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Review

Managing metastatic bone pain: New perspectives, different solutions

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ABSTRACT

Bone metastases are the most frequent cause of cancer-induced bone pain (CIBP). Although palliative radiotherapy and pharmacotherapy conducted according to World Health Organization (WHO) analgesic ladder are the treatment of choice for CIBP reduction, these methods are not always successful, especially with regard to alleviation of incidental pain. Antiresorptive drugs (bisphosphonates) are able to inhibit bone destruction (loss), proliferation of cancer cells and angiogenesis, but their prolonged use may lead to a spectrum of adverse effects. In this paper, types of bone metastases, their complications, as well as diagnostic and therapeutic implications are presented. Moreover, the paper discusses presently used CIBP treatment methods and research directions for future methods, with special focus on bone metastases.

Contents

1. Introduction

1.1. Types of bone metastases

Bone metastases can be categorized on the basis of radiological and histopathological image data and divided into osteolytic, osteosclerotic and mixed types.

Osteolytic metastases are responsible for bone destruction. These types of lesions are related with breast, lung, thyroid, kidney and multiple myeloma cancer.

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The second type of bone metastasis, referred to as the osteosclerotic type is able to stimulate new bone tissue formation and is associated with prostate and breast cancer.

The third type, called mixed metastasis, occurs mainly with lymphoma, breast and lung cancer. This type of metastasis is related to local interactions of metastatic cells with osteoclasts and osteoblasts [1,2].

Regardless of their type, metastases alter normal bone architecture and increase the risk of complications referred to as skeletal-related events (SRE) [1–3]. The processes of bone resorption and formation are closely interrelated and, although they may be impaired due to ongoing cancerogenesis, they occur at the site of the metastasis (independently of its type) in nearly all types of cancer [4]. There are two exceptions from this rule. The first is osteosarcoma (the 3rd most frequent type of cancer in children and youth) which is related to pure osteosclerotic metastasis [5] and the second is multiple myeloma giving exclusively metastases of "purely" osteolytic character [6]. In all other types of cancers, the process of bone formation is secondary to osteolysis [7].

Prostate and bladder cancers are responsible mainly for osteosclerotic (aka. osteoblastic) metastases [8], however intense osteolysis is also observed in these types of cancers. Therefore, the application of antiresorptive drugs decreases pain and risk of pathological fractures in patients with prostate cancer [9–11].

Breast and lung cancers and lymphomas lead to simultaneous osteosclerotic and osteolytic metastases. These types of lesions are therefore referred to as mixed- type metastases.

In patients with breast and lung cancer, osteolytic lesions prevail. In 25% of patients suffering from breast cancer, blastic metastasis is also present, while osteosclerotic metastases prevail in 15–20% of such patients [1,3,12]. In the case of thyroid, kidney and multiple myeloma cancers, osteolytic metastasis is the most frequent type of lesion [13].

Biochemical markers of bone turnover (i.e. cell-secreted peptides and proteins as well as cellular products of degradation) are assessed for quick evaluation of cellular activity in the bone [14]. The levels of the above-mentioned markers may be increased in female breast cancer patients even in the absence of clinical manifestations of metastases [15].

1.1.1. Osteolytic metastases

Osteoclasts are polynuclear cells adhered to the bone using αvβ3 integrin. Due to the secretion of collagenases, proteases and hydrogen ions, they are able to demineralize the bone matrix. Osteoclasts' main growth factors are called RANKL (Receptor Activators of Nuclear Factor κβ Ligand) and M-CSF (macrophage colony stimulating factor) [16,17]. RANKL activates osteoclastogenesis, prolongs the time of osteoclasts' survival by binding on these cells and their precursors' surface [18–21]. In turn, M-CSF increases RANKL expression on the surface of bone stromal cells, has a chemotactic effect on osteoclasts and prolongs their life span by inhibiting apoptosis [22].

IL-11 is another cellular factor that induces and escalates osteoclastogenesis [23]. There are many other growth factors that can directly or indirectly induce osteoclasts' formation, stimulate their activity or prolong their life span. One of them is Parathyroid Hormone-Related Peptide (PTHRP1), produced by a majority of solid tumor cells (e.g. breast cancers). PTHrP binds to PTHRP1 receptor (i.e. receptor of PTH) and induces RANKL expression on cells of stromal bone marrow (see Fig. 1) [24,25].

TGFβ, in turn, stimulates the production of PTHrP by breast cancer cells [26,27]. It has been found that PTHrP production was increased in 92% of patients with metastases from breast to bone, while the presence of this peptide was confirmed in only 50% of patients suffering from breast cancer without metastasis to bone tissue [28].

Phenotypic similarity of breast cancer cells to osteoblasts is the reason why breast cancer tends to metastasize to the bone. Barns et al. have shown ectopic expression of the transcription factor referred to as the RUNX2 protein (Runt-Related Transcription Factor 2) that stimulates bone sialoprotein (BSP) synthesis in breast cancers [29]. BSP level correlates positively with the frequency of metastasis to the bone [30]. BSP plays a role in angiogenesis, micro-calcification and protection from complement-induced cell lysis [31]. RUNX2 protein also stimulates osteoblasts' differentiation. Breast cancer and multiple myeloma cells produce cytokines that inhibit osteoblasts' activity, namely activin A and DKK-1 (dikkopf-related protein 1) [32,33]. DKK-1 is a

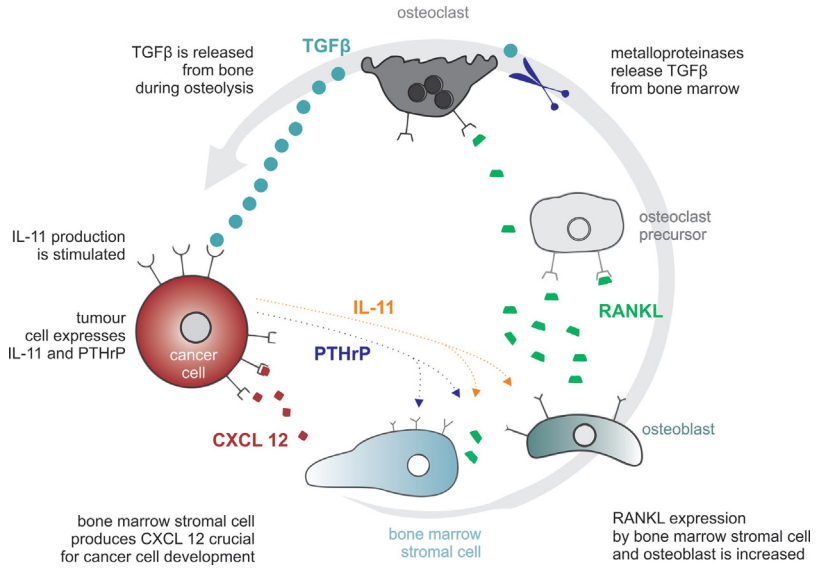

Fig. 1. A simplified scheme of osteolytic bone metastases.