibitors are not inactivated through the oxidation and are not secreted from the cell through the multi-drug resistance (MDR) carrier system [23].

Bortezomib is an example of peptide boronate proteasome inhibitors, which is used as a possible therapeutic agent for the treatment of cancer and contains boronic acid.. It is a dipeptidyl boronic acid inhibitor, which has a great specificity for 26S proteasome [25].Bortezomib inhibits the function of proteasome, by binding to the chymotrypsin-like β5 subunit of 20S particle [26].The interaction between bortezomib and proteasome is shown in Figure 2.

In 2008, U.S. Food and Drug Administration approved bortezomib for multiple myeloma patients in the form of injection. This was the result of an approval from a clinical trial, using bortezomib for multiple myeloma treatment [27].

Bortezomib interferes with the degradation or recycling of intracellular protein, by binding to the core subunits of proteasome, which induces apoptosis (Figure-3) [28].Bortezomib inactivates the nuclear factor- κB (NF-κB), by maintaining NF-κB inhibitor, IκB, [29-34].which plays a key role in stress, cell cycle or growth arrest, and apoptosis.

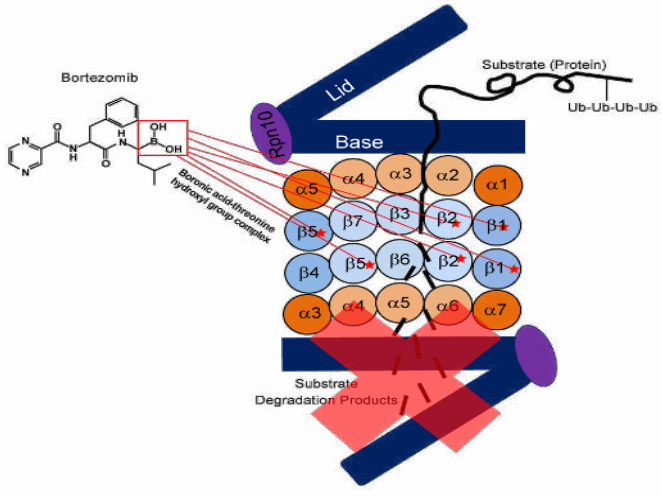

Figure2. Proteasome inhibition by bortezomib. Bortezomib is a dipeptidyl boronic acid inhibitor which inhibits the chymotrypsin threonine protease activity. Boronic acid is having high affinity to fits the

active sites of proteasome (shown as stars) and at chymotrypsin-like active site, it produces a composite with threonine hydroxyl group (Thr1) which works as a reversible inhibitor of proteasome and it is enough to inhibit proteolysis [23].

Bortezomib induces apoptosis by improving the cytochrome C release [35],inspiring the production of reactive oxygen species [36], misleading the two inhibitors p21 and p27 of cyclin-dependent kinase (CDK) and also tumor suppressor protein, p53 [31,33,35].It also increases the interpretation of tumor necrosis factor alfa, which is associated with apoptosis and activating ligand (TRAIL) and TRAIL receptors [37]. Bortezomib affects B-cell lymphoma 2 (Bcl-2) family of regulatory proteins, activation of proapoptotic Bcl-2 family of regulatory proteins [30,35,36,38]., and it is also involved in the inhibition of anti-apoptotic Bcl-2 family of regulator proteins [29,36,38]. Bortezomib inhibits proteasome and subscribe to the cell growth or cell cycle arrest through the interruption in the oscillation of cyclins A, B, D, E, but the cytotoxic activity of bortezomib may be free of cyclin D1 levels in NHL [39]. In the inclusion of NF-κB effects, the stress response can be increased, due to the different effects of proteasome inhibition on chemo sensitization and radio sensitization, especially in the cell lines, which are dependent on nuclear factor- κB (NF-κB) [40,41]. This proteasome inhibition can also affect the microenvironment through the inhibiting adhesion molecules, growth factors, and cytokines [42].

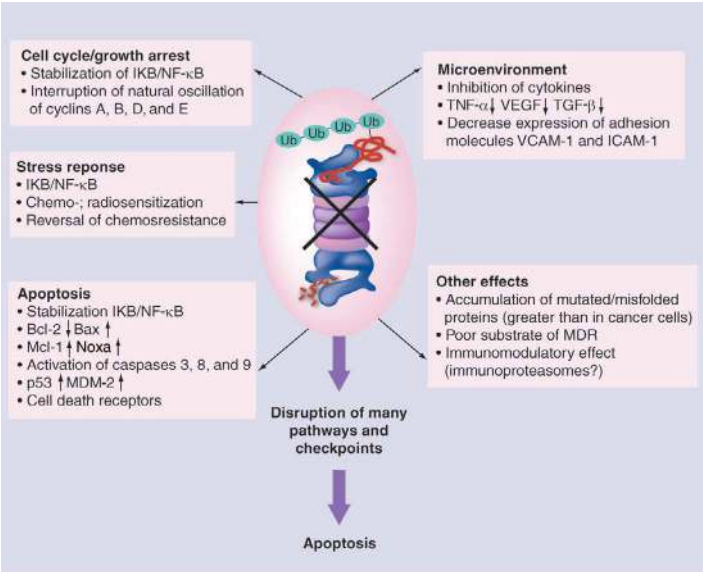

Figure 3. Bortezomib inhibitor affects multiple signaling pathways [43].

Peptide aldehydes inhibitors:

The first proteasome inhibitor was the synthetic peptide MG 132: a peptide aldehyde proteasome inhibitor, which reacts against the cysteine and serine proteases and through a nucleophilic binding. The residue of N-terminal threonine, executes a nucleophilic attack at the active site of proteasome, on the aldehyde moiety of inhibitor and construct a covalent hemiacetal adduct between the threonine residue and the inhibitor [18]. These inhibitors are immediately oxidized into the inactive acids and secreted from the cells, through multi-drug resistance (MDR) carrier system. Some of the peptide inhibitors block the activity of chymotrypsin of proteasome; even though, they are not convenient as a therapeutic agent for the cancer treatment [23].

Peptide epoxyketone inhibitors:

Recently, two peptide epoxyketone inhibitors are being tested clinically, e.g., ONX-0912 (Oprozomib) and Carfizomib. This inhibitor includes α, β-epoxyketone moiety, which is involved in the production of a morpholino compound, with N-terminal threonine residue in the proteasome and it inactivates the function of proteasome [19]. Oprozomib is the irreversible inhibitor of chymotrypsin-like subunit of proteasome and its route of administration is oral. Now, Oprozomib is in the phase I and II clinical trials, which is used for the treatment of multiple myeloma in the first line and relapsed cases [23].

Carfilzomib is also irreversible inhibitor of chymotrypsin-like subunit of immunoproteasome and proteasome, and it has also demonstrated the preclinical effectiveness for both in vivo and in vitro studies, against different hematological and solid malignancies [44]. It is used for the treatment of multiple myeloma, solid tumors, and non-Hodgkin lymphoma type diseases and its route of administration is intravenously. Now, Carfilzomib is in the phase I to III of several clinical trials and it shows synergistic effect with dexamethasone, which enhances cell death in multiple myeloma, specifically.

A study conducted by FDA for carfilzomib,analyzed on the 266 patients with relapsed multiple myeloma, who had undergone at least two prior therapies, which included bortezomib and other immunomodulatory agent. The primary efficacy endpoint was overall response rate (ORR) and it was 22.9% (95% CI: 18.0, 28.5), which consisted of one complete response, 47 partial response, and 13 very good partial responses. The average time duration was 7.8 months (95% CI: 5.6, 9.2) [27].

It distinguished that carfilzomib is particular towards the chymotrypsin-like subunit of proteasome than bortezomib [19]. The mechanism of action of carfilzomib is similar to bortezomib, but it inhibits proteasome irreversibly, it is selective for chymotrypsin-like (CT-L) active site [45].

β-lactone-γ-lactam inhibitors:

These inhibitors interact with β-lactone-γ-lactam moiety, and are used to treat malignant cells. Marizomib, from this group

of proteasome inhibitors, is a β-lactone-γ-lactam inhibitor and is an irreversible inhibitor of trypsin-like, chymotrypsin-like, and caspase-like activity of the immunoproteasome. Marizomib is recently being investigated in both Phase I and Phase II of clinical trials for the treatment of multiple myeloma, as a single agent or in combination with dexamethasone. Some reports indicated the side effects of marizomib, which include dizziness, vomiting, weight loss, nausea, fatigue, and shortness of breath. The pre-clinical and early phase clinical trials stated that marizomib is well tolerated drug for the treatment of multiple myeloma [46].

Marizomib inhibits 20S proteasome and encourages apoptosis in multiple myeloma cells, which are resistant to bortezomib and other conventional therapies, without affecting the viability of normal lymphocytes. It is totally different from bortezomib. It has long-lasting pharmacodynamic properties than bortezomib and the recovery of proteasome activity can be observed, within 24 hours, after the treatment with marizomib [47]. Data indicated that a single dose of marizomib leads to the inhibition of 20S proteasome catalytic activity. The treatment with marizomib (0.5mg/kg) projected 90-99% 20S proteasome inhibition, in whole blood and maximum 11.5% of the weight loss was observed [48].

Peptide Amide inhibitors:

Peptide amide inhibitors are natural inhibitors of proteasome such as TMC-95A, Fellutamide-B, Argyrin A, and Syringolin A. TMC-95A is isolated from a fermentation broth of Apiospora montagnei [49]. TMC-95 restrains each of the three proteasomal movement, with IC50 estimation of 5.4, 200, and 60 nm, separately. At the point when co- crystallized with the yeast proteasome, it was distinguished that TMC-95a, particularly blocks the active site of proteasome, non-covalently [50, 51].
Syringolin A is a type of macro-cyclic vinyl ketone inhibitor, which is separated from plant pathogen Pseudomonas syringae pv. Syringolin A is found to encourage the changes in the gene expression. It inhibits the function of proteasome through the hydroxyl group of catalytic threonine residue and it also causes a Michael type 1, 4-addition to the vinyl ketone moiety, in the ring of Syringolin A. Thus, it irreversibly inhibits every one of the three types of proteasomal activity and it was also distinguished that at therapeutic concentration, the rhodamine-tagged Syringolin A, specifically binds to the active site of proteasome and also labels the proteasome active sites [52].

Drugs Tested	Clinical Trial Phase	Clinical Trial Identifier	No. of Patients/Duration/Method/Study	Result Outcome
Ixazomib Citrate	Phase 3	NCT021813	652 patients, Randomized, Placebo-Controlled, Double-Blind Study	This study is currently recruiting participants.
CEP 18770	Phase 1 and Phase 2	NCT013489	11 patients, Non-Randomized, Safety/Efficacy Study, Single Group Assignment, Open Label	This study has been terminated.
MLN-2238	Phase 1	NCT021766	40 Patients, Randomized, Double-Blind, Placebo-Controlled, Safety	This study is currently recruiting participants.
Bortezomib	Phase 2	NCT004088	11 patients, 30 days, Safety/Efficacy Study, Single Group Assignment, Open Label	The whole response in an organ is defined as there is no proof clinical or biochemical signs of AGVHD. For the complete valuation, it is defined as complete resolution of rash, absence of diarrhea, and abnormal LFTs. The partial response is that one stage decrease in any organ system without deteriorating in other organ systems.
Marizomib	Phase 1	NCT0066782	22 patients, 100 months, Non-Randomized, Safety/Efficacy Study, Single Group Assignment, Open Label	This study has been completed but result is not mentioned
Carfilzomib	Phase 1	NCT02257476	30 patients, Safety Study, Single Group Assignment, Open Label	This study is currently recruiting participants.
ONX-0912 (Oprozomib)	Phase 1 and Phase 2	NCT01881789	118 patients, Non-Randomized, Safety /Efficacy Study, Parallel Assignment, Open Label	This study is currently recruiting participants

Table 3. Proteasome inhibitor drugs with its clinical trials update [53].

Conclusion

There are few types of malignant lymph proliferative diseases, which have been recognized so far, to be susceptible to the treatment with bortezomib (Proteasome inhibitor), either alone or in combination with different anti-cancer therapies. There are some clinical evidences, which favor the activity of bortezomib combination with standard treatments, like R-CHOP and Rituximab for B-cells NHL. The various long term data and clinical trials have shown promising results, in terms of safety and efficacy of combination of proteasome inhibitor with standard treatment for mantle cell lymphoma. The different combinations of proteasome inhibitors with other targeted agents, express additive or synergistic effects. The development of novel proteasome inhibitor is in progress, which can block the catalytic active site of proteasome in tumors and enhance the therapeutic effectiveness of standard chemotherapy, targeted therapy or radiation therapy, as well as reduce the resistance to irradiation and chemotherapies in tumors. A

deep study is required to completely identify the safety and the therapeutic range of proteasome inhibitors, and its effect on immune system against cancer.

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