Efficacy of Sunitinib in Patients with Renal Cell Carcinoma with Bone Metastases

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Abstract. Bone is the second most common metastatic site in patients with renal cell carcinoma presenting with metastases (mRCC) at diagnosis. Complications of metastatic bone disease, including bone pain, fractures, spinal cord compression, and hypercalcaemia, are the primary cause of decline in the quality of life of patients with mRCC. Currently, treatment for mRCC bone metastases is generally palliative. Bisphosphonates are also used; however, the efficacy of bisphosphonates in conjunction with targeted agents is currently unknown. As growth factors play a critical role in the development of bone metastases, there is a biological rationale for the use of targeted agents to treat them. We report here the case of two patients with mRCC with surgically unresectable sacral bone metastases treated with sunitinib, who are still alive with long-term stabilization of metastases of 48 and 31 months. Results suggest targeted agents such as sunitinib may be an effective treatment for bone metastases.

Approximately 30% of patients with renal cell carcinoma (RCC) present with metastatic disease (mRCC) at diagnosis; of these, 20% have bone metastases (1). Bone metastases are often one of the first signs of disseminated disease in cancer patients (2), most frequently affecting the axial skeleton with osteolytic lesions where bone resorption predominates over new bone formation (3). Bone metastases are associated with significant skeletal morbidity, including bone pain, fractures, spinal cord compression requiring surgery, and hypercalcaemia of malignancy (3). Complications from bone metastases and their subsequent treatment are the primary cause of decline in the quality of life of patients with mRCC (3). Because mRCC is non-responsive to conventional chemotherapy, radiotherapy and hormonal treatment, traditional treatment for bone metastases associated with mRCC has been largely palliative, consisting of pain relief measures, prevention of pathological fractures, and improvement of physiological function and mobility (4).

In the past, metastatic disease was associated with a poor prognosis and a 5-year survival rate of less than 10% (5). The development of targeted therapies for mRCC has improved outcomes for patients considerably. Sunitinib malate (SUTENT®, Pfizer Inc.) is an oral receptor tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3; platelet-derived growth factor receptors (PDGFR) a and b; stem cell factor receptor (KIT), FMS-like tyrosine kinase-3 receptor (FLT3) and the glial cell line-derived neurotrophic factor (RET) (6-9). In a pivotal phase III study, sunitinib significantly increased progression-free survival (from 5 to 11 months) compared with interferon-alpha (IFN-α) and extended overall survival beyond two years in treatment-naïve patients with mRCC (10). Sunitinib is now considered a reference standard of care for the first-line treatment of mRCC in patients with favourable and intermediate prognosis (11-12).

Growth factors such as PDGF and VEGF are players in metastasis to bone (13). Cytokines and growth factors derived from stromal cells as well as growth factors that are released during the bone resorption process play a critical role in the development of bone metastasis. PDGF is thought to stimulate both bone resorption and angiogenesis (14) by regulating the expression of cytokines such as interleukin (IL)-6 by osteoblasts, or by direct action on osteoclasts (15). IL-6 expression in bone metastases of RCC has been associated with hypercalcaemia (16). VEGF and VEGF receptors also play an important role in tumor growth by not only increasing angiogenesis and growth of tumor cells but also by up-regulating IL-6 and increasing osteoclast bone resorption (13). Inhibition of growth factors may potentially block bone destruction and decrease tumour burden within bone (13).
Support for the role of VEGFR in bone metastases is also provided by a recent study which identified several biomarkers associated with the occurrence of bone metastases in patients with RCC (17). These included VEGFR-1, VEGFR-2, hypoxia-inducible factor-1 alpha (HIF-1α), plasminogen activator (uPA) and plasminogen activator inhibitor-1 (PAI-1) (17).

As such, targeted agents may have a role to play in the treatment of bone metastases. Here, we report two cases of patients with RCC with surgically unresectable sacral bone metastases, treated with sunitinib.

Case Reports

Case 1. In October 1995, a 49-year-old female patient was treated by left radical nephrectomy for clear cell adenocarcinoma of the kidney, Furhman II, pT2. The patient was determined to be at favourable prognostic risk as defined by the Memorial Sloan-Kettering Cancer Centre (MSKCC) criteria and had a European Cooperative Oncology Group performance status (ECOG PS) of 0.

Ten years later, the patient was re-hospitalised with radicular lumbosacral pain of the both lower limbs and impaired sphincter function. Bone scintigraphy demonstrated pathological bone uptake in the sacrum. The chest computed tomography (CT) scan was normal. A CT scan of the lumbosacral region of the spine demonstrated an osteolytic lesion with a fracture of the S1 vertebra as well as a tilting of the S1 plateau. The corresponding tumour was 5 cm × 2.5 cm × 3 cm in size. The diagnosis of secondary clear cell adenocarcinoma metastasis was confirmed by a bone biopsy and the metastasis was treated by performing a sacral laminectomy to free the roots of the left and right S1 and S2 nerves. Additionally, an incomplete curettage of the S1 vertebra was performed. As the vertebral metastasis could not be completely resected and the curettage remained incomplete, treatment was initiated with sunitinib 50 mg/day on Schedule 4/2 in July 2007. Analysis of tumour samples indicated overexpression of several genes including those for VEGFR1 and VEGFR2, HIF-1α, uPA and PAI-1.

Following 3 months of treatment, magnetic resonance imaging (MRI) scan of the lumbosacral spine showed a stable bone lesion with the appearance of necrosis in the centre. However, the patient experienced grade 3 diarrhoea and grade 3 hand-foot syndrome, leading to sunitinib dose adjustment to 37.5 mg/day on Schedule 4/2. The patient continued to receive sunitinib at 37.5 mg/day for an additional six months. An MRI of the lumbosacral spine confirmed complete necrosis of the tumour lesion without radiological changes of its size. Sunitinib treatment was discontinued and a positron emission tomography (PET scan) was performed. Results demonstrated a focus of increased metabolic activity in the tumour lesion invading the sacrum.

Three weeks after discontinuation of sunitinib, a sacral biopsy of the tumour was taken. Histological examination did not reveal any tumour cells within the sample. Two months after discontinuation of sunitinib, the patient experienced significant functional improvement and a cessation of pain. However, 4 months after discontinuation of sunitinib treatment, a spinal MRI scan demonstrated a progression of the sacral tumour at the right transverse process. Sunitinib treatment was resumed at 50 mg/day on Schedule 4/2. This was adjusted to 37.5 mg/day following 3 months of treatment as the patient again experienced hand-foot syndrome and diarrhoea (grade II in intensity).

Overall, the patient has received sunitinib treatment for 4 years (3 years after re-initiating treatment and 4 years from the first treatment with sunitinib). Regular, five-monthly MRI scans of the sacral and lumbar spine demonstrate that the sacral lesion remains stable. In addition, the patient is not experiencing any pain and does not require any pain medication. The patient also remains free of further bone or visceral metastases (Figure 1).

Case 2. An 84-year old male patient was diagnosed, by abdominal scan, with a tumour in the left kidney in December 2006. The patient was determined to have ECOG PS of 1 and was treated with a left radical nephrectomy. The tumour was confirmed to be a clear cell adenocarcinoma, pT4 Nx R1 and the patient determined to be at favourable prognostic risk.

In June 2007, six months after the initial nephrectomy, the patient was diagnosed with a sacral metastasis located at S1, of 5 cm in size. The tumour also protruded into the epidural compartment.

Treatment was initiated with sunitinib 50 mg/day, Schedule 4/2 in July 2007. Analysis of tumour samples indicated overexpression of several genes including those for VEGFR1 and VEGFR2, HIF-1α, uPA and PAI-1 in this patient also.

Stabilisation of the sacral metastasis without further progression of the tumour into the epidural compartment was observed on an MRI scan of the lumbosacral region, performed after 3 months of treatment. The patient remained under observation with regular MRI scans of the lumbosacral region. Scans were conducted every 4 months during the first year and every 6 months thereafter.

At 31 months of treatment with sunitinib, the metastases, both sacral and epidural, remain stable.

No adverse events have been observed on sunitinib treatment; the patient remains on twice daily morphine 10 mg, twice daily pregabalin 175 mg and twice daily paracetamol 1 mg.

Discussion

Bone metastases are frequent in RCC and can result in devastating skeletal morbidities for which the efficacy of current treatments remains uncertain. Currently palliative treatment with bisphosphonates and radiotherapy is used for bone metastases...
and related pain (4). Bisphosphonates, such as zoledronic acid, are able to delay the onset of bone metastases-associated complications and to reduce the morbidity associated with those complications, but not overall mortality in such patients (18, 19). Additionally, data supporting the use of bisphosphonates was collected prior to the era of targeted agents, thus its efficacy with current agents remains unknown (20).

We report two patients with unresectable bone metastases, treated with sunitinib. Both patients achieved long-term stabilisation of surgically unresectable bone metastases, with one patient remaining stable for 48 months, and the other for 31 months. Of interest, the first patient (case 1) demonstrated a recurrence within 6 months following curettage. Additionally, bone necrosis observed in this patient, confirming sunitinib activity on tumour vasculature, suggests that arterial embolisation of bone tumour lesions prior to surgical resection may be unnecessary.

The results seen in these patients with favourable prognosis are comparable to those described by Vogl and co-workers demonstrating that patients with favourable prognosis, treated with metastasectomy followed by cytokines, achieved an overall survival of 30.5 months. This was significantly longer overall survival compared to that achieved by patients in the intermediate or poor risk categories (22 and 5.9 months, respectively), indicating that risk group classification may be correlated to response to treatment (5).

Both patients demonstrated overexpression of genes associated with the development of bone metastases (VEGFR1 and VEGFR2, HIF-1α, UPA and PA-1) in patients with RCC. Treatment with sunitinib in these patients prevented emergence of new bone lesions during the treatment period.

Furthermore, a retrospective analysis conducted by Zolnierek et al., which investigated the emergence and progression of metastatic bone lesions in patients with mRCC, showed that treatment with sunitinib reduced the incidence of new metastatic bone lesions and significantly prolonged the mean time to occurrence of new lesions compared with sorafenib (21).

The results reported in these cases, coupled with the observations of Zolnierek and co-workers (21), suggest that targeted agents such as sunitinib may be useful for the treatment of bone metastases

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References


Figure 1. Computed tomographic scan of the lumbosacral region of the patient (case 1) demonstrating presence of bone metastasis.


