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Prognostic Significance of Bone Metastases and Bisphosphonate Therapy in Patients with Renal Cell Carcinoma

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Abstract

Background: Bone metastases (BMs) are frequently present in patients with metastatic renal cell carcinoma (mRCC) and cause significant morbidity.
Objective: The purpose of this analysis was to assess the impact of BMs and bisphosphonate therapy (BT) on outcomes in mRCC.
Design, setting, and participants: We conducted a pooled analysis of patients with mRCC treated from 2003 to 2011 in phase 2 and 3 trials.
Outcome measurements and statistical analysis: Statistical analyses were performed using Cox regression and the Kaplan-Meier method.
Results and limitations: We identified 2749 patients treated with sunitinib ($n = 1059$), sorafenib ($n = 355$), axitinib ($n = 359$), temsirolimus ($n = 208$), temsirolimus plus interferon-α (IFN-α) ($n = 208$), or IFN-α ($n = 560$), with 28% ($n = 781$) having BMs. A total of 285 patients (10.4%) received BT. The presence of BMs in patients was associated with shorter overall survival (OS) when compared with patients without BMs (13.2 vs 20.2 mo, respectively; $p < 0.0001$) and shorter progression-free survival (PFS) (5.1 vs 6.7 mo, respectively; $p < 0.0008$). When stratified by risk groups, the presence of BMs was associated with shorter OS in all risk groups. The use of BT in patients with BMs was not associated with improved OS compared with patients who did not receive BT (13.3 vs 13.1 mo, respectively; $p = 0.3801$) or improved PFS (5.1 vs 4.9 mo, respectively; $p = 0.1785$). Bisphosphonate users with BMs did not have a decreased rate of skeletal-related events (SREs) compared with nonusers (8.6% vs 5.8%, respectively; $p = 0.191$). In addition, BT was associated with increased rates of hypocalcemia, renal insufficiency, and osteonecrosis of the jaw ($p < 0.0001$). Data were analyzed retrospectively.
Conclusions: We confirm that the presence of BMs is associated with shorter survival in mRCC. BT did not affect survival or SRE prevention and was associated with increased toxicity.
Patient summary: In this analysis, we demonstrate that bone metastases are associated with shorter survival in patients with metastatic renal cell carcinoma. In addition, we call into question the utility of bisphosphonate therapy in this population.

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1. Introduction

Approximately 30% of patients with metastatic renal cell carcinoma (mRCC) have bone metastases (BMs) [1]. Patients with BMs are vulnerable to significant skeletal morbidity, which can lead to quality-of-life deterioration. In addition, these patients are at risk of skeletal-related events (SREs), including pain requiring irradiation, pathologic fractures, spinal cord compression, surgery to bone, and occasionally hypercalcemia.

Skeletal lesions from mRCC are typically osteolytic on imaging. The mechanism by which mRCC induces osteolytic bone changes is unclear. In normal bone, structural integrity is maintained by way of a process of bone resorption and formation [2]. It is proposed that dysregulation of this process results in a vicious cycle of bone destruction and tumor growth [2]. Integral to the interaction of tumor cells with the bone microenvironment is the release by osteoblasts of receptor activator of nuclear factor kappa B ligand (RANKL), a cytokine critical in osteoclast differentiation and survival [2].

Osteoclast-targeted agents are used to prevent skeletal complications related to BMs and do not appear to affect survival. Bisphosphonates bind to bone and have a direct inhibitory effect on osteoclasts [3]. Zoledronic acid, a potent bisphosphonate, was approved for SRE prevention in 2002, corresponding with the cytokine era in mRCC [3]. Denosumab, a monoclonal antibody against RANKL, prevents osteoclast differentiation and survival [4]. Denosumab was approved for SRE prevention in 2010. Compared with other cancers, there are limited prospective data on the role of osteoclast-targeted therapy in mRCC.

Outcomes of patients with mRCC have improved dramatically since 2005, when agents targeting the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin pathways were introduced. Despite improvements in survival, there is increasing evidence that BMs in mRCC are associated with worse outcomes [5,6]. Understanding the prognostic impact of BMs on outcomes is critical for personalizing treatment for patients with mRCC. In addition, it is important to understand the role of osteoclast-targeted agents in patients with BMs. In this study, we used a clinical trials database of patients with mRCC to characterize BMs, evaluate their impact on survival, and investigate the role of bisphosphonate therapy (BT).

2. Patient and methods

2.1. Study design

We conducted a post hoc analysis of pooled prospective data of patients with mRCC treated in phase 2 trials (NCT00054886, NCT00077974, NCT00267748, NCT00338884, NCT00137423) and phase 3 trials (NCT00083889, NCT00065468, NCT00678392) conducted by Pfizer Oncology. We identified 2749 patients treated for mRCC between January 2003 and November 2011.

Baseline demographic, clinical, and laboratory data were collected. Data regarding osteoclast-targeted therapy were collected. Users of osteoclast-targeted therapy were defined as those receiving a bisphosphonate or denosumab at baseline or during the study period. The decision to start an osteoclast-targeted agent and the management of patients while on therapy were at the discretion of the treating physician. SREs of pathologic fractures and spinal cord compression were captured from the adverse event database. All studies in the database used Common Terminology Criteria for Adverse Events v.3.0, which did not include a category to record bone radiotherapy or surgery to the bone. Data regarding adverse events including hypocalcemia, renal insufficiency, and osteonecrosis of the jaw (ONJ) were collected. Survival data were collected for all patients.

2.2. Statistical methods

The primary outcome was to assess overall survival (OS) and progression-free survival (PFS) of patients with BMs compared with those without BMs. The secondary outcome was to assess OS and PFS of patients with BMs treated with BT compared with those not receiving BT. OS was defined as the time from initiation of therapy to death from any cause. PFS was defined as the time from initiation of therapy to date of progression or death from any cause, whichever came first. Distributions of OS and PFS were calculated using the Kaplan-Meier method. Median OS and PFS, along with 95% confidence intervals (CIs), were reported. Associations between OS and PFS were assessed using the log-rank test in univariate analysis or the Wald χ^2 test from Cox regression in multivariable analysis, adjusted for age, sex, race, and Memorial Sloan-Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups [7]. Subgroup efficacy analyses were performed in the following groups: (1) MSKCC risk groups, (2) IMDC risk groups, and (3) therapy type.

3. Results

3.1. Patient and disease characteristics

Most patients were <65 yr of age, were men, had good performance status, and had clear cell histology (Table 1). Patients received treatment with sunitinib (n = 1059), sorafenib (n = 355), axitinib (n = 359), temsirolimus (n = 208), temsirolimus plus interferon-α (IFN-α) (n = 208), and IFN-α (n = 560), of whom 1759 received first-line therapy. The presence of baseline lung metastases, liver metastases, and BMs was 77%, 28%, and 28%, respectively. With regard to risk groups, more patients with BMs had poor-risk disease compared with patients without BMs.

3.2. Bisphosphonate therapy and skeletal-related events

Of the 2749 patients in the cohort, 285 (10.4%) received BT (zoledronic acid: n = 233; pamidronate: n = 57; unspecified: n = 1), 3 of whom received more than one agent sequentially. No patient received denosumab. All 285 patients were receiving BT at baseline, and the majority continued therapy during the study period (n = 272, 95.4%). Of the 285 BT users, 23 (8.1%) were receiving calcium supplementation, and 4 (1.4%) were receiving vitamin D supplementation at baseline. Of the 781 patients with BMs, 162 (20.7%) received BT. Indications for BT in patients without documented BMs (123 of 1968) included hypercalcemia (53%), osteoporosis or prophylaxis (13%), no reason given (11%), or pain (5%). In 23 patients, BMs were recorded as the indication for BT, although BMs were not documented as a site of involvement.