Urinary \textit{N}-telopeptide (uNTx) is an independent prognostic factor for overall survival in patients with bone metastases from castration-resistant prostate cancer

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\textbf{Background:} In patients with bone metastases from castration-resistant prostate cancer (CRPC) not pretreated with a bisphosphonate elevated \textit{N}-telopeptide of type I collagen (uNTx), a marker of bone resorption, predicts skeletal-related events (SRE). The aim of this study was to assess the prognostic value of uNTx for overall survival (OS) and the incidence of SRE in patients with bone metastases from CRPC receiving zoledronic acid.

\textbf{Methods:} From 2004 to 2007, 94 patients with bone metastases from CRPC receiving zoledronic acid for at least 2 months were screened for uNTx.

\textbf{Results:} Median age was 66 years (range 46–88). Median serum prostate-specific antigen (PSA) was 66 ng/ml (0–3984) and median uNTx was 19 nmol/mM creatinine (3–489). During follow-up, 38 patients (40%) experienced an SRE. Median OS was 20 months [95% (CI) confidence interval 15–24]. In the multivariate analysis, elevated uNTx [hazard ratio (HR) 2.2 (95% CI 1.2–4.0)], serum PSA [HR 2.8 (95% CI 1.6–5.1)], and ECOG performance status were the only independent prognostic factors for OS. Median OS was 12 months (10–16) and 25 months (21–34) in patients with uNTx ≥20 nmol/mM creatinine and in those with uNTx <20 nmol/mM creatinine, respectively.

\textbf{Conclusion:} An elevated uNTx level is an independent prognostic factor for OS in patients with bone metastases from CRPC receiving a bisphosphonate.

\textbf{Key words:} bone metastasis, prostate cancer, uNTx, zoledronic acid

\textbf{Introduction}

Prostate cancer is the most common cancer and the second leading cause of death from cancer in males in most Western countries [1]. Although advanced prostate cancer is initially sensitive to androgen deprivation therapy, the disease eventually progresses to the castration-resistant status (CRPC) [2]. Most deaths related to CRPC are caused by haematogenous metastatic dissemination and subsequent tumour cell growth in distant organs, especially the skeleton, which is the site of metastases in >80% of cases [3,4].

The current standard treatment of patients with disseminated prostate cancer includes androgen deprivation therapy and other hormonal manipulations, docetaxel-based chemotherapy, and zoledronic acid [5–7]. Overall survival (OS) of patients with bone metastases from CRPC is limited, however, with median survival rates of ~19 months in recent large phase III randomised trials and only 13 [8] months in symptomatic patients. Bone metastases alter bone homeostasis resulting in reduced bone integrity and, consequently, increased skeletal complications [9]. These lesions are associated with high morbidity: pain can have devastating effects on quality of life and reduce autonomy. Skeletal-related events (SRE) are defined as any of the following events: pathologic bone fracture, bone surgery, radiotherapy delivered to the bone, and spinal cord compression [10].

Although mostly osteoblastic (bone building) radiologically, bone metastases from prostate cancer essentially exhibit both osteolytic and osteoblastic [11] features at the pathological and molecular levels as a result of increased overall bone remodelling [12]. This consists in modifications in the equilibrium between osteoblast-mediated bone formation and osteoclast-mediated resorption involved in the formation and maintenance of normal bone tissue. In human, a variety of biochemical markers of bone metabolism can provide information on tumour and bone interactions [13].
of serum alkaline phosphatase activity and of other bone formation markers can be detected in patients with bone metastases from prostate cancer [10]. On the other hand, elevation of bone resorption markers can be detected in serum and in urine, and their levels in patients with bone metastases from prostate cancer are usually higher when compared with those of patients with bone metastases from other primaries and even those with osteolytic features [14]. For example, baseline uNTx, a well-recognised marker of bone resorption, was found to predict a poor outcome in a variety of patients with bone metastases [14,15]. In contrast, a decrease in bone markers while on zoledronic acid correlates with improved survival in patients with bone metastases from breast, prostate, and lung cancers [16]. An important achievement during recent years has been the demonstration that zoledronic acid reduces the incidence of SRE in patients with bone metastases from CRPC [6] and this drug has become a standard treatment option in this setting.

However, SRE can occur on a population of bisphosphonate-treated patients despite attempts of bone resorption control. The primary objective of this study was to assess the association between elevated uNTx and clinical outcome (SRE and OS) in patients with bone metastases from CRPC receiving zoledronic acid.

patients and methods

patients

From 2004 to 2007, 94 patients with CRPC and bone metastases treated with zoledronic acid (Zometa®; Novartis Pharma AG, Basel, Switzerland; 4 mg in a 15-min infusion) at the Institut Gustave Roussy entered a prospective phase II study (AMG 162 114), which randomly assessed denosumab or zoledronic acid. Those with an uNTx >50 nmol/mM creatinine were kept on zoledronic acid. Those with an uNTx level >50 nmol/mM creatinine participated in a randomised phase II study (AMG 162 114), which randomly assessed denosumab or zoledronic acid. The patients who were randomly allocated to denosumab arm are not excluded from this study.

inclusion criteria

Inclusion criteria included prostate cancer with histological confirmation and radiographic evidence of one or multiple bone metastases, in evolution with hormonal therapy or chemotherapy, a serum testosterone level within the castrate range (<0.50 ng/ml), at least two previous injections of zoledronic acid, the last dose being given within 4 weeks before inclusion, no liver or kidney dysfunction, and a performance status (PS) of 0–2. Exclusion criteria included more than two prior SRE, a prior history of osteonecrosis of the jaw, invasive dental surgery planned during the study, radiation therapy for bone within 2 weeks, treatment with bone-targeted radioisotopes within 8 weeks, Paget’s disease, current unstable hypo- or hyperthyroidism, and a pathologic fracture during follow-up. Patients who had received zoledronic acid, the last dose being given within 4 weeks before inclusion, were excluded from this study.

uNTx assessment

Assessment of uNTx levels was centrally carried out using the method described previously [17]. Urine was obtained as a morning second-void sample, and uNTx levels were normalised according to urinary creatinine levels (nmol uNTx/nmol/l uCreatinine). Patients with an uNTx level <50 nmol/mM creatinine were kept on zoledronic acid. Those with an uNTx level >50 nmol/mM creatinine were kept on zoledronic acid. Those with an uNTx level >50 nmol/mM creatinine participated in a randomised phase II study (AMG 162 114), which randomly assessed denosumab or zoledronic acid. The patients who were randomly allocated to denosumab arm are not excluded from this study.

statistical analysis

The following variables were collected at the inclusion: PS, age, previous history of SRE, number of zoledronic acid injections, serum prostate-specific antigen (PSA), haemoglobin, alkaline phosphatase, Gleason score, and uNTx.

uNTx was characterised as normal (<20 nmol/mM creatinine) or elevated (>220 nmol/mM creatinine), the cut-off being based on the observed median value in this study.

SRE were defined as any of the following events: pathologic bone fracture, spinal cord compression, bone surgery, and radiotherapy delivered to the bone. The time to SRE was defined as the time from the date of inclusion to the first SRE. Patients who died without an SRE were censored.

OS was defined as the time between the date of inclusion and the date of death.

The association between patient characteristics and the time to SRE or survival was evaluated using the log-rank test. A multivariate analysis including the significant variables in the univariate analysis was carried out using the Cox model. All reported P values are two sided. Differences were considered statistically significant when P <0.05. OS and the incidence of SRE were determined using the Kaplan–Meier method. Statistical analyses were carried out using SAS software (Release 9.1; SAS Institute, Cary, NC).

results

patient characteristics at baseline

Patient characteristics are summarised in Table 1 and correspond to a typical population of patients with bone metastases from CRPC. Of 94 patients, 36 (38%) had previously experienced at least one SRE before inclusion. The median uNTx level was 19 nmol/mM creatinine (range 3–489). The median number of prior zoledronic acid injections was 6 (range 1–37). Sixty-eight patients (67%) received chemotherapy before inclusion.

prognostic factors for survival

After a median follow-up of 30 months [95% confidence interval (CI) 0–34], 60 deaths were observed. Median OS was 20 months (95% CI 15–24). In the univariate analysis, the factors associated with a favourable survival included uNTx <20 nmol/ml creatinine, a good PS (grade 0 or 1), serum PSA <70 ng/ml, haemoglobin >12 g/dl, and a normal alkaline phosphatase level (Table 2). Median OS was 12 months (95% CI 10–16) and 25 months (95% CI 21–34) in patients with uNTx <20 nmol/mM creatinine and in those with uNTx >20 nmol/mM creatinine, respectively (Figure 1).

Parameters associated with survival in the univariate analysis, excepted haemoglobin and alkaline phosphatase, were tested in a multivariate analysis using the Cox model. Only elevated uNTx [hazard ratio (HR) 2.2 95% CI 1.2–4.0], serum PSA [HR 2.8 (95% CI 1.6–5.1)], and PS were independent prognostic factors for OS (Table 3).

SRE during the study

During follow-up, 38 patients experienced an SRE, including pain requiring radiotherapy delivered to the bone (n = 32), spinal cord compression (n = 22), and a pathologic fracture (n = 4) (Table 4).

The median time to the first SRE was 29 months (95% CI 14–7). In the univariate analysis, there was no association...
between the uNTx level and SRE in this population of patients with CRPC already receiving zoledronic acid. Moreover, there was no association between the uNTx level and other variables (Table 5).

discussion

The unique tendency of prostate cancer to metastasise to the bone makes bone markers potential candidate prognostic factors in patients with CRPC. In this study, the uNTx level was found to be independently associated with OS. Median survival rates have been reduced by half (25 versus 12 months) in patients with elevated levels while on zoledronic acid. In contrast, uNTx was not associated to SRE in this population, perhaps because the time to death was short, thus eliminating the risk for SRE. It is important to notice that all patients were not treated by zoledronic acid after inclusion and some of them received denosumab.

Haemoglobin and alkaline phosphatase are not included in the multivariate analysis because of lack of information for 29 patients (30% of patients included in the study).

Bisphosphonates are potent inhibitors of osteoclastic bone resorption [18] that have been widely studied for the prevention of bone-related morbidity in CRPC patients. Large phase III randomised trials conducted in the 1990s established bisphosphonates as part of the standard treatment of patients with bone metastases from breast cancer, multiple myeloma, and other solid tumours [19]. Zoledronic acid was the only bisphophonate capable of demonstrating a reduction in the incidence of SRE in a randomised trial in patients with CRPC [20], while other bisphosphonates failed to achieve this result.
Based on this result, zoledronic acid has been approved for the treatment of patients with bone metastases from CRPC in most Western countries.

**Figure 1.** Overall survival.

**Table 3.** Multivariate analysis of OS

<table>
<thead>
<tr>
<th>Multivariate analysis</th>
<th>1-Year OS</th>
<th>N</th>
<th>HR (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>68%</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>uNTx (nmol/mmol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>85%</td>
<td>50</td>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>20</td>
<td>48%</td>
<td>42</td>
<td>2.2 (1.2–4.0)</td>
<td></td>
</tr>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>86%</td>
<td>30</td>
<td>1</td>
<td>0.03</td>
</tr>
<tr>
<td>1</td>
<td>67%</td>
<td>53</td>
<td>1.06 (0.6–2.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22%</td>
<td>9</td>
<td>3.12 (1.2–8.2)</td>
<td></td>
</tr>
<tr>
<td>Serum prostate-specific antigen (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70</td>
<td>82%</td>
<td>48</td>
<td>1</td>
<td>0.0005</td>
</tr>
<tr>
<td>≥70</td>
<td>52%</td>
<td>44</td>
<td>2.83 (1.6–5.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Cox model.

CI, confidence interval; HR, hazard ratio; OS, overall survival. Bold in the first column is the % of patients alive after 1 year (1-year OS), in the second column is the number of patients (N), and in column three is the Hazard ratio with 1 as the group for comparison, and the fourth column is the results of the multivariate analysis using a Cox Model. All reported P values are two sided. Differences were considered statistically significant when P < 0.05.

**Table 4.** SRE description

<table>
<thead>
<tr>
<th>SRE (n = 38)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of SRE, n (%)</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>17 (45)</td>
</tr>
<tr>
<td>2</td>
<td>11 (29)</td>
</tr>
<tr>
<td>3</td>
<td>7 (18)</td>
</tr>
<tr>
<td>4</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Spinal cord compression, n (%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16 (42)</td>
</tr>
<tr>
<td>Yes</td>
<td>22 (58)</td>
</tr>
<tr>
<td>Pathologic fracture, n (%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>34 (89)</td>
</tr>
<tr>
<td>Yes</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Antalgic radiotherapy, n (%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Yes</td>
<td>32 (84)</td>
</tr>
</tbody>
</table>

SRE, skeletal-related events.

[21,22]. Based on this result, zoledronic acid has been approved for the treatment of patients with bone metastases from CRPC in most Western countries.
In recent years, the measurement of biochemical markers of bone metabolism has become more common in trials of patients with bone metastases [23]. In a large study pooling the results of two multicentre randomised phase III clinical trials assessing zoledronic acid versus a placebo in patients with bone metastases from lung, breast, and prostate cancer, baseline uNTx levels were predictive of both SRE and survival [14,15], which reflects the key role of osteolysis in skeletal complications and outcome. In our study, uNTx levels measured during the course of zoledronic acid in patients with bone metastases from CRPC were not associated with an increased risk for SRE. The main potential explanations for this apparent discrepancy include a reduced overall incidence of SRE in these patients probably related to the systematic use of zoledronic acid, a competitive event with death in patients with elevated uNTx levels, and the lack of power of the study to identify a small difference. In contrast, elevated uNTx is an independent prognostic factor of poor survival in patients with bone metastases from CRPC. However, patients with high uNTx level have a higher serum PSA and more of them received chemotherapy before inclusion. It indicates that this group had perhaps at first sight a poor prognostic. Similar results were previously shown in patients with breast cancer and bone metastases where elevated uNTx was predictive of disease extent [24], progression-free survival, and OS [16]. A number of prognostic analyses have been conducted in patients with CRPC [25–28], although there is currently no universally recognised prognostic index in these patients. Although CRPC is mostly a bone disease, only a few prognostic studies have integrated parameters related to the bone (e.g. alkaline phosphatase or the number of bone metastases, as assessed by bone scan) in their models and none assessed parameters related to osteolysis, although high bone resorption was shown to be typical of these lesions at the pathological and molecular levels, in contrast to their classic mixed or osteoblastic phenotype on imaging [15].

The development of bone metastases from prostate cancer is the result of a complex interaction between prostate cancer cells, osteoclasts, and osteoblasts, resulting in a ‘vicious cycle’ [5,29]. Besides bisphosphonates, the main and currently most advanced attempts to target cancer cell activation of osteoclasts include denosumab, a monoclonal antibody directed at receptor activator for nuclear factor kB ligand which was shown to reduce uNTx levels significantly better than zoledronic acid in patients with bone metastases and elevated levels while on the IV bisphosphonate [17], and dasatinib, a src inhibitor, which was also demonstrated to result in decreased uNTx levels in patients with bone metastases [30]. These two agents are currently being assessed in phase III studies. Although no drug directly interfering with osteoblasts is routinely used in oncology, drugs targeting the endothelin-1 A receptor are currently being investigated. For example, ZD4054 showed promising activity in a large randomised phase II trial [31,32]. Finally, phase II clinical data indicate a possible use of a bone-targeting strategy combining chemotherapy and radiopharmaceuticals like samarium-153 [33] or strontium-89 [34].

This study indicates the importance of bone resorption markers like uNTx as an independent prognostic factor of OS in patients with CRPC. In contrast, the association with SRE was not found in this study. These results require validation in prospective studies.

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**disclosure**

None of the authors declare conflicts of interest.
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references


