Published in final edited form as:

Cancer Treat Rev. 2008 November ; 34(7): 629–639. doi:10.1016/j.ctrv.2008.05.001.

Bone markers and their prognostic value in metastatic bone disease: Clinical evidence and future directions

Robert Coleman^{a,*}, Janet Brown^{b,h}, Evangelos Terpos^{c,i}, Allan Lipton^{d,j}, Matthew R. Smith^{e,k}, Richard Cook^{f,l}, and Pierre Major^{g,m}

^aAcademic Unit of Clinical Oncology, Cancer Research Centre, Weston Park Hospital, Sheffield S10 2SJ, UK

^bCancer Research UK Clinical Centre, St. James Hospital, University of Leeds, Leeds LS9 7TF, UK

^cDepartment of Hematology and Medical Research, 251 General Air Force Hospital, 3 Kanellopoulou Street, Athens GR 11525, Greece

^dMilton S. Hershey Medical Center, Pennsylvania State University, 500 University Drive, Hershey, PA, USA

^eMassachusetts General Hospital Cancer Center, 100 Blossom Street, Boston, MA, USA

^fUniversity of Waterloo, 200 University Avenue West, Waterloo, ON, Canada N2L 3G1

^gJuravinski Cancer Centre, McMaster University, 699 Concession Street, Hamilton, ON, Canada L8V 5C2

Summary

Background—Bone metastases are prevalent among patients with advanced solid tumors. Metastatic bone disease alters bone homeostasis, resulting in reduced bone integrity and, consequently, increased skeletal complications. Biochemical markers of bone metabolism may meet an unmet need for useful, noninvasive, and sensitive surrogate information for following patients' skeletal health.

Materials and methods—Data for this review were identified by searches of PubMed, and references from relevant articles using the search terms “bone markers” or individual bone marker nomenclature, “cancer,” and “metastases.” Abstracts and reports from meetings were included

© 2008 Elsevier Ltd. All rights reserved.

*Corresponding author. Tel.: +44 114 226 5213; fax: +44 114 226 5678.

^hTel.: +44 7 920 750 563; fax: +44 1 13 246 0136.

ⁱTel.: +30 210 7463803; fax: +30 210 7464676.

^jTel.: +717 531 5960; fax: +717 531 5076.

^kTel.: +617 724 5257; fax: +617 724 3166.

^lTel.: +519 888 4567; fax: +519 746 1875.

^mTel.: +905 387 9495; fax: +905 575 6326.

Conflict of interest statement

Dr. Smith is a consultant to Novartis Oncology, Amgen Oncology, Merck, and GTx, Inc.

Dr. Coleman has received consultancy fees, speaker fees, and research funding from Novartis and has given expert testimony on their behalf.

Dr. Terpos has received an honorarium for participation in an advisory board for Novartis.

Dr. Major has received consultancy fees and participated in advisory boards for Novartis.

Dr. Brown has participated in an advisory board for Novartis.

Dr. Cook has received consultancy fees and participated in advisory boards for Novartis.

Dr. Lipton has served on a speakers' bureau, received consultancy fees, and has given expert testimony on behalf of Novartis Oncology.

only when they related directly to previously published work. Only papers published in English between 1990 and 2007 were included.

Results—Recent retrospective analyses with bisphosphonates, and particularly with zoledronic acid, have shown significant correlations between biochemical markers of bone metabolism levels and clinical outcomes, especially for bone resorption markers. Clinical results for biochemical markers of bone formation and resorption and other emerging markers of bone metabolism including bone sialoprotein, receptor–activator of nuclear factor- κ B ligand, osteoprotegerin, and other markers are presented. However, biochemical markers of bone metabolism are not yet an established surrogate endpoint for treatment efficacy.

Conclusions—Biochemical markers of bone metabolism may allow physicians to identify which patients with metastatic bone disease are at high risk for skeletal-related events or death and who may be responding to therapy. Prospective randomized clinical trials are underway to further assess the utility of markers of bone metabolism in patients with bone metastases.

Keywords

Bone alkaline phosphatase; Bone sialoprotein; C-telopeptide of type I collagen; N-telopeptide of type I collagen; Osteoprotegerin

Introduction

Bone is a common site for metastases in patients with solid tumors such as breast, prostate, lung, thyroid, and renal cancers.¹ Approximately 70% of patients with advanced prostate cancer or breast cancer will develop bone metastases, and metastatic disease is often limited to the skeleton in patients with advanced prostate cancer.² Bone metastases have been reported in up to 40% of patients with advanced solid tumors other than breast and prostate cancer. ² Moreover, almost all patients with multiple myeloma will develop bone lesions during the course of their disease.² Metastatic bone disease disrupts the normal homeostasis of bone, which is a dynamic process that involves the coupled and balanced osteoclast-mediated osteolysis and osteogenesis by osteoblasts.¹ The resulting increased and unbalanced bone metabolism leads to a loss of bone integrity, which can result in skeletal complications.

Conventional measurements of skeletal health and treatment response in metastatic bone lesions are imprecise and can only detect changes after the damage has occurred. Surrogate assessments that are simple and can rapidly and sensitively detect changes in skeletal health are needed, so that serial measurements may be easily taken to follow patient progress. Biochemical markers of bone resorption and formation may fill this area of clinical need. The ideal marker of bone metabolism would provide both sensitivity to identify patients with bone metastases or patients at high risk for negative clinical outcomes from bone metastases and specificity in monitoring skeletal health. In addition, its clinical variations would be well-defined and reference values established.

The science and clinical utility of biochemical markers of bone metabolism are still evolving; therefore, they are not yet an established surrogate measurement for clinical efficacy. Therefore, the current medical literature was surveyed using PubMed searches, and additional information was gathered from recent conference proceedings and presentations on current use and potential utility of biochemical markers of bone metabolism in the clinical setting. In this review, we present the clinically relevant biochemical markers of bone metabolism and the available evidence for their use in the metastatic bone disease setting.

Mechanisms of bone remodeling and the bone microenvironment

Bone is composed of two basic types: cortical and cancellous (trabecular). Cortical bone comprises the shafts of the long bones in the skeleton and the outer layer of all bones. It constitutes approximately 80% of the total skeletal mass.³ Cancellous bone comprises the inner structure of the vertebrae, pelvis, and the ends of the long bones. It provides a large honeycombed surface area for bone-forming cells and minerals. Although cancellous bone constitutes approximately 20% of the total skeletal mass, it contributes approximately 80% of the total bone surface area. Therefore, it is more rapidly remodeled than cortical bone, with approximately 25% renewed each year compared with only 3% of cortical bone.³

Bone homeostasis is achieved through a continuous remodeling process on the bone surface of coupled and balanced resorption of old bone by osteoclasts and formation of new bone by osteoblasts.⁴ This process is thought to be initiated in response to local mechanical stress, predominately muscle loads, and osteocytes appear to have an important role.^{5,6} Local and systemic growth factors then regulate the differentiation and activity of the osteoclasts and osteoblasts (Fig. 1).^{4,7} Normal bone remodeling begins with differentiation of osteoclasts from hematopoietic progenitor cells and their attachment to the bone surface. Macrophage-colony stimulating factor predominantly increases the pool of osteoclast precursors, and receptor-activator of nuclear factor- κ B ligand (RANKL) induces proliferation and differentiation of osteoclast precursors and inhibits apoptosis of both osteoclast precursors and mature osteoclasts.⁸ Subsequent morphologic changes allow the dissolution of the bone hydroxyapatite (mineral) and organic matrix.^{4,9} Growth factors that are released during bone resorption stimulate the differentiation of osteoblasts from mesenchymal progenitor cells.⁴ Bone formation then ensues in several steps, which include coupling the osteoblast cells to the site of recent osteolysis, secretion of matrix proteins, and mineralization of the osteoid matrix.¹⁰ In addition, osteoblasts inhibit the local differentiation of osteoclasts through the secretion of osteoprotegerin, thereby ending the process.⁴

Maintenance and repair of normal bone results in the release of enzymes, peptides, and mineral components that have been characterized as serum and urinary biochemical markers of bone remodeling.⁷ These biochemical markers are typically classified according to the metabolic process by which they are directly or indirectly produced (bone resorption or formation).⁷ Many of these markers are also produced by other tissues, and their levels could also change in response to fluctuations in other metabolic processes.⁷ However, in patients with skeletal metastases, acute changes in these marker levels typically indicate alterations in skeletal homeostasis.⁷ Moreover, most of the clinically relevant markers currently being investigated are more bone-specific factors. For these reasons, biochemical markers of bone remodeling may be an ideal tool to evaluate changes in bone turnover, such as those associated with malignant bone lesions and patient response to treatment.

Biochemical markers of bone formation and bone resorption

Skeletal health may be evaluated by various measurements such as histomorphometry, bone mineral density, and plain radiographs.^{11,12} However, each of these established methodologies has limitations. For example, histomorphometry is an expensive and invasive procedure that measures bone predominantly in the iliac crest and requires a relatively long time to obtain results. Bone mineral densitometry (dual-energy X-ray absorptiometry; e.g., to assess bone mineral density), scintigraphy (e.g., to identify areas of increased osteoblastic activity), and plain radiographs (e.g., to identify established bone lesions) are noninvasive procedures that may be performed on many sites of the skeleton with a relatively short wait for results; however, they do not reveal acute changes to bone homeostasis such as those associated with malignant bone lesions. Some physicians may assess calcium flux to gain

insight into bone metabolism, but the clinical utility is limited by technical considerations and this is not used routinely.

Some markers of bone metabolism have correlative and prognostic value, especially when combined with other clinical indicators of disease progression and treatment efficacy. They have potential use in determining the appropriate therapy in patients with bone loss and monitoring response to therapy. Levels of biochemical markers of bone metabolism may be assessed inexpensively in blood or urine samples, thereby allowing for relatively easy monitoring of skeletal health, especially in the case of acute changes.³ Indeed, because bone resorption typically precedes bone formation; bone resorption markers may provide an earlier detection system for changes in bone metabolism than bone formation markers.

Bone formation markers

By-products of osteogenesis or osteoblast-secreted factors can provide insight into the ongoing levels of bone formation (Table 1).^{13–20}

Bone-specific alkaline phosphatase—Bone-specific alkaline phosphatase (BALP) hydrolyses pyrophosphate, thereby removing an inhibitor of osteogenesis while creating the inorganic phosphate that is required for generation and deposition of hydroxyapatite.²¹ This enzyme is secreted as a “bud” from the osteoblast cell membrane to the bone matrix vesicles, allowing bone mineralization to proceed.²¹

There are several alkaline phosphatase isoforms secreted by the various organs into the serum. Predominant isoforms originate from bone, liver, intestine, and placenta.³ Because of these wide sources of activity, limited information may be obtained from a total alkaline phosphatase measurement. However, the bone-specific isoform (BALP) is a relatively specific marker for osteogenesis. Elevated BALP levels occur in Paget’s disease, renal rickets, bone cancer, osteomalacia, celiac disease, and malignant bone disease. In addition, BALP may be increased in patients with liver diseases because it is normally cleared from the serum by the liver.³

Osteocalcin—Osteocalcin (OC) is the major noncollagen protein in the bone matrix.³ It is produced by osteoblasts, odontoblasts, and hypertrophic chondrocytes and is thought to function as a localization site for hydroxyapatite crystals during bone matrix synthesis. Both osteolysis and osteogenesis release OC into the serum, from which it is eliminated via renal clearance and degradation.²² Therefore, OC levels might reflect overall bone metabolism, not just osteogenesis. In addition, detection of serum or plasma OC may be impaired by high lipid levels because of OC-lipid binding. Moreover, multiple isoforms exist in the circulation, and current assays have a limited ability to detect them all.²² Urinary OC levels may also be assayed, but, because of recovery and degradation, urinary OC levels typically reflect only basal bone turnover instead of acute changes in bone metabolism.²²

Propeptides of procollagen type I—Collagen type I comprises approximately 90% of the organic bone matrix.²³ Extracellular processing occurs before the final collagen fibril assembly wherein the N-terminal (N-terminal propeptide of procollagen type 1 [P1NP]) and C-terminal (C-terminal propeptide of procollagen type 1 [P1CP]) regions are generated in a 1:1 ratio with collagen and released into the serum. Therefore, levels of P1NP and P1CP may reflect the level of osteogenesis. However, type I collagen is synthesized in some other tissues, which may contribute to the serum P1NP and P1CP levels. Serum P1CP levels have been correlated with bone formation, and decreased levels have been reported after bisphosphonate therapy or hormone replacement therapy. Both P1NP and P1CP are removed by the liver, but P1NP can also be deposited directly into bone and has been found

to constitute 5% of the noncollagenous protein in bone. However, recent reports have suggested that P1NP has greater diagnostic validity than P1CP.²⁴ In the first study, P1NP was shown to be predictive of bone metastasis in patients with prostate cancer.²⁵ Serum levels of P1NP and prostate-specific antigen (PSA) were measured, and the development of bone metastases was evaluated after 2 years. Results showed a positive correlation between elevated levels of P1NP, PSA, and eventual development of bone metastases.²⁵ In a separate multivariate Cox analysis, P1NP was shown to be an independent predictive factor for survival in patients with prostate cancer.²⁶

Bone resorption markers

By-products of osteolysis or osteoclast-secreted factors can provide insight into the ongoing levels of bone resorption (Table 2).^{14,27–37}

Pyridinoline and deoxypyridinoline—Pyridinoline (PYD) and deoxypyridinoline (DPD) are produced from the posttranslational modification of lysine and hydroxylysine. They stabilize mature type I collagen in all major connective tissues, cross-linking the telopeptide domain of a collagen fibril to the helical region of an adjacent collagen fibril. During bone resorption, PYD and DPD are released from bone in approximately a 3:1 ratio as free molecules or attached to collagen fragments.³ They are not recovered by the bone and are excreted via the kidneys, with no known metabolic degradation.²⁴ Urinary excretion is closely related to the rate of bone resorption. Levels of PYD and DPD are not influenced by degradation of newly synthesized collagens or dietary collagen intake, and, although they are present in other tissues, bone is the major reservoir and has a higher turnover than most connective tissues. In fact, DPD is found almost exclusively in bone.³⁸ However, the contribution from soft tissues may make these markers less accurate than other markers, especially in the case of PYD. Both PYD and DPD have been found to be elevated in patients with metastatic bone disease³⁹; however, in a separate study, DPD was a more sensitive indicator of bone resorption in patients receiving bisphosphonate therapy.⁴⁰

C-telopeptide and N-telopeptide of type I collagen—C-terminal cross-linked telopeptide of type I collagen (CTX) and N-terminal cross-linked telopeptide of type I collagen (NTX) are the carboxyterminal and aminoterminal peptides, respectively, of mature type I collagen with the cross-links attached and are released during bone resorption.³ Degradation products of collagen are of various sizes and may undergo additional breakdown in the liver or kidney to their constituent amino acids. Cross-links (PYD and DPD) and are excreted in the urine. However, osteoclast-derived fragments are different from those formed in nonskeletal tissues. The cross-linked peptide is primarily attached as an alpha-2 isoform for NTX from bone and as an alpha-1 isoform from other tissues.²³ The CTX peptide exists as alpha or beta isoforms, with beta isoforms found more often in mature bone.

Assays for NTX utilize an antibody to the alpha-2 chain, which can be conveniently measured in urine or serum.²³ However, urinary results must be adjusted for urine dilution, which may add to measurement variability. Urinary CTX measurements have poor precision at concentrations lower than 200 µg/L, so serum or plasma samples are often used. Plasma CTX is more stable, but some anticoagulants interfere with the assay. Serum CTX measurements utilize an antibody to the beta isoform.

Recent studies have suggested that NTX and CTX levels may be sensitive indicators of bone metastasis development from prostate, breast, or lung cancer, as well as of osteolytic disease in multiple myeloma.^{41,42} Moreover, both react promptly and profoundly to bisphosphonate, hormonal, or chemical treatments. However, relative to NTX, CTX levels

were less elevated in patients with Paget's disease and more elevated in patients with hyperthyroidism.²³ This suggests that NTX may have greater bone specificity.

Carboxyterminal cross-linked telopeptide of type I collagen generated by metalloproteinases—Carboxyterminal cross-linked telopeptide of type I collagen generated by metalloproteinases (ICTP) is another metabolic product of mature type I collagen resorption. Immunoassays of serum ICTP detect the telopeptide portion of the collagen fragment that resides between the 2 α -1 chains.⁴³ Increased levels of serum ICTP correlate well with bone resorption levels in patients with either high or low bone turnover.²³ Serum ICTP level increases of up to 20% have been reported in patients with osteolytic metastases and rheumatoid arthritis.^{23,43} Indeed, ICTP levels are elevated in lung cancer patients with bone metastases compared with patients without bone metastases, in multiple myeloma patients with negative radiographs but positive magnetic resonance images, and in patients with hyperparathyroidism.³⁴ However, fluctuations in serum ICTP levels did not correlate with BMD changes in postmenopausal women with osteoporosis who were undergoing bisphosphonate treatment.²³ Immunochemical characterization of serum ICTP revealed that cathepsin K-mediated bone resorption by osteoclasts cleaves the collagen at the antigenic site, and the resulting ICTP fragment is therefore not detected by the assay.⁴³ However, matrix metalloproteinase-mediated release leaves the antigenic site intact, and the resulting ICTP fragment is detectable. These results explain why the current assay for ICTP is insensitive to more physiological changes in bone turnover such as those induced by estrogen or bisphosphonate treatment.

Tartrate-resistant acid phosphatase type 5b—Tartrate-resistant acid phosphatase type 5b (TRAcP-5b) is secreted primarily by activated osteoclasts and is 1 of 2 isoforms detected in human serum.²⁴ Activated macrophages secrete the second isoform, TRAcP-5a. It is produced as a latent proenzyme requiring proteolytic processing by cathepsin K or L. Osteoclasts secrete the active enzyme after they have attached to the bone surface. The enzyme then enters the circulation where it is inactivated and degraded. Therefore, catalytically active enzyme levels in the circulation reflect recently released enzyme as a result of bone resorption. Serum TRAcP-5b levels are measured using immunoassays. TRAcP-5b has been investigated recently as a marker for bone resorption with encouraging results. Changes in serum TRAcP-5b activity significantly correlated with the changes in other bone markers in patients with osteoporosis receiving hormone replacement therapy.⁴⁴ In addition, TRAcP-5b had a significant negative correlation with BMD in this study. TRAcP-5b has also been found to be elevated in patients with bone metastases from cancer,⁴¹ and in multiple myeloma, TRAcP-5b correlated with the extent of lytic disease.⁴⁵ However, some studies have suggested that TRAcP-5b may reflect osteoclast numbers rather than activity.⁴⁶

Bone sialoprotein—Bone sialoprotein (BSP) is a noncollagenous bone matrix protein secreted by osteoclasts and is part of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family. It is secreted by other cells and is present in all mineralized tissues. In vitro, BSP promotes the adhesion of osteoclasts to the bone surface and at the same concentration also inhibits the differentiation of new osteoclasts.⁴⁷ However, more recent evidence suggests that in the presence of RANKL, BSP might synergistically induce osteoclastogenesis.⁴⁸ Furthermore, BSP and RANKL were shown to have opposite effects on osteoclast survival and apoptosis. BSP contributed to osteoclast survival and decreased apoptosis. It is also thought that BSP may play a role in the nucleation of hydroxyapatite in the bone matrix.⁴⁹ Regulation of BSP activity is achieved through dephosphorylation by TRAcP.⁵⁰

Serum BSP levels are measured by immunoassays. However, BSP has been found bound to complement factor H in serum, and this complex must be disrupted to accurately measure total BSP levels.⁵¹ Elevated serum BSP levels have been reported in patients with prostate cancer, breast cancer, and colon cancer.⁵¹ In fact, BSP levels in patients with bone metastases secondary to prostate cancer were an independent prognostic factor for survival.⁵² Elevated serum BSP levels have also been reported in patients with multiple myeloma.⁵³

Osteoclast regulators

Signaling factors stimulating osteoclast activity have been investigated as markers of osteolysis (Table 2).^{14,27–37}

Receptor activator of nuclear factor- κ B ligand/osteoprotegerin—Receptor activator of nuclear factor- κ B (RANK) and its ligand (RANKL) are required for osteoclastogenesis. Osteoprotegerin (OPG) is a soluble decoy receptor that binds RANKL, thereby blocking stimulation of osteoclastogenesis. RANKL exists as 2 isoforms; a membrane-bound form and a shorter soluble form.⁵⁴ It is expressed not only in preosteoblastic and stromal cells in the bone but also in lymphoid tissue.⁵⁴ Osteoprotegerin is synthesized as a propeptide that is cleaved before secretion as a mature protein.⁵⁴ It is expressed in a number of other tissues besides bone including the cardiovascular system, the neurologic system, and the gastrointestinal system.⁵⁴ This signaling pathway has molecular interactions with other ligand-receptor systems to maintain normal bone homeostasis.

Serum levels of OPG and both soluble and total RANKL are assessed by immunoassay. Elevated levels of either protein alone or increases in the ratio of RANKL to OPG have been investigated as prognostic tools in patients with metabolic bone diseases and bone malignancies. In patients with metabolic bone disease, study results have been inconsistent, and these marker proteins are still of limited utility in clinical practice.^{55,56} In patients with bone metastases secondary to breast cancer, prostate cancer, or lung cancer, serum levels of both OPG and RANKL were elevated compared with healthy volunteers, and in prostate cancer OPG was increased in patients with bone metastases compared with patients without bone metastases.^{52,57} However, in patients with bone metastases from breast cancer or lung cancer both OPG and RANKL were not significantly elevated compared with patients without bone metastases.⁴¹ Furthermore, among patients with multiple myeloma, serum levels of soluble RANKL and the RANKL/OPG ratio were elevated and correlated with markers of disease activity.⁴² Indeed, the RANKL/OPG ratio was an independent prognostic factor for survival. Therefore, these markers may have utility in patients with hematologic malignancies.

Practical considerations for marker assessments

Most markers of bone metabolism have diurnal variations characterized by a peak after midnight and a nadir at approximately noon.²² The variation is approximately 10% for markers of bone formation and 20% for markers of bone resorption.³ Seasonal fluctuations may also occur, such as those seen for OC, which has a small peak in the winter and a slight decrease in the summer, with a nadir around July,²² perhaps because of increased sun exposure and vitamin D production during the summer months. However, no such variations in free urinary PYD and DPD levels have been reported,⁵⁸ and diurnal variations of serum BSP, OPG, and RANKL are unknown. Diurnal variations may also be altered by menopause in women. For example, in one study, the P1CP diurnal variation was approximately 2-fold higher, and the peak occurred 3 h later in osteopenic postmenopausal women than in age-matched women with normal BMD.⁵⁹ However, diurnal patterns of OC, urinary PYD, and urinary DPD were similar between groups.^{58,59} Variability because of diurnal variations may be reduced by collecting specimens at a specific time of the day.

Almost all markers of bone metabolism are also significantly influenced by the sex, age, and renal function of the individual. In fact, many markers of bone metabolism are increased in postmenopausal women who are either osteopenic or osteoporotic, although diurnal variations may not be affected. Among menopausal women, both NTX and CTX levels had a greater increase than those of PYD and DPD.²³ Bone sialoprotein levels are increased among postmenopausal women with osteoporosis compared to healthy perimenopausal volunteers and correlate well with those of NTX and PYD.⁶⁰ In addition, several small studies have suggested that bone resorption, as measured by serum CTX levels, is reduced by up to 50% after the intake of glucose, fat, or protein in healthy volunteers and is independent of age and sex.⁶¹ Reductions in these variations will require established values in each population and fasting before specimen collection.

Serum measurements of bone markers are usually performed by either radioimmunoassay or enzyme immunoassay. Current methodologies for most of the markers have intra- and interassay coefficients of variation of <10%.^{38,62} However, the differences in OC levels depend on the assay and range from 5% to 9%. In addition, serum BALP assays may have up to 15% cross-reactivity with the hepatic isoform.⁶³ Urinary NTX levels also have an intra- and interassay coefficient of variation of <10%.³⁸ Variability between urinary and serum levels of NTX and CTX have been reported to be similar and correlate well.⁶⁴

Clinical experience with biochemical markers of bone metabolism

Biochemical markers of bone metabolism may provide valuable prognostic information in patients with metastatic bone disease. These patients often have increased bone metabolism as evidenced by increases in both bone formation and resorption marker levels. Patients also often have unbalanced bone metabolism, which results in a loss of bone integrity and increased risk of skeletal complications.¹ For clinical utility, changes in biochemical markers of bone metabolism (bone markers) should correlate with the extent of the disease in patients with bone metastases.⁷ However, patients may have abnormal levels of bone markers even in the absence of bone metastases. For example, increased bone turnover occurs during androgen deprivation therapy or aromatase inhibition. Therefore, bone markers are not yet routinely used for the diagnosis of bone metastases in clinical practice, but their use as investigational tools in clinical trials is increasing.⁶⁵

Clinical evidence of correlations between bone marker levels and patient outcomes have been recently reported from retrospective analyses of large randomized trials with zoledronic acid.^{1,66} Elevated on-study bone marker levels correlated with negative clinical outcomes in patients with metastatic breast cancer, prostate cancer, or lung cancer and other solid tumors.^{1,67–69} Specifically, patients with different cancer types (e.g., breast cancer, prostate cancer, other solid tumors, and multiple myeloma) and elevated urinary NTX levels either at baseline or at their most recent assessment had an approximate 2-fold increase in their risk of disease progression and an approximate 2–3-fold increase in their relative risk of skeletal-related events (SREs: pathologic fracture, spinal cord compression, hypercalcemia of malignancy, and radiotherapy or surgery to bone) compared with patients with low NTX levels.⁶⁶ Among patients with prostate cancer, elevated NTX levels were associated with a 4.6-fold increased risk of death and a 2.7-fold increased risk of death among patients with lung cancer or other solid tumors compared with patients with low NTX.¹ Recent NTX levels had prognostic significance as a time-dependent covariate. In contrast, BALP levels were not a consistently strong prognostic indicator. In a randomized study in breast cancer patients with bone metastases, NTX levels were shown to provide valuable prognostic information.⁷⁰ Patients with elevated baseline NTX levels were found to have shorter median time to disease progression ($P = .0006$) and shorter overall median survival ($P < .0001$) compared with patients with normal baseline NTX levels. In a larger

post hoc analysis of patients with bone metastases from breast cancer, prostate cancer, lung cancer, or other solid tumors or bone lesions from multiple myeloma,⁶⁶ results showed that elevated NTX levels were associated with a significant 2-fold increased risk of disease progression and risk of skeletal complications ($P < .001$ for all). In addition, elevated NTX levels were associated with a significant 2–3-fold increased risk of experiencing a first SRE on study in patients with breast cancer, prostate cancer, or multiple myeloma ($P \leq .008$). Furthermore, elevated NTX levels were associated with a significant 4–6-fold increased risk of dying on study in all patients with solid tumors ($P < .001$ for all). There were so few patients with multiple myeloma and elevated baseline NTX levels that meaningful evaluation was not possible because of wide confidence intervals. However, other studies have provided supporting evidence for the prognostic value of NTX in patients with multiple myeloma.^{24,42,71}

The clinical prognostic value of other bone markers has also been evaluated in various types of cancer. In one study, multiple myeloma patients treated with ibandronate who had at least a 50% mean relative decrease (MRD) in CTX and at least a 30% MRD in osteocalcin levels experienced fewer SREs than those who did not.⁷² Bone sialoprotein may also be a prognostic marker for multiple myeloma. Serum BSP levels were elevated in multiple myeloma patients relative to a healthy control group ($P < .001$), and BSP levels decreased in patients who responded to chemotherapy.⁵³ Furthermore, multiple myeloma patients with normal baseline BSP levels survived longer than patients with elevated serum BSP ($P < .001$).

Results from studies of the osteoclast-regulatory protein OPG have been variable, and its utility in clinical practice is still being evaluated. Results from a recent study in patients with metastatic bone disease treated with oral clodronate indicated that although there was a sustained decrease in NTX levels in the treated group versus placebo, there was no significant change in serum OPG levels.⁷³ However, the serum RANKL/OPG ratio is emerging as an indicator of clinical outcome. In patients with refractory or relapsed multiple myeloma receiving zoledronic acid, the serum RANKL/OPG ratio increased with extent of bone disease and showed a response to thalidomide-dexamethasone treatment.⁷⁴

Normalization of bone markers from bisphosphonate therapy may correlate with improved survival in patients with metastatic bone disease. Further analyses of NTX levels after 3 months of zoledronic acid treatment in patients with either breast cancer or multiple myeloma revealed that the risks of first SRE, disease progression in bone, and death were all decreased to a greater extent in patients who had normalized 3-month urinary NTX levels.⁷⁵ In fact, patients whose NTX levels normalized on study had survival rates similar to patients with normal baseline NTX. In addition, there was a continuum of benefit, depending on the percentage decrease in NTX levels at 3 months, with larger decreases in NTX relative to baseline associated with lower risk of death.⁷⁶ Smaller studies have shown that bisphosphonate treatment with zoledronic acid produced a reduction in CTX and BALP levels that correlated with improvements in the Visual Analogue Scale for pain in patients with metastatic prostate cancer⁷⁷ and that reductions in CTX levels remained for up to 21 days after a single infusion of zoledronic acid in patients with metastatic bone disease.⁷⁸ Similarly, in another small study in patients with metastatic breast cancer who had bone pain despite treatment with clodronate or pamidronate, zoledronic acid was able to improve bone pain, and improvements correlated with a downward trend in urinary NTX levels.⁷⁹ In addition, a larger study of patients with metastatic bone disease has shown that urinary NTX levels have predictive value for bone disease progression but not for extraskelatal disease.⁸⁰

Interpretation of bone marker changes during treatment

Changes in biochemical markers of bone metabolism may provide valuable information for prediction and monitoring of response to therapy. In multiple myeloma, reductions of bone resorption markers have been observed in patients who received a combination of antimyeloma agents with zoledronic acid.⁷⁴⁻⁸¹ The reduction of NTX or CTX was greater in patients who responded to thalidomide-based regimens compared with patients who did not respond to treatment.⁸¹ Furthermore, bortezomib, a proteasome inhibitor, in combination with zoledronic acid, reduced bone resorption but had a beneficial effect on bone formation, increasing the serum levels of BALP and OC in patients with relapsed disease.⁸²

Treatment with bisphosphonates can reduce levels of bone markers, and exploratory analyses have shown strong correlations between reductions in bone marker levels and reduced risks of clinical events. However, clinical efficacy cannot be reliably inferred through assessment of markers alone. Results from the analyses of large randomized trials with zoledronic acid and pamidronate illustrate this point. In patients with metastatic breast cancer, although zoledronic acid significantly reduced the risk of SREs compared with pamidronate,⁸³ and although zoledronic acid was more effective than pamidronate in reducing NTX levels, BALP levels were found to be similar between the two treatments.⁸⁴ Conversely, in patients with multiple myeloma, the risk reduction of developing an SRE was similar between zoledronic acid and pamidronate,⁸³ despite the similarity of the relative changes in BALP and NTX levels after treatment to those observed in patients with breast cancer.⁸⁵ Thus, the accuracy of individual bone marker assessments for various malignancies has not yet been well established.

Comparisons of treatment efficacy based on assessments of a single bone marker have been made in a recent study. Information was presented whereby oral ibandronate and intravenous zoledronic acid were shown to reduce serum CTX levels to a similar extent in women with metastatic breast cancer.⁸⁶ Although additional clinical endpoints such as frequency and timing of SREs were not assessed in this study, the trial investigators stated that ibandronate demonstrated similar efficacy to zoledronic acid. However, bone markers are not established as surrogates for clinical efficacy at this time, and further validation of the use of bone markers in this context still awaits the maturation of data from ongoing clinical trials. To this end, a prospective study is under way to evaluate the clinical efficacy of oral ibandronate versus intravenous zoledronic acid in patients with metastatic breast cancer. A direct comparison across SRE endpoints is the primary objective.⁸⁷ In addition, patients will be stratified according to hormonal status. This study is expected to be complete in 2015, and interim results are eagerly anticipated.⁸⁸

Conclusions

Although biochemical markers of bone metabolism are useful tools to provide insight into the ongoing levels of skeletal metabolism, they are not sufficiently characterized surrogate measurements to definitively predict clinical outcomes in individual patients. However, evidence is accumulating regarding the prognostic value of some biochemical markers of bone metabolism. Elevated NTX levels clearly have negative prognostic implications for SREs and survival in patients with bone lesions from solid tumors or multiple myeloma, and there is a continuum of risk among all patients with bone lesions. However, not all skeletal morbidity is related to acute increases in resorption (e.g., cancer-free osteoporotic fracture), and even patients with relatively low NTX levels can develop an SRE.

Several emergent markers of bone metabolism may prove to be useful prognostic indicators, including BSP, TRAcP-5b, RANKL, and OPG. Early studies have shown encouraging results and warrant further clinical trials assessing their specificity and sensitivity in identifying metastatic bone disease and monitoring disease progression. In addition, several ongoing trials are evaluating the value of bone marker monitoring in patients with bone metastases using more established bone markers. The BISMARCK trial (cost-effective use of BISphosphonates in metastatic bone disease – a comparison of bone MARKer-directed zoledronic acid therapy to a standard schedule) is planned to enroll 1500 patients with bone metastases from breast cancer.^{89,90} Patients will be randomized to receive either zoledronic acid 4 mg every 3–4 weeks or zoledronic acid 4 mg on a marker-directed schedule based on changes from baseline NTX. The primary endpoint is the frequency and timing of SREs. Secondary endpoints include the evaluation of pain, quality of life, incidence of new bone metastases, overall survival, bone marker levels, and the utility of a “point of care” assessment for NTX. The study is expected to be complete in 2010.

Acknowledgments

The authors thank Tamalette Loh, PhD, ProEd Communications, Inc.[®], for medical editorial assistance with this manuscript. All authors were responsible for the generation of this article, controlling content from inception, analysis and interpretation of data, critically revising for intellectual content, and providing final approval of the submitted version.

Role of the funding source

Funding for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA.

References

1. Brown JE, Cook RJ, Major P, et al. Bone turnover markers as predictors of skeletal complications in prostate cancer, lung cancer, and other solid tumors. *J Natl Cancer Inst.* 2005; 97:59–69. [PubMed: 15632381]
2. Coleman RE. Skeletal complications of malignancy. *Cancer.* 1997; 80:1588–1594. [PubMed: 9362426]
3. Watts NB. Clinical utility of biochemical markers of bone remodeling. *Clin Chem.* 1999; 45:1359–1368. [PubMed: 10430819]
4. Krane SM. Identifying genes that regulate bone remodeling as potential therapeutic targets. *J Exp Med.* 2005; 201:841–843. [PubMed: 15781576]
5. de Baat P, Heijboer MP, de Baat C. [Development, physiology, and cell activity of bone]. *Ned Tijdschr Tandheelkd.* 2005; 112:258–263. [PubMed: 16047964]
6. Seeman E, Delmas PD. Bone quality – the material and structural basis of bone strength and fragility. *N Engl J Med.* 2006; 354:2250–2261. [PubMed: 16723616]
7. Fohr B, Dunstan CR, Seibel MJ. Clinical review 165: markers of bone remodeling in metastatic bone disease. *J Clin Endocrinol Metab.* 2003; 88:5059–5075. [PubMed: 14602728]
8. Tanaka S, Miyazaki T, Fukuda A, et al. Molecular mechanism of the life and death of the osteoclast. *Ann N Y Acad Sci.* 2006; 1068:180–186. [PubMed: 16831917]
9. Take I, Takahash N, Kurihara S. [Molecules which are involved in osteoclastic bone resorption: from the aspect of targets of treatment for osteoporosis]. *Clin Calcium.* 2005; 15:741–746. [PubMed: 15876734]
10. Katagiri T, Fukuda T. [Molecular mechanisms of bone formation and bone-forming factors]. *Clin Calcium.* 2005; 15:17–22. [PubMed: 15995291]
11. Thomsen JS, Ebbesen EN, Mosekilde L. Predicting human vertebral bone strength by vertebral static histomorphometry. *Bone.* 2002; 30:502–508. [PubMed: 11882465]
12. Tothill P, Hannan WJ. Precision and accuracy of measuring changes in bone mineral density by dual-energy X-ray absorptiometry. *Osteoporos Int.* 2007; 18:1515–1523. [PubMed: 17483864]

13. University of Washington Department of Laboratory Medicine Immunology Division. Bone alkaline phosphatase (BAP) in serum. 2008 [accessed 21.04.08]. Available at: <<http://depts.washington.edu/labweb/Divisions/Imm/ImmTesting/BAP.HTML>>
14. Garnero P, Buchs N, Zekri J, Rizzoli R, Coleman RE, Delmas PD. Markers of bone turnover for the management of patients with bone metastases from prostate cancer. *Br J Cancer*. 2000; 82:858–864. [PubMed: 10732759]
15. Kanakis I, Nikolaou M, Pectasides D, Kiamouris C, Karamanos NK. Determination and biological relevance of serum crosslinked type I collagen N-telopeptide and bone-specific alkaline phosphatase in breast metastatic cancer. *J Pharm Biomed Anal*. 2004; 34:827–832. [PubMed: 15019061]
16. Heuck C, Wolthers OD. A placebo-controlled study of three osteocalcin assays for assessment of prednisolone-induced suppression of bone turnover. *J Endocrinol*. 1998; 159:127–131. [PubMed: 9795350]
17. Caillot-Augusseau A, Lafage-Proust MH, Soler C, Pernod J, Dubois F, Alexandre C. Bone formation and resorption biological markers in cosmonauts during and after a 180-day space flight (Euromir 95). *Clin Chem*. 1998; 44:578–585. [PubMed: 9510865]
18. Puistola U, Risteli L, Kauppila A, Knip M, Risteli J. Markers of type I and type III collagen synthesis in serum as indicators of tissue growth during pregnancy. *J Clin Endocrinol Metab*. 1993; 77:178–182. [PubMed: 8325940]
19. Bauer DC, Garnero P, Hochberg MC, et al. Pretreatment levels of bone turnover and the antifracture efficacy of alendronate: the fracture intervention trial. *J Bone Miner Res*. 2006; 21:292–299. [PubMed: 16418785]
20. Nguyen TV, Meier C, Center JR, Eisman JA, Seibel MJ. Bone turnover in elderly men: relationships to change in bone mineral density. *BMC Musculoskelet Disord*. 2007; 8:13. [PubMed: 17316428]
21. Balcerzak M, Hamade E, Zhang L, et al. The roles of annexins and alkaline phosphatase in mineralization process. *Acta Biochim Pol*. 2003; 50:1019–1038. [PubMed: 14739992]
22. Ivaska KK, Kakonen S-M, Gerdhem P, Obrant KJ, Pettersson K, Vaananen HK. Urinary osteocalcin as a marker of bone metabolism. *Clin Chem*. 2005; 51:618–628. [PubMed: 15650032]
23. Calvo MS, Eyre DR, Gundberg CM. Molecular basis and clinical application of biological markers of bone turnover. *Endocr Rev*. 1996; 17:333–368. [PubMed: 8854049]
24. Terpos E, Politou M, Rahemtulla A. The role of markers of bone remodeling in multiple myeloma. *Blood Rev*. 2005; 19:125–142. [PubMed: 15748961]
25. Thurairaja R, Iles RK, Jefferson K, McFarlane JP, Persad RA. Serum amino-terminal propeptide of type 1 procollagen (PINP) in prostate cancer: a potential predictor of bone metastases and prognosticator for disease progression and survival. *Urol Int*. 2006; 76:67–71. [PubMed: 16401924]
26. Brasso K, Christensen IJ, Johansen JS, et al. Prognostic value of PINP, bone alkaline phosphatase, CTX-I, and YKL-40 in patients with metastatic prostate carcinoma. *Prostate*. 2006; 66:503–513. [PubMed: 16372331]
27. Coleman RE. The clinical use of bone resorption markers in patients with malignant bone disease. *Cancer*. 2002; 94:2521–2533. [PubMed: 12173317]
28. Pecherstorfer M, Seibel MJ, Woitge HW, et al. Bone resorption in multiple myeloma and in monoclonal gammopathy of undetermined significance: quantification by urinary pyridinium cross-links of collagen. *Blood*. 1997; 90:3743–3750. [PubMed: 9345061]
29. Hou MF, Tsai LY, Tsai SM, et al. Biochemical markers for assessment of bone metastases in patients with breast cancer. *Kaohsiung J Med Sci*. 1999; 15:452–460. [PubMed: 10518361]
30. Souberbielle J-C. Utilisation des marqueurs du remodelage osseux dans l'ostéoporose. *J Inf Biomed* [in French]. 2004;9–11.
31. Osteomark NTX accurate answers for osteoporosis patient management: urine ELISA, serum ELISA. 2008 [accessed 21.04.08]. Available at: <<http://www.osteomark.com/UEPerformance.cfm>>

32. Pectasides D, Farmakis D, Nikolaou M, et al. Diagnostic value of bone remodeling markers in the diagnosis of bone metastases in patients with breast cancer. *J Pharm Biomed Anal.* 2005; 37:171–176. [PubMed: 15664758]
33. Shimozuma K, Sonoo H, Fukunaga M, Ichihara K, Aoyama T, Tanaka K. Biochemical markers of bone turnover in breast cancer patients with bone metastases: a preliminary report. *Jpn J Clin Oncol.* 1999; 29:16–22. [PubMed: 10073146]
34. Jakob C, Zavrski I, Heider U, et al. Serum levels of carboxyterminal telopeptide of type-I collagen are elevated in patients with multiple myeloma showing skeletal manifestations in magnetic resonance imaging but lacking lytic bone lesions in conventional radiography. *Clin Cancer Res.* 2003; 9:3047–3051. [PubMed: 12912955]
35. Politou M, Terpos E, Nadal E, Crawley C, Apperley JF, Rahemtulla A. Prolonged effect of reduced intensity conditioning (RIC) allogeneic transplantation for multiple myeloma on biochemical markers of bone remodelling and osteoclast function: report of a case. *Haema.* 2004; 7:87–91.
36. Morena M, Terrier N, Jaussent I, et al. Plasma osteoprotegerin is associated with mortality in hemodialysis patients. *J Am Soc Nephrol.* 2006; 17:262–270. [PubMed: 16280472]
37. Guang-da X, Hui-ling S, Zhi-song C, Lin-shuang Z. Changes in plasma concentrations of osteoprotegerin before and after levothyroxine replacement therapy in hypothyroid patients. *J Clin Endocrinol Metab.* 2005; 90:5765–5768. [PubMed: 16046585]
38. Ju H-S, Leung S, Brown B, et al. Comparison of analytical performance and biological variability of three bone resorption assays. *Clin Chem.* 1997; 43:1570–1576. [PubMed: 9299935]
39. Demers LM, Costa L, Chinchilli VM, Gaydos L, Curley E, Lipton A. Biochemical markers of bone turnover in patients with metastatic bone disease. *Clin Chem.* 1995; 41:1489–1494. [PubMed: 7586522]
40. Vinholes J, Guo CY, Purohit OP, Eastell R, Coleman RE. Metabolic effects of pamidronate in patients with metastatic bone disease. *Br J Cancer.* 1996; 73:1089–1095. [PubMed: 8624269]
41. Leeming DJ, Koizumi M, Byrjalsen I, Li B, Qvist P, Tanko LB. The relative use of eight collagenous and noncollagenous markers for diagnosis of skeletal metastases in breast, prostate, or lung cancer patients. *Cancer Epidemiol Biomarkers Prev.* 2006; 15:32–38. [PubMed: 16434583]
42. Terpos E, Szydlo R, Apperley JF, et al. Soluble receptor activator of nuclear factor kappaB ligand-osteoprotegerin ratio predicts survival in multiple myeloma: proposal for a novel prognostic index. *Blood.* 2003; 102:1064–1069. [PubMed: 12689925]
43. Sassi ML, Eriksen H, Risteli L, et al. Immunochemical characterization of assay for carboxyterminal telopeptide of human type I collagen: loss of antigenicity by treatment with cathepsin K. *Bone.* 2000; 26:367–373. [PubMed: 10719280]
44. Halleen JM, Ylipahkala H, Alatalo SL, et al. Serum tartrate-resistant acid phosphatase 5b, but not 5a, correlates with other markers of bone turnover and bone mineral density. *Calcif Tissue Int.* 2002; 71:20–25. [PubMed: 12073156]
45. Terpos E, de la Fuente J, Szydlo R, et al. Tartrate-resistant acid phosphatase isoform 5b: a novel serum marker for monitoring bone disease in multiple myeloma. *Int J Cancer.* 2003; 106:455–457. [PubMed: 12845688]
46. Alatalo SL, Ivaska KK, Waguespack SG, Econs MJ, Vaananen HK, Halleen JM. Osteoclast-derived serum tartrate-resistant acid phosphatase 5b in Albers-Schonberg disease (type II autosomal dominant osteopetrosis). *Clin Chem.* 2004; 50:883–890. [PubMed: 15016726]
47. Raynal C, Delmas PD, Chenu C. Bone sialoprotein stimulates in vitro bone resorption. *Endocrinology.* 1996; 137:2347–2354. [PubMed: 8641185]
48. Valverde P, Tu Q, Chen J. BSP and RANKL induce osteoclastogenesis and bone resorption synergistically. *J Bone Miner Res.* 2005; 20:1669–1679. [PubMed: 16059638]
49. Nagata T, Bellows CG, Kasugai S, Butler WT, Sodek J. Biosynthesis of bone proteins [SPP-1 (secreted phosphoprotein-I, osteopontin), BSP (bone sialoprotein) and SPARC (osteonectin)] in association with mineralized-tissue formation by fetal-rat calvarial cells in culture. *Biochem J.* 1991; 274:513–520. [PubMed: 2006915]

50. Ek-Rylander B, Flores M, Wendel M, Heinegard D, Andersson G. Dephosphorylation of osteopontin and bone sialoprotein by osteoclastic tartrate-resistant acid phosphatase. Modulation of osteoclast adhesion in vitro. *J Biol Chem.* 1994; 269:14853–14856. [PubMed: 8195113]
51. Fedarko NS, Jain A, Karadag A, Van Eman MR, Fisher LW. Elevated serum bone sialoprotein and osteopontin in colon, breast, prostate, and lung cancer. *Clin Cancer Res.* 2001; 7:4060–4066. [PubMed: 11751502]
52. Jung K, Lein M, Stephan C, et al. Comparison of 10 serum bone turnover markers in prostate carcinoma patients with bone metastatic spread: diagnostic and prognostic implications. *Int J Cancer.* 2004; 111:783–791. [PubMed: 15252851]
53. Woitge HW, Pecherstorfer M, Horn E, et al. Serum bone sialoprotein as a marker of tumour burden and neoplastic bone involvement and as a prognostic factor in multiple myeloma. *Br J Cancer.* 2001; 84:344–351. [PubMed: 11161399]
54. Khosla S. Minireview: the OPG/RANKL/RANK system. *Endocrinology.* 2001; 142:5050–5055. [PubMed: 11713196]
55. Dovic A, Data V, Angeli A. Circulating osteoprotegerin and soluble RANKL: do they have a future in clinical practice? *J Endocrinol Invest.* 2005; 28 Suppl.:14–22. [PubMed: 16550717]
56. Rogers A, Eastell R. Review: circulating osteoprotegerin and receptor activator for nuclear factor kappaB ligand: clinical utility in metabolic bone disease assessment. *J Clin Endocrinol Metab.* 2005; 90:6323–6331. [PubMed: 16105967]
57. Mountzios G, Dimopoulos MA, Bamias A, et al. Abnormal bone remodeling process is due to an imbalance in the receptor activator of nuclear factor-kappaB ligand (RANKL)/osteoprotegerin (OPG) axis in patients with solid tumors metastatic to the skeleton. *Acta Oncol.* 2007; 46:221–229. [PubMed: 17453373]
58. Aoshima H, Kushida K, Takahashi M, et al. Circadian variation of urinary type I collagen crosslinked C-telopeptide and free and peptide-bound forms of pyridinium crosslinks. *Bone.* 1998; 22:73–78. [PubMed: 9437516]
59. Pedersen BJ, Schlemmer A, Rosenquist C, Hassager C, Christiansen C. Circadian rhythm in type I collagen formation in postmenopausal women with and without osteopenia. *Osteoporos Int.* 1995; 5:472–477. [PubMed: 8695971]
60. Shaarawy M, Hasan M. Serum bone sialoprotein: a marker of bone resorption in postmenopausal osteoporosis. *Scand J Clin Lab Invest.* 2001; 61:513–521. [PubMed: 11763409]
61. Bjarnason NH, Henriksen EE, Alexandersen P, Christgau S, Henriksen DB, Christiansen C. Mechanism of circadian variation in bone resorption. *Bone.* 2002; 30:307–313. [PubMed: 11792602]
62. Wolthers OD, Heuck C, Heickendorff L. Diurnal variations in serum and urine markers of type I and type III collagen turnover in children. *Clin Chem.* 2001; 47:1721–1722. [PubMed: 11514416]
63. Kleerekoper M. Use of bone markers in the management of women with low bone density. *Am Soc Reprod Med Menopausal Med.* 2002; 10:5–7.
64. Fall PM, Kennedy D, Smith JA, Seibel MJ, Raisz LG. Comparison of serum and urine assays for biochemical markers of bone resorption in postmenopausal women with and without hormone replacement therapy and in men. *Osteoporos Int.* 2000; 11:481–485. [PubMed: 10982162]
65. Vinholes JJ, Purohit OP, Abbey ME, Eastell R, Coleman RE. Relationships between biochemical and symptomatic response in a double-blind randomised trial of pamidronate for metastatic bone disease. *Ann Oncol.* 1997; 8:1243–1250. [PubMed: 9496390]
66. Coleman RE, Major P, Lipton A, et al. Predictive value of bone resorption and formation markers in cancer patients with bone metastases receiving the bisphosphonate zoledronic acid. *J Clin Oncol.* 2005; 23:4925–4935. [PubMed: 15983391]
67. Lipton A, Cook RJ, Major P, Smith MR, Coleman RE. Zoledronic acid and survival in breast cancer patients with bone metastases and elevated markers of osteoclast activity. *Oncologist.* 2007; 12:1035–1043. [PubMed: 17914073]
68. Hirsh V, Major PP, Lipton A, et al. Zoledronic acid and survival in patients with metastatic bone disease from lung cancer and elevated markers of osteoclast activity. *J Thorac Oncol.* 2008; 3:228–236. [PubMed: 18317064]

69. Lipton A, Cook R, Saad F, et al. Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. *Cancer*. 2008 [Epub ahead of print].
70. Ali SM, Demers LM, Leitzel K, et al. Baseline serum NTx levels are prognostic in metastatic breast cancer patients with boneonly metastasis. *Ann Oncol*. 2004; 15:455–459. [PubMed: 14998848]
71. Abildgaard N, Brixen K, Kristensen JE, Eriksen EF, Nielsen JL, Heickendorff L. Comparison of five biochemical markers of bone resorption in multiple myeloma: elevated pre-treatment levels of S-ICTP and U-Ntx are predictive for early progression of the bone disease during standard chemotherapy. *Br J Haematol*. 2003; 120:235–242. [PubMed: 12542480]
72. Menssen HD, Sakalova A, Fontana A, et al. Effects of long-term intravenous ibandronate therapy on skeletal-related events, survival, and bone resorption markers in patients with advanced multiple myeloma. *J Clin Oncol*. 2002; 20:2353–2359. [PubMed: 11981007]
73. Holen I, Hannon RA, Ellis SP, Coleman RE, Brown JE. Effects of clodronate on serum osteoprotegerin (OPG) in patients with metastatic bone disease. *Cancer Treat Rev*. 2006; 32 Suppl.:S40. [Abstract 95].
74. Terpos E, Mihou D, Szydlo R, et al. The combination of intermediate doses of thalidomide with dexamethasone is an effective treatment for patients with refractory/relapsed multiple myeloma and normalizes abnormal bone remodeling, through the reduction of sRANKL/osteoprotegerin ratio. *Leukemia*. 2005; 19:1969–1976. [PubMed: 16079895]
75. Lipton A, Hei Y, Coleman RE, Major P, Cook R. Suppression of bone turnover markers by zoledronic acid and correlation with clinical outcome. *J Clin Oncol*. 2005; 23 Suppl.:11s. [Abstract 532].
76. Lipton, A.; Hei, Y.-J.; Coleman, RE.; Major, P.; Smith, M.; Cook, RJ. Normalization of urinary N-telopeptide levels by zoledronic acid correlates with improved survival in patients with bone metastases from breast cancer; Poster presented at: the 28th Annual San Antonio breast cancer symposium; December 8–11, 2005; San Antonio (TX). Poster 3015
77. Fulfaro F, Leto G, Badalamenti G, et al. The use of zoledronic acid in patients with bone metastases from prostate carcinoma: effect on analgesic response and bone metabolism biomarkers. *J Chemother*. 2005; 17:555–559. [PubMed: 16323446]
78. Santini D, Vincenzi B, Hannon RA, et al. Changes in bone resorption and vascular endothelial growth factor after a single zoledronic acid infusion in cancer patients with bone metastases from solid tumours. *Oncol Rep*. 2006; 15:1351–1357. [PubMed: 16596210]
79. Clemons MJ, Dranitsaris G, Ooi WS, et al. Phase II trial evaluating the palliative benefit of second-line zoledronic acid in breast cancer patients with either a skeletal-related event or progressive bone metastases despite first-line bisphosphonate therapy. *J Clin Oncol*. 2006; 24:4895–4900. [PubMed: 17001071]
80. Costa L, Demers LM, Gouveia-Oliveira A, et al. Prospective evaluation of the peptide-bound collagen type I cross-links N-telopeptide and C-telopeptide in predicting bone metastases status. *J Clin Oncol*. 2002; 20:850–856. [PubMed: 11821470]
81. Tosi P, Zamagni E, Cellini C, et al. First-line therapy with thalidomide, dexamethasone and zoledronic acid decreases bone resorption markers in patients with multiple myeloma. *Eur J Haematol*. 2006; 76:399–404. [PubMed: 16480429]
82. Terpos E, Heath DJ, Rahemtulla A, et al. Bortezomib reduces serum dickkopf-1 and receptor activator of nuclear factor-kappaB ligand concentrations and normalises indices of bone remodelling in patients with relapsed multiple myeloma. *Br J Haematol*. 2006; 135:688–692. [PubMed: 17107351]
83. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer*. 2003; 98:1735–1744. [PubMed: 14534891]
84. Coleman RE, Cook R, Major P, et al. Why is zoledronic acid (Z) superior to pamidronate (P) for bone metastases from breast cancer (BC) but equivalent in multiple myeloma (MM)? *Proc Am Soc Clin Oncol*. 2003; 22 Suppl.:47. [Abstract 187].

85. Terpos E, Dimopoulos M-A. Myeloma bone disease: pathophysiology and management. *Ann Oncol.* 2005; 16:1223–1231. [PubMed: 15928069]
86. Barrett-Lee P, Murray N. Zoledronic acid versus ibandronate comparative evaluation in breast cancer patients with bone metastases: the NCRI ZICE trial. *Bone.* 2006; 38:S67. Poster 62.
87. Rivkin S. Oral ibandronate versus intravenous zoledronic acid for breast cancer patients with skeletal complications: The SWOG trial. *Bone.* 2006; 38 Suppl.:S82. [Abstract 101].
88. Paterson AH. The role of bisphosphonates in early breast cancer. *Oncologist.* 2006; 11 Suppl. 1:13–19. [PubMed: 16971735]
89. US National Institutes of Health. Clinical trials: randomized study of bone marker-directed schedule versus standard schedule of zoledronic acid in patients with advanced breast cancer metastatic to the bone. 2008 [accessed 21.04.08]. Available at: <http://www.cancer.gov/clinicaltrials/NCRI-BISMARCK>
90. UK Clinical Research Network: Portfolio Database. Cost-effective use of BISphosphonates in metastatic bone disease – a comparison of bone MARKer directed zoledronic acid therapy to a standard schedule – the BISMARCK trial. 2008 [accessed 21.04.08]. Available at: <http://public.ukcrn.org.uk/StudyDetail.aspx?StudyID=1737>

Figure 1.

Bone remodeling and regulation of bone specific markers. BALP, bone-specific alkaline phosphatase; TRAcP-5b, tartrate-resistant acid phosphatase type 5b; BSP, bone sialoprotein. Adapted with permission from Fohr et al. Clinical review 165: markers of bone remodeling in metastatic bone disease. *J Clin Endocrinol Metab* 2003;**88**(11):5059–75. Copyright 2003, The Endocrine Society.⁷

Table 1

Markers of bone formation

Marker	Normal range	Elevated values, median	Specimen	Evaluation method
BALP	Premenopausal women: 2.9–14.5 µg/L ¹³	PC patients with bone mets: 38.5 ng/mL ¹⁴	Serum	Colorimetric, IRMA, EIA
	Postmenopausal women: 3.8–22.6 µg/L ¹³	BC patients with bone mets: 45.7 µ/L ¹⁵		
	Men: 3.7–20.9 µg/L ¹³			
OC	Premenopausal women ^a : 1.0–36 µg/L ¹⁶	PC patients with bone mets: 29.8 ng/mL ¹⁴	Serum	IRMA, RIA, ELISA
	Men ^a : 1.0–35 µg/L ¹⁶			
P1CP	Women: 50–170 µg/L ^{17,18}	PC patients with bone mets: 168 ng/mL ¹⁴	Serum	RIA, ELISA
	Men: 38–202 µg/L ^{17,18}			
PINP	Women: 31.7–70.7 ng/mL ¹⁹	–	Serum	RIA, ELISA
	Men: 21–78 µg/L ²⁰			

BALP, bone alkaline phosphatase; OC, osteocalcin; P1CP, C-terminal propeptide of procollagen type 1; PINP, N-terminal propeptide of procollagen type 1; PC, prostate cancer; BC, breast cancer; Mets, metastases; IRMA, immunoradiometric assay; EIA, enzyme immunoassay.

^aEncompasses the normal range for all available assays.

Table 2**Markers of bone resorption and osteoclastogenesis**

Marker	Normal range	Elevated values, median	Specimen	Evaluation method
PYD	Adults: 19.5–25.1 nM/mM Cr27	MM patients with bone mets: 64.4 nmol/mmol Cr28	Urine	HPLC, ELISA
DPD	Adults ^a : 1.8–15.5 fmol/mol28	MM patients with bone mets ^a : 10.6–18.0 nmol/mmol Cr28 Advanced BC patients: 10.5 nmol/mmol Cr29	Urine	HPLC, ELISA
CTX	<i>Urine</i> Adults: 3.9–4.9 nM/mM Cr27 <i>Serum</i> Premenopausal women, mean: 0.29 ± 0.14 ng/mL30 Postmenopausal women, mean: 0.56 ± 0.23 ng/mL30 Men, mean: 0.30 ± 0.14 ng/mL30	<i>Urine</i> PC patients with bone mets: 621 µg/mmol Cr14 <i>Serum</i> PC patients with bone mets: 6,900 pmol/L14	Urine or serum	Urine: Crosslaps® Serum: ELISA, RIA
NTX	<i>Urine</i> Premenopausal women: 5–65 nM BCE/mM Cr31 Men: 3–63 nM BCE/mM Cr31 <i>Serum</i> Women: 6.2–19 nM BCE31 Men: 5.4–24.2 nM BCE31	<i>Serum</i> BC patients with bone mets: 30 nM BCE32	Urine or serum	Urine: Osteomark™ Serum: ELISA, RIA
ICTP	Adults: 0.76–5.24 ng/mL33	MM patients with bone mets: ~8 µg/L34	Serum	RIA
TRAcP-5b	Premenopausal women: 0.5–3.8 U/L35 Postmenopausal women: 0.5–4.8 U/L35 Men: 0.5–3.8 U/L35	–	Plasma or serum	Colorimetric, RIA
BSP	Adults: 8.0–9.4 µg/L27	–	Serum	ELISA, RIA
RANKL	Adults: 0.80 ± 0.40 pmol/L36	–	Plasma or serum	ELISA
OPG	Adults, mean: 2.42 ± 0.26 ng/L37	–	Plasma or serum	ELISA

Crosslaps is a registered trademark of Nordic Bioscience Diagnostics.

Osteomark is a trademark of Inverness Medical Innovations.

PYD, pyridinoline; DPD, deoxypyridinoline; CTX, C-telopeptide of type I collagen; NTX, N-telopeptide of type I collagen; ICTP, pyridinoline cross-linked carboxyterminal telopeptide of type I collagen; TRAcP-5b, tartrate-resistant acid phosphatase serum type 5b; BSP, bone sialoprotein; RANKL, receptor activator of nuclear factor-κB ligand; OPG, osteoprotegerin; Cr, creatinine; MM, multiple myeloma; PC, prostate cancer; BC, breast cancer; mets, metastases; BCE, bone collagen equivalents; HPLC, high-performance liquid chromatography; ELISA, enzyme-linked immunoassay; RIA, radioimmunoassay.

^aEncompasses the normal range for all available assays.