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Complications of Treatment

Cancer treatment-induced bone loss (CTIBL): Pathogenesis and clinical implications

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ABSTRACT

Osteopenia and osteoporosis are often long-term complications of anti-neoplastic treatments, defined as "cancer treatment-induced bone loss" (CTIBL). This pathological condition in oncologic patients results in a higher fracture risk than in the general population, and so has a significant negative impact on their quality of life. Hormone treatment is the main actor in this scenario, but not the only one. In fact, chemotherapies, radiotherapy and tyrosine kinase inhibitors may contribute to deregulate bone remodeling via different mechanisms. Thus, the identification of cancer patients at risk for CTIBL is essential for early diagnosis and appropriate intervention, that includes both lifestyle modifications and pharmacological approaches to prevent bone metabolism failure during anti-tumor treatments.

Introduction

The increased knowledge of cancer biology and diagnostic and therapeutic advances have considerably increased the life expectancy in a large number of cancer patients, leading to a general improvement of overall survival. However, prolonged treatment is often associated with long-term effects that negatively affect the quality of life, and have a significant social and economic impact.

In this context, unfortunately the majority of anti-tumor treatments is associated with cancer treatment-induced bone loss (CTIBL). Patients with both breast and prostate cancer may experience a decrease in bone mineral density (BMD) during hormonal therapy, resulting in osteopenia or osteoporosis that often require drug suspension. Meanwhile, chemotherapies contribute to bone mass loss either directly, through a dysregulation of osteoblast (OB) and/or osteoclast (OC) differentiation and activity, or indirectly, as a result of the development of chronic renal disorders and electrolyte abnormalities, as well as hypogonadism onset. Other mechanisms include the pro-apoptotic effect on both OBs and osteocytes as well as the accelerated differentiation of bone marrow stromal cells (BMSCs) into adipocytes [1,2]. Radiotherapy (RT), glucocorticoids (GCs) and tyrosine kinase inhibitors (TKIs) also contribute to damage bone health.

Apart from the impaired quality of life due to the increased fracture risk and bone pain, that greatly restrict daily activities, another critical condition induced by CTIBL is a tendency to generate a favorable metastatic niche for cancer [3]. Thus, the early identification of cancer patients at high risk for CTIBL is necessary to plan appropriate follow-up and adequate prevention options to preserve bone health.

Here, we review the major mechanisms according to which anti-cancer treatments affect the physiological bone turnover, as well as diagnostic and therapeutic strategies for overcoming this serious complication.

Physiology of bone turnover

The skeleton undergoes a continuous physiological remodeling, thanks to the balanced activity of OCs and OBs (Fig. 1). OCs are giant syncytial cells deriving from monocyte/macrophages that fill the Howship lacunae and exert a resorptive function by secreting protons and enzymes, such as cathepsin K, phosphatase and collagenase. On the other hand, OBs derive from mesenchymal stem cells (MSCs), fill the cavities created by OCs and deposit the morphogenic bone proteins within the mineralized matrix. Their secreting activity is synchronized through cell-to-cell contact, mediated by gap junctions [4,5]. After completing the bone formation, OBs become flat and quiescent and some of them are buried in the mineralized bone, becoming osteocytes, namely OB-like cells

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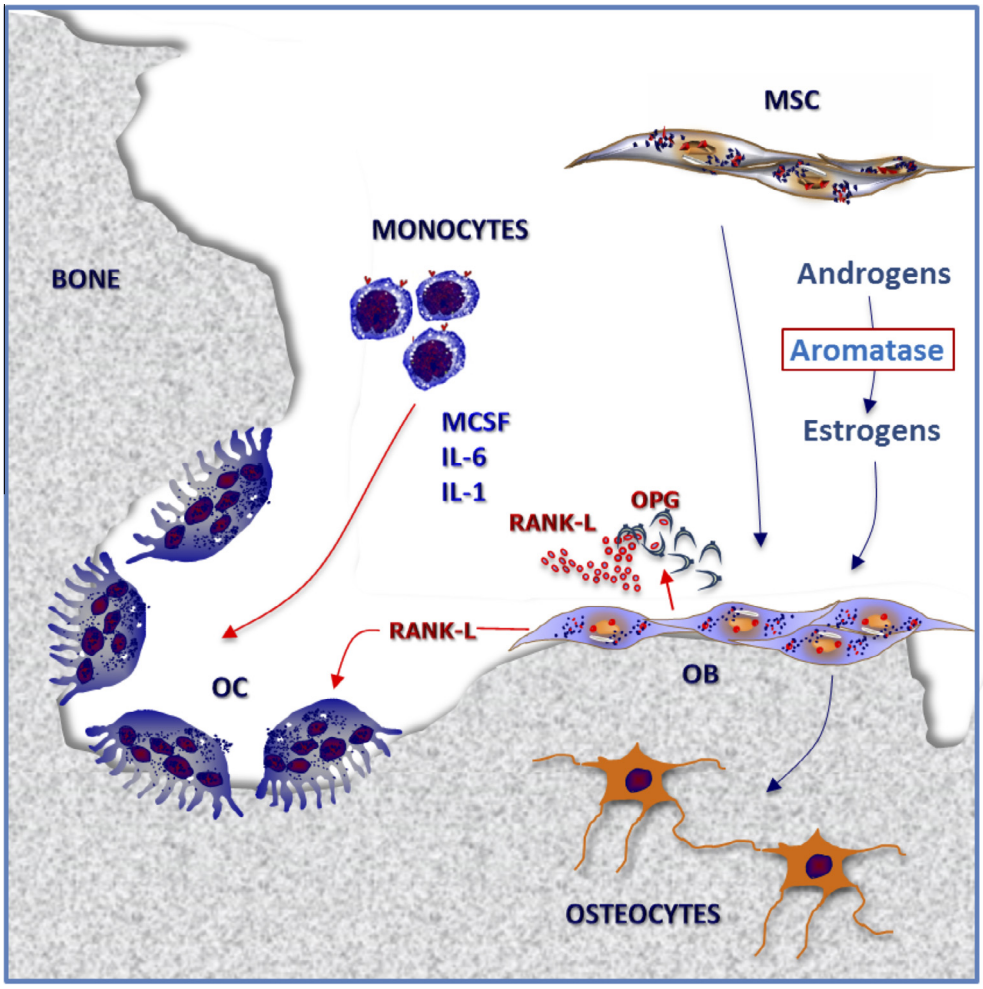

Fig. 1. Physiology of bone turnover. The balanced activity of OCs and OBs concurs in bone physiological remodeling. OCs arise from the monocyte/macrophage lineage and resorb bone matrix by secreting protons and enzymes, such as cathepsin K, collagenases, vacuolar ATPase and phosphatases. OBs derive from MSC and are responsible for bone deposition. Some of them are buried in the mineralized bone and become osteocytes, able to synthesize bone protein components. These activities are regulated by systemic and local factors, among which the RANK-L/RANK/OPG axis seems to play the major role. The dominant steroids regulating bone resorption are estrogens, that increase OB activity and proliferation while inhibiting osteoclastogenesis. Testosterone also participates in the regulation of bone turnover, by stimulating OB proliferation and inhibiting their apoptosis. The effects of this hormone are also indirect since it may be converted to estradiol through the aromatization process.

that synthesize bone proteins and express membrane dendrites acting as mechanotransducers. Indeed, these cells are interconnected through their dendritic protrusions that occupy the canaliculi which contain a proteoglycan-rich extracellular matrix. Based on this dendritic network, osteocytes detect the mechanical stimuli and secrete mediators regulating both bone formation and resorption [5,6].

This balance is finely regulated by systemic and local factors, among which the receptor activator of nuclear factor *k* B-ligand (RANK-L)/RANK/osteoprotegerin (OPG) axis plays the major role. RANK-L is a member of the tumor necrosis factor (TNF) family, produced by OBs and stromal cells. After binding to RANK, an integral membrane protein on the surface of OC precursors, RANKL drives their differentiation through the nuclear factor *k* B and Jun N-terminal kinase pathways. OPG, a soluble decoy receptor for RANK-L, is mainly secreted by cells of the OB lineage and prevents excessive OC maturation and bone resorption. Other local pro-osteoclastogenic factors include a number of cytokines, such as interleukin (IL)-6, IL-1, macrophage colony stimulating factor (M-CSF) and prostaglandins, whose function is physiologically balanced by anti-osteoclastogenic molecules such as IL-4, IL-18 and interferon (IFN)-γ [7].

Several systemic factors contribute to the regulation of calcium homeostasis and hence bone turnover. Parathyroid hormone (PTH) is a major calcium regulator and promotes its plasma increase, inducing the release of pro-osteoclastogenic cytokines by OBs. Calcium bioavailability is also increased by Vitamin D (VitD) whose active form, 1-25-dihydroxyvitamin D, is the result of double hydroxylation, that occurs primarily in the liver and then in the kidney. On one hand, VitD primes OBs to produce RANKL and M-CSF to increase bone resorption, while on the other, it enhances the intestinal absorption of calcium and phosphate and regulates the OB production of bone matrix components such as osteocalcin, osteopontin and alkaline phosphatase (ALP) [8]. A third hormone, namely calcitonin, inhibits bone resorption, although it exerts a greater role during skeletal development than in adult bone turnover [4].

Estrogens are dominant steroids regulating bone resorption, whose receptors are expressed by both OBs and OCs. These hormones increase the secretion of OPG, Insulin-like Growth Factor (IGF)-1 and Transforming Growth Factor (TGF)-β by OBs, while inhibiting the release of pro-osteoclastogenic factors, thus inducing a preponderance of bone formation over erosive activity. Testosterone also participates in the regulation of bone turnover

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