CASE 1: LUNG CANCER AND ASYMPTOMATIC BONE METASTASIS: CURATIVE VS PALLIATIVE INTENT

A 69-year-old man with a 10-pack-per-year history of smoking presented to Dr Brahmer after consulting with other physicians. He had first visited an ear, nose, and throat physician because of hoarseness. At that time, he had left vocal cord paralysis; results of a computerized axial tomography scan revealed a left hilar mass, in addition to mediastinal adenopathy. The patient underwent a bronchoscopy and biopsy. The pathology yielded adenocarcinoma, poorly differentiated, thyroid transcription factor-1 positive. Subsequent to evaluation by the ear, nose, and throat physician, the patient met with an oncologist. Results of a positron emission tomography (PET) scan showed fluorodeoxyglucose (FDG) avidity in the left lung mass, mediastinal adenopathy, and a possible right iliac bone metastasis.

Dr Brahmer: The patient then came to me for a second opinion and to discuss his treatment options. In addition to complaints of shortness of breath, cough, hoarseness, and occasional hemoptysis, he reported a recent 20-lb loss in weight, absence of bone pain, and results of a recent brain magnetic resonance image (MRI) that was negative with no neurological symptoms. His primary concern about the staging of the lung tumor was whether he had stage III disease or if it had progressed to metastatic disease. I requested an MRI, rather than a bone scan or plain x-rays. The MRI confirmed metastatic disease in the patient’s right iliac crest, which was highly suspicious and considered to be positive at that time. The next step, a biopsy, was not performed at that point.

Dr Ettinger: Were there associated symptoms?

Dr Brahmer: No, there were no associated symptoms.

Dr Langer: Would you biopsy the iliac crest?

Dr Curran: It depends how unequivocal the MRI and the PET scan are. If there is a very high pretreatment standardized uptake value by FDG-PET, plus a lesion in someone with no other osseous problems associated with age or benign morbidity, then fine. It is not a hard place to perform a needle biopsy. It would be something to consider if you thought you were going to be treating him with a multimodality approach versus palliative care.

Dr Langer: Yes, it depends on our goals: curative intent versus palliative intent. It would also depend on how convinced the radiologist was that there was metastatic disease present. If the findings are unequivocal, I probably would not proceed with biopsy. If the radiologists equivocate, I probably would consider it, particularly because it is an isolated area of metastasis.

Dr Ettinger: Let’s say it is unequivocal, and that it is stage IV disease with a solitary isolated bone metastasis. What would you do in that scenario?

Dr Curran: The 2 options to consider are: (1) treat it like stage IV disease and figure out whether he is a carboplatin-paclitaxel-bevacizumab patient; or (2) treat it like a unique oligometastatic situation. You could irradiate the iliac lesion and treat him aggressively with chemotherapy-radiotherapy, thinking there is a small subset of people with oligometastatic disease...
for whom natural history is going to be more favorable than stage IV disease.

**Dr Ettinger:** That is what I would do. Would you do that, Dr Curran?

**Dr Curran:** What volume is the central disease?

**Dr Brahmer:** It is large-volume central disease, symptomatic with hoarseness and cough, and hemoptysis.

**Dr Curran:** In my perspective, the reason to treat him with chemotherapy-radiotherapy is more a function of the symptoms and the bulkiness than the curability. You would probably want to add zoledronic acid to address the skeletal events, but I think the chemotherapy-radiotherapy is how I would start, based on the bulk of disease and the need for palliation and control.

**Dr Ettinger:** Did the patient respond?

**Dr Brahmer:** I just gave him chemotherapy.

**Dr Langer:** I would give chemotherapy; however, the history of hemoptysis would likely preclude bevacizumab. I would probably add zoledronic acid. But, if his hoarseness and cough do not respond quickly, I would certainly entertain giving aggressive radiation therapy.

**Dr Ettinger:** What happened to this patient?

**Dr Brahmer:** He had a very good response. We gave him paclitaxel and carboplatin, and at the end of the 6 cycles, we performed a repeat PET scan. The bone metastasis was not detectable by PET scan at that point, but within 5 months he recurred with a positive PET scan in the bone again, as well as in the lung.

**Dr Berenson:** Multiple sites or single?

**Dr Brahmer:** Multiple sites at that time.

**Dr Curran:** You did not initially sterilize it with radiation?

**Dr Brahmer:** No. It remains asymptomatic.

**Dr Ettinger:** I would have taken a different approach if the patient was symptomatic, had hoarseness, and if combined chemotherapy-radiotherapy had taken care of that. I would evaluate after 4500 cGy. If the patient was responding and symptomatically better, I would continue with definitive radiation therapy and persuade the radiation oncologist to irradiate the bone with the idea that this is a rare case, an isolated metastasis, and we might be able to prolong the patient's life for a reasonable period of time. I would want at least 3000 cGy, perhaps more. It is a very small port. You should administer it to an area where you cannot do much damage, unless the patient lives a long time and you are concerned about other radiation-induced effects. I have several patients exactly like that and it is now 2 years down the road. So it does happen.

**Dr Brahmer:** Yes, but people with bone metastases, even if they present initially with an isolated lesion, are frequently harboring other metastases.

**Dr Ettinger:** I agree. I think I would divide bone metastases from brain and adrenal metastases. If a patient had presented this way with a solitary brain metastasis, or a solitary adrenal metastasis, I would have taken the more aggressive approach, possibly resected those metastases, and do aggressive local concomitant chemotherapy-radiotherapy. But with a bone metastasis, I might have followed Dr Brahmer's approach.

**Dr Brahmer:** The patient has actually fared relatively well. It is now approximately 1.5 years after his initial diagnosis. He is currently on erlotinib and zoledronic acid, with stable disease, and without bevacizumab. He never required radiation to the mediastinum.

**Dr Garey:** Did you start the zoledronic acid at the same time he started chemotherapy?

**Dr Brahmer:** Yes.

**Dr Ettinger:** Did you have the patient obtain a dental consult?

**Dr Brahmer:** No, but I think that would have been a good idea.

**Dr Ettinger:** What was your initial systemic chemotherapy?

**Dr Brahmer:** Paclitaxel and carboplatin.

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**SUGGESTED READING**


CASE 2: TREATMENT OF LUNG CANCER WITH FEMORAL LESION RESULTING IN POSSIBLE COMPARTMENT SYNDROME

A 72-year-old male smoker with diabetes presented with chronic cough and progressive right hip pain. He had seen his orthopedist because of a history of chronic osteoarthritis problems and previous bilateral knee replacement. His orthopedist ordered an x-ray of his right hip, and this showed a large lytic lesion in the femur with cortical destruction. The orthopedist obtained a biopsy and the pathology was consistent with adenocarcinoma.

Dr Brahmer: Further workup revealed a left lower lobe mass and hilar adenopathy. The patient was also found to have additional small bone metastases in the ribs. No brain, liver, or adrenal metastases were detected. There was no hemoptysis, and no history of therapeutic anticoagulation. What would you do first?

Dr Curran: It sounds like he may need his femur rod and irradiated. While that is getting done, one would probably want to consider the appropriate systemic therapy in addition to zoledronic acid.

Dr Langer: Would you irradiate after the rodding?

Dr Curran: Yes.

Dr Langer: I would administer a 1-week course for the hip. I would not prolong it to 2 weeks. The symptomatic site is the hip. He is asymptomatic from the primary, or almost asymptomatic. His only pulmonary complaint is chronic cough. The first priority is to fix the hip. Otherwise, it will not matter what else you do, and systemic therapy alone is not likely to have much effect on the hip. From the description, it sounds as if he needs some kind of surgical intervention. This is where I typically get a radiology report that indicates “impending fracture,” or some other impending catastrophe. Therefore, rod and is appropriate. If the lesion is very proximal, you might need a total hip replacement, but it depends on the location.

As for postsurgical radiation, I would keep it short. I would probably put this patient on zoledronic acid along with chemotherapy. We continue to use paclitaxel and carboplatin, although I am open to other chemotherapeutic combinations. Also, I would probably administer bevacizumab because he does not have any contraindications for this. Assuming that he heals properly from his hip surgery, he would be a candidate for a clinical trial. We are currently looking at an insulinlike growth factor receptor antibody in combination with paclitaxel and carboplatin. I would not have problems putting him on that regimen in lieu of bevacizumab.

Dr Brahmer: We ended up rodning him and giving him radiation therapy, and then there was an interesting outcome. Bevacizumab was not used (this time frame preceded its availability). We used gemcitabine and carboplatin. After 4 cycles of gemcitabine and carboplatin, in addition to the radiation, his hip pain initially improved, and then he slowly had worsening pain. He also had hardening of his right thigh localized to the area of radiation therapy administration, and this site became increasingly redder. This was a diabetic patient, so we thought it was a form of cellulitis and treated him as such, but it got worse. He ended up with a compartment syndrome because it became so hard. The question was: Did the muscle in that area become necrotic in association with the radiation? I do not know if any of you have ever seen that before.

Dr Curran: You are talking about gemcitabine recall.

Dr Brahmer: Correct.

Dr Curran: Yes, but not in a patient whose surgery and area is so uncomplicated. Maybe in a setting where there is active tumor in the skin or the muscle, but I have never heard of that in this situation.

Dr Langer: I have seen it.

Dr Berenger: Gemcitabine is highly radiomimetic.

Dr Curran: Yes, but to this severity I have never seen it.

Dr Brahmer: I have never seen it to the point where a patient had to have surgery like this one.

Dr Langer: I have certainly seen reddening and, over time, fibrosis, more than I would ordinarily expect to see with standard radiation. Also, we have seen it in the chest, and in adjacent soft tissues in patients who have received gemcitabine after thoracic radiation therapy.

Dr Ettinger: How did you treat it?

Dr Brahmer: The patient had surgery, it was necrotic, and there were no infections.

SUGGESTED READING


CASE 3: NEPHROTOXICITY ISSUES IN TREATMENT OF

S1078
LUNG CANCER WITH MULTIPLE ORGAN METASTASES, INCLUDING BONE

An 80-year-old woman presented with cough and, upon workup, was found to have a lung mass. Biopsy confirmed adenocarcinoma, and further workup diagnosed metastatic non–small-cell lung cancer. Metastases were in the liver and lung at that time. She was first administered 2 cycles of gemcitabine-carboplatin and was found to have disease progression. At that point, she began complaining of bone pain, and a bone scan indicated bone metastasis.

Dr Brahmer. She received 2 cycles of gemcitabine and carboplatin. We then switched, and gave her docetaxel as a single agent for second-line treatment (this was awhile ago). We also started giving her zoledronic acid. When the patient took her first dose of zoledronic acid, her renal function was noted as “fine”; after her second dose of zoledronic acid, she presented a week later with a creatinine value of approximately 5 mg/dL. The patient was admitted to the hospital, and workup did not reveal any obstruction. She was taking an angiotensin-converting enzyme inhibitor and non-steroidal anti-inflammatory drugs, so those medications were stopped.

Dr Garey. Were these new or maintenance medications?

Dr Brahmer. They were maintenance medications. On further workup, it was believed that the creatinine rise was potentially caused by zoledronic acid. Retrospectively, the second dose of zoledronic acid was clinically administered in less than 15 minutes, or relatively quickly.

Dr Ettinger. Have you seen creatinine values of 5 mg/dL in your population?

Dr Brahmer. Yes. I had a patient a couple of weeks ago who received her first dose of zoledronic acid and became dialysis-dependent for a short period of time. It is rare, but it does occur. Over time, her creatinine values returned closer to normal.

Dr Ettinger. So you discontinued everything, the angiotensin-converting enzyme inhibitors, the non-steroidal anti-inflammatory drugs, and the zoledronic acid?

Dr Brahmer. That is correct. I did not restart the zoledronic acid because of the risk of acute renal failure.

Dr Langer. We conducted a retrospective study from the time zoledronic acid was first approved and over the following year, in which we examined the incidence of renal insufficiency. In our population at Fox Chase Cancer Center, which included a large representation of breast and lung cancer patients, and very few with myeloma, there were usually some other factors that contributed to elevated creatinine. These patients were either volume-contracted, had another contributing disease such as diabetes (or in rare instance, myeloma), or were taking other drugs with known nephrotoxicity. Therefore, there was always some complicating, confounding variable that may have contributed, or may have actually caused renal impairment. Very few people developed renal impairment without any other contributing factors. Our former fellow, Raymond McDermott from Ireland, has completed the manuscript and it is being submitted.

Dr Brahmer. It is important to be aware of what other medications these patients are taking that may make them more prone to renal insufficiency. If known, I will follow these patients closely. It is not as though we do not check a patient’s creatinine value except for the day that they come in for the zoledronic acid infusion therapy.

Dr Berenson. Do you wait every month for creatinine values to come back before you dose? Most people do not do that.

Dr Ettinger. I wait.

Dr Brahmer. Yes, our nurses wait.

Dr Garey. We have a similar practice.

Group. Most of the people here are in academics. However, in a private practice setting, physicians may give infused therapy without updated creatinine data.

Dr Ettinger. I think that is a risk because these patients are complicated enough. You have to know your patient.

Dr Langer. These patients are routinely receiving additional drugs for which we require creatinine data. Therefore, if they are taking carboplatin, they are receiving a creatinine anyway. For us, it is not so difficult because checking creatinine values is part of our standard operating procedures.

Dr Brahmer. However, if that is all they are receiving, it would be another story.

Dr Ettinger. Has anyone looked at the rate of renal insufficiency when giving zoledronic acid and whether it is more adversely affected by cisplatin than carboplatin?

Dr Berenson. That has not been systematically looked at.

Dr Garey. Because cisplatin alone causes more
nephrotoxicity than carboplatin, it would make sense that the combination of zoledronic acid with cisplatin could have a greater negative impact on renal function than if combined with carboplatin.

**Dr Brahmer:** It is an innate sense that other agents contribute to the nephrotoxicity.

**Dr Garey:** Other examples would include diuretics, certain antihyperglycemic agents such as metformin, and intravenous and oral antibiotics. Polypharmacy is common in this patient population, so it is crucial to be updated of a patient’s current medications.

**Dr Ettinger:** I see many patients as second opinions, and the wide range of polypharmacy of the patients. You must have a pharmacist right next to you to ask questions such as, “What are the interactions of these 3 antihypertensives, and these 2 diabetic antitype 2 medications?”

**Dr Garey:** In addition to medications, intravenous contrast may be a confounding factor that may predispose a patient receiving zoledronic acid to renal toxicity. Another important consideration is patient hydration status and the presence of nausea/vomiting as an adverse event from other systemic therapies, which can also lead to changes in serum creatinine.

**Dr Ettinger:** The real question is, “What is the risk?” If you have to give the patient a consent form, and you start to look at some of the language that you must include for regulatory purposes, say to the patient, “If you want to understand what the difficulties or toxicities are, get the handout on aspirin from your neighborhood pharmacist as an example—it is 3 pages long.”

**Dr Berenson:** It is a difficult issue with patient enrollment. We are now trying to enroll for a pre-myeloma trial with zoledronic acid. We were doing well, but then the lay press reports came out regarding osteonecrosis of the jaw and, suddenly, enrollment stopped. The patients were concerned that their jaws would fall off.

**Dr Garey:** I think it is a matter of making sure patients receive appropriate education from the right resources. The lay press and Internet chat rooms are not the most reliable sources of peer-reviewed data. Patients may fear the worst, as opposed to seeking out reliable information from their physician or pharmacist who is educated in the field. Patient education is a critical part of enrollment in clinical trials and standard treatment regimens so that patients feel confident that if they do experience an adverse effect, it can be treated in a timely manner.

**SUGGESTED READING**

