ELSEVIER

Urologic Oncology: Seminars and Original Investigations 30 (2012) 369–378

UROLOGIC ONCOLOGY

Review article

Biochemical markers of bone turnover and clinical outcomes in men with prostate cancer☆

Fred Saad, M.D., FRCS[a,*,1], James A. Eastham, M.D.[b], Matthew R. Smith, M.D., Ph.D.[c,2]

[a] *Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada*
[b] *Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA*
[c] *Massachusetts General Hospital, Boston, MA 02114, USA*

Received 24 May 2010; received in revised form 9 August 2010; accepted 10 August 2010

Abstract

Objectives: Disrupted skeletal homeostasis is common in patients with prostate cancer. Low bone density is common at diagnosis, and fracture risk is further elevated by the effects of androgen-deprivation therapy. Later in the disease course, bone metastases can result in skeletal morbidity. Although prostate-specific antigen (PSA) levels can provide important insights into overall disease progression, convenient, noninvasive tools for monitoring skeletal health are lacking. Biochemical markers released into serum and urine as a result of bone turnover might fulfill this unmet need. The objectives of this article are to assess current evidence examining the potential utility of bone turnover markers for monitoring skeletal health, bone disease progression, and response to antiresorptive therapies in the prostate cancer setting.

Methods: Published articles and abstracts from major oncology or urology congresses pertaining to the use of bone turnover markers to monitor skeletal health and disease progression were identified and assessed for relevance and methodologic stringency.

Results: Several randomized trials and correlative studies support the utility of bone marker level changes to assess disease progression in the metastatic setting, bone health during hormonal therapy, and response to bisphosphonate therapy. The available data support potential associations between levels of the collagen type I telopeptides (NTX and CTX) and the severity of metastatic bone disease as well as outcomes during antiresorptive therapy. Evidence linking bone marker level changes with early diagnosis of skeletal metastases is emerging. Although several markers have shown promising results in correlative studies, results from ongoing prospective trials are needed to establish the role of bone markers in this setting.

Conclusions: Bone marker levels reflect ongoing skeletal metabolism and can provide important insights into bone health and response to bisphosphonate therapy in patients with prostate cancer. The data supporting a role for bone markers to monitor skeletal disease progression and response to zoledronic acid therapy are especially strong. Bone marker assessments may complement established diagnostic and monitoring paradigms in prostate cancer.

Keywords: Bisphosphonate; Bone loss; Bone metastases; Bone mineral density; Bone turnover markers; Prostate cancer

1. Introduction

Prostate cancer is the most common malignancy in men in developed countries, and accounts for almost 20% of new cancer diagnoses in men annually [1]. This cancer shows a strong predilection for metastasis to bone, with 65% to 75% of men with castration-resistant prostate cancer (CRPC) developing bone metastases [2]. In healthy bone, homeostasis is maintained through balanced bone resorption and formation. This balance is disrupted by bone metastases [2], weakening the skeleton and increasing the risk of debilitating and potentially life-limiting skeletal-related events (SREs) such as pathologic fractures, spinal cord compression, the need for orthopedic surgery or palliative radiotherapy to bone, and hypercalcemia of malignancy (HCM) [2]. Although bone metastases from prostate cancer have an osteoblastic appearance on radiographs, they also have a strong osteolytic component [3]. Indeed, bone resorption marker levels in serum and urine are typically elevated to greater levels in patients with osteoblastic vs. osteolytic bone metastases [4].

☆ Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation.

* Corresponding author. Tel.: +1-514-890-8000 ext. 27466; fax: +1-514-412-7620.

E-mail address: fred.saad@umontreal.ca (F. Saad).

[1] Received research funding, attended advisory board meetings, and received honoraria for speaking on behalf of Novartis Oncology.

[2] Received research funding and/or served as a consultant to Amgen, Novartis, and GTx Inc.

1078-1439/$ – see front matter
http://dx.doi.org/10.1016/j.urolonc.2010.08.007

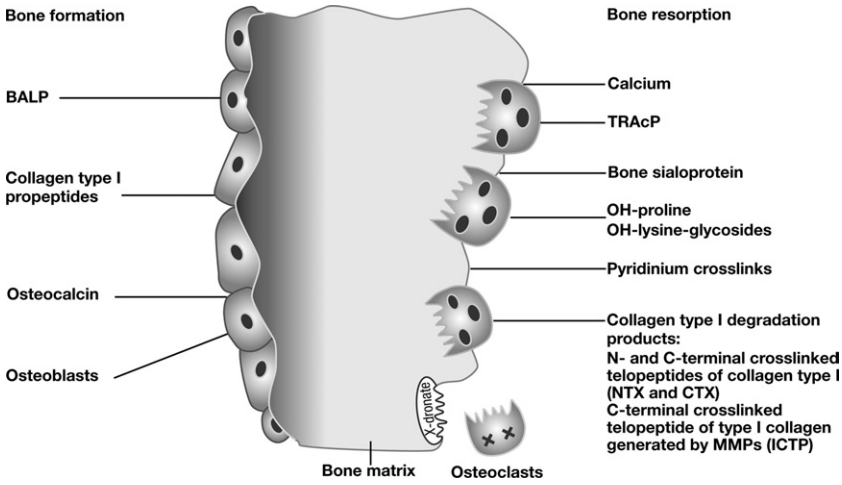

Fig. 1. Biochemical markers of bone turnover. BALP = bone-specific alkaline phosphatase; CTX = C-telopeptide of type I collagen; NTX = N-telopeptide of type I collagen; TRAcP = tartrate-resistant acid phosphatase. Adapted with permission from Fohr B, Dunstan CR, Seibel MJ. Clinical review 165: Markers of bone remodeling in metastatic bone disease. *J Clin Endocrinol Metab.* 2003;88(11):5059–75. Copyright 2003, The Endocrine Society [21].

Low bone mineral density (BMD) is common among men with prostate cancer [5,6], an observation explained at least in part by their older age. Androgen-deprivation therapy (ADT) decreases BMD at all measured sites including the hip and spine [7], and is associated with increased risk of clinical fractures [8]. In addition to potential disability, fractures can have profound ramifications for patients with prostate cancer. Fractures in patients treated with ADT and pathologic fractures in patients with bone metastases from prostate cancer have both been correlated with decreased survival [9,10]. Therefore, appropriate management of patients with prostate cancer includes preservation of bone health.

Bisphosphonates (BPs) are bone-targeted agents that inhibit osteoclast-mediated osteolysis [2]. Although several BPs are available for the prevention of SREs in patients with breast cancer [11], zoledronic acid (ZOL; 4 mg intravenous every 3–4 weeks) is the only agent with proven efficacy for the prevention of SREs in patients with bone metastases from CRPC and other solid tumors [12]. Several BPs have also demonstrated promising activity in clinical trials for the prevention of ADT-associated bone loss in men with prostate cancer [13–18]. Furthermore, investigational bone-targeted agents such as denosumab (an antibody against receptor activator of nuclear factor κ-B ligand [RANKL], a key regulator of osteoclast maturation and function) are being evaluated. Recent data indicate that denosumab can improve BMD and prevent morphometric vertebral fractures in men with prostate cancer receiving long-term ADT, providing evidence that preserving BMD in this setting can potentially prevent fractures [19].

While pharmacologic interventions to prevent bone loss may be necessary in patients with cancer, the continued administration of calcium and vitamin D is important to maintain serum ion homeostasis. In addition, patients might derive benefit from weight-bearing and resistance exercises [20].

2. Tools for assessing bone health in the prostate cancer setting

Current diagnostic tools for the assessment of skeletal health in patients with prostate cancer are limited to imaging techniques, including bone scans and magnetic resonance imaging in the bone-metastatic setting and dual-energy X-ray absorptiometry (DXA) for BMD assessments. These methods rely on changes in the physical characteristics of the skeleton because of bone metastases or ADT and other factors, respectively. However, altered bone metabolism also results in the release of characteristic enzymes and peptides (Fig. 1) [21], and changes in these marker levels can precede the measurable physical changes. Several markers can be easily measured in serum and urine samples using standardized biochemical and immunologic assays (Table 1). In recent years, randomized clinical trials and correlative studies have investigated the potential for these biochemical markers of bone turnover to provide insight into clinical parameters that currently require assessment using imaging techniques. Moreover, the relationship between bone markers and skeletal disease in advanced prostate cancer suggests that increases in bone marker levels may reflect disease progression in bone, similar to how elevated prostate-specific antigen (PSA) levels post-prostatectomy herald disease recurrence [22,23]. This review will examine the available evidence for the use of bone marker assessments in monitoring skeletal health and disease progression, predicting or diagnosing bone metastases, and evaluating response to therapy in patients with prostate cancer.

3. Literature review

Articles and published abstracts were identified by searching PubMed, HighWire, and the Web sites for inter-

Table 1
Bone turnover markers that can be measured in serum and urine

Urinary[a]	Serum	
Bone resorption	Bone resorption	Bone formation
Calcium (Ca/Cr)	N-telopeptide (S-NTX)	Bone-specific alkaline phosphatase (BALP)
Hydroxyproline	C-telopeptide (S-CTX)	Osteocalcin
N-telopeptide of type I collagen (NTX/Cr)	Type I collagen C-terminal telopeptide (ICTP)	C-terminal peptide of procollagen type 1 (P1CP)
C-telopeptide of type I collagen (CTX/Cr)	RANKL/OPG ratio	N-terminal peptide of procollagen type 1 (P1NP)
Pyridinoline (PYD/Cr)	Tartrate-resistant acid phosphatase (TRAcP)	
Deoxypyridinoline (DPD/Cr)		

[a] Bone marker levels are corrected for urinary creatinine.

national oncology and urology congresses using the keywords "prostate cancer" and "human" in combination with each of the following terms: N-telopeptide of type I collagen (NTX), C-telopeptide of type I collagen (CTX), bone-specific alkaline phosphatase (BALP), type I collagen C-terminal telopeptide (ICTP), C-terminal peptide of procollagen type 1 (P1CP), N-terminal peptide of procollagen type 1 (P1NP), RANKL, osteocalcin, BMD, and bone turnover. The search focused on primary reports of randomized trials and observational or correlative studies. Full-text articles were assessed for relevance (i.e., study size and patient selection, timing of bone marker assessments, definitions of "normal" and "abnormal" bone marker levels, methodologic stringency, etc.), and key findings are included. Articles published before the year 2000 are included only if they contained key information that was not subsequently updated.

4. Potential insights from bone marker assessments throughout the prostate cancer disease continuum

4.1. Bone marker levels and clinical outcomes in patients with skeletal metastases

Bone turnover marker levels are elevated in the majority of patients with bone metastases from CRPC, and elevated levels of both resorption and formation markers correlate with poor outcomes. In the phase III registration trial of ZOL in 643 patients with CRPC and bone metastases [12], approximately 62% had elevated urinary NTX levels (≥64 nmol/mmol creatinine) at randomization [24]. In exploratory analyses of placebo-group patients with baseline bone marker assessments ($n = 203$), markedly elevated baseline NTX (≥100 nmol/mmol creatinine) was associated with significantly worse clinical outcomes compared with NTX levels less than 100 nmol/mmol creatinine [25]. This included a 57% increased risk of SREs ($P = 0.015$), a 56% increased risk of disease progression ($P = 0.006$), and a 2.4-fold increased risk of death ($P < 0.001$) [25]. In other analyses of this study, elevated baseline levels of BALP (defined using a cutoff of 267.5 U/L, the median value for the trial population) were associated with a 49% increased risk of death ($P = 0.001$) [26]. Baseline BALP levels demonstrated an even more pronounced association with the risk of death when BALP was categorized into quartiles. Patients with BALP levels in the highest quartile had a 64% increase in the relative risk of death compared with patients who had BALP levels in the lowest quartile ($P = 0.01$) [26]. Moreover, elevated (i.e., above median) baseline BALP was significantly associated with shorter times to first events for SREs in general (relative risk [RR] = 1.81; $P < .001$), and pathologic fractures (RR = 1.60, $P = 0.02$) and palliative radiotherapy to bone (RR = 2.07; $P < 0.001$) in particular [27].

A prospective, open-label, single-arm study of the efficacy and tolerability of ZOL (4 mg q 4 weeks for 15 months) in 308 German patients with bone metastases from prostate cancer included a subset of 77 patients with periodic serum bone marker assessments, and correlative data on PSA levels and disease progression [28]. In these patients, serum levels of several bone markers (NTX, CTX, BALP, ICTP, and P1NP) were initially suppressed during monthly ZOL treatment, reaching a nadir at 12 to 24 weeks. Thereafter, bone marker levels remained suppressed in patients without bone disease progression ($n = 27$) but increased between week 24 and the end of the study (week 60) in patients with radiologic evidence of progression ($n = 50$), with statistically significant ($P < .05$) differences in P1NP, BALP, and ICTP levels [28]. Further analyses comparing 56 patients who developed one or more on-study SREs with 61 patients who did not develop SREs revealed higher baseline bone marker levels in the SRE group vs. the no-SRE group ($P = 0.006$ for P1NP, $P < 0.0001$ for NTX, and $P = 0.002$ for CTX) [29]. Cox regression analyses revealed significant correlations between increased risks of SREs and elevated baseline serum NTX as well as on-study increases in serum P1NP and ICTP [29].

Further support for the correlation between bone marker increases and bone disease progression was provided by a prospective observational study in 84 Japanese patients receiving ADT for prostate cancer with bone metastases [30]. In this study, levels of PSA, ICTP, and P1CP decreased during ADT in patients without progression of bone metastases but began to rebound in patients with bone metastases progression on serial bone scans. Furthermore, ICTP and

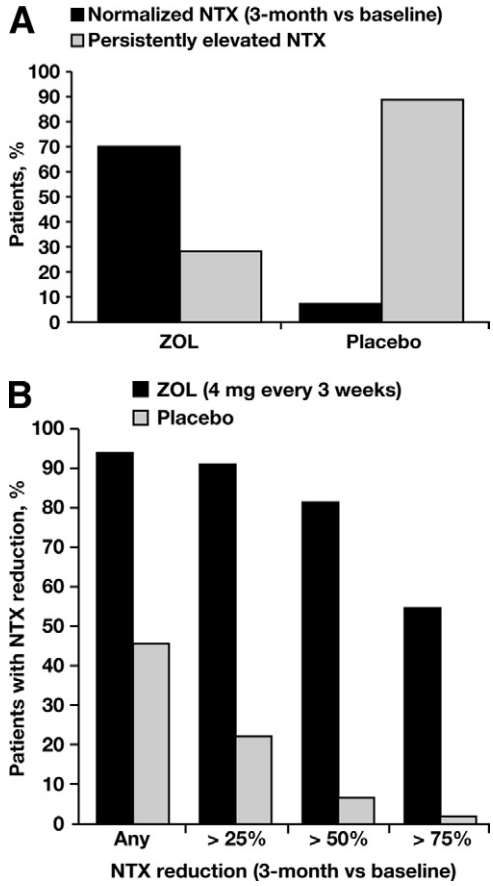

Fig. 2. Proportion of patients with elevated baseline NTX whose NTX levels at 3 months either (A) normalized or (B) demonstrated any decrease from baseline with placebo or zoledronic acid treatment. NTX = N-telopeptide of type I collagen; ZOL = zoledronic acid 4 mg q3wk. Data from Saad F [31].

P1CP outperformed PSA as predictors of bone metastases progression in this patient population [30].

4.2. Bone marker levels and clinical outcomes in patients receiving bone-directed therapy for skeletal metastases

In addition to their correlations with disease progression in bone, changes in bone marker levels also appear to correlate with outcomes during BP therapy, and the evidence is especially strong for ZOL. Although bone turnover markers are not established as surrogates for clinically relevant endpoints such as prevention of SREs, exploratory analyses of the phase III ZOL trial databases have shown that rapid normalization of elevated NTX levels during ZOL therapy is associated with improved survival in patients with bone metastases from CRPC, breast cancer, lung cancer, and other solid tumors [24]. Among the CRPC patients with bone marker assessments, approximately 70% of ZOL-treated patients with elevated baseline NTX (n = 193) normalized their NTX levels within 3 months, vs. only 8% of placebo-treated patients (Fig. 2A) [31]. Overall, 94% of ZOL-treated patients recorded decreases in NTX levels at 3 months vs. baseline, compared with less than half (46.5%) of the placebo-treated patients (Fig. 2B) [31]. Normalization of NTX levels at 3 months was associated with a 59% decrease in the risk of death ($P < 0.0001$) and a 38% decrease in the risk of subsequent SREs ($P = 0.0411$) compared with persistently elevated NTX during ZOL therapy [24]. Furthermore, reductions in NTX levels compared with baseline were associated with a continuum of survival benefits (Fig. 3A) [31], indicating that any reduction in ongoing bone turnover with ZOL may improve clinical outcomes for patients with CRPC. On the other hand, further increases in NTX levels vs. baseline, as observed in more than 50% of placebo-treated patients, correlated with increased risks of death (Fig. 3B) [31].

Data correlating outcomes with bone marker levels in patients with metastatic prostate cancer treated with bisphosphonates other than ZOL are more limited. In a study comparing the effects of pamidronate and oral clodronate in patients with metastatic bone disease (including ~30% patients with prostate cancer) patients treated with pamidronate were more likely to have symptomatic response and experience sustained improvement in pain scores compared with patients treated with clodronate [32]. Interestingly, patients treated with pamidronate also had a sustained decrease in urinary CTX relative to clodronate-treated patients.

Further data on the potential role of bone markers in patients with solid tumors was provided by recent phase II trials of denosumab, an anti-RANKL antibody [33]. In patients with bone metastases from solid tumors and elevated urinary NTX levels despite prior intravenous BP therapy (n = 111), NTX levels normalized within 13 weeks in 71% of patients receiving denosumab, compared with 29% of patients continuing BP treatment ($P < 0.001$) [33]. Bone marker patterns were similar in the prostate cancer subset (n = 50) [34]. However, these studies were not designed to assess clinical outcomes such as SREs, and further investigations will be necessary to determine whether the reductions in bone marker levels with denosumab will translate into clinical benefits, as they appear to do in the ZOL studies.

Recent studies also have begun to explore correlations between bone marker level changes and response to palliative radionuclide treatment [35]. In a pilot study in men with painful osseous metastases from prostate cancer receiving palliative Re-186 treatment, a post-treatment NTX level decrease of at least 20% correlated with 3.4-fold better palliation of bone pain (vs. men with <20% reduction in NTX levels; $P = 0.0005$) [35]. Although this study involved a small number of patients, the findings are important because none of the patients received any other therapies that could affect bone metabolism [35].

Overall, current evidence indicates that NTX and BALP levels may provide convenient, noninvasive means of assessing response to ZOL therapy at an individual level. The evidence is yet to mature for other antiresorptive agents,

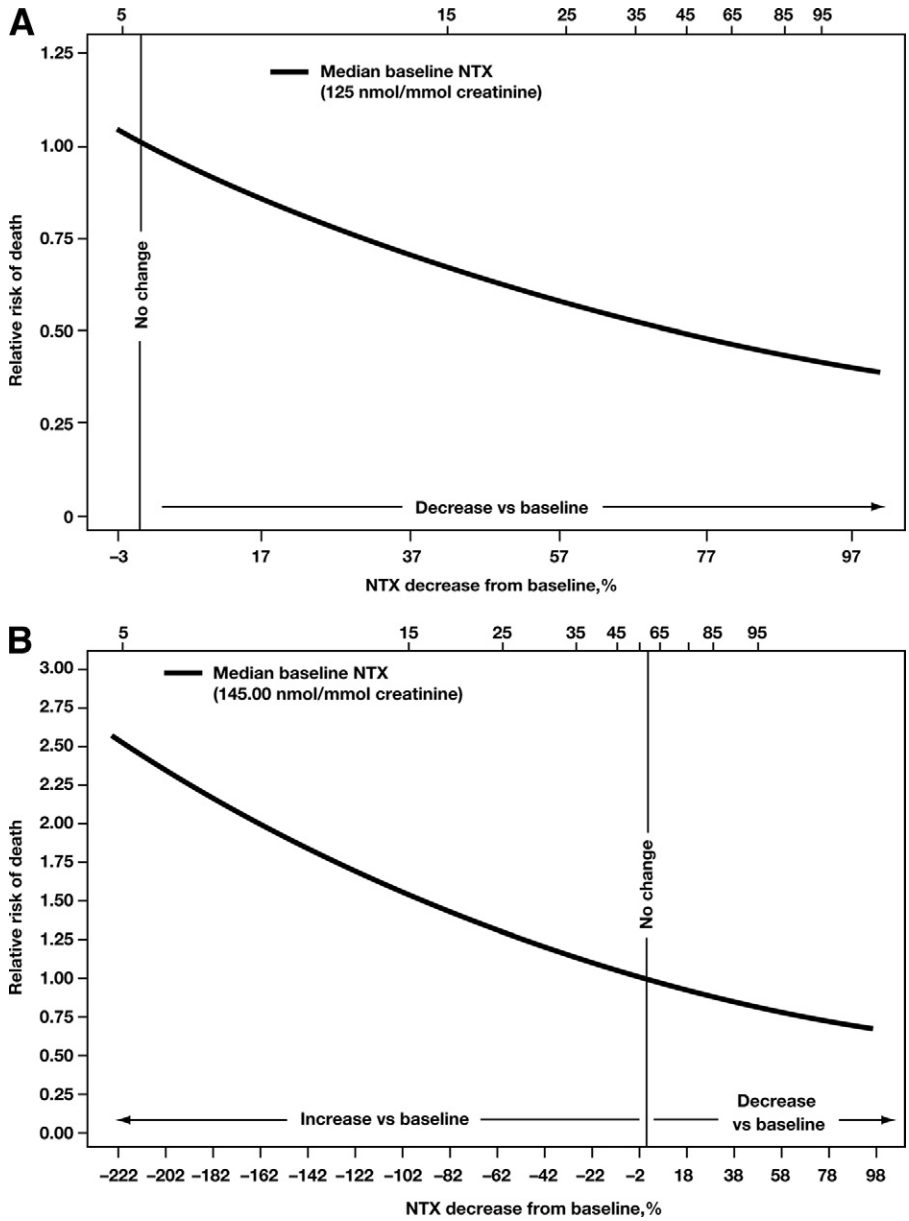

Fig. 3. Continuum of (A) survival benefits observed in patients whose NTX levels at 3 months decreased and (B) increased risk of death in patients whose NTX levels increased compared with baseline. NTX = N-telopeptide of type I collagen. Percentage NTX decrease from baseline calculated as 100 × (baseline NTX level − 3-month NTX level) ÷ baseline NTX level. Adapted from Saad F [31].

or for other modes of bone-directed therapy (e.g., radiotherapy). With increasing insights into bone marker science, we believe that assessing bone marker level responses might contribute to clinical decision-making—for example, persistently high bone marker levels during first-line antiresorptive therapy might signal the need to switch to a different bone-protective agent. Most ongoing clinical trials of antiresorptive agents in the prostate cancer setting now include prospective bone marker studies. As data from these trials mature, the potential role of bone markers in monitoring treatment response and risk of bone disease progression will be further elucidated.

4.3. Bone markers in the diagnosis of bone metastases from prostate cancer

Rising PSA levels after radical prostatectomy or during ADT are indicative of prostate cancer recurrence or overall progression. However, although elevated PSA level and rapid PSA kinetics correlate with increased risk of bone metastases [23], PSA is not specific to bone metastasis, and biochemical relapse in itself does not identify patients in need of bone-targeted therapies. Several studies have therefore evaluated the utility of elevated bone turnover marker levels as a screening tool for identifying patients who need follow-up bone scans.

In a study in 161 patients with solid tumors (breast, prostate, or lung cancer) with or without bone metastases, serum and urinary levels of bone turnover markers (various CTX isoforms, NTX, ICTP, and BALP) were significantly increased in patients with bone metastases vs. those without bone metastases ($P < 0.05$ for between-group comparisons) [36]. Moreover, elevated marker levels were detectable at early stages of skeletal involvement (<6 bone metastases), and strong linear associations were observed between bone marker levels and extent of skeletal involvement [36]. Similar results were reported in a second study ($n = 123$), wherein an increase in urinary NTX was observed to be strongly predictive of bone metastases progression (positive predictive value = 71%) [37]. Another study limited to patients with prostate cancer with ($n = 25$) or without ($n = 40$) bone metastases confirmed strong associations between the presence of skeletal disease and elevated levels of P1NP, P1CP, BALP, and ICTP [38]. Although the extent of bone disease correlated best with P1NP levels in this study, useful correlations were also observed for ICTP, BALP, and PSA [38]. In a study comparing men with prostate cancer ($n = 36$) with age-matched healthy controls ($n = 24$), levels of BALP, CTX, NTX, P1CP, and P1NP were all significantly higher in patients vs. controls ($P \leq 0.04$ for all) [39]. Moreover, bone marker levels in this study showed significant linear correlations with the extent of skeletal disease ($P \leq 0.032$) [39]. On the other hand, in a study in 155 men with prostate cancer, serum ICTP levels were not indicative of skeletal involvement in the study population as a whole [40]. However, in the subset of patients with low alkaline phosphatase (<335 IU/L) and high PSA (≥40 ng/ml) levels, ICTP levels clearly distinguished between men with and without bone metastases [40].

Bone markers may also provide insights into the sites of metastases in patients with biochemical relapse. Elevations in serum P1NP and ICTP levels were found to identify patients with bone vs. lymph node metastases in a retrospective study ($n = 64$) [41]. Interestingly, P1NP levels were found to increase up to 8 months before the first evidence of skeletal involvement by bone scintigraphy [41], indicating a potential role in identification and monitoring of patients at increased risk for bone metastases. Other studies have identified tartrate-resistant acid phosphatase 5b (TRAcP-5b) and total alkaline phosphatase as promising markers, alone or in combination with PSA [42,43]. Two other studies from a single institution have compared bone marker levels in patients with prostate cancer with ($n = 44$) or without ($n = 73$) bone metastases vs. patients with benign prostatic hyperplasia and healthy men ($n = 35$ each) [44,45]. These studies identified strong correlations between elevated osteoprotegerin (OPG) levels and the presence of bone metastases from prostate cancer [44,45]. In other studies, plasma osteopontin levels have been correlated with the incidence of distant metastases in patients with renal cell carcinoma, and bone metastases in patients with prostate cancer [46,47]. In the prostate cancer study ($n = 90$), osteopontin levels were significantly different between patients with and without bone metastases ($P < 0.001$), and combination of osteopontin levels with BALP levels indicated the presence of bone metastases with a sensitivity and specificity of approximately 90% [46].

Although small studies have consistently revealed strong associations between bone turnover markers and the presence or progression of skeletal metastases from prostate cancer, further studies are needed to identify the optimal marker for this purpose. Moreover, consistent cutoffs for marker levels are needed to distinguish between patients with and without bone metastases.

4.4. Bone marker changes during androgen-deprivation therapy

It is now well established that ADT is associated with deceased BMD and increased fracture risk [8,48]. Androgens play an important role in maintaining skeletal health in men, at least in part through peripheral aromatization to estrogens [49,50]. Indeed, the reported association of BMD with serum estradiol levels is stronger than its association with serum testosterone levels, especially in elderly men [51,52]. Thus, both orchiectomy and ADT have the potential to indirectly decrease serum estradiol levels by decreasing the amount of testosterone available for aromatization, and marked suppression of serum estrogen has been reported in men receiving ADT with gonadotropin-releasing hormone agonists (e.g., goserelin) [53]. Therefore, men who are post-orchiectomy or undergoing ADT have elevated levels of bone turnover markers [53,54]. In one study in men with advanced prostate cancer, serum NTX and BALP levels were elevated in men with castrate levels of testosterone (e.g., post-orchiectomy or during ADT) compared with hormone-naive men ($P < 0.01$ for all comparisons) [54]. However, in the group with castrate testosterone levels, significant ($P = 0.01$) further elevations in BALP levels were indicative of bone metastases, whereas NTX levels were similar in men with and without bone metastases [54].

Several studies in recent years have explored the relationship between ADT and bone turnover. However, little is known about the importance of changes in bone marker levels and subsequent challenges to skeletal integrity. Recent studies in the breast cancer setting have revealed that early increases in bone marker levels during adjuvant hormonal therapy for hormone-responsive breast cancer can predict clinically relevant decreases in BMD at later timepoints [55]. Similar correlations are likely to exist in patients receiving ADT for prostate cancer, and further evaluation in prospectively planned clinical trials and through clinical experience is needed.

Bisphosphonates such as intravenous ZOL (4 mg q 3 months) and other investigational antiresorptive therapies including subcutaneous denosumab (60 mg q 6 months) have shown activity for preventing and reversing ADT-

associated bone loss [14–19]. Several of these studies also reveal that antiresorptive therapies reverse the elevation in bone turnover observed during ADT. In 61 men with prostate cancer undergoing long-term ADT (median duration, 42 months), oral risedronate (2.5 mg daily for 6 months) significantly decreased urinary NTX levels within 3 months, increased lumbar spine (LS) BMD by 4.9% at 6 months ($P < 0.001$ vs. baseline for both), and maintained stable BMD at the femoral neck [15]. In another study in patients with prostate cancer and osteoporosis ($n = 60$) who were initiating hormonal therapy, treatment with intramuscular neridronate (25 mg q 1 month) maintained serum BALP at baseline levels and prevented further BMD loss [17]. Several clinical trials have shown that ZOL (4 mg q 3 months) prevents bone loss during ADT and increases BMD above baseline at the LS and other sites (reviewed in Saad et al) [13]. In one study of ZOL initiated during the first year of ADT in 215 men with locally advanced prostate cancer, bone marker levels (NTX and BALP) were significantly lower compared with baseline in the ZOL-treated patients (–14% to –28% for NTX and –31% to –37% for BALP; $P < 0.05$ vs. baseline for both). Moreover, changes in NTX and BALP levels were significantly associated with changes in LS BMD at 52 weeks ($P = 0.04$ and 0.02, respectively), which was 6.7% higher in the ZOL-treated group compared with placebo ($P < 0.0001$) [16]. A single study of annual ZOL treatment ($n = 44$ randomized non-osteoporotic men undergoing ADT) showed between-group differences of 7.1% in LS BMD ($P < 0.001$) and 2.6% in total hip BMD ($P = 0.004$) at 12 months [14]. In this study, a single dose of ZOL suppressed NTX and BALP levels vs. baseline for up to 1 year (mean 12-month differences from baseline were –17% and –13%, respectively) [14]. Thus, decreased levels of bone turnover markers during antiresorptive therapy correlate with preservation of BMD in men undergoing ADT for prostate cancer.

Similar findings have been reported with other bisphosphonates. In a 6-month randomized, double-blind, placebo-controlled trial in men with nonmetastatic prostate cancer receiving ADT, 35 mg weekly risedronate stabilized BMD at femoral neck and total hip at 6 months, whereas patients in the placebo arm had a significant loss at both sites (2.0%, $P = 0.004$ and 2.2%, $P = 0.001$, respectively) [56]. In addition, patients using risedronate had a significant increase in their lumbar spine BMD. The benefit in prevention of bone loss was paralleled by changes in the levels of bone turnover markers. Compared with baseline levels, both urinary NTX and CTX decreased (by 15% and 5%, respectively) in the risedronate treatment group, but increased in the placebo group (by 21% and 55%, respectively). Moreover, these changes were statistically significant ($P = 0.015$ for NTX and P = 0.01 for CTX). In another placebo-controlled study that evaluated 2 years of alendronate treatment in a similar patient population (i.e., men with nonmetastatic prostate cancer receiving ADT), alendronate treatment was associated with a significant benefit in BMD at the spine and hip vs. placebo ($P < 0.01$ for both) [57]. Overall, alendronate treatment significantly decreased urinary NTX, serum CTX, P1NP, and BSAP ($P < 0.05$, for all).

Recently, a phase III clinical trial comparing denosumab with placebo in men undergoing ADT ($n = 1,468$) provided the first evidence for reduced fracture incidence with an antiresorptive agent in this setting [19]. In this study, the incidence of new vertebral fractures at 36 months was 1.5% in the denosumab arm, vs. 3.9% in the placebo arm ($P = 0.006$) [19]. Compared with placebo, denosumab significantly improved BMD at all sites of measurement (lumbar spine, total hip, and distal radius; $P < 0.0001$ for all comparisons) [58]. Improvements in BMD with denosumab treatment were consistent across protocol-defined patient subgroups, including patients with the highest levels of bone turnover markers at study entry [58]. Denosumab also significantly decreased serum levels of bone turnover markers ($P < 0.001$ vs. placebo for each marker): 6 months after the last dose of study drug, serum levels of CTX, P1NP, and TRAcP-5b decreased by a median of 45%, 61%, and 33%, respectively, vs. baseline [19]. In contrast, placebo-treated patients recorded increases of 8% to 18% in bone marker levels compared with baseline [19].

4.5. Bone marker level changes during chemo- and glucocorticoid therapy

In addition to ADT, treatment with dexamethasone or prednisone is common in men with CRPC. Although there are no systematic reports of the effects of corticosteroids on bone turnover in the prostate cancer setting, it is well known that chronic glucocorticoid use can cause osteoporosis or exacerbate existing bone loss [59]. Not surprisingly, bone formation marker levels decrease, and bone resorption marker levels increase, during long-term glucocorticoid therapy regardless of dose [59]. Moreover, there is little known about the effects of chemotherapy on bone turnover in the CRPC setting. In one study in men with CRPC randomized to chemotherapy (docetaxel and estramustine) or ZOL, changes in bone marker levels after 1 cycle of therapy (vs. baseline) were similar between the treatment arms [60]. As it is becoming evident that bone turnover might be affected by a variety of therapeutic agents used in the prostate cancer setting, further studies are needed to distinguish between changes in bone marker levels as a direct consequence of the treatment vs. changes attributable to treatment-induced reduction in disease burden (e.g., after chemotherapy).

5. Conclusions

Skeletal homeostasis is disrupted in patients with bone metastases from solid tumors including prostate cancer, and during ADT. Biochemical markers of bone turnover provide

Table 2
Correlations of bone markers with clinical events

Bone marker/patient population	Correlations with clinical events
BALP	
In prostate cancer patients vs controls	Presence of bone metastases [61,62]
During treatment with zoledronic acid or placebo	Time to SRE, pathologic fracture [27], death [26]
CTX	
Prostate cancer	Presence of bone metastases, response to pamidronate [63]
	Shorter bone-only relapse-free survival [64]
Deoxypyridinoline	
Normal premenopausal women	Increased incidence of new vertebral fractures [65]
Hydroxyproline	
In prostate cancer patients	Presence of bone metastases [66]
ICTP	
In all tumors	Bone pain levels [67]
NTX	
In cancer patients	Presence of advanced bone disease [68]
In postmenopausal women	Time to progression and death [69]
	Predictive of survival benefit with zoledronic acid [70]
	Increased incidence of hip fracture among postmenopausal women [71]
Osteocalcin	
Prostate cancer patients	Presence of bone metastases [62]
Cancer and non-cancer patients	Presence of fracture, non-irradiated bone metastases, or Paget's disease [72]
TRAcP-5b	
In prostate cancer patients vs controls	Presence of bone metastases [62] therapy of bone metastases [73]
Cancer patients vs postmenopausal women	Presence of early bone lesions [68]

BALP = bone-specific alkaline phosphatase; BSP = bone sialoprotein; CTX = C-telopeptide of type I collagen; DPD = deoxypyridinoline; HP = hydroxylysylpyridinoline; ICTP = pyridinoline cross-linked carboxyterminal telopeptide of type I collagen; NTX = N-telopeptide of type I collagen; LP = lysylpyridinoline; SRE = skeletal-related event; TRAcP-5b = tartrate-resistant acid phosphatase 5b.

insight into ongoing rates of bone metabolism, and potentially offer a noninvasive technique to monitor bone turnover in patients with prostate cancer. In doing so, bone marker assessments may provide insight into bone health, skeletal disease progression, and response to bone-directed therapy in the prostate cancer bone metastasis setting (Table 2). In the absence of bone metastases, changes in bone marker levels may herald impending BMD loss during ADT, and also reflect potential benefit from antiresorptive therapies. Ongoing clinical trials (e.g., ZEUS, a study evaluating the activity of quarterly ZOL for delaying the onset of bone disease in patients with early stage prostate cancer) are further exploring the relationship between bone marker level changes, the risk of developing bone metastases, and effects of antiresorptive therapy in patients with prostate cancer. These studies are expected to yield important insights into the use of bone marker levels for assessing disease progression and risks of skeletal morbidity.

Overall, bone marker assessments have shown promise in the prostate cancer setting, and could potentially become important tools in screening and patient monitoring. Although bone marker assessments have no established role in routine clinical practice, and the effect of chemotherapy on bone turnover is mostly unexplored, several studies have revealed correlations between bone marker level changes during BP treatment and clinical outcomes in patients with locally advanced or metastatic prostate cancer. These data suggest that bone marker assessments may provide a useful complement to established techniques (e.g., PSA testing, total alkaline phosphatase levels, and bone scans) for identifying patients at high risk for skeletal involvement and for monitoring bone disease progression. Ongoing studies are evaluating the utility of bone marker level changes as an aid to clinical decision-making in individual patients. Results from these studies may establish bone markers as useful adjunct tools for the identification of high-risk patients and for guiding patient-management decisions in the prostate cancer setting.

Acknowledgments

The authors thank Shalini Murthy, Ph.D., ProEd Communications, Inc., for her medical editorial assistance with this manuscript.

References

[1] Garcia M, Jemal A, Ward EM, et al. Global Cancer Facts and Figures, 2007. Atlanta, GA: American Cancer Society; 2007.
[2] Lipton A. Pathophysiology of bone metastases: How this knowledge may lead to therapeutic intervention. J Support Oncol 2004;2:205–13, Discussion 13–14, 16–17, 19–20.
[3] Roato I, D'Amelio P, Gorassini E, et al. Osteoclasts are active in bone forming metastases of prostate cancer patients. PLoS One 2008;3: e3627.

[4] Demers LM, Costa L, Lipton A. Biochemical markers and skeletal metastases. Cancer 2000;88(12 Suppl):2919–26.
[5] Conde FA, Sarna L, Oka RK, et al. Age, body mass index, and serum prostate-specific antigen correlate with bone loss in men with prostate cancer not receiving androgen deprivation therapy. Urology 2004;64: 335–40.
[6] Smith MR, McGovern FJ, Fallon MA, et al. Low bone mineral density in hormone-naive men with prostate carcinoma. Cancer 2001; 91:2238–45.
[7] Berruti A, Dogliotti L, Terrone C, et al. Changes in bone mineral density, lean body mass and fat content as measured by dual energy X-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. J Urol 2002; 167:2361–7; Discussion 7.
[8] Shahinian VB, Kuo YF, Freeman JL, et al. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352: 154–64.
[9] Oefelein MG, Ricchiuti V, Conrad W, et al. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. J Urol 2002;168:1005–7.
[10] Saad F, Lipton A, Cook R, et al. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. Cancer 2007;110:1860–7.
[11] Pavlakis N, Schmidt R, Stockler M. Bisphosphonates for breast cancer. Cochrane Database Syst Rev 2005(3):CD003474.
[12] Coleman RE. Bisphosphonates: Clinical experience. Oncologist 2004;9(Suppl 4):14–27.
[13] Saad F, Adachi JD, Brown JP, et al. Cancer treatment-induced bone loss in breast and prostate cancer. J Clin Oncol 2008;26:5465–76.
[14] Michaelson MD, Kaufman DS, Lee H, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol 2007;25:1038–42.
[15] Ishizaka K, Machida T, Kobayashi S, et al. Preventive effect of risedronate on bone loss in men receiving androgen-deprivation therapy for prostate cancer. Int J Urol 2007;14:1071–5.
[16] Israeli RS, Rosenberg SJ, Saltzstein DR, et al. The effect of zoledronic acid on bone mineral density in patients undergoing androgen deprivation therapy. Clin Genitourin Cancer 2007;5:271–7.
[17] Magno C, Anastasi G, Morabito N, et al. Preventing bone loss during androgen deprivation therapy for prostate cancer: Early experience with neridronate. Eur Urol 2005;47:575–80; Discussion 80.
[18] Planas J, Trilla E, Raventos C, et al. Alendronate decreases the fracture risk in patients with prostate cancer on androgen-deprivation therapy and with severe osteopenia or osteoporosis. BJU Int 2009; 104:1637–40.
[19] Smith MR, Egerdie B, Hernandez Toriz N, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med 2009;361:745–55.
[20] Guadalupe-Grau A, Fuentes T, Guerra B, et al. Exercise and bone mass in adults. Sports Med 2009;39:439–68.
[21] Fohr B, Dunstan CR, Seibel MJ. Clinical review 165: Markers of bone remodeling in metastatic bone disease. J Clin Endocrinol Metab 2003;88:5059–75.
[22] Simmons MN, Stephenson AJ, Klein EA. Natural history of biochemical recurrence after radical prostatectomy: Risk assessment for secondary therapy. Eur Urol 2007;51:1175–84.
[23] Smith MR, Kabbinavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol 2005;23:2918–25.
[24] 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;113:193–201.
[25] 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.
[26] Cook RJ, Coleman R, Brown J, et al. Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. Clin Cancer Res 2006;12(11 Pt 1):3361–7.
[27] Smith MR, Cook RJ, Coleman R, et al. Predictors of skeletal complications in men with hormone-refractory metastatic prostate cancer. Urology 2007;70:315–9.
[28] Lein M, Wirth M, Miller K, et al. Serial markers of bone turnover in men with metastatic prostate cancer treated with zoledronic acid for detection of bone metastases progression. Eur Urol 2007;52:1381–7.
[29] Lein M, Miller K, Wirth M, et al. Bone turnover markers as predictive tools for skeletal complications in men with metastatic prostate cancer treated with zoledronic acid. Prostate 2009;69:624–32.
[30] Noguchi M, Yahara J, Noda S. Serum levels of bone turnover markers parallel the results of bone scintigraphy in monitoring bone activity of prostate cancer. Urology 2003;61:993–8.
[31] Saad F. N-telopeptide of type I collagen (NTX) response to zoledronic acid in patients with bone metastases from prostate cancer. Proceedings of the Société Internationale d'Urologie (SIU) World Uro-Oncology Update Meeting; November, 2008; Santiago, Chile. [Abstract 411].
[32] Jagdev SP, Purohit P, Heatley S, et al. Comparison of the effects of intravenous pamidronate and oral clodronate on symptoms and bone resorption in patients with metastatic bone disease. Ann Oncol 2001; 12:1433–8.
[33] Fizazi K, Lipton A, Mariette X, et al. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. J Clin Oncol 2009;27:1564–71.
[34] Fizazi K, Bosserman L, Gao G, et al. Denosumab treatment of prostate cancer with bone metastases and increased urine N-telopeptide levels after therapy with intravenous bisphosphonates: Results of a randomized phase II trial. J Urol 2009;182:509–15, Discussion 15–6.
[35] Zafeirakis A, Papatheodorou G, Arhontakis A, et al. Predictive implications of bone turnover markers after palliative treatment with (186)Re-HEDP in hormone-refractory prostate cancer patients with painful osseous metastases. Eur J Nucl Med Mol Imaging 2010;37: 103–13.
[36] Leeming DJ, Koizumi M, Byrjalsen I, et al. 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;15:32–8.
[37] 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;20:850–6.
[38] Koizumi M, Yonese J, Fukui I, et al. The serum level of the aminoterminal propeptide of type I procollagen is a sensitive marker for prostate cancer metastasis to bone. BJU Int 2001;87:348–51.
[39] Zafeirakis AG, Papatheodorou GA, Limouris GS. Clinical and imaging correlations of bone turnover markers in prostate cancer patients with bone only metastases. Nucl Med Commun 2010;31:249–53.
[40] Kataoka A, Yuasa T, Kageyama S, et al. Diagnosis of bone metastasis in men with prostate cancer by measurement of serum ICTP in combination with alkali phosphatase and prostate-specific antigen. Clin Oncol (R Coll Radiol) 2006;18:480–4.
[41] Koopmans N, de Jong IJ, Breeuwsma AJ, et al. Serum bone turnover markers (PINP and ICTP) for the early detection of bone metastases in patients with prostate cancer: A longitudinal approach. J Urol 2007;178(3 Pt 1):849–53, Discussion 53; quiz 1129.
[42] Lyubimova NV, Pashkov MV, Tyulyandin SA, et al. Tartrate-resistant acid phosphatase as a marker of bone metastases in patients with breast cancer and prostate cancer. Bull Exp Biol Med 2004;138:77–9.
[43] Salminen E, Ala-Houhala M, Korpela J, et al. Serum tartrate-resistant acid phosphatase 5b (TRACP 5b) as a marker of skeletal changes in prostate cancer. Acta Oncol 2005;44:742–7.

[44] 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; 111:783–91.
[45] Jung K, Lein M, von Hosslin K, et al. Osteoprotegerin in serum as a novel marker of bone metastatic spread in prostate cancer. Clin Chem 2001;47:2061–3.
[46] Ramankulov A, Lein M, Kristiansen G, et al. Plasma osteopontin in comparison with bone markers as indicator of bone metastasis and survival outcome in patients with prostate cancer. Prostate 2007;67: 330–40.
[47] Ramankulov A, Lein M, Kristiansen G, et al. Elevated plasma osteopontin as marker for distant metastases and poor survival in patients with renal cell carcinoma. J Cancer Res Clin Oncol 2007;133:643–52.
[48] Alibhai SM, Gogov S, Allibhai Z. Long-term side effects of androgen deprivation therapy in men with non-metastatic prostate cancer: A systematic literature review. Crit Rev Oncol Hematol 2006;60:201–15.
[49] Chang SS. Exploring the effects of luteinizing hormone-releasing hormone agonist therapy on bone health: Implications in the management of prostate cancer. Urology 2003;62(6 Suppl 1):29–35.
[50] Kastelan D, Giljevic Z, Kraljevic I, et al. Selective estrogen receptor modulators: A possible new treatment of osteoporosis in males. Med Hypotheses 2006;67:1052–3.
[51] Araujo AB, Travison TG, Leder BZ, et al. Correlations between serum testosterone, estradiol, and sex hormone-binding globulin and bone mineral density in a diverse sample of men. J Clin Endocrinol Metab 2008;93:2135–41.
[52] Paller CJ, Shiels MS, Rohrmann S, et al. Relationship of sex steroid hormones with bone mineral density (BMD) in a nationally representative sample of men. Clin Endocrinol (Oxf) 2009;70:26–34.
[53] Basaria S, Lieb J II, Tang AM, et al. Long-term effects of androgen deprivation therapy in prostate cancer patients. Clin Endocrinol (Oxf) 2002;56:779–86.
[54] Michaelson MD, Marujo RM, Smith MR. Contribution of androgen deprivation therapy to elevated osteoclast activity in men with metastatic prostate cancer. Clin Cancer Res 2004;10:2705–8.
[55] Brufsky A, Harker G, Beck T, et al. Bone-specific alkaline phosphatase (BSAP) and serum N-telopeptide (sNTX) as predictors of bone loss in postmenopausal women with early breast cancer receiving letrozole as adjuvant therapy: A 5-year study (Z-FAST). Cancer Res 2009;69(2 Suppl):[Abstract2067].
[56] Taxel P, Dowsett R, Richter L, et al. Risedronate prevents early bone loss and increased bone turnover in the first 6 months of luteinizing hormone-releasing hormone-agonist therapy for prostate cancer. BJU Int 2010. [Epub ahead of print].
[57] Greenspan SL, Nelson JB, Trump DL, et al. Skeletal health after continuation, withdrawal, or delay of alendronate in men with prostate cancer undergoing androgen-deprivation therapy. J Clin Oncol 2008;26:4426–34.
[58] Smith MR, Saad F, Egerdie B, et al. Effects of denosumab on bone mineral density in men receiving androgen deprivation therapy for prostate cancer. J Urol 2009;182:2670–5.
[59] Ton FN, Gunawardene SC, Lee H, et al. Effects of low-dose prednisone on bone metabolism. J Bone Miner Res 2005;20:464–70.
[60] Ignatoski KM, Friedman J, Escara-Wilke J, et al. Change in markers of bone metabolism with chemotherapy for advanced prostate cancer: Interleukin-6 response is a potential early indicator of response to therapy. J Interferon Cytokine Res 2009;29:105–12.
[61] Lorente JA, Valenzuela H, Morote J, et al. Serum bone alkaline phosphatase levels enhance the clinical utility of prostate specific antigen in the staging of newly diagnosed prostate cancer patients. Eur J Nucl Med 1999;26:625–32.
[62] Hegele A, Wahl HG, Varga Z, et al. Biochemical markers of bone turnover in patients with localized and metastasized prostate cancer. BJU Int 2007;99:330–4.
[63] Garnero P, Buchs N, Zekri J, et al. Markers of bone turnover for the management of patients with bone metastases from prostate cancer. Br J Cancer 2000;82:858–64.
[64] Lipton A, Chapman J, Demers L, et al. Use of elevated bone turnover to predict bone metastasis. J Clin Oncol 2008;26(Suppl):28s. Abstract 591.
[65] Seibel MJ, Naganathan V, Barton I, et al. Relationship between pretreatment bone resorption and vertebral fracture incidence in postmenopausal osteoporotic women treated with risedronate. J Bone Miner Res 2004;19:323–9.
[66] Heller W, Harzmann R, Bichler KH, et al. Urinary hydroxyproline in healthy patients and in prostate patients with and without bone metastases. Curr Probl Clin Biochem 1979;9:249–56.
[67] Berruti A, Dogliotti L, Gorzegno G, et al. Differential patterns of bone turnover in relation to bone pain and disease extent in bone in cancer patients with skeletal metastases. Clin Chem 1999;45(8 Pt 1):1240–7.
[68] Koizumi M, Takahashi S, Ogata E. Comparison of serum bone resorption markers in the diagnosis of skeletal metastasis. Anticancer Res 2003;23(5b):4095–9.
[69] Ali SM, Demers LM, Leitzel K, et al. Baseline serum NTx levels are prognostic in metastatic breast cancer patients with bone-only metastasis. Ann Oncol 2004;15:455–9.
[70] Coleman RE, Cook RJ, Saad F, et al. Meta-analysis of effects of zoledronic acid on survival in patients with metastatic bone disease and high bone turnover. Cancer Treat Rev 2008;34:S89 [Abstract P81].
[71] Erem C, Tanakol R, Alagol F, et al. Relationship of bone turnover parameters, endogenous hormones and vitamin D deficiency to hip fracture in elderly postmenopausal women. Int J Clin Pract 2002;56: 333–7.
[72] Slovik DM, Gundberg CM, Neer RM, et al. Clinical evaluation of bone turnover by serum osteocalcin measurements in a hospital setting. J Clin Endocrinol Metab 1984;59:228–30.
[73] Capeller B, Caffier H, Sutterlin MW, et al. Evaluation of tartrate-resistant acid phosphatase (TRAP) 5b as serum marker of bone metastases in human breast cancer. Anticancer Res 2003;23(2A): 1011–5.