The Novel Polyamine Analogue CGC-11093 Enhances the Antimyeloma Activity of Bortezomib

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Abstract

Multiple myeloma (MM) is an incurable plasma cell malignancy. The recent successes of the proteasome inhibitor bortezomib in MM therapy have prompted investigations of its efficacy in combination with other anticancer agents. Polyamines play important roles in regulating tumor cell proliferation and angiogenesis and represent an important therapeutic target. CGC-11093 is a novel polyamine analogue that has completed a phase 1 clinical trial for the treatment of cancer. Here, we report that CGC-11093 selectively augments the in vitro and in vivo antimyeloma activity of bortezomib. Specifically, the combination of CGC-11093 and bortezomib compromised MM viability and clonogenic survival, and increased drug-induced apoptosis over that achieved by either single agent. Xenografts of MM tumors treated with this combination had marked increases in phospho-c-Jun-NH2-kinase (JNK)-positive cells and apoptosis, and corresponding reductions in tumor burden, tumor vasculature, and the expression of proliferating cell nuclear antigen and the proangiogenic cytokine vascular endothelial growth factor. Furthermore, inhibition of JNK with a pharmacologic inhibitor or by selective knockdown blunted the efficacy of CGC-11093 and bortezomib. Therefore, CGC-11093 enhances the antimyeloma activity of bortezomib by augmenting JNK-mediated apoptosis and blocking angiogenesis. These findings support the study of the use of the combination of bortezomib and CGC-11093 in MM patients that fail to respond to frontline therapy. [Cancer Res 2008;68(12):4783–90]

Introduction

The polyamines putrescine, spermidine, and spermine are small-chained, cationic molecules present in all organisms that play essential roles in many biological processes, including cell proliferation and angiogenesis. Polyamine homeostasis is frequently disrupted during malignant transformation, and this augments intracellular polyamine levels. Precisely how this response occurs is not resolved, but it often involves increased expression or activity of polyamine biosynthetic enzymes and suppression of catabolic enzymes in the pathway. Augmented polyamine levels in cancer has served as a longstanding platform for the design of targeted agents for the prevention and treatment of cancer (1, 2). Indeed, agents such as difluoromethylornithine (DFMO), a suicide inhibitor of ornithine decarboxylase (ODC), a rate-limiting enzyme in polyamine biosynthesis, have shown potent in vivo chemopreventive activity (3). However, DFMO, with one exception, has failed to show antitumor activity in clinical trials, and this is likely due to marked increases in polyamine transport by malignant cells (4, 5).

Several polyamine analogues have been generated that can modulate the biosynthetic or catabolic enzymes of the pathway, and those that induce polyamine catabolism can generate hydrogen peroxide and aminoaide products that are toxic to the tumor cell (6–10). However, some polyamine analogues can have significant antitumor effects without affecting polyamine catabolism.

Multiple myeloma (MM) remains an incurable plasma cell malignancy, and this has spurred tremendous efforts toward developing novel therapeutic strategies to improve outcome. The proteasome inhibitor bortezomib (Velcade) has made great strides in the clinic in treatment of MM and earned fast-track Food and Drug Administration approval in 2003 (11–13). Based on this success, novel combination therapies with bortezomib are being tested for efficacy and for their potential in circumventing drug resistance in MM. CGC-11093 is a novel polyamine analogue that has completed a phase I trial for the treatment of cancer (14, 15). Given the important role of polyamines in pathways targeted by the mechanism of action of bortezomib, we hypothesized that CGC-11093 may enhance its therapeutic efficacy. Here, we report that in cell line and xenograft models of MM, CGC-11093 increases the antiangiogenic properties of bortezomib and augments bortezomib-mediated apoptosis via a c-Jun-NH2-kinase (JNK)-dependent mechanism. This study provides a basis for the further evaluation of this combination in the clinical setting for chemorefractory MM.

Materials and Methods

Cells and cell culture. NCI-H929 and U266 human MM cells, and H157 and A549 human lung cancer cells (from American Type Culture Collection) were maintained in RPMI 1640 with 10% fetal bovine serum at 37°C with 5% CO2 as previously described (7, 16–18). Primary human peripheral blood mononuclear cells (PBMC) were obtained from healthy individuals after informed consent.

Drugs. CGC-11093 was provided by Cellgate, Inc. Bortezomib was purchased from the St. Jude Children’s Research Hospital Pharmacy. The JNK inhibitor SP600125 was obtained from EMD Biosciences. N1,11-bis(ethyl)norspermine (DENSPM) was obtained from Genzyme.
Quantifying drug-induced cytotoxicity. Drug-related effects on cell viability were assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay as described (16). Proapoptotic effects of in vitro drug exposure were quantified by propidium iodide/fluorescence-activated cell sorting (PI/FACS) analysis of sub-G₀-G₁ DNA content as described (16, 19).

Colony assays. Cells were treated for 24 h with the indicated concentrations of bortezomib and CGC-11093. Drug-treated cells were washed twice in PBS and seeded in Methocult methylcellulose medium (Stem Cell Technologies) and incubated for 10 d in a humidified incubator at 37°C with 5% CO₂. Colonies were stained with 0.5% 2,3,5-triphenyltetrazolium chloride (Sigma) and were scored manually (20).

Xenograft studies. Logarithmically growing U266 and NCI-H929 MM cells were centrifuged, washed twice in PBS, and counted. Immunodeficient Scid mice (Jackson Labs) were inoculated s.c. with 3 x 10⁷ cells suspended in a 200-μL mixture of 100 μL of HBSS and 100 μL of phenol red-free Matrigel (BD Biosciences). Ten mice bearing tumors from each cell line xenograft were randomized into different treatment groups when tumors became palpable. Tumor-bearing mice were either treated with vehicle (PBS, control) or with therapeutic agents with the following schedule and dose: CGC-11093 at 50 mg/kg once weekly and bortezomib at 1 mg/kg twice weekly, or the combination of CGC-11093 (50 mg/kg once weekly) and bortezomib (1 mg/kg twice weekly). Mice were monitored daily throughout the 21-d treatment schedule. All mice were humanely euthanized at the end of the experiment. Tumors were immediately excised from euthanized mice, weighed, measured with digital calipers, and snap-frozen in liquid nitrogen.

Terminal deoxynucleotidyl-transferase–mediated dUTP nick-end assay. Terminal deoxynucleotidyl-transferase–mediated dUTP nick-end assay (TUNEL) was performed to quantify apoptotic cells in xenograft tumor sections using the Dead End kit (Promega) with the assistance of an autostainer (DAKO). The assay was carried out according to the manufacturer’s instructions with the following modifications: TBS containing Tween 20 (TBS-T) buffer was used for all washes, DAKO proteinase K was substituted for the proteinase K included in the kit, and endogenous peroxidases were blocked for 5 min with 3% H₂O₂. Slides were counterstained 3 min with 1:10 dilution of hematoxylin (DAKO), dehydrated, and coverslipped. Apoptotic cells were scored manually under ×20 magnification.

Immunohistochemistry. The following reagents were obtained from commercial sources: rat anti-mouse CD34 antibody (PharMingen), mouse anti-human proliferating cell nuclear antigen (PCNA) antibody, ARK biotinylation kit, Target Retrieval buffer, 3,3′-diaminobenzidine (DAB), horseradish peroxidase–conjugated streptavidin (SA-HRP), TBS-T buffer (all from DAKO), and biotinylated rabbit anti-rat antibody (Vector). Slides of 5 to 6 μm sections cut from formalin-fixed paraffin-embedded tissues were deparaffinized in xylene and rehydrated. Heat-induced epitope retrieval in target retrieval buffer was performed in a steamer at 96°C for 30 min. The slides were allowed to cool for 30 min and were placed in TBS-T before assay. Immunohistochemistry assays for PCNA and CD34 were performed at room temperature using a DAKO autostainer. The assay was carried out according to the manufacturer’s instructions with the following modifications: TBS containing Tween 20 (TBS-T) buffer was used for all washes, DAKO proteinase K was substituted for the proteinase K included in the kit, and endogenous peroxidases were blocked for 5 min with 3% H₂O₂. Slides were counterstained 3 min with 1:10 dilution of hematoxylin (DAKO), dehydrated, and coverslipped. Apoptotic cells were scored manually under ×20 magnification.

High performance liquid chromatography analyses. Intracellular levels of polyamines present in xenograft tumors were quantified by high performance liquid chromatography (HPLC) analysis of dansylated derivatives as previously described (24).

Immunoblot analyses. Protein extracts were subjected to SDS-PAGE electrophoresis and transferred to nitrocellulose membranes as described previously (16, 19). The antibodies used were as follows: anti–phospho-JNK (Biosource), anti-JNK (Cell Signaling), and anti-actin (Sigma). The
anti–phospho-JNK and anti-JNK antibodies detect both JNK1 and JNK2 (23). RNA interference. A custom siRNA sequence (AGAAUGCUACCUCU- CUUUUU) that simultaneously targets JNK1 and JNK2 and a control siRNA targeting luciferase were both synthesized by Dharmacon. NCI-H929 and U266 cells were transfected with JNK1/2 siRNA or control siRNA with the Nucleofector II device (Amazia Biosystems) as described (20). After 24 h, cells were treated with bortezomib and CGC-11093 as indicated. Drug-induced apoptosis was quantified by PI/FACS. The efficiency of JNK1/2 knockdown was confirmed by immunoblotting.

Statistical analyses. All analyses were performed with the assistance of GraphPad Prism software version 4.0a (GraphPad Software) as described (16). A P value of <0.05 was considered statistically significant.

Spermidine/spermine N-acetyltransferase and spermine oxidase enzyme assays. NCI-H929 or U266 MM cells, or H157 or A549 lung cancer cells, were treated with DENSPM (10 μmol/L), CGC-11093 (10 μmol/L), bortezomib (2 mmol/L), or CGC-11093 plus bortezomib for 48 h. Cells were harvested, washed in ice-cold PBS, resuspended in buffer containing 5 mmol/L HEPES and 1 mmol/L DTT [for spermidine/spermine N′-acetyltransferase (SSAT) assays] or in buffer containing 0.083 mol/L glycine [pH 8.0 for spermine oxidase (SMO) assays], and frozen at −80°C. Protein concentration was determined by Bradford assays, and SSAT or SMO enzyme assays were performed as described (7, 17, 18).

Results
CGC-11093 enhances the antimyeloma activity of bortezomib. Manipulating polyamine levels regulates pathways controlling cell proliferation and angiogenesis, which are also modulated by bortezomib (1, 2). Therefore, we hypothesized that the novel polyamine analogue CGC-11093 would augment the anticancer effects of bortezomib. To test this, the human U266 and NCI-H929 MM cells, well-established models of human MM, were treated with 10 μmol/L CGC-11093, 2 mmol/L bortezomib, or combination of these agents for 48 h. The cytotoxic effects of drug treatment were determined by MTT assay. In both MM cells, CGC-11093 produced only a modest cytotoxic response compared with bortezomib, which significantly reduced viability, especially of NCI-H929 cells. However, CGC-11093 significantly enhanced the antimyeloma activity of bortezomib in both cell lines (Fig. 1A). Bortezomib is preferentially toxic to malignant cells (19, 25), and to address whether the same property held for this combination, we exposed PBMC from two healthy donors to both agents. Importantly, the cytotoxic effects of both agents were minimal in normal PBMC and significantly less than that observed for MM cells (Fig. 1A); therefore, this combination has a favorable therapeutic index, at least in vitro.

To assess whether the effects of the combination of CGC-11093 and bortezomib were due to the induction of MM cell apoptosis, PI/FACS analyses were performed. In MM cells treated with CGC-11093 and bortezomib, there were significant increases in the percentages of apoptotic cells over that achieved by exposure to either single agent (Fig. 1B). Finally, clonogenic assays were performed to evaluate the prolonged in vitro effects of CGC-11093 and bortezomib on the growth and survival of MM cells. Again, CGC-11093 enhanced the ability of bortezomib to inhibit the clonogenic survival of both NCI-H929 and U266 MM cells (Fig. 1C). Collectively, these data suggest that CGC-11093 enhances the anticancer activity of bortezomib.

CGC-11093 cooperates with bortezomib to reduce tumor burden in MM xenografts. To investigate the potential in vivo benefit of combining CGC-11093 with bortezomib, xenograft studies were performed. NCI-H929 and U266 MM cells were implanted s.c. into the flanks of Scid mice. Tumor-bearing mice were randomized into groups of 10, and treatment was initiated with the following schedule for 21 days: bortezomib at a dose of 1 mg/kg twice weekly, CGC-11093 at a dose of 50 mg/kg once

Figure 2. Bortezomib and CGC-11093 reduce tumor burden in MM xenografts. A, NCI-H929 and U266 human MM cells were injected s.c. into the flanks of Scid mice. Mice with palpable tumors were randomized into groups of 10 and were treated for 21 d as described in the Materials and Methods. Mice were humanely euthanized at the end of the study, and tumors were excised and weighed. Columns, mean; bars, SD; n = 10 per group; *, P < 0.05. B, bortezomib and CGC-11093 are well-tolerated in vivo. Xenograft studies were carried out as described in the Materials and Methods. Body weight was determined immediately after euthanasia at the end of the study to quantify drug-induced weight loss. Columns, mean; bars, SD; n = 10 per group. C, effects of bortezomib and CGC-11093 on polyamine pools in MM tumors. Tumor tissue was snap frozen in liquid nitrogen immediately after euthanasia. Tissue was processed and HPLC analyses were performed to determine the intratumoral levels of spermidine, spermine, and putrescine. Columns, mean; bars, SE; n = 3; *, P < 0.05.
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Polyamines play key roles in controlling tumor cell proliferation, angiogenesis, and other signaling cascades (1, 2). Considering this, interfering with polyamine function is a highly attractive strategy for cancer therapy. To assess the effects of CGC-11093 and/or bortezomib on polyamine pools, HPLC analyses (24) of putrescine, spermidine, and spermine pools were performed on the tumor tissue from NCI-H929 and U266 xenografts. CGC-11093 and bortezomib treatment caused modest reductions in the levels of all three polyamines in NCI-H929 tumors. In contrast, both agents stimulated significant reductions in polyamine pools in U266 tumors, which are more sensitive to these agents in vivo. Interestingly, bortezomib treatment led to more dramatic reductions in polyamine pools than CGC-11093 in U266 xenografts, and the combination of these agents resulted in lower levels of each individual polyamine than that achieved by either single agent (Fig. 2B).

Polyamine analogues can often induce two key catabolic enzymes of the polyamine pathway, SSAT or SMO (7, 17, 18). Given the effects of the CGC-11093 plus bortezomib combination treatment on polyamine pools, we evaluated whether CGC-11093, bortezomib, or CGC-11093 plus bortezomib treatment of U266 or NCI-H929 MM cells affected the activity of SSAT or SMO. As controls, the effects of the well-characterized polyamine analogue DENSPM on the activity of SSAT and SMO in H157 and A549 cells lung cancer cells (7, 17, 18) were assessed in parallel, respectively. As expected, DENSPM led to marked induction in SSAT and SMO enzyme activity in lung cancer cells (Supplementary Fig. S1). By contrast, there was little to no effect of CGC-11093 on the activity or expression of either SSAT or SMO in U266 or NCI-H929 MM cells, and bortezomib or bortezomib plus CGC-11093 also had no effect on their activity or expression (Supplementary Fig. S1; data not shown). Therefore, polyamine depletion seen in the MM xenografts treated with the bortezomib plus CGC-11093 combination seems independent of the effects of these agents on SSAT or SMO.

CGC-11093 and bortezomib inhibit tumor cell proliferation and provoke apoptosis. Immunohistochemical analyses were then performed to determine the mechanism(s) by which CGC-11093 augmented the anticancer activity of bortezomib. Previous studies have established that bortezomib inhibits the proliferation of malignant cells and induces apoptosis in both tumor and endothelial cells (21, 22). To determine effects of these agents on tumor cell proliferation, paraffin-embedded tumor sections were stained with an anti-PCNA antibody. As expected, bortezomib treatment led to more dramatic reductions in polyamine pools than CGC-11093 in U266 xenografts, and the combination of these agents resulted in lower levels of each individual polyamine than that achieved by either single agent (Fig. 2C).

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Angiogenesis is impaired in CGC-11093/Bortezomib-treated MM. Angiogenesis is essential for the development and progression of both hematologic and solid malignancies, where new vessels deliver oxygen and nutrients to the burgeoning tumor (28). As such, agents that block angiogenesis are highly desired in cancer therapy (29). Suppression of angiogenesis is an important component of the anticancer activity of bortezomib and is thought to largely occur via inhibition of nuclear factor-κB, which induces the expression of many proangiogenic factors, including VEGF (21, 22).

Interestingly, several studies have reported that polyamines are essential for angiogenesis (30–33), and we thus tested if CGC-11093 augmented the antivascular effects of bortezomib. To assess this, we quantified two variables of angiogenesis: intratumoral vascularity, as determined by CD34 expression, and VEGF expression. As expected, bortezomib reduced the size and number of vessels in both NCI-H929 and U266 tumors. Tumors from mice treated with CGC-11093 also displayed a marked decrease in vessel size, yet only had a modest reduction in overall vessel counts. Notably, the bortezomib/CGC-11093 combination further reduced vessel size and density over that achieved with single-agent treatments (Fig. 4A–B).

The effects of the bortezomib/CGC-11093 combination on vessel number and density could be due to effects on the expression of angiogenic cytokines. We therefore assessed the effects of this combination regimen on the expression of VEGF in xenograft tumors derived from both MM cell lines. Tumors from mice treated with CGC-11093 also displayed a marked decrease in vessel size, yet only had a modest reduction in overall vessel counts. Notably, the bortezomib/CGC-11093 combination further reduced vessel size and density over that achieved with either single agent (Fig. 4A–B).

The ability of these agents to target two different aspects of angiogenesis, neovascularization and VEGF production, thus effectively cancels this important neoplastic process.

Bortezomib and CGC-11093 stimulate JNK activity in vivo. We and others have shown that JNK activation plays critical roles in
mediating bortezomib-induced apoptosis (23, 35–38). Because disruption of polyamine homeostasis augments JNK activity (39–41), we hypothesized that JNK would also mediate the combination effects of bortezomib and CGC-11093. To test if CGC-11093 modulated bortezomib-stimulated JNK activity in vivo, immunohistochemistry was performed with antibodies that detect both phospho-JNK1 and phospho-JNK2 (active JNK) or total JNK1/2 in tumor tissue from NCI-H929 and U266 xenografts. Total JNK1/2 levels in NCI-H929 and U266 tumors were not affected by treatment with bortezomib and/or CGC-11093. In contrast, phospho-JNK1/2 was modestly increased in CGC-11093–treated tumors, was augmented 2.5- to 3-fold in bortezomib-treated xenografts, and was induced ~3.5-fold in bortezomib/CGC-11093–treated MM tumors (Fig. 5A–B). Therefore, increased JNK1/2 phosphorylation is associated with the proapoptotic effects of the bortezomib/CGC-11093 combination treatment.

**Discussion**

MM has long been considered an incurable malignancy with an extremely poor clinical prognosis. Concerted efforts in the field of MM therapy over the last decade are now, however, changing outcome. In particular, the proteasome inhibitor bortezomib (Velcade) has made a major mark in MM treatment (11–13). Bortezomib has also showed promising preclinical and clinical activity in a number of other cancer models (19, 21, 42–44), and its success is likely linked to its multifaceted mechanisms of action, where it inhibits tumor cell proliferation and angiogenesis, stimulates the death of malignant and endothelial cells, and disrupts several prosurvival signaling cascades. The utility of bortezomib is further enhanced by the virtue that it can be effectively combined with other classes of anticancer agents, including histone deacetylase inhibitors, death ligands such as TRAIL, topoisomerase inhibitors, alkylating agents, and several others (19, 22, 23, 42, 44, 45).

Dysregulation of the polyamine pathway has been known for several decades to be involved in transformation and malignant

**Figure 6.** JNK contributes to bortezomib/CGC-11093–induced apoptosis. A, CGC-11093 augments bortezomib-induced JNK1/2 phosphorylation in NCI-H929 and U266 MM cells in vitro. Immunoblotting with antibodies that detect both JNK1 and JNK2 (23) was used to detect the expression levels of phospho- and total JNK1/2 as described in the Materials and Methods. B, the pan-JNK inhibitor SP600125 significantly impairs bortezomib/CGC-11093–induced apoptosis. NCI-H929 cells were treated with 2 nmol/L bortezomib, 10 μmol/L CGC-11093, or the combination in the presence and absence of 25 μmol/L SP600125 for 48 h. Drug-induced apoptosis was quantified by PI/FACS; n = 3; *, P < 0.05. C, knockdown of JNK1/2 with siRNA. A dual-targeting siRNA sequence was used to simultaneously knockdown JNK1 and JNK2 expression in NCI-H929 and U266 cells as described in the Materials and Methods. Immunoblotting confirmed efficient knockdown of JNK1 and JNK2. D, knockdown of JNK1/2 compromises bortezomib/CGC-11093–induced apoptosis. NCI-H929 and U266 cells were transfected with JNK1/2 siRNA or nontargeted control siRNA as described in the Materials and Methods. Transfected cells were treated with 2 nmol/L bortezomib, 10 μmol/L CGC-11093, or the combination for 48 h. Drug-induced apoptosis was quantified by PI/FACS; n = 3; *, P < 0.05; con, control.
progression. DFMO was developed as a suicide inhibitor of a rate-limiting enzyme in polyamine biosynthesis (ODC) as a cancer therapeutic. However, DFMO largely failed in this arena, due to the ability of malignant cells to maintain polyamines by increasing polyamine uptake from the microenvironment (1, 2). However, lessons learned from the DFMO experience have been used to generate novel agents targeting the polyamine pathway (2). Theoretically, such agents should effectively lower intracellular polyamine levels, but these can also be active even without affecting the pools of endogenous natural polyamines. CGC-11093 is a member of this latter class of novel polyamine analogues and has completed a phase I clinical trial for cancer therapy.

Based on the regulatory role of polyamines in pathways and processes that are targeted by bortezomib, we hypothesized that CGC-11093 would enhance the anticancer activity of bortezomib. In support of this notion, our in vitro assays showed efficacy of this combination in impairing the clonogenic potential of MM cells, and that this was due to the ability of CGC-11093 to augment bortezomib-induced apoptosis. Finally, the ability of CGC-11093 to augment the antymyeloma activity of bortezomib was validated in two different MM xenograft models.

Rather unexpectedly, our analyses showed that bortezomib alone reduced the levels of polyamines in U266 xenograft tumors. Disruption of polyamine homeostasis after bortezomib treatment has not been previously reported. Indeed, bortezomib diminished polyamine pools much more effectively than CGC-11093, an agent that was designed specifically for this purpose. The combined ability of these agents to decrease polyamines in vivo directly correlated with sensitivity, where effects were more pronounced in the U266 xenografts, which responded more dramatically to drug treatment than NCI-H929 tumors. The mechanism(s) by which bortezomib modulates polyamine pools is presently not clear, but this is not associated with the induction of the polyamine catabolic enzymes SSAT or SMO. Similarly, the CGC-11093 polyamine analogue alone does not overtly affect the expression or activity of SSAT or SMO, so its combined effects with bortezomib in decreasing polyamines must occur through other means. Regardless, future studies are warranted to address whether polyamine-related effects represent an important component of the anticancer mechanism of action of bortezomib.

Our xenograft analyses and in vitro studies established that bortezomib and CGC-11093 cooperate to inhibit MM cell proliferation and to induce cell death. Furthermore, CGC-11093 also had moderate antiangiogenic properties alone and augmented this aspect of the mechanism of action of bortezomib. The inhibitory effect of CGC-11093 on such a fundamental process in tumor biology suggests that it may also combine effectively with other classes of anticancer agents. Interestingly, the antiangiogenic effects of CGC-11093 have also been shown in a model of macular degeneration (46). Indeed, CGC-11093 and other structurally related compounds have entered clinical trials as potential therapeutics for this disease.

We focused on the role of JNK as a potential regulator of cell death induced by the CGC-11093/bortezomib combination as we and others have shown that JNK activation contributes to bortezomib-induced apoptosis (23, 35–38). Furthermore, polyamines have been reported to control JNK activity (39–41), and thus, we hypothesized that CGC-11093 would augment JNK activity stimulated by bortezomib. Indeed, analyses of phospho-JNK expression in xenograft MM tumors revealed that CGC-11093 augmented activation of JNK by bortezomib, and similar effects were also manifest in vitro. Finally, pharmacologic and siRNA-mediated inhibition of JNK significantly impaired bortezomib/CGC-11093–induced apoptosis, establishing that JNK is indeed a critical regulator of the anticancer activity of these agents.

Collectively, these findings show that the CGC-11093 polyamine analogue enhances the antymyeloma activity of bortezomib, and that this occurs by augmenting its ability to inhibit tumor cell proliferation and angiogenesis and to stimulate cell death via a JNK-mediated mechanism. Notably, both agents displayed minimal toxicity to normal human PBMCs in vitro and were well-tolerated in vivo; i.e., there seems to be a therapeutic index for this combination. These findings thus provide a platform for the design of a clinical trial to evaluate the efficacy of CGC-11093 in combination with bortezomib for MM patients that are refractory to conventional agents.

Disclosure of Potential Conflicts of Interest

R.A. Casero: Commerical research support, Cellgate, Inc.; consultant, Cellgate, Inc.
L.J. Marton: Employee, Progen Pharmaceuticals; ownership interest, Wisconsin Alumni Research Foundation. The other authors disclosed no potential conflicts of interest.

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References


26. Table 2 shown in the paper.


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