Published in final edited form as:
Clin Genitourin Cancer. 2011 December ; 9(2): 81–88. doi:10.1016/j.clgc.2011.07.001.

Pilot trial of bone-targeted therapy combining zoledronate with fluvastatin or atorvastatin for patients with metastatic renal-cell carcinoma

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Abstract

Objective—The biologic rationale for this study came from the observation that bisphosphonates and statins affect bone metastasis in different ways; thus, combination therapy may provide synergistic benefit. This pilot trial evaluated the efficacy and safety of combining a bisphosphonate and statin in patients with renal-cell carcinoma (RCC) metastatic to bone.

Methods—Patients with RCC and bone metastasis received zoledronate and fluvastatin or atorvastatin. Patients were monitored clinically and by imaging for skeletal events. Concentrations of the bone-resorption markers deoxypyridinoline (DPD) and N-telopeptide (NTX) and the bone-formation marker bone-specific alkaline phosphatase (BSAP) were monitored for changes during treatment.

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CONFLICT OF INTEREST DISCLOSURES

This work was supported in part by a grant from Novartis Pharmaceuticals Corporation, East Hanover, New Jersey. Financial conflicts of interest to disclose: Shi-Ming Tu served on an Advisory Board sponsored by the Novartis Pharmaceuticals Corporation. The other authors have no conflicts of interest to disclose.

Results—Eleven patients were enrolled and followed for a median time of 6 months. The median time to first skeletal-related event for all patients was 9.0 months. Seven (63%) patients experienced skeletal events with a median time to first skeletal-related event of 4.0 months (range, 3–18 months); Four patients (36%) did not experience any skeletal events for a median of 12 months of follow-up (range, 2–28 months). Four patients (36%) demonstrated treatment responses with development of sclerosis in lytic bone lesions. Differences in the median changes in biomarker levels between patients who had a skeletal event and those who did not were statistically significant for DPD and NTX ($P = 0.03$ and 0.01, respectively) but not for BSAP ($P = 0.4$). The regimen was well tolerated, with few adverse reactions related to study drugs.

Conclusion—Although the use of bone-targeting therapy combining zoledronate and fluvastatin or atorvastatin affected certain bone biomarkers and provided bone response in several patients with RCC and bone metastasis, we could not demonstrate a statistically significant improvement in time to skeletal events.

Keywords

Bisphosphonate; Statin; Bone metastasis; Renal-cell carcinoma

1. Introduction

Renal-cell carcinoma (RCC) accounts for 3% of all adult malignancies, with 58,000 new diagnosed cases and 12,000 deaths estimated for 2010 [1. RCC is the tenth-leading cause of cancer death in the United States [1]. Metastatic RCC is associated with a 5-year survival rate of 0%–10% and a median survival time of 7–11 months [2,3].

Skeletal lesions develop in about half of the patients with metastatic RCC, and 80% of these bone metastases become evident within 3 years of the original diagnosis [4–6]. The median interval from the time of diagnosis to the first skeletal metastasis is about 8.5 months [7]. These skeletal metastases account for 10% of all pathologic fractures and 5% of all spinal cord compressions in patients with cancer [8]. The median survival of patients with multiple skeletal metastases in RCC is about 1 year [9,10], although patients with a solitary skeletal lesion tend to have a more protracted clinical course, with a 5-year survival rate reported between 30% and 60% [7, 11, 12].

Bisphosphonates have been shown to reduce the incidence of bone-related events in patients with metastatic RCC [13]. Their mechanisms of action include inhibition of tumor adherence to the bone matrix, reduction of osteoclast development from precursors, disruption of bone resorption, inhibition of angiogenesis, and reduction of interleukin-6 (IL-6) production from bone stromal cells [14,15]. Bisphosphonates inhibit the mevalonate pathway (Fig. 1), which eventually prevents the prenylation of the Rho and RAS proteins, resulting in induction of apoptosis of osteoclasts and tumor cells [16]. It has been suggested that the effect of the bisphosphonate zoledronate, for example, on osteoclasts and osteoblasts can be enhanced by concurrent treatment with a statin. In the case of RCC, the concurrent administration of statin therapy theoretically could increase skeletal protection, because the statin compounds have been shown to stimulate bone formation in vitro and in rodents [17]. The results of some epidemiologic studies have also suggested that these compounds increase bone mineral density and reduce the risk of fracture [18,19]. In mouse models, statins have induced a decrease in the number of distant metastases [20]. We speculate that because they target different steps in the mevalonate pathway than the bisphosphonates do, the statins provide a synergistic effect when administered concurrently with zoledronate, thus enhancing zoledronate’s therapeutic benefit for the treatment of skeletal metastasis of RCC [21].

During normal bone remodeling, osteoclastic and osteoblastic activity is coupled, resulting in a balanced rate of bone resorption and formation. To further explore bone turnover activity, we undertook this pilot trial in patients with RCC metastatic to the bone with the intent of dissecting skeletal metastasis into discrete bone epithelial compartments that can be objectively and individually measured. Serum bone–specific alkaline phosphatase (BSAP) is the most specific and sensitive marker of bone formation currently available, and substantial correlation between the BSAP concentration and the presence of skeletal metastases and extent of bone involvement has been demonstrated [22,23]. In addition, increased osteoclastic activity leads to osteolytic skeletal metastases, and studies have shown that increased concentrations of urinary deoxypyridinoline (DPD, a cross-link product of pyridinium) and N-telopeptide (NTX, a type I collagen telopeptide), which can be used as biochemical markers of collagen degradation and bone resorption, correlate with the number of bone metastases [22,23]. We believe that analysis of the compartmental activities of skeletal metastasis in serial serum and urine specimens from patients who undergo bone-targeted therapy for RCC will help to clarify the heterogeneity of the disease and correlate the effect of therapy on a particular therapeutic target with response.

In this study, focused on patients with RCC and predominantly skeletal metastases, we planned to acquire preliminary data on the effects of a bone-targeted regimen on clinical outcomes, as defined by time to skeletal events, calcification of lytic lesions, and changes in the levels of bone markers. The bone-targeted regimen consisted of the bisphosphonate zoledronate and a statin, either fluvastatin (Lescol; Novartis Pharmaceuticals Corp., East Hanover, NJ) or atorvastatin (Lipitor; Pfizer, Inc., New York, NY). An additional aim of this study was to collect useful preliminary information for the future design of more definitive studies to test the validity of therapy targeted at skeletal metastases in RCC and other malignancies.

2. Patients and Methods

2.1. Study design

This was a single-arm, pilot trial conducted at The University of Texas MD Anderson Cancer Center. The protocol was approved by the institutional review board, and the study was conducted in accordance with the provisions of the Declaration of Helsinki and its amendments and with the Good Clinical Practice Guidelines. All patients provided written informed consent to participate before they were enrolled in the study.

2.1.1. Inclusion and exclusion criteria—To be included in this study, patients had to have confirmed RCC, including image-evident skeletal metastases and an Eastern Cooperative Oncology Group (Zubrod) performance status score of 0–2. Initially, patients with metastases to other organs were excluded, but owing to the difficulty we encountered in enrolling patients who had only skeletal metastases, the protocol was amended to bypass this criterion if the other criteria were met. Patients of child-bearing potential were required to use an adequate method of contraception. Patients received targeted agents for their RCC at the discretion of their treating physician.

Patients were excluded if they had poor dentition, had recently undergone a major dental procedure, or had current active dental problems, including tooth or jaw infections and dental or fixture trauma. They were also excluded if they had a current or prior diagnosis of osteonecrosis of the jaw. Patients taking gemfibrozil, nicotinic acid, phenytoin, or ketoconazole or other antifungal agents were also excluded.

2.1.2. Drug treatment—All patients received standard-of-care treatments before, during, and after study participation at MD Anderson. The study drugs were administered on an

outpatient basis. Zoledronate was given as a 4-mg intravenous infusion once every 4 weeks, but the dosage was adjusted to achieve the same area under the curve as achieved in patients with a creatinine clearance (CrCl) rate of 75 mL/min. Thus, patients with a CrCl rate of > 60 mg/dL received the full 4-mg dosage; those with a rate of 50–60 mL/min received 3.5 mg; those with a rate of 40–49 mL/min received 3.3 mg; and those with a rate of 30–39 mL/min received 3.0 mg of zoledronate. Either fluvastatin or atorvastatin was given orally at a dosage of 40 mg and 20 mg daily, respectively. Patients were given a statin independent of pre-existing conditions. Those already on a statin were converted to a uniform statin for the purpose of the study. If patients are already on a statin different than atorvastatin prior to enrolling in this study, the following guidelines were utilized in determining the atorvastatin doses; if converted atorvastatin dose ≤ 20 mg daily, start atorvastatin 20 mg daily, if the converted dose > 20 mg daily, start atorvastatin at the respective doses using the conversion table.

2.1.3. End points and follow-up—The primary study end point was efficacy of the treatment regimen as assessed by time to skeletal events, defined as a metastatic site's requiring radiotherapy or any surgical intervention (e.g., embolization, radiofrequency ablation, intrathecal catheter placement), or complications from skeletal metastatic lesions (e.g., pathologic fracture, spinal cord compression).

Secondary end points included response of skeletal metastasis to therapy, defined as the development of calcification in the metastatic lesions as determined on computed tomography (CT) scans obtained at least every 2 months (± 5 days) and interpreted by a dedicated MD Anderson radiologist; changes in the concentrations of the bone-formation marker BSAP and the bone-resorption markers DPD and NTX; and the effect of the bone-targeted therapy on serum cholesterol levels every 2 months. Every 8–12 weeks, we also assessed the patients for safety and tolerability of the regimen, as indicated by the occurrence of painful symptoms, muscle symptoms, and acute and cumulative toxic reactions, measured by monitoring concentrations of blood urea nitrogen, creatinine, alkaline phosphatase, lactate dehydrogenase, electrolytes, calcium, phosphate, albumin, and alanine and aspartate aminotransferases. The concentration of creatine kinase (CK) was measured in the event of acute muscle or joint pain or tenderness, and if it was > 10 times the upper limit of normal (ULN), treatment with the statin was discontinued. If the CK concentration was 3–10 times the ULN, the patient was continued on the study treatment but was evaluated weekly for symptoms and CK concentration.

Finally, we stratified all patients into risk categories by using the prognostic criteria of Motzer et al [24] and determined whether there was any correlation between risk level and response to therapy.

2.2. Statistical analysis

The patients' clinical histories, laboratory results, and treatment responses were collected from their medical records and from MD Anderson's computerized data management system (NETPASS or ClinicStation). Time-to-event analysis was performed. Survival data were obtained from the clinical records or from the Social Security Death Index interactive search Web site [20]. Analysis to compare differences between the changes in the biomarker levels was performed by using Wilcoxon's rank-sum test with SAS version 9.0 (SAS Institute Inc., Cary, NC) and S-Plus version 8.0 (Tibco Software, Inc., Somerville, MA) software. The level of statistical significance was set at $P < 0.05$.

Efficacy will be assessed using the Simon's two-stage optimal design, based on the primary endpoint (i.e., time to skeletal event) at 6 months after bone-targeted therapy. The treatment will be considered promising if the probability of event-free survival (p) at 6 months is 80%

or higher, and will be considered unworthy of further investigation if p at 6 months is 60% or lower. The sample size of 38 is chosen to differentiate between p=80% and p=60% with 90% power at a significance level of 0.1.

3. Results

3.1. Patients and treatments

Our original intent was to evaluate 38 patients, but the study was terminated after 11 patients had been enrolled due to lack of efficacy. The enrollment period was October 1, 2006, through January 31, 2008. All patients had conventional-type RCC; the tumor in 2 patients also had sarcomatoid features. Six patients had only skeletal metastasis (patients 1, 4, 5, 8, 9, 10; Table 1). All patients were men; their median age at enrollment was 56.6 years (range, 42–71 years). Ten patients had previously undergone nephrectomy, and 3 had also previously undergone embolization of the metastatic skeletal lesion.

In total, 7 patients had been exposed to sunitinib: 1 had received sunitinib before enrollment in our study, and 5 received concurrent treatment with sunitinib during the study (Table 1). One of those 5 continued treatment with sunitinib after the study's end. Three patients had been exposed to sorafenib: 2 had received sorafenib before enrollment in our study, and 1 received concurrent therapy with sorafenib and interferon during the study. Finally, 1 patient had previously been treated with bevacizumab and erlotinib.

The median length of follow-up was 6 months (range, 2–28 months) (Table 2). The patients received a median of 6 doses of zoledronate as well as daily statin throughout the study period. Five of the patients received fluvastatin and 6, atorvastatin, during our study (Table 1).

3.2. Treatment response

Median time to the occurrence of a first skeletal event, as defined in the Methods section, for all patients was 9 months (95 % confidence interval: 4.1 – 18.1). Seven patients (63.6%) experienced a skeletal event over a median time of 4 months (range, 3–18 months) (Table 2). The other 4 patients (36.4%) did not experience skeletal events for median duration of follow-up of 12 months.

Four patients' tumors responded to treatment, as demonstrated on CT scanning (Table 2), including sclerosis formation in and calcification within or on the rim of the metastatic skeletal lesions. Imaging also revealed that 9 patients experienced progressive disease (PD) during the study: 3 developed a new skeletal metastasis, 4 experienced progression of their existing skeletal metastasis, and 2 developed new metastatic lesions in sites other than the bone (1 in the brain and 1 in the lung).

Our risk stratification of the 11 patients according to Motzer et al's prognostic criteria (Table 1) showed that 2 had a favorable-risk status and 9 had an intermediate-risk status. All patients' corrected calcium levels were within the normal range (8.3–10.5 mg/dL) throughout the study. All patients were anemic (hemoglobin concentration < 15 g/dL) throughout the study; 1 patient experienced a single clinically significant decrease in hemoglobin concentration to 8.9 g/dL, but with no intervention, his average concentration remained > 10 g/dL. Although 4 patients had initial lactate dehydrogenase concentrations greater than the ULN (range, 313–618 IU/L), they were < 1.5 times the ULN.

When all patients' biomarker data were considered together, according to our initial plan, the median DPD level did not change from baseline (range: +4 to −8.2 nmol/mmol), whereas the median change in NTX level from baseline was − 11 nmol/mmol (range, +15 to

−63 nmol/mmol) and the median change in BSAP level from baseline was −4.1 μg/L (range, +2.9 to −51.8 μg/L) (Table 3 and Fig. 2). Further review of the data, however, revealed significant findings when we grouped the patients according to whether they experienced a skeletal event during the study (Table 4): Group A (patients 2, 5, 8, and 10) did not experience a skeletal event (new metastatic lesion was not considered a skeletal event), but those in Group B (patients 1, 3, 4, 6, 7, 9, and 11) did. On analysis by group, the median changes from baseline in DPD, NTX, and BSAP levels in group A were −2.6 nmol/mmol (−38.5%), −33.5 nmol/mmol (−77.9%), and −4.3 μg/L (−36.8%), respectively. In group B, the respective median changes from baseline were +0.4 nmol/mmol (+12.9%), +1.0 nmol/mmol (+7.7%), and −1.9 μg/L (−17.8%). The differences between the median changes in biomarker levels between the patients who experienced a skeletal event during the study and those who did not were statistically significant for DPD and NTX levels ($P = 0.03$ and 0.01, respectively) but not significant for BSAP ($P = 0.4$).

Also, the median decrease in cholesterol concentration from baseline was 25 mg/dL (Table 3 and Fig. 3), and all but 2 patients (numbers 1 and 5) had final concentrations of < 200 mg/dL.

3.3. Safety and tolerability

Overall, the combination regimen of zoledronate and either fluvastatin or atorvastatin was well tolerated, with only a few adverse events recorded as “probably” or “definitely” related to the study treatments. The adverse events that occurred were in large part secondary to the use of the concurrent TKIs rather than to zoledronate or the statins. Only 2 patients experienced a grade 4 adverse event, both of which were categorized as “unrelated” to study medications; 1 patient experienced a transient ischemic attack, which was believed to have been caused by another medication, and the other patient experienced bone pain secondary to the metastatic lesions and skeletal progression of disease. (No other adverse events that were deemed unrelated to the study treatments are addressed here.) No “definitely,” “probably,” or “possibly” related WHO classification grade 3 adverse events were reported.

Desquamatory rash was the only WHO grade 2 adverse event categorized as “definitely” related to the study drugs, and fever, fatigue, and lymphopenia were the only WHO grade 1 and 2 events that were classified as “probably” related to the study drugs. The great majority of the grade 1 and 2 adverse reactions that occurred were considered “possibly” related to the study treatments.

Six patients discontinued treatment because of progression of their skeletal lesion(s) and 2 others, because of progression of their non-skeletal lesion(s) (Table 2). One patient withdrew his consent to continue his participation in the study. Two patients had to be withdrawn from the study because of worsening renal function (1 of them was also 1 of the 8 patients who experienced PD). One patient was still being treated according to the study protocol at the time of writing this manuscript. No deaths occurred during the study period.

4. Discussion

The objectives of this pilot trial were to assess the efficacy of a bone-targeted regimen on the time to and the radiographic response of skeletal metastatic events, as well as to evaluate changes in biomarkers of bone resorption and formation and the regimen’s safety. Our results suggest that a combined bone-targeted regimen of a bisphosphonate and a statin administered concurrently with standard therapy in this small group of patients with RCC and predominantly bone metastases was comparable with historical data. We did not demonstrate a statistically significant difference in time to the development of skeletal metastatic events.

Zoledronate has been shown to delay the onset of skeletal-related events and progression of skeletal disease in patients with advanced RCC [13]. In that study, retrospective subset analysis showed that the median times to a skeletal event were 4.6 and 2.4 months for patients who received antineoplastic therapy combined with zoledronate (8/4 mg) or placebo, respectively. The median time to a skeletal event was not reached for those patients who received antineoplastic therapy plus zoledronate (4 mg) in that study [13]. In another study, which combined zoledronate with thalidomide and interferon-γ the median time to a skeletal event was 2.8 months [6]. Our results was comparable with those from previous studies: the median time to a skeletal event was 9.0 months using zoledronate combined with the newer antineoplastic agents and a statin.

We also demonstrated a radiographically visible treatment response in 4 patients (36%), with the development of a sclerotic border around the metastatic lesions. However, since patients also received concurrent TKIs, we acknowledge that the antitumor response was likely due to the combined treatment. In a previous study [13], bone response or formation of sclerosis in osteolytic lesions was observed in 7% of RCC patients who received zoledronate plus antineoplastic therapy but in none of those patients who received antineoplastic therapy alone. In another study, 13% of those who received zoledronate combined with thalidomide and interferon-γ showed a bone response [6]. To our knowledge, the rate of sclerosis formation in osteolytic lesions among patients with RCC who receive TKIs, mammalian target of rapamycin inhibitors, or combined therapies using these agents has not been previously reported in the literature. It remains to be determined whether a radiographic bone response is associated with delayed skeletal events. In our study, 2 of the 4 patients who had a bone response on CT scans experienced a skeletal event (Table 1, patients 1 and 3).

Objective measurement of specificity and sensitivity values is inaccurate in small patient populations, but we demonstrated a correlation between bone-resorption marker concentrations and skeletal events. We showed that the changes in concentrations of the bone-resorption markers DPD and NTX from baseline to the end of the study were statistically significantly different between patients who experienced skeletal events during the study and those who did not, whereas the change in the bone-formation marker BSAP was not.

Whether the statin treatment contributed to any delays in skeletal events requires further investigation. Statins are widely used, and measurement of serum cholesterol levels could be a convenient and meaningful end point to determine their efficacy in delaying skeletal events. Decreasing the serum cholesterol concentration to < 200 mg/dL was achieved in all but 2 patients in this study, 1 each in groups A and B, even though the median total change was small, a decrease of only 25 mg/dL, or 9.2%. Those 2 patients had a final cholesterol level > 200 mg/dL because they had only 2 measurements, at baseline and at 1 follow-up, since they were in the study for a short time.

In conclusion, the results of this pilot study suggest that combining a bone-targeted regimen containing a bisphosphonate and a statin with standard therapy is feasible and safe. We could not demonstrate any statistically significant improvement in time to skeletal events for a small cohort of patients with RCC and predominant skeletal metastases. Additional studies need to be performed to confirm these preliminary findings.

Acknowledgments

This work was supported in part by the National Institutes of Health through MD Anderson's Cancer Center Support Grant, CA016672. The authors thank Karen Phillips, ELS, for editorial assistance.

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Clinical Practice Points

- Multiple studies have demonstrated the importance of bisphosphonate treatment in skeletal metastatic disease from various malignancies, including genito-urinary cancers.
- We sought to improve the skeletal outcome by adding statins to bisphosphonates, two agents that work in the same mevalonate pathway, to obtain synergistic effect.
- Currently, there is no clinical evidence to support this combination treatment. We attempted to evaluate the combined regimen in a pilot phase II study of patients with skeletal metastasis from renal cell carcinoma.
- We did not demonstrate any statistically significant improvement in time to skeletal events.
- However, the use of bone-targeting therapy combining a statin and a bisphosphonate affected certain bone biomarkers and provided bone response in several patients with RCC and bone metastasis.
- Whether bone-targeted therapy enhances the clinical benefits of certain anti-cancer therapeutics in select patients with renal cell carcinoma and bone metastasis needs further investigation in the future.

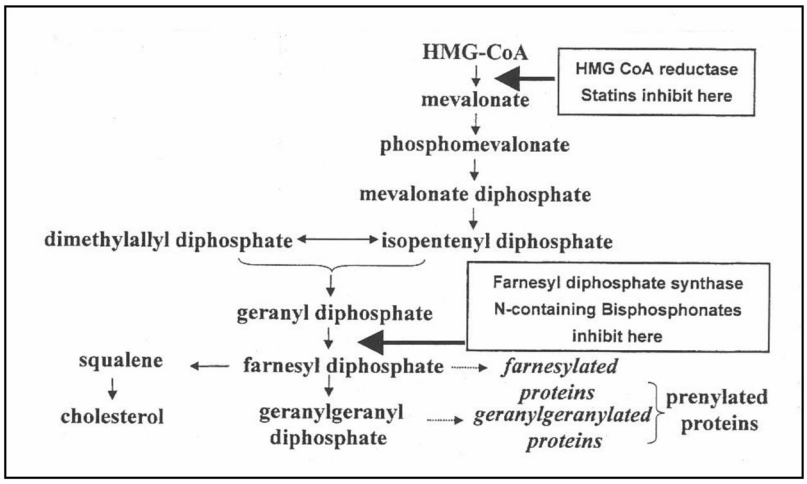

Fig. 1.

Diagram of the mevalonate pathway demonstrates sites of synergistic inhibition for statins and bisphosphanates. Inhibiting prenylated proteins, indicated at the bottom right, eventually inhibits the Rho and RAS intracellular cascades, which contribute to cell cycle arrest and induction of apoptosis, respectively.

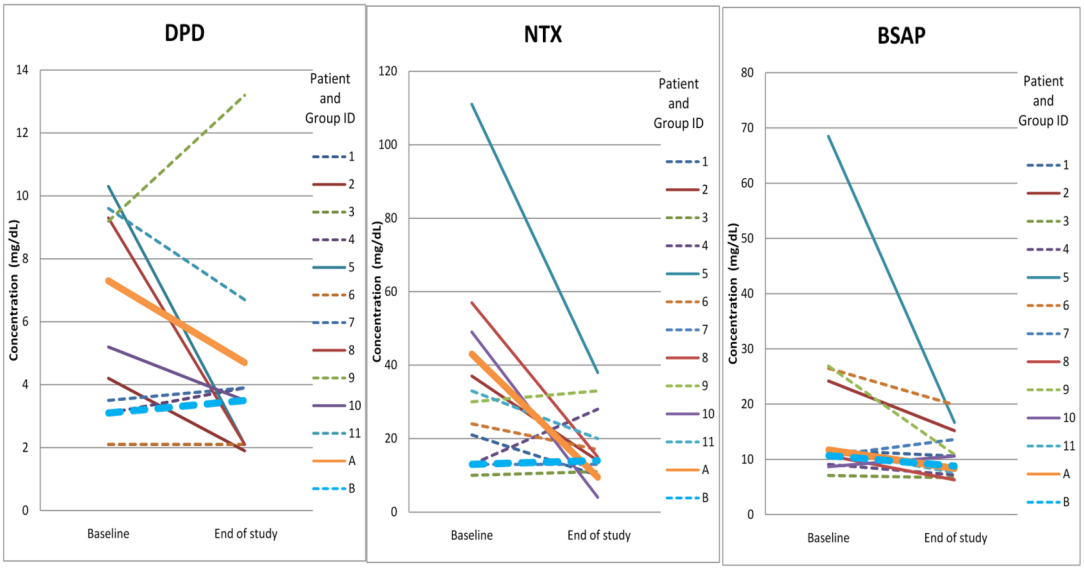

Fig. 2.

Graphs illustrate the median serum concentrations of the bone-specific biomarkers over the course of the study, by both patient (relatively thinner lines) and group (relatively thicker lines). Solid lines represent patients who did not experience a skeletal event during the study (Group A), whereas dashed lines represent patients who experienced a skeletal event (Group B). Notice the differences in the changes in median deoxypyridinoline (DPD) and N-telopeptide (NTX) levels between the different patients and groups and the relative lack of these changes in the median bone-specific alkaline phosphatase (BSAP) levels ($P = 0.03$, 0.02, and 0.66, respectively).

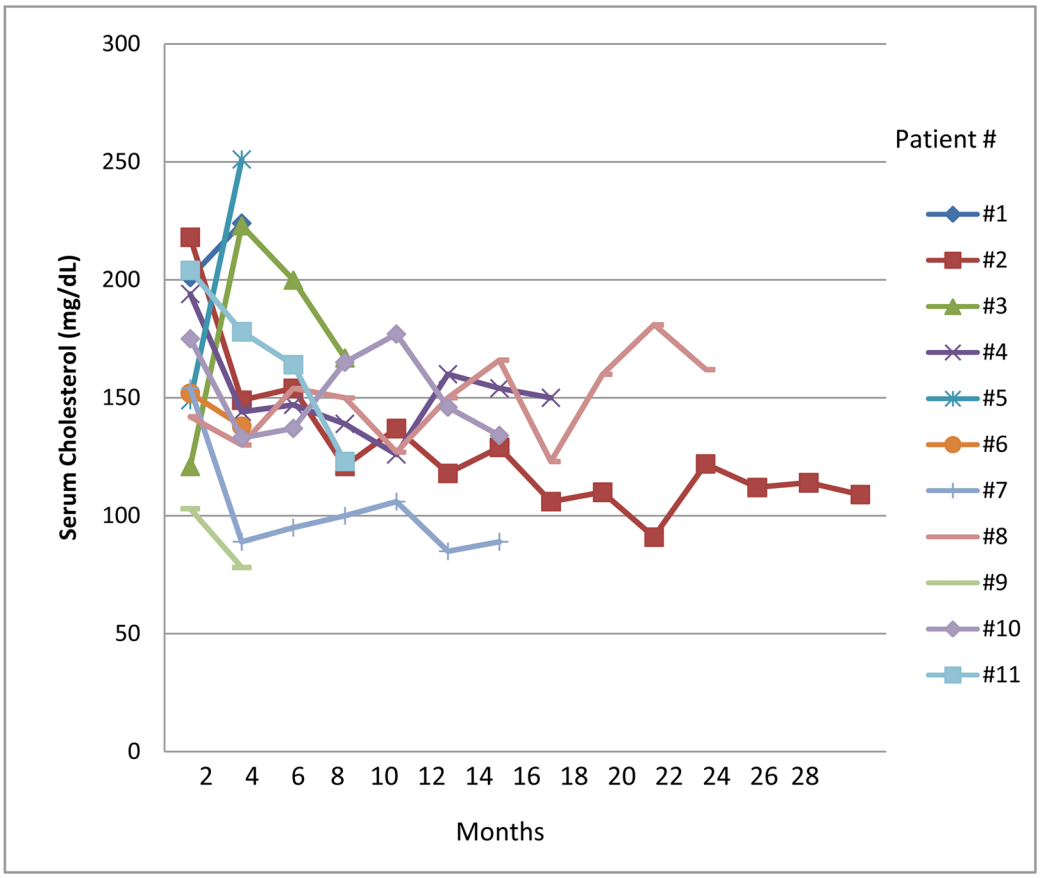

Fig. 3.

The patients' serum cholesterol concentrations were measured every 2 months. Graphs illustrate the changes in cholesterol over the course of the study. Notice that only 2 patients (numbers 1 and 5) had a concentration > 200 mg/dL when they discontinued from the study; this resulted from only 2 measurements having been taken because of their short study participation. Note also that in the case of 1 patient (number 3), the concentration increased to > 200 mg/dL but subsequently decreased and stayed below that level. The remainder of the patients' cholesterol concentrations both started and stayed at < 200 mg/dL.

Table 1

Patients' characteristics and treatments

Patient no.[a]	Age (yrs)	Other metastasis	Pathology	Motzer Prognostic Criteria[b]	Statin used[c]	Prior treatment[d]	Concurrent treatment[e]
1	60	Bone only	Conventional	Intermediate	F	Nephrectomy	Sunitinib
2	42	Pleura	Conventional	Intermediate	A	Nephrectomy	Sorafenib, interferon
3	62	Mediastinum, hilum, lung	Conventional	Intermediate	F	Nephrectomy, sorafenib	Sunitinib
4	56	Bone only	Conventional	Favorable	A	Nephrectomy, sorafenib	None
5	52	Bone only	Sarcomatoid features	Intermediate	F	Nephrectomy	None
6	49	Lung	Sarcomatoid features	Intermediate	F	Radiotherapy	None
7	58	Pleura	Conventional	Favorable	F	Nephrectomy, embolization, bevacizumab, erlotinib, sunitinib	None
8	56	Bone only	Conventional	Intermediate	A	Nephrectomy, radiotherapy, embolization	Sunitinib
9	55	Bone only	Conventional	Intermediate	A	Nephrectomy, embolization	Sunitinib
10	62	Bone only	Conventional	Intermediate	A	Nephrectomy, radiotherapy	Sunitinib
11	71	Liver	Conventional	Intermediate	A	Nephrectomy	None
Median	**56.6**						

[a] All patients were men.

[b] Reference 11.

[c] A, atorvastatin; F, fluvastatin.

[d] Treatments administered before patients' study enrollment.

[e] These treatments were administered during the study along with the zoledronate and either fluvastatin or atorvastatin.

Table 2

Patients' clinical and skeletal outcomes

Patient no.	Follow-up time (months)	No. of skeletal lesions	Skeletal outcome	Time to skeletal event (months)	No. of zolendronate doses	Radiologic response (on CT)	Reason for discontinuation from trial
1	4	6	PD	4	4	Yes	PD (also patient withdrew consent)
2	**13**	**1**	**No skeletal event**	**n/a**	**14**	**No**	**PD, new lung metastasis (bone stable)**
3	6	2	PD	6	6	Yes	PD of bone metastasis (required XRT)
4	18	5	PD	18	18	No	PD of bone metastasis (required cryoablation)
5	**2**	**3**	**No skeletal event**	**n/a**	**2**	**Yes**	**PD, new brain metastasis (bone stable)**
6	3	5	New skeletal metastasis	3	3	No	PD, new bone metastasis
7	4	1	PD	4	3	No	PD and worsening renal function
8	**28**	**7**	**No skeletal event**	**n/a**	**28**	**Yes**	**Still undergoing treatment**
9	3	8	New skeletal metastasis	3	3	No	PD, new bone metastasis and L2/4 vertebral fracture
10	**11**	**1**	**No skeletal event**	**n/a**	**11**	**No**	**Worsening renal function (bone stable)**
11	9	4	New skeletal metastasis	9	9	No	PD, new bone metastasis
Median	**6**	**4**		**9**	**6**		
Median length of follow-up for all patients				**6 months**			
Median length of follow-up of patients who experienced no skeletal event during the study (Group A)				**12 months**			
Median time to skeletal event for patients who experienced events during the study (Group B)				**4 months**			

Abbreviations: CT, computed tomography; PD, progression of disease; n/a, not applicable; XRT, radiotherapy.

Table 3

Changes from baseline concentrations of bone-specific biomarkers and cholesterol during the study, by patient

	DPD concentration: normal range, 2.1–8.1 mol/mmol[a]			NTX concentration: normal range, 9–60 nmol/mmol[a]			BSAP concentration: normal range, 7–18.3 μg/L[a]			Cholesterol concentration: normal, < 200 mg/dL		
Patient no.	**Baseline**	**Final**	**Change**	**Baseline**	**Final**	**Change**	**Baseline**	**Final**	**Change**	**Baseline**	**Final**	**Change**
1	ND	ND	—	21	10	−11	11.7	10.6	−0.9	201	224	+23
2	4.2	1.9	−2.3	37	14	−25	24.2	15.2	−9.0	218	109	−109
3	ND	ND	—	10	11	1	7.1	6.7	−0.4	121	167	+46
4	3.1	3.9	+0.8	13	28	+15	9.1	7.2	−1.9	194	150	−44
5	10.3	2.1	−8.2	111	38	−63	68.5	16.7	−51.8	149	251	+102
6	ND	ND	—	24	17	−7	26.5	19.9	−6.6	125	138	−13
7	3.5	3.9	+0.4	13	13	0	10.7	13.6	+2.9	154	89	−65
8	9.3	2.1	−7.2	57	15	−42	10.7	6.3	−4.4	142	162	+20
9	9.2	13.2	+4.0	30	33	+3	26.9	10.9	−16.0	103	78	−25
10	5.2	3.5	−1.7	49	4	−45	8.7	10.6	+1.9	175	134	−41
11	9.6	6.7	−2.9	33	20	−13	11.7	7.6	−4.1	204	123	−81
Median change		0 mol/mmol			−11 nmol/mmol			−4.1 μg/L			−25 mg/dL	

Abbreviations: DPD, deoxypyridinoline; NTX, N-telopeptide; BSAP, bone-specific alkaline phosphatase; ND, not done.

[a]The normal ranges given are those used in our laboratory.

Table 4

Changes from baseline in median bone-specific biomarker and cholesterol concentrations during the study, by patient group[a]

	Median DPD concentration Normal range: 2.1–8.1 nmol/mmol[b]				Median NTX concentration Normal range: 9–60 nmol/mmol[b]				Median BSAP concentration Normal range: 7–18.3 μg/L[b]				Median cholesterol concentration Normal < 200 mg/dL			
Group	**Baseline**	**Final**	**Change**	**% Change**	**Baseline**	**Final**	**Change**	**% Change**	**Baseline**	**Final**	**Change**	**% Change**	**Baseline**	**Final**	**Change**	**% Change**
A	7.3	4.7	−2.6	−38.5	43.0	9.5	−33.5	−77.9	11.7	7.4	−4.3	−36.8	162.0	151.5	−10.5	−4.7
B	3.1	3.5	+0.4	+12.9	13.0	14.0	+1.0	+7.7	10.7	8.8	−1.9	−17.8	154.0	129.0	−25.0	−9.2
P value				**0.03**				**0.01**				**0.4**				**n/a**

Abbreviations: DPD, deoxypyridinoline; NTX, N-telopeptide; BSAP, bone-specific alkaline phosphatase; n/a, not available.

[a]Group A (patients 2, 5, 8, and 10) did not experience a skeletal event during the study period. Group B (patients 1, 3, 4, 6, 7, 9, and 11) did experience a skeletal event during the study.

[b]The normal ranges given are those used in our laboratory.