Luteinizing Hormone-Releasing Hormone (LHRH)-I Antagonist Cetrorelix Inhibits Myeloma Cell Growth In vitro and In vivo

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Abstract
The objective of this study was to determine the effects of an luteinizing hormone-releasing hormone (LHRH)-I antagonist, Cetrorelix, on human multiple myeloma (MM) cells and to elucidate the mechanisms of action. We showed that LHRH-I and LHRHR-I genes were expressed in MM cell lines and primary MM cells. Treatment with Cetrorelix inhibited growth and colony-forming ability of myeloma cells, including cell lines resistant to arsenic trioxide, bortezomib, or lenalidomide. Cetrorelix induced apoptosis in myeloma cells including primary myeloma cells. In addition, Cetrorelix inhibited the growth of human myeloma cells xenografted into mice without any apparent side effects. Cetrorelix downregulated the nuclear factor-kappa B (NF-kB) pathway activity and the expression of cytokines, including interleukin 6, insulin-like growth factor 1, VEGF-A, and stromal-derived factor 1, important for myeloma cell growth and survival in myeloma cells and/or marrow stromal cells from myeloma patients. Cetrorelix decreased the phosphorylation of extracellular signal regulated kinase 1/2 and STAT3 in myeloma cells, two crucial pathways for myeloma cells growth and survival. Moreover, the expression of p21 and p53 was increased, whereas that of antiapoptotic proteins Bcl-2 and Bcl-xL was reduced by Cetrorelix. Our findings indicate that Cetrorelix induces cytotoxicity in myeloma cells through various mechanisms and provide a rationale for investigating Cetrorelix for the treatment of MM. Mol Cancer Ther; 10(1); 148–58. ©2010 AACR.

Introduction
Multiple myeloma (MM) is the second most common hematologic cancer in the United States, representing 10% of all hematopoietic malignancies (1). It is incurable, although novel approaches such as the use of proteasome inhibitor bortezomib, have improved the treatment outcome (2, 3). However, the majority of patients with refractory or relapsed disease show resistance to these therapies (4, 5). Thus, the development of novel agents to treat MM remains an important task.

We observed in our gene array experiments that RPMI 8226 myeloma cells expressed the luteinizing hormone-releasing hormone (LHRH)-I antagonist, Cetrorelix, on human multiple myeloma (MM) cells and to elucidate the mechanisms of action. We showed that LHRH-I and LHRHR-I genes were expressed in MM cell lines and primary MM cells. Treatment with Cetrorelix inhibited growth and colony-forming ability of myeloma cells, including cell lines resistant to arsenic trioxide, bortezomib, or lenalidomide. Cetrorelix induced apoptosis in myeloma cells including primary myeloma cells. In addition, Cetrorelix inhibited the growth of human myeloma cells xenografted into mice without any apparent side effects. Cetrorelix downregulated the nuclear factor-kappa B (NF-kB) pathway activity and the expression of cytokines, including interleukin 6, insulin-like growth factor 1, VEGF-A, and stromal-derived factor 1, important for myeloma cell growth and survival in myeloma cells and/or marrow stromal cells from myeloma patients. Cetrorelix decreased the phosphorylation of extracellular signal regulated kinase 1/2 and STAT3 in myeloma cells, two crucial pathways for myeloma cells growth and survival. Moreover, the expression of p21 and p53 was increased, whereas that of antiapoptotic proteins Bcl-2 and Bcl-xL was reduced by Cetrorelix. Our findings indicate that Cetrorelix induces cytotoxicity in myeloma cells through various mechanisms and provide a rationale for investigating Cetrorelix for the treatment of MM. Mol Cancer Ther; 10(1); 148–58. ©2010 AACR.
treated with Cetrorelix, an augmented expression of Fas, Fas ligand, Bcl-xL, Bax, and caspase 3 and reduced expression of Bcl-2 have been reported (19).

These findings prompted us to examine cultured human MM cells and primary myeloma cells for the presence of LHRH-I and LHRHR-I and to determine the effects of the LHRH antagonist Cetrorelix on cell growth. Our work shows that Cetrorelix induces apoptosis and inhibits the growth of myeloma cells, including some cell lines resistant to arsenic trioxide (ATO), bortezomib (BZM), or lenalidomide, in vitro and in vivo. This effect is likely exerted through the suppression of NF-κB pathway and expression of several key growth/survival factors of myeloma cells, including IL-6 (interleukin 6), IGF-1 (insulin like growth factor 1), VEGF-A, SDF1-α (stromal-derived factor 1-α), expressed by myeloma cells and/or myeloma bone marrow stromal cells (BMSC) from myeloma patients; inhibition of the activation of ERK (extracellular signal regulated kinase) and STAT3 pathways; upregulation of p53 and p21 expression; and downregulation of Bcl-2 and Bcl-xL expression. Altogether, these findings support the merit of further evaluation of LHRH-I antagonists in the treatment of MM.

Materials and Methods

Reagents and antibodies

The LHRH-I antagonist Cetrorelix [Ac-D-Nal(2), D-Phe (4Cl)2, D-Pal(3), D-Cit6, D-Ala10]LH-RH [Nal(2) is 3-(2-naphthyl)alanine, Pal(3) is 3-(3-pyridyl)alanine, and Cit is citrulline], was originally synthesized in our laboratory (25). Cetrorelix was dissolved in distilled water containing 5% mannitol (vehicle solution for injection). Antibodies against phospho-ERK1/2, ERK1/2, phospho-STAT3, STAT3, p21, p27, p53, Mcl-1, Bcl-2, Bcl-xL (Cell Signaling Technology), CD138, LHRHR-I (Abcam), β-actin (Sigma-Aldrich), and Alexa 647–conjugated phospho-NF-κB p65 (RelA; Becton Dickinson) were purchased from the indicated vendors.

Myeloma cell lines and primary cell cultures

Dexamethasone-sensitive (MM.1S) and -resistant (MM.1R) human MM cell lines were kindly provided from The Methodist Hospital and the M. D. Anderson Cancer Center Department of Lymphoma and Myeloma Tissue Bank. Usage of these samples was approved by the institutional review board of The Methodist Hospital Research Institute.
and 5'-TTTTCTGCCAGTGCTTCTTT-3' for human IL-6, and 5'-TTCCGAACGTGAGCCTTGAT-3' and 5'-TTTGCGTCGTCGTCGGT-3' for human 18SrRNA. Each sample was measure in triplicate, and the results were analyzed as previously reported (28).

**Sequencing and BLAST analysis**

PCR products of LHRH-I and LHRHR-I genes, purified using QIAquick Gel Extraction Kit (Qiagen), were sequenced at Baylor College of Medicine Sequencing Core Laboratory. These were then submitted through the NCBI server for BLAST analysis to confirm the expression of these genes.

**Immunohistochemistry**

The immunohistochemistry using antibody against CD138 and LHRHR-I were done on bone marrow biopsies from a MM patient with previously reported methods (29).

**Western blotting analysis**

Cells were treated as specified in the figure legends, collected, and immunoblotted with the antibodies listed earlier using previously described methods (26).

**Growth inhibition assay, colony assay, and evaluation of apoptosis**

Myeloma cells were treated as specified in each figure legend. The growth inhibitory effect on MM cell lines was then assessed by MTT assays (Chemicon International) as previously described (26). Colony formation was assayed by soft-agar method as shown (26). The induction of apoptosis was evaluated using the Annexin V assay (BD Pharmingen) as reported previously (26).

**Flow cytometric evaluation of caspase 3 activity**

Cells were treated as specified in the figure legends, collected, and caspase 3 activity was evaluated by flow cytometry using previously described methods (26).

**Transient transfection of siRNA**

The scrambled siRNA (siSCR; catalogue no. sc-37007) and siRNA to knock down LHRHR-I (catalogue no. sc-4002) were obtained from Santa Cruz Biotechnology, Inc. RPMI 8226 cells were transfected with siRNA, using the RNAiFect transfection system (Qiagen) as reported (26). Cells were incubated at 37°C for 40 hours before replating onto 12-well plates. Cells were allowed to attach overnight (about 8 hours), then treated with Cetrorelix for 24 hours, followed by apoptosis and Western blot.

**Animal study**

The pLenti7.3/V5-GFP/luciferase plasmid developed at our laboratory, along with packaging mix, was transfected into 293FT with Lipofectamin 2000 according to the manufacturer’s procedure. RPMI 8226 cells were transduced with the collected virus particles and stably transduced cells were purified on the basis of GFP expression by an Aria flow cytometer (BD Biosciences). Then, cells were injected intravenously into sixteen 8- to 10-week-old female NOD/SCID II2rg−/− mice (Jackson Laboratory). For imaging, each mouse was anesthetized and imaged in a Xenogen/Caliper IVIS 200 optical scanner (Wave- metrics) at approximately 10 minutes following the i.p. administration of d-luciferin (150 mg/kg). Semiquantitative region of interest analysis was conducted with the dedicated software Living Image v3.1. The mice were subjected to imaging weekly after injection. As soon as the imaging study showed tumor growth, the mice were injected i.p. daily with vehicle (5% mannitol; n = 8 mice) or Cetrorelix (75 μg per mouse per day; n = 8 mice) and imaged every week for 8 weeks to monitor the tumor size. The mice were sacrificed when signs of discomfort emerged or when the tumor volume exceeded 2.0 cm. All experiments were conducted in accord with NIH guidelines and with approval of The Methodist Hospital Research Institute Committee for the Protection of Animals in Research.

**Statistical analysis**

Statistical analysis was conducted with the SPSS 11.5, using t test or 1-way ANOVA.

**Results**

**Expression of LHRH and LHRHR in MM cells lines and plasma cells from myeloma patients or healthy donors**

Because there is no information on the expression of LHRH and receptor in MM cells, we first determined the expression of LHRH-I and LHRHR-I by RT-PCR in 3 myeloma cell lines and samples from myeloma patients. As presented in Figure 1A, amplified products with the predicted size of 139 bp (LHRH-I) and 128 bp (LHRHR-I) were observed in human MM cell lines RPMI 8226, MM.1S, and U266 and in CD138+ plasma cells from bone marrow samples of healthy donors (NM1–5) and myeloma patients (MM1–5). Products from RPMI 8226 cDNA were sequenced and confirmed by BLAST analysis as a part of human LHRH-I and LHRHR-I genes. MM cell lines Dox40, MM.1R, ATOR, BZMR, KAS-6/1, and KAS-6/R10R all have LHRH-I and LHRHR-I expression, verified by PCR (data not shown). Western blot also revealed that the LHRHR-I is expressed in MM cells lines and primary myeloma cells (Fig. 1B). The immunohistochemical staining showed that LHRHR-I was expressed by the neo-plastic CD138+ plasma cells (Fig. 1C). We next studied by qRT-PCR the expression levels of LHRHR-I in CD138+ plasma cells and CD138− cells from bone marrow samples of control individuals and myeloma patients. As shown in Figure 1D, the neo-plastic plasma cells showed the highest level of expression of LHRHR-I, whereas there were no significant differences among normal CD138+ cells and CD138− cells from controls or myeloma.
patients. This raises the possibility of targeting LHRH-R-I for the treatment of myeloma patients.

**Cetrorelix decreases MM cell growth and colony-forming ability**

To investigate the effect of LHRH-R-I antagonist on myeloma cell growth, we used the Cetrorelix to treat 8 MM cell lines, including the RPMI 8226--derived ATO- or BZM-resistant cells, and KAS-6/1--derived, lenalidomide-resistant myeloma cells generated in our laboratories. Cetrorelix treatment reduced cell growth after 48 hours in all cell lines. At the concentration of 1 to 2 μmol/L (a concentration comparable with the previous studies; ref. 16), a 20% to 50% decrease of cell growth as compared with the vehicle was seen and a maximal response was reached at 4 μmol/L (Fig. 2A). Importantly, although RPMI 8226--ATOR cells, RPMI 8226-BZMR, and KAS-6/R10R cells show resistance to ATO, BZM, and lenalidomide, respectively (Fig. 2A inset), they remained sensitive to Cetrorelix treatment. The growth inhibition was further confirmed by colony formation assays (Fig. 2B), showing that Cetrorelix (1 μmol/L) reduced colony-forming ability of the two MM cell lines tested.

**Cetrorelix induces apoptosis in MM cells**

The changes of cell growth and viability indicated earlier suggested the induction of cell death by Cetrorelix in MM cells. Therefore, we investigated the Cetrorelix-induced apoptosis with flow cytometry. As shown in Figure 3A, as compared with controls, treatment with Cetrorelix for 24 hours significantly increased apoptosis in MM cells in a dose-dependent manner. We also investigated the effect of Cetrorelix on caspase-mediated apoptosis. Results showed that Cetrorelix significantly induced the activities of caspase 3 in RPMI 8226, MM.1S, and U266 cells (Fig. 3A). Furthermore, Cetrorelix showed a similar cytotoxic effect in all primary MM CD138+ cells. Of note, there were no significant toxicities to CD138-/C0 cells (Fig. 3B), suggesting that the toxicity of Cetrorelix is specific to myeloma cells. We next explored whether this Cetrorelix-induced apoptosis is mediated through LHRH-R-I. Compared with siSCR-transfected cells, the apoptosis was largely abrogated by the
Figure 2. Effects of Cetrorelix on the growth and colony-forming ability of MM cells. A, RPMI 8226, RPMI 8226-Dox40, MM.1S, MM.1R, ATOR, BZMR, KAS-6/1, and KAS-6/R10R cells were cultured in 96-well plate and treated with Cetrorelix (1, 2, 4, and 8 μmol/L). The MTT analysis was done after 48 hours of culture. Inset, RPMI 8226 and ATOR were cultured and treated with ATO (0, 1, 2, 4, 8, and 16 μmol/L); RPMI 8226 and BZMR were cultured and treated with BZM (0, 1.25, 2.5, 5, 10, and 20 nmol/L) to show the resistance to ATO and BZM, respectively; KAS-6 and KAS-6/R10R were cultured and treated with lenalidomide (0, 0.1, 1, 10, and 100 μmol/L) to show the resistance. The MTT analysis was done after 48 hours of culture. Data are mean ± SD of 3 independent experiments. *, P < 0.05; **, P < 0.01 versus vehicle. The reduction in cell viability (¼ (1 – relative viability normalized to vehicle)) caused by Cetrorelix (4 μmol/L) in different MM cell lines are shown in the table. B, RPMI 8226 and MM.1S cells were cultured in agar with 1 μmol/L Cetrorelix in a 6-well plate. After 2 weeks, the dishes were stained with methylene blue and colonies were photographed and counted. Data are mean ± SD of 3 independent experiments. **, P < 0.01 versus vehicle. Representative images of colonies are presented.
Cetrorelix Inhibits Myeloma Cell Growth In vitro and In vivo

Figure 3. Effects of Cetrorelix on the apoptosis of MM cells. A, left, RPMI 8226, MM.1S, and U226 cells were cultured in 6-well plates and treated with Cetrorelix (1, 5, and 10 μmol/L) for 24 hours and the analysis for apoptosis was done. Right, RPMI 8226, MM.1S, and U226 cells were cultured in 6-well plates and treated with Cetrorelix (5 μmol/L) for 24 hours and the analysis for caspase 3 was done. Data are mean ± SD of 3 independent experiments, normalized to vehicle treatment. **, P < 0.01 versus vehicle. B, CD138+ and CD138− cells from primary MM samples (MM1–5) were cultured in 6-well plate and treated with Cetrorelix (5 and 10 μmol/L) for 24 hours and the analysis for apoptosis was done. C, RPMI 8226 cells were transfected with siSCR or siRNA to knockdown LHRHR-I. Forty hours after transfection, cells were replated and cultured overnight, allowed to attach, and then treated with Cetrorelix for another 24 hours. Cells were collected for apoptosis as well as Western blot to determine the knockdown efficiency. Data are mean ± SD of 3 independent experiments, normalized to vehicle treatment. **, P < 0.01 versus siSCR control.

Cetrorelix inhibits myeloma cell growth in vivo

To show the in vivo activity of Cetrorelix, we next treated NOD/SCID I12rg−/− mice bearing human myeloma RPMI 8226 tumors with Cetrorelix. At a dose of 75 μg Cetrorelix per animal per day, a dose lower than the previous studies (30, 31), bioluminescence imaging began to show significantly decreased tumor volume with Cetrorelix treatment at 4 weeks (Fig. 4A and B) and the inhibition of tumor growth continued for the 8-week duration of the experiment. The Kaplan–Meier survival curve revealed that there was a significant improvement in overall survival of mice treated with Cetrorelix compared with vehicle-treated mice (Fig. 4C; P < 0.05).

Cetrorelix regulates the expression of cytokines and NF-κB pathway

To understand the mechanisms involved in the induction of cytotoxicity by Cetrorelix in myeloma cells, we conducted several studies. First, because several cytokines expressed by myeloma cells and/or the microenvironment have been shown to be important for myeloma cell growth and survival through autocrine and/or

LHRHR-I knockdown with siRNA transfection. This result suggested that the LHRHR-I is necessary for Cetrorelix to function in myeloma cells. The remaining apoptosis effect may come from the residual LHRHR-I or another unknown target receptor (Fig. 3C).
paracrine signaling, we evaluated the effects of Cetrorelix on these cytokines and growth factors. Thus, we used a qRT-PCR to assess the effect of Cetrorelix on mRNA expression of IL-6, IGF-1, VEGF-A, A proliferation-inducing ligand (APRIL), B-cell–stimulating factor-3 (BSF3), SDF1-α, and TGF-β in RPMI 8226 cells and BMSCs established from myeloma patients when they were cocultured. As shown in Figure 5A, Cetrorelix significantly decreased the mRNA expression for IL-6, IGF-1, VEGF-A, APRIL, BSF3, SDF1-α, and TGF-β in RPMI 8226 cells. In addition, Cetrorelix also significantly decreased the expression of mRNA for IL-6, VEGF-A, and BSF3 in BMSCs. Because LHRH pathway has been shown to induce activation of NF-κB (32), and many of these cytokines expression are regulated by NF-κB pathway (33, 34), we further examined the effect of Cetrorelix on NF-κB activity in the MM coculture system. The phosphorylation of p65 (RelA), an indicator for NF-κB activation, was significantly decreased after 6 hours of Cetrorelix treatment in both MM cells and BMSCs (left and right panels, respectively, Fig. 5C). This suggests that the decreased NF-κB activity and the decreased expression of these cytokines, which are important for myeloma cell growth and survival, may play a role in Cetrorelix-induced cytotoxicity and growth inhibition.

Figure 4. Cetrorelix is active in an MM xenograft model. A, NOD/SCID Il2rg−/− mice bearing RPMI 8226 tumors were injected i.p. daily with vehicle (n = 8) or Cetrorelix (75 μg/mouse/day; n = 8) for 8 weeks. Tumor volume was monitored with bioluminescence imaging and a representative example from each group is shown. Color gradation scale ranges from purple (low signal; low tumor burden) to red (high signal; high tumor burden). Units are 10⁶ photons/cm²/sr. B, mice receiving Cetrorelix or vehicle were imaged weekly. The images were analyzed using Living Image software, and a region of interest tool was used to measure the fluorescence efficiency. Data are mean of 8 independent experiments. **, P < 0.01 versus vehicle. C, the Kaplan–Meier survival curve for mouse groups that received Cetrorelix (n = 8) or vehicle (n = 8).
Cetrorelix regulates the phosphorylation of STAT3 and ERK: expression of cell-cycle–related and apoptosis-related proteins

We next examined whether Cetrorelix inhibited signaling pathways important for myeloma growth and survival, including STAT3, ERK, JNK (c-jun NH, kinase), and AKT pathways. As shown in Figure 5B, Cetrorelix markedly inhibited phosphorylation of STAT3 and ERK. We then studied the influence of Cetrorelix on cell-cycle–related and apoptosis-related protein expression in myeloma cells (Fig. 6). Results showed that Cetrorelix increased the expression of genes inhibiting cell cycling, p21 and p53, but decreased the expression of antiapoptotic genes, including Bcl-2 and Bcl-xL. These results suggest that Cetrorelix generates antmyeloma effects through various pathways important for the survival and growth of myeloma cells. Of note, JNK and AKT did not show significant changes with Cetrorelix treatment (data not shown).

Discussion

Various investigators showed that Cetrorelix inhibits in vivo and in vitro growth of human ovarian, endometrial, mammary, and prostatic cancers (13, 15–18, 21–24). Here, we report that Cetrorelix induced cell growth inhibition and apoptosis in multiple myeloma cells. To the best of our knowledge, our study is the first to show the antitumor properties of Cetrorelix in a hematologic malignancy.
Marrow milieu can secrete cytokines such as TNF- 

α, IL-6, VEGF, IGF-1, APRIL, SDF1- 

α, and TGF- 

β in BMSCs. Our findings suggest that the cell-cycle regulatory genes p53 and p21 play significant roles in Cetrorelix-induced growth inhibition. p53 is known to induce cell- 

cycle arrest and apoptosis. p21 is an inhibitor of cyclin- 

dependent kinases and plays a critical role in controlling the cell cycle. It is known that p21 can be upregulated by both p53-dependent and p53-independent pathways (22). In our study, the expression of p53 protein was increased in association with the increase of p21 protein, suggesting that Cetrorelix-induced upregulation of p21 may be mediated by p53. Although RPMI 8226 is regarded as a mutant p53-expressing cell line, RPMI 8226 cells still produce small amounts of wild-type p53 with correct conformation (44, 45).

Our results revealed that the LHRH-I and LHRHR-I were expressed in myeloma cells lines and the expression levels of LHRH-I were upregulated in the neoplastic

Figure 6. Cetrorelix regulates the phosphorylation of ERK and STAT3; expression of cell-cycle-related and apoptosis-related protein. A, RPMI 8226 cells were starved overnight and cultured without cytokine. Cells were then exposed to Cetrorelix (5 μmol/L) for 0, 1, 6, and 12 hours. Lysates from unstimulated or stimulated myeloma cells were immunoblotted with either anti-phospho-specific ERK antibody and then reprobed with anti-ERK antibody or with anti-phospho-specific STAT3 antibody and reprobed with anti-STAT3 antibody. The membrane was reprobed again with anti-actin antibody as a loading control. Data are from 3 independent experiments. B, RPMI 8226 and MM.1S cells were starved overnight and cultured without cytokines. Cells were then exposed to Cetrorelix (5 μmol/L) for 12 hours. Lysates from unstimulated or stimulated myeloma cells were immunoblotted with anti-p21, anti-p27, anti-p53, anti-Bcl-2, or anti-Bcl-xL antibody. The membrane was reprobed again with anti-actin antibody as a loading control. Data are from 3 independent experiments.
myeloma cells from patients compared with normal plasma cells from controls (Fig. 1). These results agree with those of gene expression profiling study database from Multiple Myeloma Genomics Portal (http://www.broadinstitute.org/mmgp/home). In that database, LHRH-I and LHRHR-I are expressed in neoplastic plasma cells isolated from all patients of MGUS (monoclonal gammopathy of undetermined significance), smoldering myeloma, and MM of different prognostic subtypes. Although we do not observe significantly different expressions of these genes among these groups of plasma cell dyscrasias, the wide expression of LHRHR-I in myeloma patients suggests that targeting these molecules may represent a treatment option for most of myeloma patients.

In conclusion, our results show for the first time that Cetrorelix significantly suppressed growth of multiple myeloma cells in vitro and in vivo through various mechanisms. In addition, we found that RPMI 8226-derived, ATO- and BZM-resistant cells are sensitive to Cetrorelix treatment. The proteasome inhibitor BZM and ATO are recent additions to the MM treatment armamentarium, and both drugs show significant beneficial effects in myeloma treatment (46, 47). However, more than 50% of patients with refractory or relapsed diseases show resistance to BZM or ATO treatment (4, 5). Future studies, including clinical trials, are warranted to evaluate the possible benefits of using Cetrorelix in the treatment of myeloma patients.

Disclosure of Potential Conflicts of Interest

Dr. Andrew V. Schally is a co-inventor on the patent for LHRH antagonist Cetrorelix, which is assigned to Tulane University School of Medicine.

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