Title

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Journal

Endocrine Related Cancer, 21(5)

ISSN

1351-0088

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Publication Date

2014-09-22

DOI

10.1530/erc-14-0387

Peer reviewed

Zoledronic acid at the time of castration prevented castration-induced bone metastasis in mice

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Abstract

Androgen deprivation therapy (ADT) is known to cause bone loss in a majority of patients with castration-resistant prostate cancer (CRPC). A study published in this issue of *Endocrine-Related Cancer* by Ottewell and colleagues shows that ADT increased bone resorption and triggered growth of disseminated prostate cancer (CaP) cells to form bone metastasis using an *in vivo* model. However, prevention of bone decay by weekly administration of zoledronic acid (ZOL) at the time of castration prevented ADT-induced tumor growth in bone. Recently, two publications from Japan have demonstrated that ZOL combined with ADT improved outcomes for patients with treatment-naïve CaP with bone metastasis. The mechanistic cause for these patients having an improved overall survival compared with those who were treated with ZOL after ADT initiation or before metastasis development was never explained. Ottewell and colleague's study now suggests that it is the bone loss caused by ADT that promoted bone metastasis, and if ZOL is administered at the time of ADT initiation, it would prevent this bone loss and prolong skeletal-related event-free survival.

Key Words
- androgen deprivation therapy
- bone loss
- zoledronic acid
- prostate cancer

Endocrine-Related Cancer (2014) **21**, C11–C14

Zoledronic acid and castration-induced bone metastasis

Over the past 25 years, prostate-specific antigen (PSA) screening and improved treatment modalities have significantly increased overall survival (OS) of patients with localized CaP; however, the survival rate of patients who develop metastatic CaP (mCaP) remain unchanged (Wu *et al.* 2014). In 75–80% of patients with mCaP, the bone will be the first and most prominent metastasis site (Roodman 2004). Metastasis alters normal bone remodeling processes, resulting in fractures and spinal cord compression (Jimenez-Andrade *et al.* 2010). In addition, the metastatic tissue replaces normal bone marrow, resulting in anemia. While metastasized tumor cells stimulate osteoclast-mediated bone resorption, growth factors released from the resorbed bone further advance the metastasized tumor colonies (Logothetis & Lin 2005). This leads to an imbalance between bone resorption and bone formation, thereby enhancing skeletal-related events (SRE).

However, treatment for mCaP may result in additional loss of skeletal integrity. Patients with mCaP are treated with androgen deprivation therapy (ADT) as standard of care, usually with leutenizing hormone-releasing

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DOI: 10.1530/ERC-14-0387

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hormone (LHRH) agonists such as leuprolide or goserelin acetate. ADT increases bone resorption and is a known risk factor for osteoporosis (Krupski *et al*. 2004). ADT is also administered to patients with high risk localized or locally advanced CaP with no radiological evidence of metastasis. Most of these patients will eventually progress and develop castration-resistant prostate cancer (CRPC), initially with no detectable metastasis. Eventually many of these patients may develop bone metastasis, but it is not known whether the SRE are a result of, or independent of, treatment for advanced disease. An article in this issue of *Endocrine-Related Cancer* now suggests, based on studies in a preclinical model of CRPC, that ADT can stimulate the development of bone metastasis via osteoclast-mediated mechanisms (Ottewell *et al*. 2014).

In this study, the authors investigated the effects of ADT on bone metastasis by castrating 12-week-old *Balb/c* nude mice that had disseminated, hormone insensitive, *Ar*-null PC-3 tumors growing in the long bones (Ottewell *et al*. 2014). The study showed that castration resulted in increased osteoclast activity and bone resorption, thus leading to increased bone turnover and significant bone volume loss in nude mice. Castration following PC-3 cells i.p. injection triggered the growth of disseminated cancer cells and resulted in a substantial increase in tumor in bone. A significant advantage in this study is the use of 12-week-old mice compared with the 4 to 6-week-old mice that is normally used. 90% of 6-week old animals had detectable skeletal tumor growth following injection of PC-3 cells to intact male mice, compared to 10% of 12-week old animals. This difference was attributed to the higher rate of bone turnover in younger animals (Ottewell *et al*. 2014). However, upon castration, there was a substantial increase in tumor growth in bone of the 12-week-old animals (70% castrated animals developed bone metastasis), accompanied by a $>40\%$ loss in trabecular bone compared with controls. This rate of bone metastasis was comparable with that of the 6-week-old mice, and hence the authors conclude that this was due to the higher bone turnaround in the 12-week-old animals upon castration (Ottewell *et al*. 2014). Therefore, it has been investigated whether prevention of bone turnaround would inhibit this effect.

Bisphosphonates, such as zoledronic acid (ZOL), are commonly used to inhibit the bone resorbing activity of osteoclasts by binding to the mineralized bone surface, thereby increasing bone volume (Gartrell & Saad 2014). Intravenous ZOL was approved in 2002 to treat patients with bone metastasis from prostate cancer, which significantly reduced the frequency of SREs while prolonging the time to develop SREs (Saad *et al*. 2002). In addition, ZOL significantly lowered pain in patients with bone metastasis; however, so far, there has been no significant difference in disease progression or OS. In these studies, ZOL was administered to patients after the metastasis had initiated. The paper by Ottewell *et al*. (2014), on the other hand, shows that in the same preclinical model, ZOL administered at the time of ADT initiation prevented subsequent relapses in bone metastatic lesions.

In this study, nude mice were injected PC-3 cells i.c. and received weekly administration of saline or ZOL 3 days before sham operation or castration. ZOL treatment inhibited osteoclast activity in both sham and castration groups, and a significant reduction in tumor growth in bone was observed in castrated animals treated with ZOL compared with castrated control (20 vs 70% of mice bearing tumors) animals. ZOL treatment did not alter the number of animals with skeletal tumors in the intact mice – but instead caused a reduction in size of skeletal tumors (Ottewell *et al*. 2014). These observations were in keeping with those of a large-scale human study, in which use of ZOL in men who were at risk for developing metastases failed to prevent the onset of mCaP (Wirth *et al*. 2014). Thus, by itself ZOL is incapable of preventing metastasis caused by factors other than castration.

In the castrated mice, on the other hand, ZOL caused an increase in bone volume back to levels seen in intact animals. However, lytic lesion formation reduced to similar levels upon ZOL administration in both intact and castrated mice, and similar numbers of single tumor cells were observed in bone in all the experimental groups. Thus, CaP cells homed to bones in all animals, but failed to form overt tumors unless the bone turnover was increased by subsequent castration. Similarly, ZOL did not prevent metastasis or invasion, but prevented the growth or colonization of the invading cells in the bone microenvironment altered by castration. Thus, neither ZOL nor ADT alone was effective, but in combination, they prevented further progression of disease, but only when the two were administered together and simultaneously.

The timeliness of the study is due to some recent reports indicating the advantages of using ZOL in combination with ADT in patients with mCaP. The observations of Ottewell *et al*. are borne out by recent clinical studies, which also show the benefits of ZOL administration in the neoadjuvant setting. A Phase II trial of ZOL combined with ADT for treatment-naïve CaP with bone metastasis showed an encouraging SRE-free OS rate at 24 months in Japanese patients (Nozawa *et al*. 2013).

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Another study, also from Japan, showed that ZOL improved outcomes in patients with hormone-naïve mCaP (Okegawa *et al*. 2014). The study by Ottewell *et al*. (2014) is coincidentally showing the same in a preclinical setting.

In both of the clinical studies (Nozawa *et al*. 2013, Okegawa *et al*. 2014), ZOL was given as an initial treatment with ADT in treatment-naïve patients with metastatic prostate cancer. In the study by Ottewell *et al*., ZOL was also administrated before the initiation of ADT, thus provided the biological evidence to the clinical settings that administration of ZOL before, or at the same time to, the initiation of ADT could inhibit prostate cancer relapse in bone. In contrast, other studies where ZOL had been administered 6-months following ADT did not show any significant advantage in the treatment arm in comparison with the control arm (Smith *et al*. 2014). Ottewell *et al*. (2014) may have a possible explanation for this discrepancy. They postulate that ADT induces rapid changes to the bone environment and that ZOL must be administered at the time of ADT to prevent ADT-induced bone modifications which in turn cause disease progression.

This is not to say that the study by Ottewell *et al*. (2014) is without any drawbacks. First, in clinical scenarios, most disseminated prostate cancer cells are androgen naïve, express androgen receptors and are responsive to ADT. In the current study, PC-3 cells, one of the most commonly used CaP bone metastasis models, do not represent the majority of prostate cancers because the PC-3 cells are AR negative and androgen-insensitive. Unfortunately, one of the drawbacks of CaP research is that no naturally bone metastasizing tumor models are currently available; therefore, the authors likely had to deal with the hand that they were dealt. Secondly, prostate cancer patients usually receive ADT with already growing tumors. In this study, ADT and ZOL were administrated before the tumor developed, which was not necessarily the clinical situation. However, the resemblance to the clinical results show that nevertheless, ZOL in both the preclinical and the clinical studies was able to prevent further bone damage and likely will prevent additional metastases as well.

Conclusions

In summary, the study by Ottewell and colleagues demonstrated that castration resulted in growth of disseminated tumor cells in bone through osteoclast-mediated mechanisms. It is the first biological evidence indicating that ZOL, when administrated to prostate cancer patients at the time of ADT, can prevent prostate cancer relapse in bone. Such findings, with the recent clinical studies together, presented a novel treatment strategy that can benefit prostate cancer patients with SRE.

Declaration of interest
The authors declare no conflict of interest. The work reported here does not represent the views or opinions of the Department of Veteran Affairs or the United States Government.

Funding
This commentary did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Author contribution statement
Conception and design: P M Ghosh. Writing, review and/or revision of the manuscript: A C Gao and P M Ghosh.

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Received in final form 19 August 2014
Accepted 1 September 2014
Made available online as an Accepted Preprint
2 September 2014

http://erc.endocrinology-journals.org
DOI: 10.1530/ERC-14-0387

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