Bone Turnover Markers as Predictors of Skeletal Complications in Prostate Cancer, Lung Cancer, and Other Solid Tumors

Janet E. Brown, Richard J. Cook, Pierre Major, Allan Lipton, Fred Saad, Matthew Smith, Ker-Ai Lee, Ming Zheng, Yong-Jiang Hei, Robert E. Coleman

Background: Whether bone markers have prognostic value in patients with bone metastases is unknown. We investigated this question in patients with bone metastases secondary to prostate cancer and to non–small-cell lung cancer (NSCLC) and other solid tumors assigned to the placebo arms of two phase III trials of zoledronic acid. Methods: Levels of the urinary bone resorption marker N-telopeptide and the serum bone formation marker bone-specific alkaline phosphatase were assessed every 3 months for patients with prostate cancer (n = 203) or NSCLC or other solid tumors (n = 238) and were categorized as low or high. Patients were monitored for skeletal-related events, bone disease progression, and death. The relative risks (RRs) and 95% confidence intervals (CIs) for these outcomes were estimated for patients with high versus low levels of each marker using intensity-based multiple event and Cox regression models. All statistical tests were two-sided. Results: In each disease group and overall, high levels of each marker at the beginning of the study were statistically significantly associated with an increased risk of negative outcomes. Use of recent marker assessments as time-dependent covariates gave even greater prognostic significance. High N-telopeptide levels were a stronger prognostic indicator of negative outcomes than bone-specific alkaline phosphatase levels. In recent assessments, patients with high N-telopeptide levels had an increased relative risk of skeletal-related events (prostate cancer, RR = 3.25, 95% CI = 2.26 to 4.68, P < .001; NSCLC and other solid tumors, RR = 1.79, 95% CI = 1.15 to 2.79, P = .010), disease progression (prostate cancer, RR = 2.02, 95% CI = 1.48 to 2.74, P < .001; NSCLC and other solid tumors, RR = 1.91, 95% CI = 1.16 to 3.15, P = .011), and death (prostate cancer, RR = 4.59, 95% CI = 2.82 to 7.46, P < .001; NSCLC and other solid tumors, RR = 2.67, 95% CI = 1.85 to 3.85, P < .001) compared with patients with low N-telopeptide levels. Conclusions: Baseline and recent bone marker levels were predictive of negative clinical outcomes in patients with bone metastases secondary to prostate cancer and to NSCLC and other solid tumors. N-telopeptide levels were more consistent prognostic indicators than bone-specific alkaline phosphatase for all tumor types, reflecting the key role of osteolysis in the development of skeletal complications. [J Natl Cancer Inst 2005;97:59–69]

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See “Notes” following “References.”

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The skeleton is the most common site of tumor metastasis, and skeletal complications from bone metastases present a major challenge in disease management (1). Such complications, referred to as skeletal-related events, include pathologic fractures, spinal cord compression, hypercalcemia, and severe bone pain. Each of these complications may substantially reduce quality of life and, in some cases, hasten death (1–3). Bone is the most frequent, typically the first, and often the only site of metastasis in patients with advanced prostate cancer (4), and the median survival after the diagnosis of bone metastases ranges from 12 to 53 months (5). Bone is also a relatively frequent site for symptomatic metastases in patients with other solid tumors, including lung, thyroid, renal, and bladder cancers (1). Furthermore, these patients, of whom up to 40% will present with bone metastases at cancer diagnosis, have an ongoing risk of skeletal morbidity and often experience severe bone pain (1).

Metastatic bone disease perturbs the tightly coordinated processes of coupled and balanced osteoclast-mediated bone resorption and osteoblast-mediated bone formation that are involved in repair and maintenance of normal bone tissue (6). The result is often increased but unbalanced bone turnover that leads to a loss of structural integrity and consequent skeletal complications (7). Substantial evidence has shown that bisphosphonates can reduce skeletal complications from malignant bone disease, and bisphosphonates are now recommended as standard therapy in breast cancer and multiple myeloma (7–10).

Biochemical markers of bone metabolism, which reflect both the formation and resorption of bone (11), can provide valuable insight into tumor and bone interactions and the effects of therapy on this dynamic process. Metastatic bone disease is typically associated with a marked increase in bone resorption. Clinical studies (mainly in breast cancer and myeloma) suggest that bone resorption markers, particularly the N-telopeptide of type I collagen, is associated with the presence and extent of metastases (12,13), prognosis (11,14,15), and response to treatment (11,13–19). Other markers of bone resorption include pyridinoline–cross-linked peptides and deoxypyridinoline–cross-linked peptides. Bone formation markers, mainly bone-specific alkaline phosphatase and osteocalcin, have also been investigated (18,20), but their association with clinical characteristics appears to vary depending on the tumor type, the nature of bone metastases, and the effects of treatment.

Despite the frequency of skeletal complications from metastatic bone disease, only a few studies have investigated the relationship between bone marker levels and the development of skeletal complications. Lipton et al. (19) reported that normalization of bone markers was associated with a reduction in fractures in breast cancer patients treated with the bisphosphonate pamidronate (n = 21), although this relationship was not statistically significant. Additionally, pamidronate-treated patients whose N-telopeptide levels failed to reach normal levels had a statistically significantly higher incidence of bone disease progression (P = .03). A recent study of bisphosphonate ibandronate in patients with multiple myeloma also demonstrated that patients with low levels of bone resorption and formation markers experienced fewer skeletal complications (21). Brown et al. (22) recently reported a statistically significant correlation between N-telopeptide levels and a range of skeletal complications in 121 bisphosphonate-treated patients with breast or prostate cancer. However, detailed and larger studies of the predictive role of biochemical markers of bone metabolism for skeletal complications have not been reported in patients with prostate cancer or in patients with solid tumors other than those of the breast.

Recently, results from two large international randomized placebo-controlled phase III trials on the treatment of metastatic bone disease with zoledronic acid (Zometa; Novartis Pharma AG, Basel, Switzerland/Novartis Pharmaceuticals Corporation, East Hanover, NJ) have been reported (23–26). One trial enrolled prostate cancer patients with bone metastases (23) and showed a 41% reduction in the risk of skeletal morbidity, a sustained beneficial effect on bone pain, and a reduction in bone marker levels among patients who received zoledronic acid. The second trial enrolled patients with bone metastases secondary to lung cancer (non–small-cell lung cancer [NSCLC]) or other solid tumors (excluding breast or prostate cancer) (24–26) and found that the median time to the first skeletal complication was statistically significantly prolonged and the total risk of skeletal morbidity was reduced by 31% among patients who received zoledronic acid compared with patients who received placebo. These trials provided the first objective evidence of the clinically significant benefits of bisphosphonate therapy in such patients and led to the regulatory approval of zoledronic acid (4 mg via a 15-minute infusion every 3 to 4 weeks) as an important component of care for patients with bone metastases.

These clinical trials (23–26) provide extensive laboratory and clinical databases for correlative studies to determine whether biochemical markers of bone metabolism are associated with the risk of skeletal complications, progression in bone disease, and death in patients with bone metastases. Herein, we present the results of such analyses using data from the placebo arms of the NSCLC and other solid tumor trial (Protocol 011) (24–26) and the prostate cancer trial (Protocol 039) (23).

Patients and Methods

Patients and Study Design

In this exploratory cohort study, data were analyzed from the placebo arms of the double-blind placebo-controlled international phase III zoledronic acid trials in patients with bone metastases from NSCLC and other solid tumors (Protocol 011) (25) and from prostate cancer (Protocol 039) (23). Patients participating in each trial gave written informed consent. These trials were approved by the research ethics committees of the participating institutions.

Protocol 011 enrolled 773 bisphosphonate-naive patients (aged 18 years or older) with radiologic evidence of bone metastases who were receiving appropriate antineoplastic therapy. Patient enrollment and study treatment took place from August 1998 through January 2001. Our current analyses were performed using available bone marker data collected over a period of 21 months from the 238 patients in the placebo arm. These patients were stratified according to primary tumor type (NSCLC [n = 115] or other solid tumor [n = 123]). Other eligibility requirements in protocol 011 included Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 and serum creatinine level of ≤3.0 mg/dL (265 μmol/L).
Protocol 039 enrolled a total of 643 bisphosphonate-naïve patients (aged 18 years or older) with biochemical disease progression while receiving hormonal therapy and objective past or present evidence of bone metastases. Patient enrollment and study treatment took place from June 1998 through January 2001. Other eligibility requirements in the protocol included ECOG performance status of ≤2, serum testosterone level of <50 ng/dL, corrected serum calcium level of ≥8.0 mg/dL, and serum creatinine level of ≤3 mg/dL. Exclusion criteria included prior treatment with cytotoxic chemotherapy (other than estramustine), radiation therapy within 3 months of study entry, a requirement for strong narcotic therapy for bone pain, or severe cardiovascular disease. The current analyses were performed using bone marker measurements that were available over a period of 24 months from 203 patients in the placebo arm.

**Patient Evaluation**

A skeletal-related event was defined as a pathologic bone fracture (vertebral or nonvertebral), spinal cord compression, surgery to bone, and radiotherapy to bone. Hypercalcemia of malignancy was not included as a skeletal-related event in these analyses. In addition, a change in antineoplastic therapy to palliate bone pain was included in analyses of prostate cancer patients. For patients in the prostate cancer group, a radionuclide bone scan was performed at baseline, 6 months, 15 months, and 24 months and a bone survey was carried out every 3 months. For patients in the NSCLC and other solid tumor group, a radionuclide bone scan and a bone survey were performed at baseline and then every 3 months and were analyzed at a central radiologic facility (WorldCare, Cambridge, MA) by individuals who were blinded to treatment to minimize bias and maximize evaluation consistency. Disease progression was defined as the appearance of any new bone lesion or the progression of existing bone metastases, as determined by assessment of radiographs. In the present analyses, only deaths occurring on-study were considered.

**Bone Marker Assessment**

For the study of patients with NSCLC and other solid tumors, N-telopeptide and bone-specific alkaline phosphatase assessments were performed at one central laboratory (Mayo Medical Laboratories, Mayo Clinic, Rochester, MN). For the study of patients with prostate cancer, assessments of N-telopeptide and bone-specific alkaline phosphatase were performed in five laboratories, depending on the location of the patients (Mayo Medical Laboratories, Rochester, MN; Bio Analytical Research Corporation, Ghent, Belgium; Laboratorio Bioquimica Medica, Buenos Aires, Argentina; Fleury Laboratories, Sao Paulo, Brazil; and Bio-Imaging Technologies, Newtown, PA).

N-telopeptide was assessed from second voided morning urine samples using the Vitro ECI Immunodiagnostic System competitive assay (Johnson & Johnson Ortho-Clinical Diagnostics, Raritan, NJ) (27). Urinary marker levels were normalized relative to urinary creatinine levels, and samples were required to contain ≥5 mg/dL creatinine to ensure validity of the sample. The coefficient of variation in the creatinine measurements was 4.8% to 12.4%. Normal ranges were based on a sampling of more than 100 adults without any evidence of cancer. Serum bone-specific alkaline phosphatase levels were assessed using a chemical inhibition and differential inactivation assay (28). Samples were rejected from the analysis if there was evidence of hemolysis. The coefficient of variation was 5.1% to 9.8%.

**Statistical Methods**

Levels of urinary N-telopeptide were characterized as low (<100 nmol/mmol creatinine) or high (≥100 nmol/mmol creatinine), with the cut-offs corresponding to approximately the upper limit of normal in postmenopausal women and in men receiving androgen deprivation therapy (29). However, the normal range for urinary N-telopeptide varies according to age, sex, and endocrine function, with the upper limit of normal for healthy young adults being approximately 50 nmol/mmol creatinine, and analyses were also performed using this cut-off level. The level of bone-specific alkaline phosphatase was characterized as low (<146 IU/L) or high (≥146 IU/L), with the cut-off value selected on the basis of available data for the normal range of bone-specific alkaline phosphatase.

Cumulative incidence plots were generated to estimate the proportion of patients with at least one skeletal-related event over time for each baseline marker category (low or high N-telopeptide and low or high bone-specific alkaline phosphatase levels) (30–32), and corresponding Kaplan–Meier estimates were computed for the time to death (33). Cox regression models were used to assess the association between bone marker levels and the time to the first skeletal-related event, progression of bone disease, and death (30–32). Martingale residual plots were examined to check the plausibility of the assumptions underlying the proportional hazards and multiplicative intensity models (34). Intensity-based multiple event regression models were also applied to assess the predictive significance of marker levels for skeletal-related events because these events may occur repeatedly over time (30).

For each outcome (all skeletal-related events, first skeletal-related event, detection of disease progression, and death), univariate regression models were applied using baseline marker values (low or high N-telopeptide and low or high bone-specific alkaline phosphatase levels). The predictive significance of the most recent (on-study) marker assessments was also assessed by univariate analyses using the marker level group (high/low) as a time-varying covariate. Marker assessments were scheduled at baseline, at 1 month, and every 3 months thereafter. However, to minimize the impact of missed assessments, values were carried forward for up to 6 months. After a 6-month period with no marker assessment, patients were no longer included in the risk set until they received a subsequent marker assessment, at which time they reentered the risk set. Recent marker measurements were available only for patients who had survived to the time of the assessment. Two-sided statistical analyses were performed, and results were considered statistically significant if \( P \leq .05 \). All statistical analyses were carried out using S-plus Version 6.0 (Insightful Corporation, Seattle, WA) on a Sun (Ultra 10) workstation.

**RESULTS**

**Baseline Characteristics**

The baseline demographics of patients in the current analysis are presented in Table 1. Overall, data were available for a total of 441 patients who received placebo from both randomized trials, with a total of 189.1 patient-years at risk. There were 359
and 438 patients with N-telopeptide and bone-specific alkaline phosphatase assessments, respectively.

Prostate cancer patients for whom at least one marker assessment was available (n = 203) had a median age of 73 years (range = 37–90 years) and a median prostate-specific antigen level of 61 ng/mL. The majority of the patients (91%) had an ECOG status of 0 or 1, and 37% had experienced a skeletal-related event before study entry. Levels of N-telopeptide were evaluated for 200 patients, and levels of bone-specific alkaline phosphatase were evaluated for 202 patients. The total at-risk observation period was 117.7 patient-years. Baseline N-telopeptide levels were low for 106 (53%) patients and high for 94 (47%) patients. Baseline bone-specific alkaline phosphatase levels were low for 46 (22.8%) patients and high for 156 (77.2%) patients.

In the NSCLC and other solid tumor group, the study population (n = 238) included more men than women, but the distribution was well matched and median age was similar (Table 1). Patients with NSCLC accounted for approximately 48% of the study population, which also included patients with small-cell lung cancer (8%), renal cell carcinoma (8%), head and neck cancer (2%), thyroid cancer (1%), cancer of unknown primary type (7%), and other solid tumors (26%). The median time since diagnosis of bone metastases to study entry was less than 2 months and was consistent between groups. Most patients had an ECOG performance status of 0 or 1, and 73% had already experienced a skeletal-related event before study entry. The total at-risk observation period was 71.4 patient-years. Baseline levels of N-telopeptide were low in 110 (69.2%) patients and high in 49 (30.8%) patients. Baseline bone-specific alkaline phosphatase levels were low in 109 (46.2%) patients and high in 127 (53.8%) patients.

### Skeletal-Related Events: Number, Type, and Distribution

Table 2 lists the number of each type of skeletal-related event for the 454 skeletal-related events that occurred among the study population (231 in the prostate cancer patients and 223 in the NSCLC and other solid tumor population). Consistent with previous observations on the relative occurrence of different skeletal-related events (23,35,36), the most frequent events were radiotherapy to bone and pathologic fractures, which accounted for 53% and 31%, respectively, of skeletal-related events in the total population. These two types of event accounted for 48% and 32%, respectively, of the total skeletal-related events in the placebo arms of two randomized trials of zoledronic acid to treat bone metastases.

<table>
<thead>
<tr>
<th>Category</th>
<th>Prostate cancer</th>
<th>NSCLC and other solid tumors</th>
<th>Total patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pathologic fractures</td>
<td>73</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>24</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>Nonvertebral fractures</td>
<td>49</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>Radiotherapy to bone</td>
<td>110</td>
<td>130</td>
<td>69</td>
</tr>
<tr>
<td>Surgery to bone</td>
<td>11</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>19</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Change in antineoplastic therapy</td>
<td>18</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total No. of SREs</td>
<td>231</td>
<td>223</td>
<td>110</td>
</tr>
</tbody>
</table>

*NSCLC = non-small-cell lung cancer; SRE = skeletal-related event; ECOG = Eastern Cooperative Oncology group.

Table 2. Number of skeletal-related events (SREs) among patients with prostate cancer, non-small-cell lung cancer (NSCLC), or other solid tumors enrolled in the placebo arms of two randomized trials of zoledronic acid to treat bone metastases*
patients from the prostate cancer study and 58% and 32%, respectively, of the total skeletal-related events in patients from the NSCLC and other solid tumor study.

Survival Data and Number of Observations

For the prostate cancer patients, median survival was 16.8 months and the mean observation time was 16.0 months (95% confidence interval [CI] = 13.0 to 17.6 months). In this context a month was defined as 28 days. A total of 1004 N-telopeptide and 1069 bone-specific alkaline phosphatase marker assessments were available for the prostate cancer patients. Allowing for the 6-month carry-forward, the number of assessments increased to 1097 and 1130 for N-telopeptide and bone-specific alkaline phosphatase, respectively.

For the NSCLC and other solid tumor patients (7,37), median survival was 5.6 months (6-month survival rate = 45.1%) for patients with NSCLC and 6.9 months for patients with other solid tumors (6-month survival rate = 58.3%). Thus, although the study period was up to 21 months, the numbers of patients surviving at longer times was relatively small, with a median observation time of 6.4 months (95% CI = 5.5 to 7.3 months). A total of 511 N-telopeptide and 797 bone-specific alkaline phosphatase measurements were available; allowing for the 6-month carry-forward, the number of assessments increased to 558 and 845 for N-telopeptide and bone-specific alkaline phosphatase, respectively.

Proportion of Patients With a Skeletal-Related Event

The number of patients with at least one skeletal-related event was recorded for each time interval between bone marker evaluations. The proportion of patients with at least one skeletal-related event during the first month of follow-up was computed according to baseline marker status. In addition, the proportion of marker assessments followed by at least one skeletal-related event was computed over the course of follow-up. These data were analyzed as a function of high and low N-telopeptide levels and high and low bone-specific alkaline phosphatase levels (Fig.1). In all cases, patients with high baseline N-telopeptide or bone-specific alkaline phosphatase levels had a greater incidence of skeletal-related events between the baseline and 1-month assessments (Fig. 1, A and B) than the patients with low baseline levels of the corresponding marker. For the prostate cancer group, 11.7% of patients with high N-telopeptide levels and 3.8% of patients with low levels had a skeletal-related event during the first month, as did 9.0% of patients with high bone-specific alkaline phosphatase levels and 2.2% of patients with low levels. For the NSCLC and other solid tumor group, 20.4% of patients with high N-telopeptide levels and 12.7% of patients with low levels had a skeletal-related event during the first month, as did 19.7% of patients with high bone-specific alkaline phosphatase levels and 10.1% of patients with low levels.

The proportions of patients with a skeletal-related event after any subsequent assessment (Fig. 1,C and D) reflect the same overall pattern of increase in skeletal-related events for those patients in the groups with high bone marker levels. Notably, although the incidence of skeletal-related events was higher in patients with higher marker levels, such skeletal-related events occurred in all patient groups during each assessment period, indicating that all patients with bone metastases have some risk of skeletal-related events, even if their bone marker levels are low.

Time Course of Negative Clinical Outcomes

High N-telopeptide levels at baseline were associated with an increased rate of first skeletal-related events for patients in the prostate cancer and the NSCLC and other solid tumor groups, and this increased rate was maintained throughout the study period (Fig. 2, A and B). The corresponding curves for the proportion of patients who died on-study show a markedly increased survival of those patients with low N-telopeptide levels compared with those with high N-telopeptide levels (Fig. 2, C and D). For patients in the prostate cancer group, the median survival time was 11.9 months (95% CI = 8.1 to 16.0) for patients with high N-telopeptide levels at baseline compared with 22.8 months (95% CI = 18.6 to 28) for those with low levels. For patients in the NSCLC and other solid tumors group,
the median survival time was 3.2 months (95% CI = 2.8 to 5.0 months) for patients with high N-telopeptide levels at baseline compared with 8.2 months (95% CI = 6.6 to 11.8 months) for those with low levels.

The time courses of negative clinical outcomes based on bone-specific alkaline phosphatase baseline levels are shown in Fig. 3. In all cases, the proportion of patients with at least one skeletal-related event and the proportion of patients who died were greater for patients with high bone-specific alkaline phosphatase levels at baseline than for those with low levels. However, the differences in proportions between the high and low categories were at times smaller with bone-specific alkaline phosphatase than with N-telopeptide, suggesting that N-telopeptide discriminates more effectively between patients with poor and better prognoses than bone-specific alkaline phosphatase.

Relative Risks by N-Telopeptide Levels

For the total study population, patients with high N-telopeptide levels at baseline (using a cut-off point of 100 nmol/mmol creatinine) had a higher risk of experiencing a skeletal-related event (RR = 1.59, 95% CI = 1.17 to 2.14, \( P = .003 \)) and had a shorter time to a first skeletal-related event (RR = 1.76, 95% CI = 1.28 to 2.44, \( P = .001 \)) and disease progression (RR = 1.60, 95% CI = 1.22 to 2.11, \( P = .001 \)) and a higher risk of death (RR = 2.65, 95% CI = 2.06 to 3.42, \( P < .001 \)) than patients with low N-telopeptide levels at baseline (Table 3). When the on-study N-telopeptide values were used in the analysis, the association with N-telopeptide was stronger, with patients in the high N-telopeptide level group having more than a 2.5-fold (RR = 2.54, 95% CI = 1.95 to 3.32) increased risk of a skeletal-related event, a
Table 3. Relative risks (RRs) and 95% confidence intervals (CIs) associated with negative outcomes for patients with prostate cancer, non-small-cell lung cancer (NSCLC), and other solid tumors considered separately and together, accordingly to bone marker level category

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prostate cancer</th>
<th>NSCLC and other solid tumors</th>
<th>Total patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR 95% CI</td>
<td>RR 95% CI</td>
<td>RR 95% CI</td>
</tr>
<tr>
<td><strong>Baseline N-telopeptide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRE</td>
<td>1.57 1.09 to 2.26</td>
<td>1.62 0.96 to 2.74</td>
<td>1.59 1.17 to 2.14</td>
</tr>
<tr>
<td>Time to first SRE</td>
<td>1.72 1.15 to 2.57</td>
<td>1.85 1.08 to 3.18</td>
<td>1.76 1.28 to 2.44</td>
</tr>
<tr>
<td>Disease progression</td>
<td>1.56 1.13 to 2.15</td>
<td>1.76 1.06 to 2.93</td>
<td>1.60 1.22 to 2.11</td>
</tr>
<tr>
<td>Death</td>
<td>2.40 1.73 to 3.33</td>
<td>3.03 2.06 to 4.46</td>
<td>2.65 2.06 to 3.42</td>
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<tr>
<td><strong>On-study N-telopeptide</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SRE</td>
<td>3.25 2.26 to 4.68</td>
<td>&lt;.001</td>
<td>2.54 1.95 to 3.32</td>
</tr>
<tr>
<td>Time to first SRE</td>
<td>3.05 1.96 to 4.72</td>
<td>&lt;.001</td>
<td>2.53 1.84 to 3.47</td>
</tr>
<tr>
<td>Disease progression</td>
<td>2.02 1.48 to 2.74</td>
<td>&lt;.001</td>
<td>1.99 1.53 to 2.58</td>
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<tr>
<td>Death</td>
<td>4.59 2.82 to 7.46</td>
<td>&lt;.001</td>
<td>3.29 2.49 to 4.36</td>
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<td><strong>Baseline bone-specific alkaline phosphatase</strong></td>
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<tr>
<td>SRE</td>
<td>1.85 1.15 to 2.98</td>
<td>.012</td>
<td>1.50 1.14 to 1.99</td>
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<tr>
<td>Time to first SRE</td>
<td>1.88 1.11 to 3.18</td>
<td>.018</td>
<td>1.61 1.20 to 2.19</td>
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<tr>
<td>Disease progression</td>
<td>1.27 0.88 to 1.83</td>
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<td>1.49 1.13 to 1.96</td>
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<td>Death</td>
<td>1.83 1.19 to 2.83</td>
<td>.006</td>
<td>1.62 1.28 to 2.04</td>
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<td><strong>On-study bone-specific alkaline phosphatase</strong></td>
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<tr>
<td>SRE</td>
<td>3.03 1.67 to 5.51</td>
<td>&lt;.001</td>
<td>2.20 1.63 to 2.96</td>
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<td>Time to first SRE</td>
<td>3.10 1.66 to 5.81</td>
<td>&lt;.001</td>
<td>2.16 1.57 to 2.97</td>
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<td>Disease progression</td>
<td>1.64 1.09 to 2.48</td>
<td>.018</td>
<td>1.81 1.34 to 2.45</td>
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<tr>
<td>Death</td>
<td>3.19 1.58 to 6.42</td>
<td>.001</td>
<td>2.02 1.52 to 2.67</td>
</tr>
</tbody>
</table>

*High bone-specific alkaline phosphatase (≥146 IU/L) versus low bone-specific alkaline phosphatase (<146 IU/L) levels. Referent group = patients in the low-level category.

shorter time to a first skeletal-related event (RR = 2.53, 95% CI = 1.84 to 3.47), approximately a twofold increased risk (RR = 1.99, 95% CI = 1.53 to 2.58) of bone progression, and more than a threefold increased risk (RR = 3.29, 95% CI = 2.49 to 4.36) of death (P<.001 in every case) than patients in the low N-telopeptide level category.

For the prostate cancer group, compared with patients with low N-telopeptide levels, patients with high N-telopeptide levels at baseline were found to be at a statistically significantly increased risk for skeletal-related events (RR = 1.57, 95% CI = 1.09 to 2.26, P = .015), to have a shorter time to a first skeletal-related event (RR = 1.72, 95% CI = 1.15 to 2.57, P = .008), and to be at higher risk of bone disease progression (RR = 1.56, 95% CI = 1.13 to 2.15, P = .006) and death (RR = 2.40, 95% CI = 1.73 to 3.33, P<.001) (Table 3). A high N-telopeptide level assessed on-study was associated with a more than threefold increased risk of experiencing a skeletal-related event (RR = 3.25, 95% CI = 2.26 to 4.68), a shorter time to a first skeletal-related event (RR = 3.05, 95% CI = 1.96 to 4.72), a twofold increased risk of disease progression (RR = 2.02, 95% CI = 1.48 to 2.74), and more than a 4.5-fold increased risk of death (RR = 4.59, 95% CI = 2.82 to 7.46) compared with patients with low N-telopeptide levels at the respective time point (P<.001 for all comparisons).

For the NSCLC and other tumor group, high baseline N-telopeptide levels were associated with a non-statistically significantly increased risk of a skeletal-related event (RR = 1.62, 95% CI = 0.96 to 2.74, P = .073) and a statistically significantly shorter time to a first skeletal-related event (RR = 1.85, 95% CI = 1.08 to 3.18, P = .026), an increased risk of bone disease progression (RR = 1.76, 95% CI = 1.06 to 2.93, P = .029), and a more than a threefold increase in the risk of death (RR = 3.03, 95% CI = 2.06 to 4.46, P<.001).

When the on-study N-telopeptide values were considered, patients in the high N-telopeptide level group had an almost twofold increase in the risk of a skeletal-related event (RR = 1.79, 95% CI = 1.15 to 2.79, P = .010), a shorter time to a first skeletal-related event (RR = 1.97, 95% CI = 1.22 to 3.20, P = .006) or an increased risk of disease progression (RR = 1.91, 95% CI = 1.16 to 3.15, P = .011), and a more than 2.5-fold increased risk of death (RR = 2.67, 95% CI = 1.85 to 3.85, P<.001) compared with patients in the low N-telopeptide level group.

We also estimated the relative risks of clinical outcomes associated with N-telopeptide levels with the cut-off point for high and low levels set at 50 nmol/mmol creatinine (Fig. 4). For patients in the prostate cancer group, baseline N-telopeptide values were statistically significantly predictive of a skeletal-related event occurrence, the time to a first skeletal-related event, the risk of bone disease progression, and death. As with the 100 nmol/mmol creatinine cut-off category, the relative risks were generally higher and the statistical significance greater for the on-study values than for the baseline values, although the latter were, nevertheless, strongly predictive. For patients in the NSCLC and other tumor group, using the 50 nmol/mmol creatinine cut-off, the relative risks of negative clinical outcomes were also consistently greater for patients in the high N-telopeptide level category. For the baseline values, statistical significance was almost reached (P = .051) for a skeletal-related event, and the relative risk of death was more than twofold greater than for patients in the lower N-telopeptide level group (P<.001). Using on-study values, the relative risk of a skeletal-related event occurrence and the time to a first skeletal-related event were both approximately 2.0 (P = .014 and .007, respectively), and the relative risk of death was more than 3.5 (P<.001).
Relative Risks by Bone-Specific Alkaline Phosphatase Marker Levels

For the total population, compared with patients who had low baseline bone-specific alkaline phosphatase levels, patients with high bone-specific alkaline phosphatase levels were at a statistically significantly increased risk of experiencing a skeletal-related event (RR = 1.50, 95% CI = 1.14 to 1.99, P = .004), a shortened time to a first skeletal-related event (RR = 1.62, 95% CI 1.20 to 2.19, P = .002), an increased risk of bone disease progression (RR = 1.49, 95% CI 1.13 to 1.96, P = .004), and an increased risk of death (RR = 1.62, 1.28 to 2.04, P<.001). The strength of the association between on-study bone-specific alkaline phosphatase levels and risk of skeletal-related events (P<.001), progression of bone disease (P<.001), and death (P<.001) was even greater than that found for the baseline levels.

For patients in the prostate cancer group, compared with patients who had low baseline bone-specific alkaline phosphatase levels, patients with high bone-specific alkaline phosphatase levels had a statistically significantly increased risk of experiencing a skeletal-related event (RR = 1.85, 95% CI = 1.15 to 2.98, P = .012) or of dying (RR = 1.83, 95% CI = 1.19 to 2.83, P = .006). By using on-study values, the relative risks for negative clinical outcomes were even greater for both skeletal-related events (RR = 3.03, 95% CI = 1.67 to 5.51, P<.001) and death (RR = 3.19, RR = 1.58 to 6.42, P = .001). There was no statistically significant increase in the risk of bone lesion progression for patients with elevated bone-specific alkaline phosphatase levels at baseline (RR = 1.27, 95% CI = 0.88 to 1.83, P = .205), but patients with high on-study bone-specific alkaline phosphatase levels had a statistically significant 1.6-fold increase in the risk of disease progression compared with patients who had low on-study bone-specific alkaline phosphatase levels (RR = 1.64, 95% CI = 1.09 to 2.48, P = .018).

For patients in the NSCLC and other tumor group, a high bone-specific alkaline phosphatase level at baseline was also associated with an increased risk of negative clinical outcomes compared with patients with low baseline bone-specific alkaline phosphatase levels (Table 3). High bone-specific alkaline phosphatase levels at baseline were associated with a statistically significant 1.5-fold increase in risk in the time to a first skeletal-related event (RR = 1.49, 95% CI = 1.02 to 2.17, P = .041), a
1.8-fold increase in risk for disease progression (RR = 1.77, 95% CI = 1.19 to 2.64, \( P = .005 \)), and a 1.5-fold increase in risk of death (RR = 1.53, 95% CI = 1.15 to 2.03, \( P = .003 \)). Patients with high bone-specific alkaline phosphatase levels on-study had statistically significantly increased risks for all negative clinical outcomes (Table 3). However, there were fewer increased risks associated with high bone-specific alkaline phosphatase levels than with high N-telopeptide levels.

**Analyses of the NSCLC Patient Stratum**

A separate analysis was performed on the NSCLC patient stratum to determine whether the findings were maintained within this group. For baseline N-telopeptide levels, using a cut-off of 100 nmol/mmol creatinine, relative risks of a skeletal-related event occurrence, time to a first skeletal-related event, bone disease progression, and death were 1.66 (95% CI = 0.79 to 3.53, \( P = .183 \)), 1.99 (95% CI = 0.80 to 4.96, \( P = .140 \)), 3.49 (95% CI = 1.42 to 8.62, \( P = .007 \)), and 4.67 (95% CI = 2.78 to 7.84, \( P < .001 \)), respectively, for patients with high levels compared with those with low levels. For the on-study measurements, the risks of negative clinical outcomes were greater for patients in the high N-telopeptide level group than for those in the low-level group, but only the risk of death was statistically significantly increased (RR = 3.51; 95% CI = 2.13 to 5.79, \( P < .001 \)). When the bone-specific alkaline phosphatase analyses were carried out for the NSCLC stratum, the risks of negative clinical outcomes were greater for patients with high bone-specific alkaline phosphatase levels than for those with low levels, regardless of whether baseline or on-study assessments were used, but the magnitude of the relative risks and the level of statistical significance were lower than those for N-telopeptide, possibly because of the smaller number of patients in the NSCLC analysis. These results suggest that, despite the reduced statistical significance, the predictive relationships for N-telopeptide and bone-specific alkaline phosphatase levels for the NSCLC group paralleled those of the other tumor types.

**Discussion**

The large databases from two international multicenter randomized phase III clinical trials of zoledronic acid in patients with bone metastases provided a unique opportunity to explore the association between biochemical markers of bone metabolism and clinical outcomes, including skeletal-related events, disease progression, and death in this setting (25). Because the phase III studies included large numbers of patients receiving a placebo, the association between bone marker levels and clinical outcomes could be explored in bisphosphonate-naïve patients. Before our current investigation, no large and statistically robust study had investigated the association between bone marker levels and clinical outcomes, such as skeletal-related events, disease progression, or death.

For patients in the prostate cancer group, those with high marker levels had a higher risk of negative clinical outcomes than patients with low marker levels. For N-telopeptide, baseline marker levels were statistically significantly predictive of skeletal-related events, time to a first skeletal-related event, disease progression, and death (all \( P \) values ≤ .015), and for bone-specific alkaline phosphatase, baseline marker values were statistically significantly predictive of skeletal-related events, time to a first skeletal-related event, and death but not of disease progression. Compared with baseline marker levels, recent (i.e., on-study) marker levels had even greater predictive significance. Patients whose recent N-telopeptide levels were high had a two- to fourfold increased risk of development of skeletal-related events, disease progression, or death (\( P < .001 \)) within the 3 months after this assessment compared with patients who had recent low N-telopeptide levels.

For patients in the NSCLC and other solid tumor group, the analysis also revealed a statistically significant association between baseline N-telopeptide levels and time to a first skeletal-related event (\( P = .026 \)) and risk of disease progression (\( P = .029 \)) and death (\( P < .001 \)), but not of the occurrence of skeletal-related events (\( P = .073 \)), with the relative risk of death on-study being >3 for those with high N-telopeptide levels. A similar pattern was seen in those patients who had high baseline levels of bone-specific alkaline phosphatase. When on-study marker levels were used instead of baseline levels, the marker levels became even more strongly predictive of skeletal-related events, time to a first skeletal-related event, disease progression, and death. The relative risks were greater for patients with high N-telopeptide levels relative to those with low levels than for patients with high bone-specific alkaline phosphatase levels relative to those with low levels. It is noteworthy that, although separate analyses could be performed for patients with NSCLC and for patients with other solid tumors, the similarities in the baseline characteristics of patients in these subgroups, the frequency and distribution of skeletal-related events among the various types, and the tests for homogeneity (data not shown) all suggest that it is valid to consider these patients as a single group.

For all tumor types evaluated, therefore, the data indicate statistically significant relationships between levels of biochemical markers of bone metabolism and clinical outcomes, and the magnitudes of the relative risks were similar. When the total patient population (\( n = 441 \)) was considered (i.e., patients with prostate cancer, NSCLC, and other tumor types), both N-telopeptide and bone-specific alkaline phosphatase levels were highly predictive of the occurrence of skeletal-related events, the time to a first skeletal-related event, and the occurrence of disease progression and death, with \( P \) values generally < .001. The markers were predictive whether baseline marker values or the updated on-study marker values were used, although the association with skeletal-related events and death on-study values were generally more statistically significant. However, overall, N-telopeptide levels were more consistent prognostic indicators than bone-specific alkaline phosphatase levels for all tumor types, including prostate cancer, reflecting the key role of osteolysis in the development of skeletal complications.

The increases in N-telopeptide and bone-specific alkaline phosphatase levels probably reflect tumor growth in bone. However, serum bone-specific alkaline phosphatase levels may also increase to balance localized or systemic increases in osteolytic activity or increase as an indication of bone formation to repair bone lesions that have responded to treatment. Increased bone-specific alkaline phosphatase levels can have both positive and negative prognostic implications, depending on the situation. Therefore, although bone-specific alkaline phosphatase levels showed statistically significant associations with outcome in this analysis, such an association may not be broadly applicable,
especially in patients whose bone lesions are responding to treatment.

The finding that baseline marker levels were predictive of skeletal-related events and death is important because it can be argued that baseline marker assessments allow more time for appropriate intervention. However, marker levels might be expected to change during the course of the disease for a number of reasons, including treatment. Although not all patients were receiving cytotoxic chemotherapy at baseline, many patients began cytotoxic therapy regimens during the course of the trials, and these therapies would be expected to influence bone metabolism and marker levels. Patients may have experienced changes in marker levels on-study in response to the effects of antineoplastic therapy or to disease progression or regression. Although it is not surprising that recent marker levels are better predictors of skeletal complications than baseline levels, an increase in bone marker levels often precedes an event by several months, thus providing another opportunity for treatment interventions. In this regard, high N-telopeptide or bone-specific alkaline phosphatase levels at baseline or at any time during the course of the disease might indicate that more aggressive intervention strategies are needed to prevent skeletal morbidity. It may be appropriate, therefore, for marker levels to be assessed at regular intervals during the course of metastatic bone disease.

The cut-offs that we used to define high N-telopeptide (≥100 nmol/mmol creatinine) and high bone-specific alkaline phosphatase (≥146 IU/L) levels in these analyses correspond approximately to the upper limit of normal in postmenopausal women and in men receiving androgen deprivation therapy and represent a practical approach in the patient groups studied. However, we would not claim that these cut-offs represent a definitive categorization but rather that they illustrate the value of the approach. Analyses using an N-telopeptide cut-off of 50 nmol/mmol creatinine (corresponding approximately to the upper limit of normal in healthy young adults) (Fig. 3) showed relative risks similar to those in the analyses using the 100 nmol/mmol creatinine cut-off. Other analyses are also possible. For example, comparing moderate N-telopeptide (≥50 nmol/mmol creatinine) and high N-telopeptide (≥100 nmol/mmol creatinine) levels with low N-telopeptide (<50 nmol/mmol creatinine) levels showed that the relative risks for patients in the high-level group were consistently greater than those for patients in the moderate-level group, which, in turn, were consistently greater than the risks for the patients in the low N-telopeptide level group, illustrating that a continuum of risk exists (data not shown).

Data for bisphosphonate-naïve patients with breast cancer and multiple myeloma are not available in as large trial populations as for the prostate and NSCLC and other solid tumor groups because bisphosphonates are already standard therapy in the treatment of such patients. However, in a recent large trial comparing zoledronic acid with pamidronate in breast cancer and multiple myeloma, N-telopeptide levels were also found to be predictive of skeletal complications (Coleman R, unpublished data, February 2004). Thus, the risk of skeletal complications in metastatic bone disease may depend on the rate of bone resorption and be independent of the primary tumor type.

The results of this study may have considerable implications for the management of patients with bone metastases. For patients with prostate cancer, although this analysis cannot address the possibility of a causal link between increases in bone metabolism markers and clinical outcomes, it does suggest that reducing bone turnover could have a positive effect on disease progression and might improve survival. However, the clinical outcome of patients is not associated solely with levels of biochemical markers of bone metabolism, and other factors are clearly at work. Therefore, bone marker measurements provide additional insight but should not replace established clinical endpoints for comparisons between bisphosphonate therapies. Nonetheless, reductions in bone marker levels during treatment show associations with improved clinical outcome in the clinical trial setting. For example, although reductions in bone resorption marker levels were reported during treatment with either zoledronic acid or pamidronate in separate trials, patients treated with zoledronic acid appeared to have greater reductions from baseline in their N-telopeptide levels than patients treated with pamidronate (25,38,39). It is interesting to note that, in placebo-controlled trials of zoledronic acid (23) and pamidronate (38) in prostate cancer patients, only zoledronic acid has been associated with clinical efficacy (i.e., a clinically significant reduction in skeletal-related events and pain).

Because survival after diagnosis of bone metastases is relatively short for patients with NSCLC and other solid tumors, methods are needed to predict skeletal complications in a shorter timescale than is possible with current imaging methods. From the results of our current study, the use of bone marker data may make a major contribution to this need by identifying those patients at highest risk who warrant the highest priority for intervention to prevent skeletal complications.

This study was limited specifically to patients who did not receive bisphosphonates. However, in the future, most patients with bone metastases are likely to be exposed to bisphosphonates. In view of the strength of the relationships observed in this study, it is important to determine whether the relationships are maintained, that is, whether bone marker levels remain predictive, in patients who are receiving bisphosphonate therapy. Analyses of bone marker data in the treatment arms of these trials and other large phase III studies evaluating the role of zoledronic acid in metastatic bone disease are underway.

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NOTES

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