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Oxidative Stress and Proteasome Inhibitors in Multiple Myeloma

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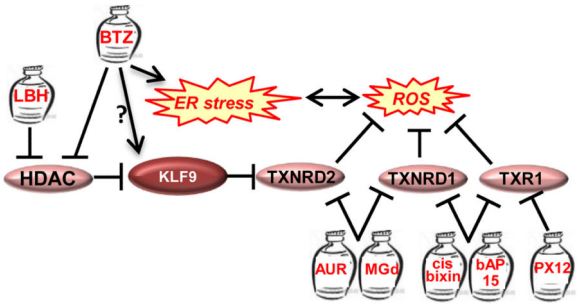
Abstract

Multiple myeloma is a form of plasma cell neoplasm that accounts for approximately 10% of all hematological malignancies. Recently, several novel drugs have been discovered that almost doubled the overall survival of multiple myeloma patients. One of these drugs, the first-in-class proteasome inhibitor bortezomib (Velcade) has demonstrated remarkable response rates in multiple myeloma patients, and yet, currently this disease remains incurable. The major factor undermining the success of multiple myeloma treatment is a rapidly emerging resistance to the available therapy. Thus, the development of stand-alone or adjuvant anti-myeloma agents becomes of paramount importance. Overproduction of intracellular reactive oxygen species (ROS) often accompanies malignant transformation due to oncogene activation and/or enhanced metabolism in tumor cells. As a result, these cells possess higher levels of ROS and lower levels of antioxidant molecules compared to their normal counterparts. Unbalanced production of ROS leads to oxidative stress which, if left unchecked, could be toxic for the cell. In multiple myeloma cells where high rates of immunoglobulin synthesis is an additional factor contributing to overproduction of ROS, further induction of oxidative stress can be an effective strategy to cope with this disease. Here we will review the available data on the role of oxidative stress in the cytotoxicity of proteasome inhibitors and the use of ROS-inducing compounds as anti-myeloma agents.

Graphical abstract



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1. Multiple Myeloma

Multiple myeloma arises from oncogenic transformation of plasma cells, a type of white blood cell normally responsible for producing antibodies [1,2]. Multiple myeloma cells accumulate in the bone marrow where they interfere with the production of normal blood cells. The progression of multiple myeloma can be subdivided in stages, which are characterized by the proliferation of a single clone of plasma cells producing homogenous monoclonal (M) protein, also known as abnormal immunoglobulin, and is often assessed by measuring the amount of M protein in the serum [2-4]. The first stage, monoclonal gammopathy of undetermined significance (MGUS), is characterized by less than 30g/l of M protein in the serum or less than 10% plasma cells in the bone marrow and the absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia or bone lesions [3,4]. Smouldering multiple myeloma (SMM), the next stage of the disease, is characterized by a M protein serum concentration of 30g/l or greater and/or 10% or more plasma cells in the bone marrow with no end-organ damage and is thought to precede multiple myeloma [2,5]. Progression to multiple myeloma from SMM occurs in approximately 10% cases a year vs progression to multiple myeloma from MGUS which accounts for approximately 1% of patients annually. Multiple myeloma is characterized by serum concentration of M protein of 30g/l or greater and/or 10% or more plasma cells in the bone marrow accompanied by end-organ damage, which is the indicator for treatment [2].

Plasma cells have the distinct ability to secret antibodies and therefore are committed to massive Ig synthesis, assembly and secretion [6]. In fact, due to this reason, even non-transformed plasma cells undergo substantial endoplasmic and oxidative stresses that are usually associated with the higher rates of protein biosynthesis and secretion [7]. The oncogenic transformation of plasma cells results in even higher protein synthesis rates ultimately leading to exacerbation of the ER stress and oxidative stress [8].

2. Oxidative Stress

Oxidative stress emerges as a result of the excessive production of reactive oxygen species (ROS) or their insufficient elimination by antioxidants [9,10]. The major sources of ROS in the cell include mitochondria (~80%), peroxisomes (where fatty acid oxidation takes part) and endoplasmic reticulum (where the oxidative protein folding occurs [11-13]). ROS detoxification in the cell involves 2 major systems: glutathione (GSH) and thioredoxin (TRX) [14,15]. The GSH system consists of GSH, glutathione peroxidases (GPX) and glutathione s-transferases (GST). GSH, GPX and GST contribute to ROS detoxification by reducing hydrogen peroxides or hydroperoxides using GSH as a substrate [14]. The TXN system includes TXN, thioredoxin reductases (TXNRD) and NADPH [15,16], and functions via reduction of the intracellular disulfides and direct quenching of ROS [16]. ROS detoxification can also occur through superoxide dismutases (SODs) that metabolize superoxide anion (O_2^-) into oxygen and hydrogen peroxide, and catalases converting hydrogen peroxide into oxygen and water [17].

Cancer cells produce higher amounts of ROS than normal cells due to oncogene activation and/or increased metabolic activity [17-19]. In these cells, elevation of ROS levels has been

shown to promote proliferation and enhance motility and invasion [18,19]. Reciprocally, antioxidants have been for a long time considered as tumor suppressing agents [20-24]. However, recently the opposite functions of antioxidants have been reported. Antioxidant N-acetylcysteine (NAC) promoted tumor progression in mouse models of oncogene-induced lung carcinogenesis [20] and increased lymph node metastasis in mouse model of melanoma [25]. Similarly, metastasizing melanoma cells have been shown to undergo metabolic changes leading to resistance to oxidative stress [26], Furthermore, recently it became apparent that tumors utilize several mechanisms of oxidative stress suppression, [27,28] the most common of which is upregulation of NRF2, a key transcriptional activator of antioxidant genes [29,30-32].

Accordingly, overproduction of ROS was identified as an inhibitor of tumor cell proliferation, viability and various transformed phenotypes [20-24;33-36]. The latter effects of ROS caused significant attention to the mechanisms regulating their production and utilization in cancer cells [35,36], and the potential exploitation of these mechanisms in novel antineoplastic agents [37]. As a result, a number of anticancer drugs that directly induce oxidative stress have been approved for treatment of several types of malignancies [37]. However none of these agents are being routinely used for treatment of multiple myeloma.

2.1. Modulators of Oxidative Stress in Multiple Myeloma Patients

The association of multiple myeloma progression with the depletion of antioxidants and the increase of pro-oxidant molecules in patient serum has been described in several reports [38-42]. Estimated serum levels of antioxidants such as superoxide dismutase (SOD1), glutathione peroxidase, catalase and vitamins C and E were lower, whereas serum levels of oxidative stress markers (including malondialdehyd and advanced oxidation protein products) were higher in multiple myeloma patients compared to healthy individuals [38-42]. Accordingly, activities of antioxidants preventing lipid peroxidation such as paraoxonase (PON1) and arylesterase (ARE) were lower in multiple myeloma patient sera [43,44]. Levels of 8-isoprostane, a product of fatty acid peroxidation, were on the contrary higher in multiple myeloma patients [43]. Moreover, decreased activities of ARE and PON1 were proposed as poor prognosis markers for a subgroup of multiple myeloma patients [44]. Additionally, serum levels of scavenger receptor class A member 3 (SCARA3), a protein protecting cells from oxidative stress, inversely correlated with myeloma progression in patients [45]. However, the molecular mechanisms underlying enhanced myelomagenesis under conditions of elevated oxidative stress in patient serum have not been reported.

Only a handful of papers describe genetic events occurring in multiple myeloma cells in the course of its progression that primarily affect intracellular redox status. Thus, overexpression of ACA11, an orphan box H/ACA class small nucleolar RNA (snoRNA) [46] was detected in cells from multiple myeloma patients as a result of t(4;14) chromosomal translocation [46]. Importantly, ACA11 was shown to inhibit oxidative stress in cultured multiple myeloma cells [46]. Additionally, higher *SOD1* mRNA levels or epigenetic silencing of glutathione peroxidase 3 gene (*GPX3*, sensitizes cells to oxidative stress) associated with multiple myeloma progression and poor prognosis [47,48].

2.2. The Role of Oxidative Stress in Cytotoxicity of Proteasome Inhibitors

Discovery of the proteasome inhibitor bortezomib (BTZ) (Velcade) has dramatically improved the overall survival of multiple myeloma patients when used as a single agent or in combination with conventional drugs such as dexamethasone [49,50]. Recently, two more proteasome inhibitors have been approved for treatment of relapsed multiple myelomas including those refractory to BTZ treatment: carfilzomib (CFZ) (Kyprolis) [51] and ixazomib (Ninlaro) [52]. These proteasome inhibitors function via reversible (BTZ, IXZ) or irreversible (CFZ) inhibition of the 20S subunit of the proteasome [49-52].

Proteasome inhibition results in accumulation of unfolded proteins, which trigger endoplasmic reticulum (ER) stress [53,54]. An unresolved ER stress, which is considered a major mediator of the cytotoxicity of proteasome inhibitors, has been shown to cause cell death via multiple pathways including overproduction of reactive oxygen species (ROS) [53,54]. Indeed, oxidative stress has been identified as an important mechanism of BTZ cytotoxicity in myeloma and non-myeloma cells [55,57,58]. For example, ROS generation has been shown to precede the initiation of BTZ-induced apoptotic cascade [59,60]. Furthermore, co-treatment with the antioxidant tiron rescued from BTZ-induced ROS generation and cell death [61,62]. In mantle cell lymphoma patients, high basal antioxidant activity was associated with reduced responsiveness and a worse outcome following BTZ treatment [63].

Oxidative stress resulting from proteasome inhibition has been long considered a byproduct of the ER stress [56]. The enzymatic components involved in ER stress-dependent ROS production include protein disulfide isomerase (PDI) [64], endoplasmic reticulum oxidoreductin (ERO-1) [64], NADPH oxidase complexes [65], and mitochondrial electron transport enzymes [65].

Under normal conditions, ERO-1 and PDI catalyze protein folding by oxidizing the cysteine residues of nascent proteins in order to form correct disulfide bonds [66]. ERO-1 uses a (FAD)-dependent reaction to transfer electrons from PDI to molecular oxygen (O_2) [67,68]. Incomplete reduction of oxygen results in the generation of ROS and ER protein-folding induced-oxidative stress [64,65]. Under conditions of ER stress, the activity of these enzymes is increased due to an elevated burden of unfolded proteins, thus higher amounts of ROS are produced as a byproduct, increasing oxidative stress.

Depletion of the glutathione (GSH) buffer system is an additional way by which oxidative stress is increased during times of ER stress [69]. GSH is used in reducing incorrect disulfide bonds, thus the presence of misfolded proteins decreases the GSH/GSSG ratio, altering the redox environment in the ER [70].

ROS produced as a byproduct of protein folding contribute only partially to the generation of oxidative stress during ER stress. Systems involved in calcium homeostasis make up another important component of ROS generation. Thus, oxidative stress can be mediated by Ca^{2+} leakage from the ER into the cytosol [71]. Ca^{2+} influences ROS production by the mitochondria via stimulation of the tricarboxylic acid cycle and oxidative phosphorylation, resulting in greater O_2 consumption [71-73]. Ca^{2+} leakage from the ER also results in

cytochrome c release from the mitochondria impairing the electron transport system and resulting in altered mitochondrial membrane potential, and as a result, production of ROS [71-73].

In addition, oxidative stress is generated as a by-product of increased mitochondrial respiration, because high levels of ATP are needed to sustain the protein folding machinery, which is a highly ATP-dependent process [74].

There is mounting evidence suggesting that NADPH oxidase complexes (NOX) are important sources of ROS during ER stress [75-79]. The NOX family of enzymes uses oxygen to mediate electron transfer via NADPH, releasing $O2^{-}$ as a by-product [75]. NOX2 [76] and NOX4 [75,77-79] are the only 2 isoforms that have so far been reported to contribute to ER stress. NOX2 causes a CHOP-mediated apoptosis in response to ER stress, and NOX2 deficiency protects mice from tunicamycin-dependent induction of apoptosis in renal cell [76]. NOX4 is induced in human vascular smooth cells during ER stress caused by the oxygenated lipid product, 7-ketocholesterol or tunicamycin [77]. Furthermore, NOX4-associated ROS alters UPR signaling and promotes the activation of RAS [79]. It is noteworthy that in addition to being a byproduct of ER stress, ROS may actually induce ER stress [76,77].

Although oxidative stress and ER stress appear to intertwine, the exact role of oxidative stress in inducing proteasome inhibitor-dependent ER stress is not well-understood. Recently, our group has identified a novel mechanism of BTZ- and CFZ-dependent induction of oxidative stress in multiple myeloma cells. We started with the identification of the transcription regulator Kruppel-like Factor 9 (KLF9) as a mediator of cytotoxicity of BTZ and histone deacetylase (HDAC) inhibitor LBH589 (panobinostat) [80,81]. In the same study we utilized a microarray-based global expression dataset that was generated for multiple myeloma cells collected from patients with relapsed myeloma before treatment with BTZ or high dose dexamethasone [82]. In combination with patient clinical response and survival data, this database serves as a valuable tool for establishing correlations between gene expression profiles and clinical outcome. Thus, we determined that KLF9 levels were significantly elevated in BTZ-responders (with no significance with regard to dexamethasone outcomes) [81]. In tissue culture settings, KLF9 levels in multiple myeloma cells correlated with BTZ-dependent suppression of histone deacetylases 1 and 2 (HDAC1 and HDAC2), and were independently increased by LBH589 [81].

A follow-up study by our group revealed that KLF9 is a ubiquitous inducer of oxidative stress acting via transcriptional repression of the gene for anti-oxidant protein thioredoxin reductase II (TXNRD2) [83]. TXNRD2 is essential for the maintenance of intracellular redox status and suppression of oxidative stress [37].

In a separate report we demonstrated that TXNRD2 levels decrease in multiple myeloma cells treated with BTZ and CFZ, whereas partial transcriptional repression of TXNRD2 in untreated multiple myeloma cells causes oxidative stress, ER stress and death similar to those induced by BTZ or CFZ [84] (Figure 1) [84]. Accordingly, TXNRD2 overexpression

suppresses BTZ- or CFZ-induced ER stress and cell death in *in vitro*, and decreases efficacy of BTZ against multiple myeloma xenografts in immunocompromised mice [84].

2.3. Oxidative Stress Inducing Agents as Adjuvants for Proteasome Inhibitor Therapy

Tumor cells possess higher basal ROS levels than their normal counterparts and thus may be more vulnerable to the oxidative stress induced by chemotherapeutic agents. Several such agents that directly increase intracellular ROS levels have been already approved for treatment of multiple malignancies including lung, breast ovarian and pancreatic cancers, as well as different forms of leukemias and lymphomas [reviewed in 17]. In multiple myeloma, with the exception of arsenic trioxide (which has demonstrated only limited efficacy [85,86]), no drugs primarily inducing oxidative stress are currently being used in clinic. Yet, data obtained in cultured cells and/or preclinical settings strongly suggest that induction of oxidative stress is a promising myeloma treatment strategy.

Treatment of multiple myeloma cells with selective inhibitor of thioredoxin 1 (TRX1) PX-12 (1-methylpropyl 2-imidazolyl disulfide) or auranofin, a coordinated gold compound that inhibits thioredoxin reductases 1 and 2 (TXNRD1,2) [87], leads to ROS-dependent apoptosis [88]. Similar results were obtained with genetic inhibition of TRX1 or TXNRD1 [88]. Our group demonstrated that depletion of TXNRD2 via shRNA induces death in multiple myeloma cells [84]. Moreover, BTZ-resistant multiple myeloma cells express higher levels of TRX1 and TXNRD2 compared to parental cells [84,88]. Interestingly, auranofin (which has been FDA approved for the treatment of rheumatoid and juvenile arthritis, Felty's syndrome, and psoriatic arthritis [87]) substantially reduced tumor burden and improved survival in a transgenic mouse model of Chronic lymphocytic leukemia [89]. These data suggest that auranofin could be used for treatment of multiple myeloma either as a stand-alone agent or in combination with proteasome inhibitors.

Indeed, combinational treatment of multiple myeloma cells with BTZ and other ROS-inducing agents demonstrated promising results in several studies. Thus, inhibition of the dimerization of the oncoprotein mucin 1 C-terminal subunit (MUC1-C) [90] in multiple myeloma cells with a cell-penetrating peptide GO-203 not only synergized with BTZ via upregulation of intracellular ROS but also re-sensitized BTZ-resistant multiple myeloma cells to BTZ treatment [91]. Similarly, co-treatment of multiple myeloma cells with carfilzomib, a next generation analog of bortezomib, and LBH589 (panobinostat), a novel broad-spectrum inhibitor of HDACs, resulted in ROS-dependent apoptosis [92]. LBH589 has been recently approved for treatment of patients with relapsed and refractory multiple myeloma [80]. Although several mechanisms have been proposed for LBH589-dependent generation of ROS [93-95], it is worth noting that KLF9 has been reported by us previously to mediate LBH589 cytotoxicity in multiple myeloma cells [81] and thus could account, at least in part, for the LBH-dependent oxidative stress in these cells. Several other histone deacetylase inhibitors cooperated or synergized with BTZ in inducing oxidative stress and apoptosis in multiple myeloma cells *in vitro*, including sodium butyrate and suberoylanilide hydroxamic acid [95], PXD101 (belinostat, Beleodaq), [96], and KD5170 [97].

A number of agents the cytotoxicity of which in multiple myeloma cells depend on the ability to induce oxidative stress have been identified within past fifteen years. These drugs

include i)b-AP15 a small molecule inhibitor of the ubiquitin specific peptidase that also possess anti-TXR and anti-TXNRD activities [98]; ii) cis-bixin, a constituent of a plant *Bixa Orellana*, that also inhibits activity of TXR and TXNRD1 [99]; iii)motexafin gadolinium (Xcytrin), an inhibitor of TXNRD and ribonucleotide reductase [100]; iv)imexon (Amplimexon/NSC-714597), a cyanoaziridine derivative that induces oxidative stress via not completely identified mechanism [101-104]; v) chaetocin, a nonspecific inhibitor of histone methyltransferases [105]; vi)parthenolide, a natural product from the plant *Tanacetum parthenium* with anti-inflammatory activity [106]. However, further testing is required to assess their efficacy in preclinical models and the ability to cooperate with proteasome inhibitors.

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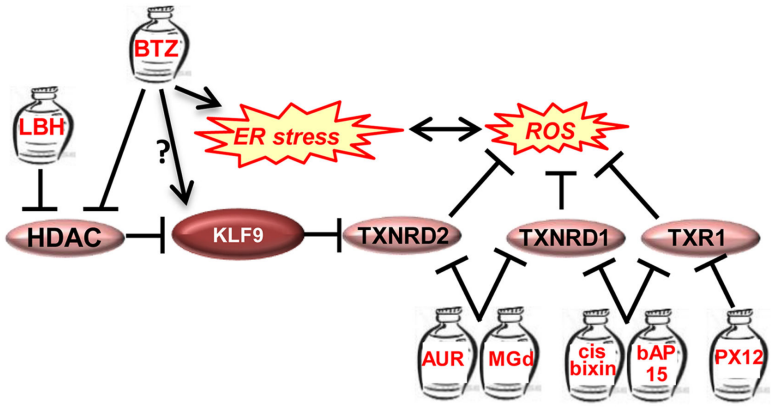

Figure 1. Inhibition of Antioxidants in Multiple Myeloma Cells

See details in the text. Genes are shown by ovals, jars represent drugs. LBH=LBH589, BTZ=bortezomib, AUR=auranofin, MGd= Motexafin gadolinium.