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REVIEW

Formation Mechanism of Bone Metastases

Sezer SAĞLAM

Department of Medical Oncology, T.C. Demiroglu Bilim University Faculty of Medicine, Istanbul-*Turkey*

Introduction

When cancer becomes metastatic, a clinical picture shows that it cannot be completely cured. Over the past 20 years, immense progress has been made in cancer treatment with new chemotherapy drugs and target-specific medicines. With the increase in median survival, cancer-related morbidity has increased and diversified. For example, the uncommon leptomeningeal metastasis rate is increasing. The rate of metastasis to the bone also increases in gastrointestinal cancers.

The two types of bone metastases are: osteolytic and osteoblastic. The cytokine profile of both metastases is different.[1] Although we have come a long way in pathogenesis, it is not fully understood.

Molecular studies have shown that the tumor cell secretes exosomes and cytokines into the blood before metastasizing to the bone. The metastatic cell needs suitable soil in order to settle in the bone. This is called the seed and soil hypothesis.

The bone and bone marrow are supplied by capillaries, and they overlap. Due to this structure, bone marrow, bone cortex, osteoblasts and osteocytes, osteoclasts encounter high blood flow. This is one of the elements that facilitate metastasis by hematogenous way.[2]

For example, more metastasis occurs since blood supply is higher in the metaphyseal region of long bones.[3]

The bone marrow is a major site for metastasis due to its endothelial and trabecular structure, high blood supply, having stem cells in its pores, and its slow blood flow in large sinusoids.[4]

Osteoblasts and osteoclasts are the two most important cells in bone metastases. Osteoclasts are multinucleated cells from the monocyte-macrophage family root. They are responsible for breaking down (de-mineralize) the bone with the acidic (proteases) products it produces. In this way, tumors or their products (cytokines) can initiate the osteolytic process by activating osteoclasts.[5]

On the other hand, osteoblasts originate from mesenchymal stem cells and carry out bone formation. RANKL (Receptor activator of nuclear factor kappa-B ligand), secreted by osteoblasts, interacts with the RANK receptor in osteoclasts and initiates the lytic cycle in the bone.[6]

Proteins that are effective in bone metastases and are drivers in this regard are RANK, RANK-Ligand, and OPG (Osteoprotegerin). They are proteins that belong to the TNF (Tumor Necrosis Factor) group.[7] These proteins belonging to the TNF family are proteins that have active roles in all cell groups in the body except the bone. Of these, RANK is also known as TRANCE receptor or TNFRSF11A. (Receptor activator of nuclear factor κappa-B). While RANK is a transmembrane protein, the other two (RANKL, OPG) are soluble predominantly in blood.

The first discovery of the existence of RANK is not made in bone but rather is made when it was first shown to be an effective protein in stimulating T-cell and dendritic cells.[7] Its role in osteoclastogenesis was later defined together with RANK-Ligand.[8] The role of OPG, the other member of the family, in the development of both the bone and the immune system will be studied later.[9]

What Happens with RANK and RANK-Ligand Interaction

It has been shown that the increase in RANK causes immunosuppression in macrophages. It has been shown

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Dr. Sezer SAĞLAM
T.C. Demiroğlu Bilim Üniversitesi Tıp Fakültesi,
Tıbbi Onkoloji Anabilim Dalı,
İstanbul-Turkey
E-mail: saglam@istanbul.edu.tr

that natural killer cells also secrete RANKL, and when RANKL is inhibited, immunosuppression is lifted. The metastasis ability of tumors increases with increased RANK; The RANK-RANK-Ligand interaction has also been proven to play an immunosuppressive role.

Another important area of RANK and RANKL is intrauterine breast development. It has been observed that if RANK and RANKL are genetically ablated in knockout mice, alveolar formation in the breast does not occur. It has been shown that RANKL progresses ER+breast cancers and increases angiogenesis. It has been shown that if RANK expression is high, the risk of recurrence increases in patients with ER (estrogen receptor) negative cancer.[10] When medroxyprogesterone was introduced, the RANKL level increased 3000 times and progression was observed in breast cancer.[11]

The contribution of the mutation in the BRCA1 and two genes to the development of breast cancer is known. When the healthy breast tissue of patients with mutations in the BRCA gene and undergoing prophylactic breast surgery without any tumor development was examined, it was found that RANK receptor positivity was high. It has been shown that if RANKL is inhibited by denosumab, if RANK activation is reduced indirectly, ductal proliferation in the breast is reduced.[12]

On the other hand, when RANKL is active, it increased the expression of bone in all subgroups of EGFR. Thus, the "soil and seed hypothesis" that the tumor cell could lay the groundwork for metastasis was proven for the first time.[13] In addition, the interaction between RANK and RANKL attracts tumor cells to the bone environment.[14] Further, such interaction that attracts the bone environment occurs in other tumors.[15] For example, in lung cancers, RANKL inhibition has also been shown to reduce osteolytic lesions in the bone.[16] We can say that RANKL opens a suitable settlement area for cancer cells in the bone.

OPG (Osteoprotegerin)

The third TNF family member in the RANK and RANKL triangle is OPG. OPG is an endogenous, natural inhibitor of RANKL. OPG, like its other members, is a protein secreted from the GiS epithelium, lung, breast, skin, endothelium, B-cells and sometimes tumor endothelium.[17] It has also been shown that POG is an important factor in the organogenesis of the breast in the intrauterine period.[18]

The prognostic importance of OPG and RANKL in breast cancer was first reported by Rachner et al.[19] The RANKL and OPG rates of 509 patients with stage I-II-II breast cancer were examined. RANKL/OPG ratio was found to be higher in those with positive lymph node involvement. In case when OPG was high, death from breast cancer was statistically increased ($p=0.005$). The factors leading to bone metastasis ultimately shorten cancer survival.

The RANKL level was also found to be 33% higher ($p<0.0001$) in the presence of tumor cells circulating in the blood. For the first time in a prospective clinical study, it was found that bone metastasis increased in patients with high RANKL blood levels ($p=0.01$).

Bisphosphonates and OPG-RANK, RANKL Relationship

Bisphosphonates have been used for cancer-related bone metastases since 2000. The first product, pamidronate, then zolendronic acid, was available in the market. Accumulating scientific evidence show that bisphosphonates increase OPG and RANKL even if they are undesirable.[20-22] In addition, it has been shown that the use of zolendronic acid under glucorticoid treatment, although undesirable, increases the RANKL level.[23] It has also been shown that the use of zolendronic acid in patients with bone metastases, including lung, breast, and prostate cancer, increases the OPG level by 96%.[24] Using denosumab, OPG does not increase and RANKL level decreases.[25] We mentioned above that increased OPG and RANKL levels decrease cancer-related survival.

MAF Gene and Bone Metastasis

The MAF gene has been known as an oncogene since the 1990s. The abbreviation comes from v-maf, Musculo-Aponeurotic Fibrosarcoma, which originates from retrovirus in chickens. It has seven separate proteins. It contributes to the formation of multiple myeloma.[26] It has been proven that the amplification of MAF gene directly increases and is responsible for bone metastasis in xenografts carrying breast cancer cells.[27] FISH positivity of the MAF gene was found to be 23% in invasive breast cancer in AZURE, which is a study on zolendronic acid conducted to prevent postoperative adjuvant bone metastasis in breast cancer. The interesting aspect of the study was that disease-free survival and overall survival were shorter in breast cancer patients in whom zolendronic acid was used and were positive for MAF.[28] This study shows that it would be appropriate to look at the MAF gene as a standard

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in patients with metastatic breast cancer. In those with the MAF gene (+), the use of zolendronic acid should be interpreted as contraindicated.

Clinical Effects of Bone Metastasis

Classification is needed to evaluate bone metastases or drugs effective in their treatment. Not all bone metastases increase morbidity. Therefore, four types of bone metastases that directly affect morbidity have been determined as the endpoint for the studies. These are:

1. Pathological fracture formation
2. Need for radiotherapy to the bone
3. Surgical intervention on the bone
4. Formation of spinal cord compression

All of these cause bone pain, but a symptomatic subgroup called bone pain has not been established in the classification.[29]

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