Dear Colleague:

The incidence of renal cell carcinoma (RCC) has been rising over the last 2 decades, and is now about 31,000 cases/year. Skeletal involvement is common among patients with RCC. Approximately one third of these patients will develop osseous metastases. This is an important turning point in the disease, because approximately 81% of such patients will require radiation therapy, 42% will have a long-bone fracture, and 29% will require orthopedic surgery or develop hypercalcemia during the subsequent course of their disease. Through the case of a 65-year-old man with bone metastases, this newsletter illustrates how the latest data on bisphosphonates affect the care of patients with RCC.

The first part of this 5-part Tx Reporter series, New Currents in Treatment of Bone Metastases: A Case-Based Approach, included an overview of bone metastases and bisphosphonates. This was followed by case-based newsletters on bone metastases in breast cancer (Part 2) and prostate cancer (Part 3). This series continues here with the case of an RCC patient with bone metastases. Part 5 will address the use of bisphosphonates in preventing skeletal complications of lung cancer. This 5-part series allows an in-depth look at specific patient populations and information on applying the data on bisphosphonates to actual clinical practice.

Each issue is an independent activity consisting of a Tx Reporter newsletter and an audio CD featuring an interview of the expert faculty on related issues. Each issue is also accompanied by a recent reprint with information that has largely determined the current standard of care. This series focuses on the next generation of bisphosphonate therapy. However, fair balance is critical to this discussion, and the faculty and I also present data on other bisphosphonates.

I hope that you enjoy the series and find it helpful and informative.

Yours truly,

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This Tx Reporter series discusses the use of bisphosphonates to help prevent skeletal-related events in patients with bone metastases from solid tumors. This fourth issue contains the case of a 65-year-old man who develops metastatic renal cell carcinoma. This continuing professional education activity also includes the enclosed audio CD, in which Dr. Lipton discusses:

- Prognosis of renal cell carcinoma (RCC) with osseous metastases
- Studies of bisphosphonates, including the retrospective analysis of zoledronic acid, in patients with metastatic RCC
- The impact of concomitant nonosseous metastases on the decision to use bisphosphonates
- Appropriate candidates for bisphosphonate therapy
- The risk of renal toxicity in patients with RCC who have undergone nephrectomy
- The most appropriate dosing schedule and duration of zoledronic acid in patients with RCC
- Cost-effectiveness of bisphosphonate therapy
- The clinical significance of markers of bone resorption

Download this 5-part series—New Currents in Treatment of Bone Metastases: A Case-Based Approach—available at www.projectsinknowledge.com/oncol/
New Currents in Treatment of Bone Metastases: A Case-Based Approach: Bone Metastases in Renal Cancer

**Case Description**
Mr. K, a 65-year-old Caucasian man with a history of hypertension, presented in November 2000 with back pain and blood in his urine. Mr. K was an employee of the state government, had a 35-year history of smoking cigarettes, and reported being a social drinker. His family history included a mother with lung cancer. A palpable mass in his right abdomen was found on physical examination. A computed tomography scan showed a 12-cm mass in his right kidney. Bone scan was negative. Later that month, Mr. K underwent right nephrectomy. It was determined that he had a 12-cm tumor invading the renal vein inferior vena cava with positive lymph nodes.

**Adjuvant Therapy in Renal Cell Carcinoma**

**Question 1:** Would you recommend adjuvant therapy for Mr. K?

1. Yes, with interferon alfa-NL
2. Yes, with interleukin-2
3. No

**Discussion**
Adjuvant therapy has not been proven to have clinical benefits in RCC. In a phase III study of 283 patients with pT3–4a and/or node-positive disease, interferon alfa-NL did not improve survival (5.1 versus 7.4 years with observation; P = .09) or relapse-free survival (2.2 versus 3.0 years, respectively; P = .33). Similarly, a phase III study of 69 patients with resected locally advanced (T3–4 or N1–3) or metastatic (M1) high-risk RCC was terminated early when it was determined that at least a 30% improvement in disease-free survival could not be attained with high-dose interleukin-2.

**Case Continues**
CT scan of the chest and abdomen was negative in 2001. In February 2002, Mr. K reported hip and rib pain. Bone scan showed multiple metastases.

**Correlates of Longer Survival in RCC**
- Presentation without metastases
- Long disease-free interval between nephrectomy and first metastases
- Appropriate skeletal location
- Solitary metastases

**Source:** Althausen P, et al.

**Discussion**
RCC frequently metastatizes to bone, and metastasis often occurs before the primary cancer has been diagnosed. Prognosis appears to vary, with many reports indicating a life expectancy of 12 to 24 months following development of osseous metastasis. However, a report from Massachusetts General Hospital found that these patients can live for quite a number of years, with 90% survival at 6 months, 84% at 1 year, 55% at 5 years, and 39% at 10 years. In that study, longer survival correlated with presentation without metastases, long disease-free interval between nephrectomy and first metastases, appendicular skeletal location, and solitary metastases.

On the other hand, five factors have been reported to be associated with shorter survival in patients with RCC: Karnofsky performance status <80%, serum lactate dehydrogenase level >1.5 times the upper limit of normal, hemoglobin less than the lower limit of normal, "corrected"...
serum calcium >10 mg/dL, and lack of prior nephrectomy. Among those with none of these risk factors, median survival time was 20 months, versus 10 months for those with one or two risk factors and 4 months for those with three or more risk factors.1

Correlates of Shorter Survival in RCC
- Karnofsky PS <80%
- Serum lactate dehydrogenase level >1.5 x upper limit
- Hemoglobin < lower limit of normal
- "Corrected" serum calcium >10 mg/dL
- Lack of prior nephrectomy

Treatment of RCC with Bone Metastases

Question 2: What treatment would you offer Mr. K at this point?

a. Chemotherapy
b. Interleukin-2
c. Interferon alfa-2a
d. Interferon alfa-NL
e. Pamidronate
f. Zoledronic acid
g. No therapy

(e) Unfortunately, bone metastases rarely respond to systemic treatment. Results with chemotherapy have been disappointing, possibly due to overexpression of a multidrug resistance gene or to a high glutathione content in RCC cells. Interleukin-2 and interferon alfa have generated some interest, but response rates tend to be low (15%-20%). Pamidronate has not been studied in patients with metastatic RCC. However, evidence does support use of zoledronic acid to prevent skeletal complications in this population. Recently, the results of a phase III, placebo-controlled study of zoledronic acid revealed a treatment benefit in patients with lung or other solid tumors. Zoledronic acid prolonged the time to first skeletal event (other than hypercalcemia) by 2 months and reduced the percentage of patients who develop skeletal-related events. A skeletal event was defined as pathologic fracture, spinal cord compression, radiation therapy to bone, or surgery to bone.2

Because of the poor prognosis of metastatic RCC and the limited treatment options, a retrospective analysis was performed to assess the benefit of zoledronic acid in the subgroup of 74 patients with RCC in this placebo-controlled, phase III lung and other solid tumors study. About three fourths of these patients had one to three bone lesions and a previous skeletal-related event prior to study entry. In the patients with RCC, zoledronic acid (4 mg IV administered over 15 minutes every 3 weeks) significantly reduced the proportion of patients with skeletal-related events compared with placebo (37% versus 74%, respectively; P = .015). It is noteworthy that the proportion of patients who developed a skeletal-related event during placebo treatment was twofold higher in the RCC subgroup compared with the entire population (74% versus 44%, respectively), suggesting that bone metastases from RCC are associated with a higher risk of skeletal-related events than are metastases from other solid tumors.3

Zoledronic acid also significantly reduced the mean skeletal morbidity rate (2.68 versus 3.38 events/y; P = .014) and extended the time to first event (median not reached versus 72 days for placebo; P = .006). A multiple-events analysis demonstrated that the risk of developing a skeletal-related event was reduced by 61% compared with placebo (hazard ratio = 0.394; P = .008).4 The median time to progression of bone lesions was significantly longer in patients treated with zoledronic acid compared with patients who received placebo (236 versus 89 days; P = .014). In addition, median survival showed a trend favoring zoledronic acid (29% versus 216 days; P = .179), but did not achieve statistical significance. The most common adverse events reported by patients with RCC included bone pain, nausea, anemia, fatigue, vomiting, and pyrexia. Serious adverse events were reported by 48% of the patients given 4 mg of zoledronic acid compared with 68% of those given placebo.5 It is noteworthy that only two of the patients with RCC who received 15-minute infusions of zoledronic acid experienced a renal-related adverse event, compared with three patients who received placebo. This suggests that renal toxicity is not more common among patients with RCC, the majority of whom have only one kidney at the time of bisphosphonate therapy.

Case Continues

Mr. K began treatment with zoledronic acid 4 mg IV Q3wk in late February 2002. The Q3wk dosing schedule was selected because it was used in the clinical trial evaluating this drug in renal cancer patients with bone metastases.6 Studies in breast cancer and multiple myeloma allowed dosing of zoledronic acid Q3–4wk,7 but dosing at the 4-week interval has not been assessed in RCC. By June 2002, Mr. K’s pain had decreased and bone scan indicated stable disease. However, a routine chest x-ray in August 2002 indicated new lesions in his lungs.

Managing Progressive Metastatic Disease

Question 3: What would your next management strategy be?

a. Discontinue zoledronic acid and initiate systemic therapy (eg, interleukin or interferon)
b. Continue zoledronic acid and initiate systemic therapy (eg, interleukin or interferon)
c. Continue zoledronic acid without additional therapy
d. Discontinue all therapy; initiate hospice care
(b) Zoledronic acid should be continued and systemic therapy initiated. Mr. K has stable bone disease, and inhibition of further bone resorption and prevention of skeletal complications remain important goals of treatment. In clinical studies, zoledronic acid was continued irrespective of disease progression or even the development of skeletal-related events.

Case Continues

Mr. K is currently continuing on zoledronic acid, which has been well tolerated. He has also been receiving interferon therapy (6 mIU/m² SQ TIW). Interferon has been well tolerated overall, with some low-grade fever and chills. The lung tumor showed partial response, and Mr. K is continuing interferon and zoledronic acid. His bone disease remains stable.

Discussion

In this case, Mr. K has been receiving zoledronic acid for over 1.5 years, and thus far has avoided skeletal complications of his disease. Mr. K has tolerated zoledronic acid well, and has not experienced renal toxicity.

Conclusion

Adjuvant therapy following nephrectomy for RCC has not been shown to be beneficial. Similarly, systemic therapies (eg, interleukin and interferon) for primary treatment of metastatic disease are of limited efficacy. Bisphosphonates have been found beneficial in a wide variety of cancer types. A small (N = 79) retrospective analysis found zoledronic acid to have significant clinical benefit in RCC patients with bone metastases. The striking reduction in the proportion of patients with a skeletal-related event and the delay in time to bone disease progression suggest that patients with RCC may be exquisitely sensitive to the effects of zoledronic acid. Prospective studies are needed to confirm these findings.

References

New Currents in Treatment of Bone Metastases: A Case-Based Approach, Part 4
Bone Metastases in Renal Cancer

Instructions for Documentation of Participation in This Activity:
To receive an acknowledgment of your participation for CME/CE credit, please complete the following steps:

1. Carefully read this newsletter and listen to the audio CD.
2. Complete the Posttest below, selecting the most appropriate response to each question.
3. Complete the Evaluation.

If you complete these steps and score 70% or higher, Projects In Knowledge will mail you an acknowledgment of participation for up to 1 hour of CME credit for physicians, 1 contact hour of credit for pharmacists, or 1.2 contact hours for nurses within 6 weeks of receipt of your materials. If you score lower than 70%, Projects In Knowledge will notify you by mail and you will be given another chance to take the Posttest.

This activity is designed as part of a 5-part series on treatment of bone metastases. We encourage you to complete the entire series for a full discussion of the topic.

Name __________________________________________________________________ Degrees/Credentials _________________

Mailing Address _____________________________________________________________________________________________

City _____________________________________________________________________ State ________ ZIP ________________

Phone ________________________________________________ Fax _________________________________________________

E-mail _____________________________________________________________________________________________________

Please indicate your answers below:

1. In a recent study of patients with pT3–4a and/or node positive RCC, adjuvant interferon α-NL improved survival significantly.
   a. True
   b. False

2. In RCC patients, bone metastasis often occurs before the primary cancer is diagnosed.
   a. True
   b. False

3. A phase III, placebo-controlled study reported that patients experienced a reduction in mean skeletal morbidity rate and an extension in the time to first skeletal event when treated with:
   a. Pamidronate
   b. Zoledronic acid
   c. Interferon alfa
   d. Interleukin-2
   e. None of the above
4. A multiple event analysis indicated that treatment with this therapy reduced the risk of a skeletal event by __________ compared with placebo.
   a. About 10%
   b. More than 25%
   c. More than half
   d. More than three quarters

5. Renal toxicity associated with bisphosphonate therapy is more common among patients with RCC than those with other solid tumors.
   a. True
   b. False

6. In a Massachusetts General Hospital study on patients with RCC, longer survival correlated with:
   a. Presentation without metastases
   b. Long disease-free interval between nephrectomy and first metastases
   c. Appendicular skeletal location
   d. Solitary metastases
   e. All of the above

7. Bone lesions associated with metastatic RCC tend to be:
   a. Lytic
   b. Blastic
   c. Mixed lytic and blastic

8. Which of the following patients with RCC and osseous metastases might not be a good candidate for bisphosphonate therapy?
   a. A patient with ECOG performance status of 1
   b. A patient with serum creatinine 2.8 mg/dL
   c. A patient with ECOG performance status >2 due to significant brain, liver, or lung metastases
   d. A patient with ECOG performance status >2 due to bone pain
   e. All of the above would be good candidates for bisphosphonate therapy

9. If a patient has shown a serum creatinine increase of ≥0.5 mg/dL since the previous measurement and creatinine is still <3 g/dL, Dr. Lipton recommends:
   a. Discontinuing bisphosphonate therapy
   b. Switching to pamidronate
   c. Increasing the infusion time to 30–60 minutes
   d. Increasing the infusion volume to 500–1000 mL
   e. Both c and d

10. The optimal duration of bisphosphonate therapy is:
    a. 12 months
    b. 24 months
    c. Until a skeletal event occurs
    d. Undetermined

Thank you for your participation.
Instructions: Please complete this survey, along with the Posttest, and mail or fax (both sides) to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424; fax: 973-890-8866.

1. Please rate the extent to which you achieved the learning objectives:

   - Review the incidence of bone metastasis among patients with renal cancer.
   - Describe the complications caused by bone metastases in the clinical management of renal cancer.
   - Discuss the safety and efficacy of currently available agents and next generation bisphosphonates.
   - Consider the use of intravenous therapy in the treatment armamentarium to delay and reduce skeletal complications of bone metastases in patients with renal cancer.

2. Please rate the relevance of the objectives to the overall purpose/goals of the educational activity:

   The goal of this activity is to provide an overview of bone metastases and the latest developments in preventing related skeletal complications using bisphosphonate therapies. Please rate the extent to which each objective was related to the goal of the activity.

3. Please rate the overall value of this enduring material:

4. Course was free from commercial bias:

   If you “Disagree” or “Strongly Disagree,” why? ....................................................................................................................................................
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New Currents in Treatment of Bone Metastases: A Case-Based Approach, Part 4
Bone Metastases in Renal Cancer
CME/CE PARTICIPANT EVALUATION

5. Please rate the level of the material presented:
   ❑ ❑ ❑

6. Please list any changes in your practice that you would consider making as a result of participating in this activity:

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7. Please rate your interest in self-directed or distance learning in the following formats: Very Interested Moderately Interested Not Interested
   a. Audioconference ❑ ❑ ❑
   b. Videoconference ❑ ❑ ❑
   c. Enduring materials (audio CDs, videotapes, monographs) ❑ ❑ ❑
   d. Internet (online discussions with experts, educational activities) ❑ ❑ ❑
   e. Multimedia (online, CD-ROM) ❑ ❑ ❑

8. Please tell us how long it took you to complete this course (in minutes):
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9. Please list topics and/or experts you would find interesting and professionally relevant for future CME activities:

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10. Follow-up:
    As part of our ongoing continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our CME courses on professional practice. Please indicate your willingness to participate in such a survey:
    ❑ Yes, I would be interested in participating in a follow-up survey.
    ❑ No, I’m not interested in participating in a follow-up survey.

   Additional comments about this activity:
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Thank you for your participation.