Journal of Bone Oncology 4 (2015) 18–23

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Review Article

Use of urinary markers in cancer setting: A literature review

Leonard Chiu [a], Erin Wong [a], Carlo DeAngelis [b], Nicholas Chiu [a], Henry Lam [c], Rachel McDonald [a], Natalie Pulenzas [a], Julia Hamer [a], Nicholas Lao [a], Edward Chow [a,*]

[a] Rapid Response Radiotherapy Program, Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
[b] Department of Pharmacy, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
[c] Medical Library, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 7 October 2014
Accepted 26 January 2015
Available online 27 February 2015

Keywords:
Urinary markers
Bone metastases
Cancer
Diagnostic use
Prognostic use
Directing therapy

ABSTRACT

Introduction: In bone metastases, the disruption of normal bone processes results in increased resorption and formation rates, which can often be quantitatively measured by biomarkers in the urine and blood. The purpose of this review is to summarize relevant studies of urinary markers used as a diagnostic and/or prognostic tool, as well as its potential and advances in directing therapy.

Methods: A literature search was conducted using Ovid MEDLINE (1950 to July 2014), EMBASE (1950 to 2014 week 30) and Cochrane Central Register of Controlled Trials (3rd Quarter 2014) to identify studies that detailed the use of urinary markers in the cancer setting, specifically involving markers for bone metastases. Search terms included "urinary markers", "cancer", and "bone metastases".

Results: A total of 35 articles, with 24 original studies, were identified. In general, urinary markers can be used to detect early signs of bone metastases prior to skeletal imaging, but still must be used in conjunction with imaging to avoid false positive results. The use of urinary markers, such as N-telopeptide, as a prognostic tool remains controversial, but can provide information on the relative risk of skeletal related events (SREs), disease progression, as well as death. Finally, while urinary markers have shown to be potentially useful in confirming the efficacy of bone metastases treatments, exploring the appropriate dosages for treatment, and directing therapy, it is still unclear to what extent urinary markers should be reduced by.

Conclusion: The potential use of urinary markers in the management of bone metastases is promising as it can allow for earlier and more convenient detection of bone metastases in comparison to other techniques. However, additional studies involving prospective clinical trials are suggested to further examine the potential of urinary markers in developing appropriate treatment strategies and endpoints, especially in developing a clearer protocol on the extent urinary markers should be reduced by to correlate with achievement of clinical benefit.

1. Introduction

Bone metastases are a common complication in advanced cancer patients. The incidence of bone metastases at postmortem examination is 73% for patients with primary breast cancer and 68% for patients with primary prostate cancer [1]. In bone metastases, what typically is a tightly regulated process of bone resorption and formation, is disrupted by the interaction of tumor cells with osteoclasts and osteoblasts in the bone [2]. The disruption of normal bone processes by the disease usually results in increased resorption and formation rates, which can often be quantitatively measured by biomarkers in the urine and blood of patients.

The focus of this review is on urinary markers. As the process of urination is a natural body process, obtaining urinary markers is certainly a very convenient procedure. Examples of urinary markers include: calcium, hydroxyproline, N-terminal cross-linked telopeptide of Type I collagen (NTX), and C-terminal cross-linked telopeptide of Type I collagen (CTX), pyridinoline crosslinks (PYD), and deoxypyridinoline crosslinks (DPD).

Despite the convenience of urinary markers, their capabilities should not be underestimated. Urinary markers are still in need of further validation to enter routine clinical practice; however they are becoming increasingly important in the management of bone metastases. Changes in bone are often too slow for detection by imaging; therefore urinary markers can provide an alternative

* Correspondence to: Department of Radiation Oncology, Odette Cancer Centre Sunnybrook Health Sciences Centre, 2075 Bayview Avenue Toronto, ON Canada M4N 3M5. #Tel.: +1 416 480 4998; fax: +1 416 480 6002.
E-mail address: Edward.Chow@sunnybrook.ca (E. Chow).

http://dx.doi.org/10.1016/j.jbo.2015.01.002

method to evaluate changes in disease status, even before such changes become clinically evident. Thus, urinary markers could potentially serve as a convenient and important diagnostic tool [3].

Many studies over the past 20 years have shown the potential of urinary markers in the detection of the presence of bone metastases [3–11], the use of urinary markers for its prognostic value in bone disease [2,4,12–20], as well as directing therapy for bone metastases patients [2,6,12–18,21–25]. The purpose of this review is to summarize relevant studies reporting the potential and advances in using urinary markers in the management of bone metastases.

2. Methods

A literature search was conducted using Ovid MEDLINE (1950 to July 2014), EMBASE (1950 to 2014 week 30) and Cochrane Central Register of Controlled Trials (3rd Quarter 2014) to identify studies that detailed the use of urinary markers in the cancer setting, specifically involving markers for bone metastases. Search terms included "urinary markers," "cancer," and "bone metastases." Articles written in languages other than English were omitted from consideration.

3. Results

We identified a total of 34 articles, with 23 original studies, that detailed the use of urinary markers as a diagnostic tool, prognostic tool, or in directing therapy for patients with bone metastases. The results of the 23 original studies are summarized in Table 1. The criterion for inclusion was strictly for studies that examined urinary markers; as such, there are many more studies in the literature not included that examines other bone markers exclusively. Studies that included both urinary markers and other bone markers were not omitted.

3.1. Diagnostic use of urinary markers

The diagnostic potential of urinary markers in bone metastases is documented by seven studies in our search, indicating a relationship between increasing levels of urinary markers and the presence of metastatic bone disease [3–11]. Most commonly, the increase of urinary pyridinoline (PYD) and deoxypyridinoline (DPD) were seen as a possible indicator for bone metastases [4–7,10,11].

In a study by Ikeda et al., patients with new or recurrent prostate cancer with bone metastases were determined to have a higher urinary excretion of urinary pyridinoline (PYD) and deoxypyridinoline (DPD) than patients with benign prostatic hypertrophy (BPH), or with prostate cancer and no bone metastases [5]. The authors concluded that PYD and DPD appeared to be a useful marker for evaluating the activity of bone metastases [5].

Another study by Vinholes et al. confirmed the specificity of PYP and DPD as bone resorption markers in patients with bone metastases [6]. The study found that pyridinoline and deoxypyridinoline levels were increased in 70% of bone metastases patients when compared to healthy reference controls, while urinary calcium, previously thought to be a suitable indicator of bone metastases in early studies [26,27], was increased in only 40% of patients [6].

Cross-linked C-telopeptide collagen (CTX) and cross-linked N-telopeptide collagen (NTX) have also been used as urinary markers with the potential of identifying the presence of bone metastases [8,9,12,14–16,18]. In the study by Garnero et al., 39 patients with prostate cancer and bone metastases had CTX levels greater than 149% of healthy control levels [15]. Moreover, there was no increase in urinary markers for prostate cancer patients without bone metastases, further highlighting the possibility of CTX as a bone metastases identifier [15]. Many studies in which urinary NTX levels were used as a marker for bone metastases have been reported [14,15,25]. In fact, in a study by Demers et al., NTX measurement had the most significant association with the probability of bone metastases of all other urinary markers, with urinary DPD the second most predictive marker [4]. The significance of NTX levels over other markers was also determined in a study by Lipton et al. [22].

However, while urinary markers show much promise in being diagnostic tools for patients with bone metastases, urinary markers are currently not absolutely necessary nor sufficient for the diagnoses of the disease. Urinary markers can detect early signs of bone metastases before skeletal imaging, but imaging is still necessary to diagnose bone metastases with certainty. Elevated urinary markers may be present even in those without malignant diseases, which explain why they are always used in conjunction with imaging to avoid false positive results.

3.2. Prognostic use of urinary markers

The use of urinary markers as a prognostic tool has also been explored in many studies in the literature [2,4,12–20]. While other bone markers such as serum bone alkaline phosphatase (BAP) [2], serum BSP [28], serum PINP [29], and serum ICTP [30] have proved useful in the prognostic setting, NTX has been shown to be the most consistent urinary marker for prognostic use [2,30,31].

For example, Brown et al. monitored 238 patients with bone metastases secondary to prostate cancer, non-small cell lung cancer (NSCLC), and other solid tumors. Patients with high urinary NTX levels had an increased relative risk (RR) of SREs, disease progression, and death compared with patients with low NTX levels. The authors concluded that baseline NTX levels were most predictive of negative clinical outcomes [12].

An exploratory cohort analysis by Coleman et al. also found similar predictive potential in NTX [2]. Urinary measurements of NTX and serum bone alkaline phosphatase (BAP) were obtained from 1824 bisphosphonate-treated patients. Patients were grouped into categories of low (<50 nmol/mmolcreatine), moderate (50–99 nmol/mmolcreatine), or high (>100 nmol/mmolcreatine) NTX levels. Risk of skeletal complications and disease progression increased by 2-fold in patients with high and moderate NTX levels compared with patients with low NTX levels. Compared with patients with low NTX levels, risk of death on study increased 4- to 6-fold with high NTX levels, and 2- to 4- fold in patients with moderate levels [2].

Despite many studies supporting the prognostic capability of urinary markers, there have been a few studies that have not confirmed these findings [19,20]. Specifically, Petriolo et al. found that bone markers were not prognostic of survival in patients with hormone-resistant prostate cancer and bone metastases treated with chemotherapy [19], while Seibel et al. concluded in their study that bone markers could not predict bone metastases in breast cancer patients [20]. Siebel later explained that the contradiction of conventional results were possibly due to the long-term variability of markers of bone turnover in patients with breast cancer [32]. In addition to the risk of attaining false positive results [33], the variability of markers is another limitation that has prevented urinary markers from being routinely used in clinical practice for prognostic value. It also reveals the inconsistency in results that may arise from similar studies with different patient cohorts. This heterogeneity should be more clearly distinguished between studies, and future research should focus on developing endpoints that are specific to certain patient cohorts. Nevertheless,