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Invited critical review

Tartrate-resistant acid phosphatase isoform 5b (TRACP 5b) as a serum maker for cancer with bone metastasis

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ABSTRACT

The spread of cancer to bone is considered a terminal event. Two main types of bone metastasis can manifest, i.e. osteoblastic and osteolytic. Irrespective of metastatic type, uncoupled bone remodeling is always present and perpetuates a vicious cycle of excess bone resorption and destruction. Biochemical markers of bone metabolism are potentially useful to diagnose metastatic bone disease and to monitor treatment response in cancer patients. Tartrate-resistant acid phosphatase isoform 5b (TRACP 5b) is a biochemical marker of osteoclast number and activity. Mounting evidence has demonstrated serum TRACP 5b as a useful marker of bone resorption and therefore bears clinical applicability in diagnosis and management of metabolic and pathologic bone diseases. Serum TRACP 5b is among one of the many bone resorption biochemical markers that have been studied to be a surrogate marker of bone metastasis in cancer patients. Its serum level may reflect the degree of lytic bone metastasis and, in turn, the tumor burden within the bone milieu. This review summarizes the development of specific immunoassays for serum TRACP 5b as well as current evidence for its exploitation as a biomarker for diagnosis, treatment response, and prognosis in various cancers with high incidence of bone metastasis including breast, prostate, lung, and multiple myeloma.

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1. Introduction

Seventy thousand Taiwanese [1] and 1.5 million Americans are diagnosed with cancer every year [2]. Thirty to seventy percent of them will develop bone metastasis at some time during the course of their disease [3–6]. Once bone metastasis is discovered, the disease is incurable, regardless of the original site of the cancer. Discovery and refinement of specific and sensitive methods to diagnose bone metastasis, follow treatment response and disease progression and to assess prognosis in patients with bone metastasis are high priority issues in cancer management. Radiological imaging techniques have been used for decades and have evolved continually to serve these purposes better. However, they have several limitations [7]. Changes in imaging are relatively slow to respond and it is difficult to justify frequent repeated studies. Some reflect only local disease, while others do not discriminate healing lesions from progressive ones [8]. They are relatively expensive and have attendant health risks themselves from repeated exposures. Now, biochemical markers of bone metabolism are being used increasingly to overcome some of these limitations and to exploit their advantages. Biomarkers reflect systemic activity and are cheaper and safer. They can be used more frequently over time to follow treatment. They can be used in selective combinations of formation markers and resorption markers depending on whether bone lesions are osteoblastic or osteolytic in nature [9]. The goals for bone markers in cancer have been defined recently and the merits and limitations of some of the older ones have been reviewed [10]. Early results indicate that bone markers have an important role to play now and in the future.

One of the newest markers of osteoclasts and bone resorption, tartrate-resistant acid phosphatase 5b (TRACP 5b) has been verified as an adjunctive test for following anti-resorptive treatment in post-menopausal women at risk for osteoporosis and fracture [11,12]. It has also been recently under consideration as a bone marker in the cancer setting [13,14], but it has not been used in most of the larger clinical trials on this topic. Since TRACP 5b has the unique application among resorption markers as a measure of systemic osteoclast number, it could provide new and useful information in the overall evaluation of bone metabolism in patients with bone metastasis. This review will summarize the literature on TRACP 5b in cancer highlighting its unique properties and the rationale for its use.

2. Cancer and bone

Cancer can affect the skeletal system through both metastatic and humoral mechanisms. Firstly, cancer cells can metastasize to bone and act locally and directly by activating osteoclasts through the critical receptor activator of NF-kappa B ligand (RANKL)/receptor activator of NF-kappa B (RANK)/osteoprotegerin (OPG) pathway [15]. Cancer cells do not have the machinery to destroy the bone themselves. Instead, they could either stimulate the osteoblasts or the stromal cells of the bone marrow by direct contact with them or indirectly by secreting cytokines by a paracrine manner [15]. The stromal cells in turn could activate osteoblast as well. Subsequently, activated osteoblast could produce RANKL which can further act on the receptor RANK on osteoclast [15]. OPG is a natural decoy receptor for RANKL secreted by bone marrow stromal cells that can reduce the activation of osteoclast and thus serves a regulatory function in normal bone metabolism. After being activated, osteoclast precursors proliferate and differentiate. While they resorb bone, the stored growth factors in the mineralized matrix including transforming growth factors (TGF)-β, insulin-like growth factors, fibroblast growth factors, platelet-derived growth factor and bone morphogenetic proteins are released [16], which in turn could stimulate the growth of cancer cells and osteoblasts. Thus a vicious cycle of bone destruction by metastasis ensues. Secondly, cancer cells may elaborate such factors as parathyroid hormone-related protein (PTHrP), 1,25-$(OH)_2D_3$, parathyroid hormone (PTH), interleukin (IL)-1, IL-6, TGF-β, and tumor necrosis factor that influence bone indirectly by disrupting normal calcium homeostasis through the target organs of bone and kidney [17,18]. The resulting consequences are mainly hypercalcemia and, rarely, oncogenic osteomalacia [16]. Thirdly, cancers of osseous origin can affect bone directly and cause local complications including pain, pathological fractures, and immobility of the afflicted region [16]. The remainder of this review will focus on aspects of cancer metastasis to bones.

The most frequent cancers which metastasize to bones include breast, prostate, multiple myeloma, lung, renal, thyroid, and melanoma (Table 1) [19–28]. Breast cancer and prostate cancer account for about 80% of all metastatic bone cancers [29]. This is due to their high overall prevalence and their relatively long clinical courses. For patients with breast and prostate cancers, approximately 70% will develop bone metastases [26–28]. Two types of bone metastases, i.e. osteoblastic and osteolytic, have been characterized. In breast cancer, most bone lesions are osteolytic in appearance with approximately 20–30% being mixed osteolytic and osteoblastic on X-ray images [30,31]. In prostate cancer, bone lesions are characteristically osteoblastic in appearance [32]. Bone lesions in multiple myeloma are mostly osteolytic in nature, but approximately 3% may manifest as osteoblastic lesions [33]. In other cancers including lung, renal, thyroid, and melanomas, osteolytic lesions are mainly observed [32]. In osteolytic bone metastasis, the osteoclast plays the major role. In osteoblastic bone metastasis from prostate cancer, for example, the tumor cells secret endothelin-1 and other factors to

Table 1
Incidence of bone metastases in different cancers [19–28].

Primary site	Incidence of bone metastases (%)
Breast	70–73
Kidney	30–35
Liver	14–28
Lung	35–36
Melanoma	23–49
Myeloma	75–85
Testis	26–30
Thyroid	28–42
Prostate	65–90