Bone effects of mammalian target of rapamycin (mTOR) inhibition with everolimus

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Abstract

Patients with breast cancer face substantial challenges to bone health from bone metastases, as well as from chemotherapy and endocrine therapies that generally elicit disease control at the cost of increased bone turnover. Consequently, maintaining bone health is of critical importance for these patients. Recently reported results from BOLERO-2 showed significant clinical benefits with adding everolimus to exemestane therapy in postmenopausal women with estrogen-receptor-positive breast cancer recurring or progressing despite nonsteroidal aromatase inhibitor therapy. Moreover, exploratory analyses from BOLERO-2 showed that adding everolimus may have beneficial effects on bone turnover and progressive disease in bone in this patient population. These results are supported by preclinical studies in which mTOR inhibition was associated with decreased osteoclast survival and activity. Thus, everolimus therapy may be able to ameliorate the negative effects of estrogen suppression on bone health. This review discusses the effects of mTOR inhibition on bone health during endocrine therapy.

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1. Introduction

Maintaining bone health is important for patients with breast cancer because both the cancer itself and the therapies used to treat the disease can negatively affect bone. Bone health challenges for patients with breast cancer commonly stem from adjuvant endocrine therapy- and chemotherapy-induced bone loss in patients with early disease and disease progression in bone (i.e., bone metastases) in patients with advanced disease. Skeletal complications associated with bone metastases in patients with advanced disease can be exacerbated by preexisting osteoporosis [1]. Following surgical resection of the tumor, depending on the biology of the disease and risk of recurrence, patients with breast cancer may require adjuvant chemotherapy and/or endocrine therapy. In particular, endocrine therapies used to treat hormone-receptor-positive (HR+) breast cancer often negatively impact bone health. In contrast with endocrine therapies, the mammalian target of rapamycin (mTOR) inhibitor, everolimus, appears to have a positive effect on bone in patients with advanced breast cancer [2].

Recently reported results from the phase 3 BOLERO-2 trial in postmenopausal women with HR+ breast cancer progressing despite nonsteroidal aromatase inhibitor (NSAI) therapy showed significant clinical benefits with adding everolimus to exemestane [3]. Notably, exploratory analyses from BOLERO-2 showed that adding everolimus also may have the beneficial effects of reducing bone turnover and breast cancer progression in bone in this patient population [2]. The former observation in particular, although explained by preclinical data, may be potentially unexpected when combined with an endocrine-based treatment regimen. This review will discuss how breast cancer, endocrine therapies, and mTOR inhibition with everolimus influence bone health.

2. Breast cancer and bone

Breast cancer can influence the cells involved in bone metabolism (i.e., osteoblasts and osteoclasts) in a manner that promotes cancer metastasis and growth and has adverse effects on bone health. Molecular signaling between bone cells and breast cancer cells can lead to a destructive cycle that promotes the growth and dissemination of bone metastases [4]. The release of growth factors (e.g., endothelin-1 and transforming growth factor-β family members) during bone remodeling can stimulate proliferation of dormant breast cancer cells [4]. This in turn promotes the development and progression of metastases. Furthermore, breast cancer cells can secrete factors that also promote osteolysis, resulting in a vicious cycle of tumor growth and bone destruction [4]. Because breast cancer preferentially metastasizes to the skeleton, bone metastases, a painful and potentially debilitating complication, develop in 65–75% of patients with advanced breast cancer [4,5]. As a result, maintaining bone health is of critical importance for patients with breast cancer. Unfortunately, many anticancer therapies used to treat the disease can adversely affect bone health.

Although a cornerstone for treating HR+ disease, endocrine therapies (especially aromatase inhibitors [AI]) used to treat breast cancer are often detrimental to bone health [6–13]. Estrogen is one of several local and systemic factors that influence normal bone homeostasis, which is maintained through continuous remodeling by osteoclasts (bone resorption) and osteoblasts (bone formation) [14]. One mechanism through which estrogen acts on bone is through the receptor activator of nuclear factor-kappa B (RANK)/osteoprotegerin pathway, wherein RANK ligand (RANKL) induces osteoclast activity and osteoprotegerin acts as a physiologic inhibitor of RANKL [15–18]. Indeed, preclinical studies have shown that suppression of estradiol can reduce osteoprotegerin expression and increase RANKL expression [15,16,18,19]. Therefore, estrogen suppression leads to increased osteoclast-mediated bone resorption in response to elevated RANKL and decreased osteoprotegerin levels.

Exploratory analyses from the NCIC MA.14 trial also suggest an increased risk of bone metastasis in patients with high bone resorption levels during adjuvant endocrine therapy [20]. These analyses examined the association of disease recurrence in bone only with serum beta C-terminal telopeptide of type I collagen (B-CTX). Of the 621 patients in the original study, 123 had disease recurrence at 7.9 years median follow-up. Nineteen (3.1% of the 621) experienced bone-only recurrence and 47 (7.5% of the 621) had recurrence in bone and other sites. In these patients, elevated pretreatment serum B-CTX was associated with decreased bone-only recurrence-free survival (P = .02). Although awaiting confirmation in other studies [21], these data support the concept that increased bone turnover fosters an environment ideal for breast cancer metastasis and growth in some patient populations.

3. Effect of endocrine therapies on bone

Much of the data regarding bone effects of endocrine therapies derive from the adjuvant setting. Historically, tamoxifen was the treatment of choice for endocrine-responsive breast cancer and has been shown to preserve bone mineral density in postmenopausal, but not premenopausal, women [22,23]. However, fracture risks remained similar in postmenopausal women receiving tamoxifen compared with those who did not receive this therapy. Aromatase inhibitors (e.g., anastrozole, letrozole, exemestane) are more effective anticancer agents than tamoxifen and have largely replaced tamoxifen as the treatment of choice for hormone-responsive breast cancer in postmenopausal women [22,24–26]. Because AIs prevent peripheral estrogen production, they suppress estrogen levels beyond what happens during natural menopause. This activity is critical for treating hormone-responsive breast cancer.
but also leads to accelerated bone loss, which can compromise bone health [6,9–12,23].

Nonsteroidal aromatase inhibitors (i.e., letrozole, anastrozole) inhibit aromatase activity in a reversible manner, and are often the first type of hormonal therapy used in patients with HR+ breast cancer. However, these agents have been associated with bone loss occurring at more than twice the rate of physiologic postmenopausal bone loss [7,27,28]. This leads to an increased risk of fractures [6,25,28,29], potentially resulting in increased morbidity and mortality [30]. For example, analyses of the ATAC and MA.17 trials showed that adjuvant anastrozole or letrozole was associated with increased bone turnover [7,27,28]. Overall, estrogen depletion attained with NSAI therapy has been associated with reduced bone mineral density and elevated fracture risk [7,14,31–33].

The steroidal AI, exemestane, exerts irreversible effects on aromatase activity and is often used to treat patients with advanced breast cancer whose disease progressed on NSAI (i.e., anastrozole or letrozole). However, a study in healthy postmenopausal women showed that the effects of exemestane on bone markers are different from letrozole and anastrozole [9]. Furthermore, exemestane also has been associated with increased levels of bone resorption and bone formation markers [6,7,10]. In addition, several studies, including bone substudies of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial, have shown that exemestane therapy is associated with increased levels of bone resorption and bone formation markers [6,7,11,12,34,35]. Additionally, patients in the TEAM study who received adjuvant exemestane also had a significantly higher fracture rate compared with those who received tamoxifen [35].

In contrast with AIs, fulvestrant, a selective estrogen receptor (ER) downregulator, has been shown to have minimal effects, neither positive nor negative, on bone health [36–38]. For example, serum bone-specific alkaline phosphatase (BSAP), N-terminal propeptide of procollagen type I (P1NP), and C-terminal telopeptide (CTX) levels were measured in a pilot study of 14 postmenopausal women with advanced breast cancer who derived clinical benefit with fulvestrant (250 mg/month) [37]. The data indicate that there were no significant differences from baseline to any assessed time-point for BSAP, P1NP, or CTX levels. Changes in the levels of these same bone markers also were evaluated in a larger phase 2 study evaluating the adjuvant use of fulvestrant 250 mg/month versus fulvestrant 500 mg/month in postmenopausal women with newly diagnosed breast cancer (N = 211) [38]. As with the small pilot study, there were no significant differences in bone marker levels at any time point compared with baseline or across treatment arms [38]. Together, these studies may suggest that, unlike other endocrine therapies, fulvestrant has a neutral effect on bone health. However, as it is indicated for use after other endocrine therapies, the neutral effects on bone might not be sufficient for postmenopausal women who have lost bone mineral density due to previous endocrine therapy.

Everolimus, an mTOR inhibitor, is not an endocrine therapy. However, the mTOR pathway intersects with multiple endocrine signaling pathways in breast cancer cells. Crosstalk can occur between the ER pathway and those of other growth factors, leading to tumor progression as well as resistance to endocrine therapy. Inhibition of the mTOR pathway with everolimus may enhance sensitivity to endocrine therapy and delay recurrence [39]. Indeed, this agent has been shown to enhance the efficacy of endocrine therapy in patients with HR+ advanced breast cancer [3]. Furthermore, based on the cellular functions influenced by the mTOR pathway, it is possible that everolimus may exert a protective effect on bone.

4. Effect of everolimus on bone

The serine–threonine kinase, mTOR, regulates cell growth, angiogenesis, and cell survival [40]. However, activation of the mTOR signaling pathway also is associated with endocrine resistance in breast cancer [41–45]. Everolimus, an oral inhibitor of mTOR, has been shown...
to enhance the efficacy of endocrine therapy (i.e., exemestane) in postmenopausal women with HR+ advanced breast cancer recurring or progressing during/after NSAI therapy [46,47]. Notably, based on analyses from the BOLERO-2 trial, everolimus was approved recently by the United States Food and Drug Administration and the European Medicines Agency for use in this patient population [46,47].

4.1. Preclinical

Research has demonstrated that there is crosstalk between estrogen-mediated and growth factor-mediated signaling pathways in breast cancer. For example, there is growing evidence supporting a close interaction between ER signaling and PI3K/Akt/mTOR signaling. The mTOR pathway is a key central regulator of cell growth and proliferation, and mTOR forms 2 different protein complexes, mTORC1 and mTORC2 [48]. The mTORC1 complex is responsible for ligand-independent activation of the ER [48]. Additionally, estradiol can suppress the apoptosis induced by inhibition of PI3K/Akt/mTOR signaling [49]. Hyperactivation of the PI3K/Akt/mTOR signaling pathway is an important mediator of endocrine resistance in HR+ breast cancer cells [42]. Furthermore, agents that inhibit PI3K/Akt/mTOR signaling have shown anticancer activity in endocrine resistant breast cancer cell lines. For example, everolimus in

![Fig. 2. mTOR inhibition decreases bone resorption, decreases osteoclast maturation, and increases osteoclast apoptosis (mouse models). (A) Inhibition of bone resorption by rapamycin. Rabbit bone marrow cells were seeded on bovine bone slices in 96-well plates and cultured in the absence or presence of rapamycin, at indicated concentrations. Release of collagen-I C-terminal telopeptides (CTX) into the culture medium was measured after 72 h. Data are mean ± SD (n = 3); bar is 100 μM. (B) Osteoclastogenesis was assessed in the absence or presence of rapamycin (30 nM, days 2–7). TRAP staining (left panels) of mouse bone marrow/MB 1.8 cell coculture (day 7) and quantification of TRAP activity (right panel) by a fluorescent assay. Values are mean ± SD (n = 8); bar is 100 μM. (C) Purified osteoclasts were treated with rapamycin (100 nM) for 20 h. Immunofluorescence image (overlay) of osteoclast nuclei stained with Hoechst No. 33342 (blue) together with FITC-phalloidin (green) to visualize nuclei and the actin cytoskeleton. Using corresponding phase-contrast images, cell outlines were traced (red) and superimposed for selected osteoclasts showing advanced induction of apoptosis. Bar is 100 μM. Abbreviations: CTX, C-telopeptide of type I collagen; mTOR, mammalian target of rapamycin; TRAP, tartrate-resistant acid phosphatase. Reprinted by permission from Macmillan Publishers Ltd.: Cell Death Differ. 2003;10:1165–1177, © 2003 [53].]
combination with letrozole has been shown to synergistically inhibit proliferation of estrogen-receptor-positive (ER+) breast cancer cells [50]. Moreover, everolimus in combination with endocrine therapy also has been shown to reverse resistance to endocrine therapy in ER+ breast cancer cell lines expressing a constitutively active AKT protein (an upstream activator of mTOR signaling and a potential mediator of endocrine resistance) [51]. Notably, anticancer synergy with the combined use of mTOR and mevalonate pathway inhibitors has been postulated in osteosarcoma, suggesting that mTOR inhibition also might have a positive impact on disease burden in bone [52].

In addition to these anticancer effects, preclinical studies suggest that mTOR inhibition may have other effects in patients with breast cancer, most notably, a potential beneficial effect on bone. In fact, preclinical evidence suggests that mTOR signaling is involved in bone remodeling [52–58]. These effects are likely exerted via signal transduction by cytokines through the mTOR pathway, which decreases osteoclast apoptosis and promotes osteoclast survival (Fig. 1) [53]. One cytokine pathway influenced by mTOR that is critical for osteoclast growth and differentiation is the RANK/osteoprotegerin pathway [53,56].

Fig. 3. The effects of everolimus on osteoblast differentiation (mouse osteoblast cell line MC3T3). MC3T3 cells were cultured to confluency, followed by induction of differentiation using an osteogenic stimulus. Treatment with indicated concentrations of everolimus started at the beginning of cultures. The results in the graph are means of two independent experiments, each done in duplicate. The IC50 value was 13.5 nM. Abbreviation: ALP, alkaline phosphatase. Reprinted from Bone, 35, Kneissl M, et al., Everolimus suppresses cancellous bone loss, bone resorption, and cathepsin K expression by osteoclasts, 1144–1156, © 2004, with permission from Elsevier [54].

Fig. 4. Everolimus treatment decreased bone loss associated with estrogen deprivation (rat models). (Top row) μCT images of the proximal tibia metaphysis; (Middle row) Osteoclast morphology on TRAP-stained 4-μm microtome sections of the proximal tibia metaphysis (400×); (Bottom row) Bone mineralization pattern visualized by fluorochrome label uptake (alizarin red and calcein green) (200×). Abbreviation: OVX, ovariectomized. Reprinted from Bone, 35, Kneissl M, et al., Everolimus suppresses cancellous bone loss, bone resorption, and cathepsin K expression by osteoclasts, 1144–1156, © 2004, with permission from Elsevier [54].
In this signaling cascade, RANKL is a major determinant of osteoclast-mediated bone resorption, which is suppressed by osteoprotegerin, a physiological inhibitor of osteoclast function [59,60]. Notably, downregulating mTOR via suppression of mTOR phosphorylation in the ST2 bone marrow-derived stromal cell line has been shown to lead to upregulation of osteoprotegerin [56].

Other factors that reflect osteoclast activity may also be influenced by mTOR inhibition. These include cathepsin K, the main osteoclast-derived protease responsible for digesting collagen type I in bone [54]. Cathepsin K mRNA expression and protein levels in human osteoclasts decreased substantially after treatment with everolimus [54]. Evaluating CTX levels is an established measure of bone resorption and can be used as an indirect measure of the effect of mTOR inhibition on bone. Notably, a study in cultured rabbit bone marrow cells demonstrated that treatment with the mTOR inhibitor rapamycin decreased production of CTX (Fig. 2A) [53]. Suppression of cathepsin K and CTX levels suggest that mTOR inhibition may lead to decreased bone resorption.

In addition to these indirect effects, animal models demonstrate that inhibition of the mTOR pathway decreases bone resorption [53,54]. For example, inhibiting mTOR in mice decreased osteoclast maturation (Fig. 2B) and increased osteoclast apoptosis (Fig. 2C) [53], suggesting that blocking the mTOR pathway may lead to a protective effect on bone. It is important to note that differentiation of osteoblasts, bone formation cells, also can be affected by mTOR inhibition. In the MC3T3 mouse osteoblast cell line, everolimus inhibited alkaline phosphatase, a marker of osteoblast differentiation, albeit only at higher concentrations (IC50 13.5 nM) (Fig. 3) [54]. Although everolimus inhibited differentiation of both osteoclasts and osteoblasts in vitro, experiments in ovariectomized rats showed that everolimus ameliorates bone loss associated with estrogen deprivation (Fig. 4) [54]. These animal studies suggest that mTOR inhibition may exert a bone-preserving effect. Together, these preclinical data outline a potential mechanism by which everolimus could ameliorate the negative bone effects of endocrine therapy in patients with advanced breast cancer.

4.2. Clinical

The phase 3 BOLERO-2 trial demonstrated that the addition of everolimus to exemestane treatment significantly improved progression-free survival (PFS) in postmenopausal
women with HR+ advanced breast cancer progressing on prior NSAI therapy [3]. In addition to the positive PFS results of the overall trial, everolimus also may have a positive effect on bone health in this patient population.

Although other clinical studies of mTOR inhibitors in patients with breast cancer have reported results, these did not include any bone-specific endpoints [61,62]. In contrast, exploratory analyses in BOLERO-2 evaluated the effect of everolimus on bone marker levels and progressive disease in bone (Table 1) [2]. Bone marker data suggest that everolimus suppresses bone turnover and reverses the increases in bone resorption associated with both progressive disease in bone and effects of exemestane treatment on normal bone turnover. Adding everolimus to exemestane therapy also reduced the incidence of breast cancer progression in bone (i.e., appearance of new bone metastases or progression of preexisting bone metastases) in the overall patient population (N = 724; \( P = .04 \), Gray’s test) [2]. Furthermore, the reduction of progressive disease in bone also was significantly lower in the subset of patients with bone metastases at baseline (n = 556; \( P = .02 \), Gray’s test). Positive bone effects with everolimus were in addition to the reported improvements in PFS, clinical benefit rate, and quality of life with everolimus [63].

In addition to reducing disease progression in bone, everolimus might help protect bone health. In BOLERO-2, a marked increase in osteoclast metabolism (i.e., BSAP), bone formation (i.e., P1NP), and bone resorption (i.e., CTX) marker levels was observed in the placebo plus exemestane arm at weeks 6 and 12 relative to baseline [2]. In contrast, there was a significant decrease in these same marker levels with everolimus plus exemestane at weeks 6 (26.4% for BSAP, 55.9% for P1NP, and 35.9% for CTX; \( P < .001 \) for all) and 12 (20.3% for BSAP, 66.2% for P1NP, and 40.5% for CTX; \( P \leq .005 \) for all) relative to baseline. Furthermore, these effects were not influenced by baseline bisphosphonate use or the presence of bone metastases at baseline (Table 1) [2]. The elevated bone marker levels reported in the placebo plus exemestane arm suggests that the rates of bone turnover are higher with exemestane therapy alone. This may be consistent with prior reports in postmenopausal women receiving adjuvant exemestane therapy for breast cancer [6,9–12]. Overall, the results of the BOLERO-2 exploratory analyses suggest that everolimus may protect bone health, potentially compensating for the negative bone effects associated with exemestane therapy.

5. Conclusions

In contrast with AIs and fulvestrant, everolimus may have beneficial effects on bone metabolism, potentially reducing bone resorption and contributing to a bone-protective effect. This benefit might be particularly relevant to postmenopausal women who have previously received NSAIs for a long period, and therefore may have experienced substantial bone loss. Preclinical evidence indicates that mTOR inhibition reduces osteoclast differentiation and survival and shows that treatment with everolimus ameliorates bone loss due to estrogen deprivation in rat models. These findings provide support for the beneficial bone effects of everolimus observed in the BOLERO-2 study. The observed reduction of progressive disease in bone with everolimus, including delaying progression of existing bone lesions, could be the net result of several mechanisms: anticaner effect on bone metastases consistent with the overall significant improvement in PFS, direct effects of mTOR inhibition on osteoclast survival and subsequent bone resorption, or a combination of these and other as yet undetermined mechanisms [53,54,57,59,60].

The potential benefits of mTOR inhibition with everolimus are of great clinical importance. For example,
utilizing everolimus therapy to reduce bone turnover in patients receiving endocrine therapy for advanced breast cancer may help patients maintain bone mineral density, thereby avoiding osteoporotic fractures and maintaining quality of life. Additionally, the protective effects of everolimus on bone differentiate this agent from endocrine therapies for HR+ breast cancer, as some of these (particularly AIs) have a negative effect on bone. Although the data are compelling, a definite clinical benefit cannot be established solely on the basis of these exploratory analyses, and insights from clinical trials of everolimus in the adjuvant setting are awaited. Notably, the ability of targeted therapies, especially kinase inhibitors, to alter osteoclast survival and function is the subject of substantial clinical research. Ongoing studies are investigating potential bone-directed effects of several targeted agents in advanced breast cancer (Table 2) [3,64–71], and results from these studies may provide additional avenues for preserving bone health in addition to achieving disease control in postmenopausal women with advanced breast cancer.

These data also suggest that earlier (adjuvant) use of everolimus may be beneficial to postmenopausal women with ER+ breast cancer. Potential adjuvant benefits with everolimus may derive from overcoming endocrine resistance and restoring/enhancing endocrine sensitivity, especially in patients at high risk for breast cancer recurrence during standard adjuvant endocrine therapy (e.g., based on prognostic factors and multigene risk scores). Currently, several adjuvant trial protocols are being developed and discussed by the global investigator community to evaluate the potential role of adjuvant everolimus in postmenopausal women with ER+ breast cancer [72,73].

Conflict of interest statement

Peyman Hadji has received honoraria, unrestricted educational grants, and research funding from Amgen, AstraZeneca, GlaxoSmithKline, Eli Lilly, Novartis, Pfizer, and Roche.

Robert Coleman has received honoraria (speaking and advisory boards) from Amgen and Bayer and has given expert testimony on behalf of Novartis.

Michael Gnant has received research support from GlaxoSmithKline, Sanofi-Aventis, Novartis, and Roche; has been a consultant to Merck and Novartis; and has received honoraria (speaking, advisory boards, etc.) and travel support from Amgen, Pfizer, Novartis, GlaxoSmithKline, Bayer, Sandoz, AstraZeneca, and GenomicHealth.

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References


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[64] U.S. National Institutes of Health. Randomized phase II trial of letrozole with or without dasatinib as first and second-line treatment for hormone receptor-positive, HER2-negative post-menopausal breast cancer that is unresistant, locally recurrent or metastatic. http://clinicaltrials.gov/ ct2/show/NCT00696072?term=NCT00696072&rank=1. NLM Identifier: NCT00696072. Updated June 18, 2012 [accessed 03.08.12].


Biography

Peyman Hadji, M.D., Ph.D., is Head of the Department of Endocrinology, Reproductive Medicine and Osteoporosis and professor of Obstetrics, Gynaecology and Endocrinology
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