Skeletal Complications in Patients with Bone Metastases from Renal Cell Carcinoma and Therapeutic Benefits of Zoledronic Acid

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ABSTRACT

Bone metastases in patients with renal cell carcinoma are associated with a high risk of skeletal complications. Therefore, a subset analysis of a larger clinical trial was performed to determine the efficacy of zoledronic acid in renal cell carcinoma patients. Patients with bone metastases from solid tumors other than breast or prostate cancer (n = 773) were randomized to receive zoledronic acid or placebo via 15-minute infusion every 3 weeks for 9 months. Patients were monitored for skeletal-related events, which were defined as pathological fracture, spinal cord compression, radiotherapy, or surgery to bone. Among the subset of 74 patients with renal cell carcinoma, 46 patients were treated with 4 mg of zoledronic acid or placebo. Significantly fewer patients treated with 4 mg zoledronic acid had a skeletal-related event (37% versus 74% for placebo, P = 0.015), and zoledronic acid significantly prolonged the time to first skeletal-related event (median not reached at 9 months versus 72 days for placebo; P = 0.006). Zoledronic acid significantly reduced the annual incidence of skeletal-related events by ~21% (mean 2.68 versus 3.38 events per year for placebo, P = 0.014) and significantly reduced the risk of developing a skeletal-related event by 61% compared with placebo (risk ratio = 0.394, P = 0.008) by multiple event analysis. Median time to progression of bone lesions was also significantly extended with zoledronic acid treatment (P = 0.014). Zoledronic acid is the first bisphosphonate to significantly reduce skeletal morbidity and significantly prolong time to bone lesion progression in patients with bone metastases from renal cell carcinoma.

INTRODUCTION

The incidence of renal cell carcinoma diagnosis has increased by ~40% during the past 3 decades (1). During this time, overall 5-year survival rates have changed very little (1). At diagnosis, ~20% of patients with renal cell carcinoma have metastatic disease (most frequently in the lung, bone, liver, or brain), and up to 35% of renal cell carcinoma patients will develop bone metastases during disease progression (2). Bone metastases can result in severe bone pain and debilitating skeletal complications, including pathological fractures, spinal cord compression, the need for orthopedic surgery to treat or prevent pathological fractures, and the need for palliative radiotherapy to bone (3). These events represent painful and debilitating changes in patient lives. For example, a recent study (4) in patients with prostate cancer found that skeletal complications were associated with diminished health-related quality of life. Therefore, delaying or preventing skeletal complications is an important and meaningful clinical benefit for patients with renal cell carcinoma and bone metastases (5).

Zoledronic acid (4 mg via 15-minute infusion every 3 weeks) was shown recently to significantly reduce the risk of skeletal complications in a retrospective subset analysis of patients with renal cell carcinoma in a randomized, double-blind, placebo-controlled clinical trial (6).

BONE METASTASIS FROM RENAL CELL CARCINOMA

The skeleton is the most common site of distant metastasis from solid tumors, in general, and is second only to the lung as a target site in patients with renal cell carcinoma (2). The natural history of bone metastases from renal cell carcinoma was evaluated recently by Zekri et al. (2) in a 5-year review of 103 patients with metastatic renal cell carcinoma who were receiving standard therapy. Thirty-one (30%) patients developed bone lesions. The most commonly affected sites were the pelvis and ribs (48% of patients for each) and the spine (42%). Other common sites included long bones and the skull (Table 1; ref. 2). These lesions were associated with substantial morbidity (Table 2; ref. 2); >80% of patients require palliative radiotherapy to bone and ≥40% of patients experience long-bone fractures. Typically, bone lesions are poorly responsive to standard cytotoxic or immunologic therapies (7, 8), and patients often experience multiple complications during the course of their disease. In a recent trial of zoledronic acid, 74% of renal cell carcinoma patients with bone metastases who were randomized to receive placebo (n = 19) had at least one skeletal complication during 9 months, and these patients experienced an average of three to four skeletal complications per year (6). Therefore, renal cell carcinoma patients with bone metastases are at high risk of skeletal complications.

Monitoring patients with renal cell carcinoma for bone metastasis by either bone scans or plain X-ray films is an...
Bisphosphonates are highly effective inhibitors of osteoclast-mediated bone resorption (12) and have become an integral component of the treatment of bone metastases. The new-generation bisphosphonate zoledronic acid is the most potent bisphosphonate currently available (13) and has demonstrated broad clinical utility in patients with a range of solid tumors, including renal cell carcinoma.

### EFFECT OF ZOLEDRONIC ACID ON SKELETAL COMPLICATIONS IN PATIENTS WITH BONE METASTASES FROM RENAL CELL CARCINOMA

The clinical benefit of zoledronic acid was investigated recently in a randomized, double-blind, placebo-controlled, Phase III trial in patients with bone metastases from solid tumors other than breast cancer or prostate cancer, including non–small cell lung cancer, renal cell carcinoma, and bladder cancer (n = 773; ref. 14). Overall, zoledronic acid significantly reduced skeletal morbidity. Among renal cell carcinoma patients in this trial, there was a very high incidence of skeletal-related events and heavy burden of disease from bone metastases compared with patients in the overall trial population and the subgroup of patients with non–small cell lung cancer (14). A subset analysis revealed that 4 mg of zoledronic acid was especially efficacious in patients with renal cell carcinoma (6).

In the absence of a prospective randomized trial in patients with bone metastases from renal cell carcinoma, which is needed for definitive conclusions, this post hoc subset analysis provides important insight into skeletal morbidity and treatment benefits in this setting.

The Phase III trial of zoledronic acid in patients with solid tumors enrolled 74 patients (10%) with renal cell carcinoma. Patients were randomized to treatment with either zoledronic acid (4 or 8 mg), administered as a 15-minute i.v. infusion every 3 weeks, or placebo, and all of the patients received daily oral supplements of calcium and vitamin D. Patients with baseline prostate cancer, zoledronic acid was shown to significantly decrease skeletal complications (14). Therefore, zoledronic acid provides a new option for the palliative care of patients with bone metastases from a variety of solid tumors, including renal cell carcinoma.

### Table 1 Distribution of bone metastases from renal cell carcinoma

<table>
<thead>
<tr>
<th>Site</th>
<th>Patients, n (%) (N = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvis</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Ribs</td>
<td>15 (48)</td>
</tr>
<tr>
<td>Spine</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Femur</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Humerus</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Skull</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Clavicle</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Ulna</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Tibia</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

NOTE. Adapted with permission from Zekri et al. (2).

### Table 2 Skeletal-related events in patients with bone metastases from renal cell carcinoma (N = 31) during 5 years of follow-up

<table>
<thead>
<tr>
<th>Skeletal-related event</th>
<th>Patients, n (%)</th>
<th>Events, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td>25 (81)</td>
<td>37</td>
</tr>
<tr>
<td>Long-bone fractures</td>
<td>13 (42)</td>
<td>15</td>
</tr>
<tr>
<td>Hypercalcemia of malignancy</td>
<td>9 (29)</td>
<td>16</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>9 (29)</td>
<td>12</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>4 (13)</td>
<td>4</td>
</tr>
</tbody>
</table>

NOTE. In this study, 32 of the 72 patients (44%) who did not have evidence of metastatic bone disease also developed hypercalcemia of malignancy. Adapted with permission from Zekri et al. (2).

important aspect of patient care. Bone lesions associated with renal cell carcinoma are typically osteolytic (i.e., they appear as less dense bone on plain radiographs). The radiographic appearance of bone metastases can be osteolytic, osteoblastic, or mixed, depending on the nature of the primary cancer and the interactions between tumor cells and the bone microenvironment (9, 10). Osteolytic bone lesions form when metastatic tumors secrete osteoclast-stimulating factors, which trigger increases in osteoclast-mediated bone resorption. In contrast, osteoblastic lesions form when metastatic tumor cells release factors that stimulate new bone formation by osteoblasts. An example of the radiologic appearance of pelvic bone lesions is presented in Fig. 1 (11). Although both osteolytic and osteoblastic lesions have been reported in patients with renal cell carcinoma, bone lesions associated with renal cell carcinoma are typically osteolytic and are generally very aggressive. In the recent review by Zekri et al., (2) radiologic assessments were available for 28 of the renal cell carcinoma patients with bone metastases. Approximately 71% of bone lesions were primarily osteolytic, 18% were osteoblastic, and 11% were mixed in radiographic appearance. All of the malignant bone lesions, regardless of their radiologic characteristics, are associated with significant increases in bone metabolism and increased risk of skeletal complications.

Bisphosphonates are highly effective inhibitors of osteoclast-mediated bone resorption (12) and have become an integral component of the treatment of bone metastases. The new-generation bisphosphonate zoledronic acid is the most potent bisphosphonate currently available (13) and has demonstrated broad clinical utility in patients with a range of solid tumors. In the first large-scale, randomized, placebo-controlled trial of a bisphosphonate in solid tumors other than breast cancer or prostate cancer, zoledronic acid was shown to significantly decrease skeletal complications (14). Therefore, zoledronic acid provides a new option for the palliative care of patients with bone metastases from a variety of solid tumors, including renal cell carcinoma.

![Fig 1] The radiologic appearance of osteolytic bone metastases. The pelvic radiograph of a patient with osteolytic metastases demonstrates the loss of bony tissue that is characteristic of osteolytic bone lesions. Reprinted with permission from Mundy (11).
serum creatinine levels $>3$ mg/dL ($265 \mu$mol/L) were excluded from the study, and treatment was withheld if serum creatinine increased to $\geq$ mg/dL during the trial (14). After randomization, the 8-mg dose of zoledronic acid was reduced to 4 mg (8/4 mg group) by protocol amendment because of renal safety concerns. Efficacy conclusions were not drawn from the 8/4-mg zoledronic acid mixed-treatment group ($n = 28$). Patients who completed the 9-month core phase of the trial were allowed to extend their assigned double-blind treatment for up to 21 months (15).

Although the overall trial was stratified using non–small cell lung cancer and other solid tumors (with no breakdown for renal cell carcinoma) for randomization, baseline disease and demographic factors for the renal cell carcinoma subset were, nonetheless, generally well balanced between the 4-mg zoledronic acid ($n = 27$) and placebo arms ($n = 19$), as described previously (6). Median age was 64 years in the 4-mg zoledronic acid group and 65 years in the placebo group, and median time from initial diagnosis to study entry was 25.5 and 21.2 months, respectively. Patients randomized to the 4-mg zoledronic acid arm had slightly higher pain scores [bone pain index composite score (on a scale of 0 to 10) of 4.3 compared with 3.3 for placebo], and 78% of patients in the zoledronic acid group had Eastern Cooperative Oncology Group performance status of 0 or 1 compared with 95% for placebo. The primary end point of this trial was the proportion of patients who experienced at least one skeletal-related event defined as pathological fracture, need for palliative radiotherapy to bone, need for orthopedic surgery to treat or prevent a pathological fracture, or spinal cord compression. Secondary efficacy endpoints included time to first skeletal-related event, skeletal morbidity rate (mean skeletal-related events per year), proportion of patients with each individual type of skeletal-related event, time to bone lesion progression, Andersen-Gill multiple event analysis (using a 21-day window to control for related events; ref. 16), and survival. For all of the secondary endpoints, hypercalcemia of malignancy was also included as a skeletal-related event (6).

In the renal cell carcinoma subset, the proportion of patients in the placebo group with an skeletal-related event was higher than that reported in any other patient group (14, 17) illustrating the aggressive nature of bone metastases from renal cell carcinoma. For example, in the 9-month analysis of the placebo-arm patients, 74% of renal cell carcinoma patients experienced at least one skeletal-related event (6) compared with 44% for the overall trial population, 45% for the non–small cell lung cancer stratum, and 43% for the other solid tumor stratum (14). Indeed, because patients with renal cell carcinoma were composed of $\sim20\%$ of the other solid tumor stratum, the proportion of patients with tumors other than non–small cell lung cancer or renal cell carcinoma who experienced at least one skeletal-related event was even lower than 43%. Therefore, compared with patients with other primary cancers, patients with bone metastases from renal cell carcinoma in this trial were at higher risk of skeletal complications.

Zoledronic acid was significantly more effective than placebo across the primary and most secondary endpoints in the renal cell carcinoma subset. During the 9-month trial, zoledronic acid significantly reduced the proportion of patients with any skeletal-related event by 50% (37% versus 74% with placebo, $P = 0.015$; ref. 6). Moreover, zoledronic acid consistently reduced the proportion of patients with each type of skeletal-related event. These reductions were consistent with, but more profound than, those seen in the overall trial population and in the stratum of patients with non–small cell lung cancer (14).

Similar to the overall trial population, zoledronic acid significantly prolonged time to first skeletal-related event. Most renal cell carcinoma patients in the placebo group experienced their first on-study skeletal-related event within 2.5 months of study entry. However, time to first skeletal-related event was significantly delayed in the patients treated with 4 mg of zoledronic acid (median not reached at 9 months versus 72 days for placebo; $P = 0.006$; Fig. 2; ref. 6). Furthermore, zoledronic acid significantly delayed the time to first pathological fracture (median not reached at 9 months versus 168 days for placebo; Fig. 3; ref. 6). Zoledronic acid also significantly reduced the skeletal morbidity rate by $\sim21\%$ (2.68 versus 3.38 events per year for placebo; $P = 0.014$). The skeletal morbidity rate in this subset is similar to that reported for patients with osteolytic lesions from breast cancer (6, 18), which is generally higher than that in patients with most other solid tumors (19).

**Fig. 2** Kaplan-Meier estimates of time to first skeletal-related event in patients with bone metastases from renal cell carcinoma during a 9-month trial of zoledronic acid. Data presented are for the 4-mg zoledronic acid and placebo groups. The number of evaluable patients in each group is listed for each of the time points. NR, not reached; SRE, Skeletal-related event. Cancer, Vol. 98, No. 5, 2003, pp. 962–9. Copyright © 2003 American Cancer Society. Adapted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. (6).
Using a prospectively planned Andersen-Gill multiple event analysis that incorporates the incidence and timing of all of the skeletal-related events throughout the study and accounts for inter- and intrapatient variations in the event rate (16), patients treated with zoledronic acid had a significant 61% reduction in the risk of skeletal-related events during the 9-month trial compared with the placebo group (risk ratio, 0.394; 95% confidence interval, 0.193 to 0.806; \( P = 0.008 \); ref. 6). The risk reduction of skeletal-related events was more profound in the renal cell carcinoma subset than in the overall patient population (31% risk reduction; ref. 20) and greater than that seen in other patient populations. These data indicate that patients with renal cell carcinoma are at high risk for skeletal-related events because of the clinically aggressive nature of their bone lesions, thus, have the potential to receive greater clinical benefit from treatment with zoledronic acid.

Zoledronic acid also had clinically observable effects on bone lesions in these patients and delayed time to progression of bone lesions. During the trial, 2 renal cell carcinoma patients (7%) treated with 4 mg of zoledronic acid compared with no patients in the placebo arm had partial responses in their bone lesions, as assessed by a central blinded radiologist (15). Overall, 48% of patients in the 4-mg zoledronic acid arm had either stable disease or partial responses in their bone lesions, compared with only 21% of patients in the placebo arm (15). Although the progression of visceral metastases and overall disease progression were not reported, it is likely that these were also delayed in the 4-mg zoledronic acid treatment arm compared with the placebo arm, based on the trend toward increased survival in the zoledronic acid-treated patients (as discussed below). The increased incidence of bone lesion response during bisphosphonates therapy is consistent with prior reports from below). The increased incidence of bone lesion response during multiple myeloma. Notably, in the renal cell carcinoma subset, the profile of renal-related adverse events was similar in the 4-mg zoledronic acid and placebo groups (Table 3; ref. 6). Therefore, 4 mg of zoledronic acid is not associated with any significant risk of decreased renal function in patients with renal cell carcinoma.

Zoledronic acid was well tolerated in patients with renal cell carcinoma (6). The adverse-event profile of 4 mg of zoledronic acid was similar to that of placebo. Adverse events that occurred more frequently in patients treated with zoledronic acid included nausea, fatigue, pyrexia, rigors, and lower-limb edema (19). These events are consistent with the effects of the acute-phase reaction that is known to occur in some patients after initial bisphosphonate infusion (22). Acute-phase reactions are typically more common after the first few infusions of bisphosphonates and rarely occur after subsequent infusions. Consistent with the reported analgesic effects of bisphosphonates (23), more patients in the placebo group reported bone pain (63% compared with 52% in the 4-mg zoledronic acid treatment group); however, this analysis did not distinguish between severe and moderate events (6). A larger proportion of patients in the placebo group experienced at least one serious adverse event (68% compared with 48% for the 4-mg zoledronic acid group), the most common of which were aggravated malignant neoplasm, bone pain, dehydration, dyspnea, and pneumonia.

In patients with renal cell carcinoma, many of whom have received unilateral nephrectomy for treatment of their primary cancers, preserving function in the remaining kidney is especially important. Therefore, renal function was closely monitored in this trial (6). Because of concerns regarding renal function, the 8-mg dose was reduced to 4 mg during the trial and is not recommended; moreover, only the 4-mg dose is approved for clinical use. Notably, in the renal cell carcinoma subset, the profile of renal-related adverse events was similar in the 4-mg zoledronic acid and placebo groups (Table 3; ref. 6). Therefore, 4 mg of zoledronic acid is not associated with any significant risk of decreased renal function in patients with renal cell carcinoma.
Zoledronic acid also improved clinical outcome in a retrospective subset analysis of patients with bone metastases in renal cell carcinoma (6). The results from the 21-month extension phase confirmed and extended those of the extension phase of the trial (15). The results from the 21-month extension data of this trial confirmed and extended the findings reported previously (6). On the basis of guidelines for patients with breast cancer (24) who experience skeletal complications at a rate comparable with that reported in patients with breast cancer (24), use of i.v. bisphosphonate therapy should be considered in any patient with radiographic evidence of bone metastases.

The median time to first pathological fracture was not reached in the 4-mg zoledronic acid group even at the 21-month time point. The safety data were consistent with those of the 9-month core analysis.

**CONCLUSIONS**

Before the introduction of zoledronic acid, palliative therapy for bone metastases secondary to renal cell carcinoma was a significant unmet medical need. Zoledronic acid (4 mg via 15-minute infusion) is the first bisphosphonate to significantly delay or prevent skeletal complications in patients with renal cell carcinoma in a randomized placebo-controlled trial (6). The prevention and delay of skeletal-related events represent meaningful clinical benefits to patients with advanced cancer (5). The 21-month extension data of this trial confirmed and extended the results reported previously (6). On the basis of guidelines for patients with breast cancer (24) who experience skeletal complications at a rate comparable with that reported in patients with renal cell carcinoma (6, 21), use of i.v. bisphosphonate therapy should be considered in any patient with radiographic evidence of bone metastases.

Zoledronic acid also improved clinical outcome in a retrospective subset analysis of patients with bone metastases from renal cell carcinoma. In addition to preventing and delaying the onset of skeletal-related events, zoledronic acid improved bone-lesion responses and significantly prolonged the time to bone-lesion progression. These results provide additional clinical evidence of the potential antitumor effects of bisphosphonates on bone metastases. Evidence from preclinical models has shown that zoledronic acid significantly reduces skeletal tumor burden in a variety of animal models (25). Although the results of this subset analysis are extremely encouraging, this analysis represents a limited clinical experience. Therefore, larger prospective studies in patients with bone metastases from renal cell carcinoma are warranted.

**OPEN DISCUSSION**

**Dr. Robert Figlin:** Most of us use this drug in patients with bony metastases. How will this common practice impact on the interpretation of results from target-specific therapy in relation to time to progression and overall survival, when they’re really just Phase II trials? Jim, you didn’t have bony metastases patients on your trial, but did patients whose disease progressed, progress with bony disease?

**Dr. James Yang:** No, not so much. It wasn’t a prominent finding, but we had very sensitive criteria for tumor progression.

**Dr. Figlin.** It seems like it’s this third of the population of patients that have bony metastases that would be candidates for this therapy plus target-specific therapy.

**Dr. Michael Gordon: These data make it a bit difficult to even consider excluding bisphosphonate therapy in patients with bone metastases going on to an investigational study.**

**Dr. Allan Lipton:** I agree completely. The ideal thing would be to have a large cooperative group go back and do the proper prospective randomized study, but that’s never going to be done in the United States.

**Dr. Gordon:** It’s probably too late. The study to do it in would have been the CALGB randomized trial with interferon interferon plus bevacizumab with a second randomization.

**Dr. Figlin:** What do people think about the interpretation of these Phase II trials in populations with bony metastases? Because it looks like progression is going to be slowed down if these data are correct.

**Dr. Gordon:** It sounds like one answer would be stratification for bone metastasis or no bone metastasis.

**Dr. Figlin:** In a Phase III trial?

**Dr. Walter Stadler:** A controlled Phase II trial that has stable disease or nonprogression as an endpoint is the answer.

**Dr. Tim Eisen:** IL-6 may be playing a role, particularly in the bone, where it is thought to be a renal cell growth factor. Were there data from this study?

**Dr. Lipton:** No, this was not measured in this study. There is no serum left over to look at IL-6.

**Dr. Atkins:** Do we know how this drug might impact the clearance of some of the other drugs or any pharmacological interactions that might be worrisome?

**Dr. Lipton:** I don’t think that’s been looked at. We’re doing right now a zoledronate/imatinib mesylate study in patients with bone metastases, looking at some drug-drug interactions to see if there is anything of concern.

**Dr. Gordon:** The best data for the bisphosphonates come from the myeloma patient population, where there are good data from Ken Anderson’s lab indicating that probably aside from inhibiting bone resorption, it does have some direct effect on the
tumor that is presumably antiangiogenic. It has been 4 years that his group has been proposing that pamidronate was antiangiogenic in some manner.

**Dr. Daniel George:** In terms of a recommendation, in prostate cancer when we do our trials on hormone refractory disease, we routinely require that all of the patients are maintained on androgen deprivation therapy. I don’t think it would be unreasonable to say, if you were going to stratify for bone metastasis, that this is a part of the standard.

**Dr. Atkins:** I don’t think we can say in a trial that everybody should go on zoledronate.

**Dr. Gordon:** So then the challenge becomes, if you’re doing a randomized Phase II trial and you have a control arm, then at least you have something to gauge the impact of the zoledronate on. If you’re going to do a straight Phase II to look at activity or time to progression endpoint, do we need to exclude patients with bone metastases from those studies to be able to get a signal? Because the worst-case scenario is getting an incorrect signal, unless you just say the signal may be distorted by the presence of patients with bone metastases, but if it’s positive, we are going to proceed to a Phase III trial and we’ll account for that by stratification and randomization.

**Dr. Atkins:** I’m still curious about the actual data here and how convincing it is. I’m struggling because half the people are dead at 11 months, yet the median time to an event is 21 months. How many people are really being assessed at the median when there aren’t that many people who remain alive?

**Dr. Lipton:** Doesn’t it say that there is a subset, a small number, that’s really doing very well?

**Dr. Atkins:** Is that enough to say that for every patient with bone metastasis or for every trial that we’re doing that we should legislate that they should all get zoledronate? I’m not sure of that.

**Dr. Figlin:** In people who are being treated with frontline therapy at the time of first relapse in all of the trials that we’ve talked about, there is going to be a population of patients that have bony metastases as part of their spectrum. I personally would have difficulty withholding zoledronate from that population, yet I would want to be sure that I’m still assessing the innovative strategy that I’m trying to test.

**Dr. Atkins:** We give it to practically everybody, but in a patient with asymptomatic bony metastases, there might be a concern about extra toxicity or some potential interference with the pharmacology of the experimental agent that you’re testing.

**Dr. Figlin:** But those are also the patients who are most likely to benefit from the agent, right? Because you’re trying to prevent the first skeletal-related event.

**Dr. Yang:** These data are very scant. For our few bony metastasis patients, none of them get zoledronate unless they have other specific indications, so this is really not a preventive or prophylactic routine therapy.

**Dr. Figlin:** What would the design of the trial be to definitively answer prospectively the question about a bisphosphonate in metastatic kidney cancer with bony metastases?

**Dr. Lipton:** If you now have the luxury of a large study, maybe you ought to be stratifying the bone metastases patients or making sure they’re treated uniformly, so it doesn’t interfere with what you’re looking at as the main purpose of the trial.

**Dr. Atkins:** It’s going to be an issue, because all of the new agents are being studied in either first or second line. Consequently, patients may only get one shot at this class of drugs and be excluded from subsequent trials when a study of a combination with a bisphosphonate might make more sense.

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