1. Introduction

Bone is the most common site for metastases—most often the spine, followed by the pelvis, hip, femur, and skull. Bone metastases can occur whenever cancer cells relocate to bone from a primary tumour but are of particular clinical importance in prostate and breast cancers because of the high incidence and relatively long clinical courses of these diseases. Approximately 70% of patients with advanced prostate or breast cancer have evidence of metastatic bone...
disease at post mortem [1]. Tumours are usually incurable once they have metastasized to bone: 5-y survival rates are 25% and 20% for metastatic prostate and breast cancer, respectively [2]. Bone metastases can cause severe pain, increased fracture risk, and hypercalcaemia [3]. Spinal metastases can cause spinal cord compression and severe neurologic impairment [4]. Such effects can have a marked impact on quality of life (QoL) and activities of daily living.

Treatment of cancer can also compromise bone health. Androgen-deprivation therapy (ADT), such as the inhibition of testosterone using gonadotropin-releasing hormone (GnRH) agonists, is a standard treatment for men with metastatic prostate cancer (PCa) and is increasingly used in patients with localised disease. However, ADT is associated with reduced bone mass. In men with PCa receiving ADT, annual rates of reduction in bone mineral density (BMD) in the lumbar spine, total hip, and femoral neck are 5–10-fold higher than in patients with PCa not receiving ADT or healthy age-matched controls [5]. This reduction in BMD translates into an increased risk for skeletal complications: A large study of the medical records of patients surviving at least 5 yr after diagnosis of PCa revealed a relative risk of fracture of 1.45 (95% confidence interval, 1.36–1.56) among those who received nine or more doses of GnRH agonist in the first 12 mo after diagnosis [6]. The issue of ADT-related bone loss is becoming more pertinent as the benefits of early treatment of PCa with ADT become apparent [7]. This, along with trends for earlier diagnosis, can result in patients receiving ADT for a decade or longer—a considerable time frame over which bone loss may progress.

Recent advances in the treatment of primary cancers have stimulated greater interest in therapeutic options for the treatment of secondary bone tumours. Current treatments for bone metastases, such as external beam radiation therapy, radiopharmaceuticals, and surgery, are primarily palliative. Therapies that reverse the bone disease associated with these tumours and potentially improve outcomes are therefore in demand. Our understanding of the pathophysiology underlying bone disease associated with cancer and its treatments is growing, and new avenues for therapeutic intervention are being identified.

2. Evidence acquisition

This article is based on a presentation at an Amgen-sponsored satellite symposium held at the European Association of Urology Congress in Stockholm, Sweden, in March 2009. Published evidence to support the presentation was acquired and reviewed through a nonsystematic PubMed search.

3. Evidence synthesis

3.1. Balanced formation and resorption in healthy bone

Bone architecture is determined by the balance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation. Bone turnover remains in a steady state when these two processes are coupled. Under normal conditions, the formation, function, and survival of osteoclasts is regulated by a number of factors belonging to the tumour necrosis factor (TNF) receptor family, which either prevent or promote osteoclast activity. Three of these factors make up a molecular triad implicated in the regulation of both normal and pathological bone metabolism: RANK, RANK Ligand and osteoprotegerin (OPG), an endogenous decoy receptor for RANK Ligand.

RANK is a transmembrane signalling receptor expressed on osteoclast precursor cells and activated osteoclasts [8]. RANK Ligand is an essential mediator of osteoclast formation, function, and survival [9,10]. It is expressed by osteoblasts and bone stromal cells and, by binding to RANK, stimulates osteoclast precursors to form and differentiate into activated osteoclasts [11,12]. RANK Ligand thereby promotes bone resorption, as summarised in Fig. 1. Subcutaneous injection of human recombinant RANK Ligand into mice has been shown to accelerate bone turnover and reduce bone volume, density, and strength [13]. By contrast,
the downregulation of RANK Ligand expression by means of targeted deletion of a transcriptional enhancer of the RANK Ligand gene in mice results in increased bone mass and a reduction in the rate of bone turnover [14].

OPG is a soluble member of the TNF receptor family and is secreted by osteoblasts [15]. By acting as a decoy receptor for RANK Ligand, OPG inhibits the binding of RANK Ligand to RANK and also reduces the half-life of membrane-bound RANK Ligand [16]. Thus, OPG blocks osteoclast differentiation, promotes apoptosis of activated osteoclasts, and reduces osteoclast adhesion to the bone surface, with a net effect of reduced osteoclast activity [17–19]. The role of OPG in maintaining bone mass is evident from studies in adolescent and adult OPG-deficient mice, which have reduced total bone density, severe trabecular and cortical bone porosity, marked thinning of the parietal bones of the skull, and a high incidence of fractures [20].

3.2. Dysregulated bone metabolism in cancerous states

Bone metastases are associated with dysregulated bone metabolism and can be associated with increases in bone resorption (osteolytic) and abnormal new bone formation (osteoblastic). Accordingly, bone metastases are identified as either osteolytic or osteoblastic in nature, depending on their radiographic appearance [21,22]. Metastases associated with PCA are generally described as osteoblastic, whereas those associated with breast or renal cancer are primarily osteolytic, based on x-ray evidence [21,23]. However, lesions are rarely at one end of this spectrum and tend to be heterogeneous. Studies in an animal model of osteoblastic PCA in which osteoblast and osteoclast activity were inhibited either separately or in combination showed that osteoblast and osteoclast activities drive the progression of PCA-associated bone lesions in a cooperative manner [21]. Furthermore, histomorphometric analysis of bone metastases in men with PCA revealed direct evidence for osteoclast-dependent bone resorption [24]. In fact, osteoclast activity may be a prerequisite for both osteoblastic and osteolytic lesions [22]. Thus, the osteoclast and the factors that regulate its formation, function, and survival clearly play important roles in the metastasis of a range of tumours to bone.

3.3. The vicious cycle of tumour growth and bone loss: the role of RANK Ligand

The RANK Ligand pathway underlies the pathological disturbances in bone resorption observed in patients with bone metastases. The equilibrium between the opposing effects of RANK Ligand and OPG becomes disrupted, disturbing the normal rates of bone resorption and formation and leading to abnormalities in bone architecture. Indeed, many disease states that are characterised by abnormally high rates of bone resorption are associated with elevated expression of RANK Ligand and reduced expression of OPG [25]. Preclinical models of metastatic bone disease have provided evidence suggesting that RANK Ligand contributes to a vicious cycle of tumour growth and bone destruction. As tumour cells invade bone, they secrete growth factors such as fibroblast growth factor (FGF), platelet-derived growth factor, transforming growth factor-β (TGF-β), bone morphogenetic peptide, and insulin-like growth factor 1. Together, these factors stimulate osteoblasts to produce and release RANK Ligand, which in turn activates osteoclasts and leads to bone resorption [25]. Bone metastases therefore increase bone resorption through increased expression of RANK Ligand, which overwhelms the neutralising effect of OPG. Bone resorption is then exacerbated further by osteoclast-mediated release of various bone-derived growth factors such as TGF-β and FGF, which promote further tumour growth, thus

Fig. 2 – RANK Ligand mediates a vicious cycle of tumour growth and bone resorption. Adapted from Roodman [25].

PTHrP = parathyroid-hormone-related peptide; BMP = bone morphogenetic peptide; TGF-β = transforming growth factor β; IGF = insulin-like growth factor; FGF = fibroblast growth factor; VEGF = vascular endothelial growth factor; ET1 = endothelin 1; PDGF = platelet-derived growth factor.
perpetuating a vicious cycle of tumour growth and bone resorption (Fig. 2) [21,25–27].

The negative effects on bone strength that result from ADT may also be mediated through the RANK Ligand pathway. There is evidence from patients with chronic renal failure (which is commonly associated with abnormalities in sex hormone concentrations) that testosterone levels are negatively correlated with levels of soluble RANK Ligand [28], suggesting that RANK Ligand may also have a role in bone loss that arises from treatment with GnRH agonists.

3.4. Inhibition of RANK Ligand as a therapeutic target

Given the apparent importance of the RANK Ligand pathway in the pathology of osseous tumour growth, osteoclastogenesis, and bone resorption and the important role of osteoclasts in both osteolytic and osteoblastic metastatic bone lesions, the RANK Ligand pathway is an attractive therapeutic target for the prevention and management of bone lesions that are secondary to a range of primary tumours as well as the prevention of cancer treatment-induced bone loss (CTIBL). Even when considering bone metastases secondary to PCa, in which the pathophysiology may be less dependent on osteoclast function than the more osteolytic lesions associated with breast cancer, the importance of RANK Ligand is apparent. In men with PCa, expression of RANK Ligand is greater in tumour cells derived from bone metastatic lesions than in cells from the primary tumour or other metastases [29]. There is also evidence that serum levels of OPG are elevated in patients with PCa that has metastasized to bone, suggesting a possible compensatory response to increased expression and activity of RANK Ligand [30,31]. It has also been suggested, however, that inhibition of tumour-associated osteolysis via elevated OPG may underlie the osteoblastic nature of bone lesions that are secondary to PCa [32]. Crucially, inhibition of RANK Ligand through the use of recombinant OPG in xenograft models of PCa has been shown to suppress the growth of existing tumours and prevent the formation of new metastases [33,34]. Along with concordant evidence for the protective role of recombinant OPG in more osteolytic bone metastases, such as those secondary to breast cancer [35], these findings demonstrate that inhibition of RANK Ligand represents a promising therapeutic approach.

Denosumab is a fully human monoclonal antibody (IgG2) developed to specifically target RANK Ligand. Essentially, it mimics the effects of endogenous OPG, binding RANK Ligand with high affinity and specificity. Through this binding, denosumab prevents the binding of RANK Ligand to RANK and thus inhibits osteoclast-mediated bone resorption (Fig. 3) [36]. As a result of its effects on osteoclast formation, function, and survival, denosumab is being studied in patients with osteoporosis, multiple myeloma, and rheumatoid arthritis as well as bone metastases, osseous tumour growth, and CTIBL. Ongoing trials are examining whether denosumab can block osteoclast-mediated bone destruction and whether it disrupts the vicious cycle of tumour growth and bone resorption in metastatic PCa.

4. Conclusions

The coordinated activity of osteoclasts and osteoblasts ensures a balance between bone resorption and formation during the turnover of normal healthy bone. Osteoclast formation, function, and survival are regulated primarily by RANK Ligand and the two receptors to which it binds: RANK and OPG. In healthy bone, the RANK Ligand pathway facilitates the balance between bone formation...
and resorption; however, an increase in the level of RANK Ligand promotes bone resorption, and this underlies osteolysis in bone metastases. Excessive bone resorption can be prevented by inhibiting RANK Ligand, thereby downregulating the formation, function, and survival of osteoclasts. Bone loss associated with ADT may also be mediated by the RANK Ligand pathway. With this in mind, the therapeutic potential of denosumab, a fully human monoclonal antibody against RANK Ligand, is being investigated in clinical trials. This agent may block osteoclast-mediated bone destruction, thereby disrupting the vicious cycle of metastatic bone destruction in a range of cancers, including PCA [3], and potentially reducing bone loss associated with ADT.

Conflicts of interest

The author has acted as a consultant for Novartis AG, as a consultant and speaker for General Electric Company, and as a researcher for Novartis AG, Johnson & Johnson, Amgen, Bayer AG, immatics biotechnologies GmbH, and Photocure ASA.

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