Complete Metabolic Remission with Gefitinib in a Hemodialysis Patient with Bone Metastases from Non-small Cell Lung Cancer

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Abstract. Gefitinib is highly active in patients with advanced or metastatic non-small cell lung cancer (NSCLC) harboring activating mutation of the epidermal growth factor receptor (EGFR) gene. The feasibility and the degree of response to treatment with gefitinib in patients with chronic renal failure (CRF) undergoing hemodialysis has not yet been fully described in literature. We describe the case of a 70-year-old man with CRF undergoing hemodialysis three times-a-week who developed vertebral and rib bone metastasis three years after lobectomy. The bone biopsy confirmed the pulmonary origin and pyrosequencing analysis revealed deletion in E746-E750 of exon 19. We started daily administration of 250 mg gefitinib with no changes in the hemodialysis schedule. Gefitinib was well-tolerated without any adverse event. After three months, the 18F-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomographic/computed tomography (FDG PET/CT) showed complete metabolic remission of bone lesions. The patient is still under treatment and maintains response (30 months to date). To our knowledge, this is the first description of complete metabolic remission in this type of patient. In conclusion, gefitinib has been safely administered to a patient with NSCLC with EGFR-activating mutation undergoing chronic hemodialysis and its use has achieved an excellent and prolonged response on bone metastases.

In most cases, the majority of patients with non-small cell lung cancer (NSCLC) are diagnosed with advanced or metastatic stage of disease. Some types of comorbidities contraindicate any chemotherapy, even with a single agent. This is the case of those with advanced chronic renal failure. The development of new targeted therapies that have a more favorable toxicity profile are of great interest for this type of patient (1, 2). Patients undergo hemodialysis for chronic renal failure now have a longer survival than ever. For this reason, many patients develop different kinds of cancer, including NSCLC (3).

Gefitinib is an orally-active, selective tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR) that demonstrates a high rate of response in patients harboring EGFR activating mutations (4, 5). The drug is well-tolerated and is metabolized in the liver (6). The feasibility of the use of gefitinib in patients with chronic renal failure undergoing hemodialysis has not been well-documented in the literature except for one case report (7). To our knowledge, the efficacy of gefitinib in this type of patients has not yet been reported. Here, we describe a case with a complete and prolonged response on bone metastases from NSCLC.

Case Report

A 70-year-old man, non-smoker, with chronic renal failure due to vascular/hypertensive nephropathy for 12 years, and with end-stage renal disease (ESRD), was on hemodialysis three times-a-week since June 2006. The patient developed a lung adenocarcinoma of the right middle lobe in December 2006. He underwent right middle lobectomy in January 2007 for pT1, G2, N0, M0 NSCLC (stage IA).

In July 2010, the computed tomography (CT) scan of the thorax demonstrated a coin lesion of 7 mm of the upper right lobe, suspected to be relapse. The case was discussed for the first time in September 2010 with medical oncologists. In October 2010, a 18F-fluoro-2-deoxy-D-glucose (18F-FDG) positron-emission tomographic (PET)/CT scan was performed. The pulmonary coin lesion was metabolically-quiescent, but the PET/CT showed several areas of

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hyperactivity in bone, in particular, the first right rib, transverse process of C7, body of D1 and D2. All these areas were osteolytic and were suspicious of recurrence. After a collegial meeting, we decided that it was necessary to have a histological confirmation that the bone lesions were due to NSCLC.

A CT-guided bone biopsy of the first right rib and of D1 was performed on January 2011. The histological examination confirmed adenocarcinoma consistent with primary lung cancer. Because standard treatment for metastatic NSCLC was not acceptable due to chronic renal failure, we examined EGFR mutations. Pyrosequencing analysis revealed the deletion of 15 nucleotides (2236-2250) in E746-E750 of exon 19.

In March 2011, PET/CT was repeated due to the elapsed time since the previous scan. Fortunately, the areas of hyperactivity on bone were stable and no new lesions appeared (Figure 1A).

In April 2011, radiotherapy (20 Gy/five sessions) was carried out to C6-D3 to reduce the risk of occurrence of spinal compression; we then obtained written informed consent from the patient and he started daily administration of 250 mg gefitinib with hemodialysis three times-a-week. Hemodialysis was performed using polysulphone capillary dialyser (F10-HPS; Fresenius, Bad Homburg, Germany).

At the start of gefitinib therapy, the calcium concentration in dialysate was 1.25 mmol/l. The treatment was well-tolerated, without any adverse event except for cutaneous rash of grade 1. During the first three months of therapy, the patient underwent prophylaxis of bisphosphonate-related osteonecrosis of the jaw, after careful preventive dentistry evaluation, as suggested by many authors (8, 9). The PET/CT after three months of gefitinib therapy demonstrated a complete metabolic remission of all the bone lesions (Figure 1B), even of those outside the field of radiotherapy (i.e., first right rib). The patient continued the treatment with gefitinib (250 mg/day).

From July 2011, the infusion of zoledronic acid at full dose (4 mg) was administered 24 h before the next hemodialysis session. Before infusion of zoledronic acid, the serum levels of calcium, 25(OH) vitamin D, parathyroid hormone, carboxy-terminal telopeptide of type I collagen (CTX) and bone alkaline phosphatase (ALP) were 8.7 mg/dl, 24.2 ng/ml, 107 pg/ml, 1.96 μg/l, and 36 U/l, respectively. After zoledronate, the patient developed mild (nadir 8.0 mg/dl after 30 days), but prolonged (four months), hypocalcemia, which was treated with oral and intravenous calcium supplementation, and oral 1,25-Dihydroxyvitamin D3. All the other laboratory values remained unchanged, except for CTX, which rapidly decreased to 0.30 μg/l.

Unfortunately, after the second administration of zoledronic acid at a dose reduced by 50% (2 mg), significant weakness and ataxia appeared. Thus, we suspended the administration of the bisphosphonate, with remission of all the symptoms. The CT scan of the brain excluded the existence of secondary lesions.

All other restaging with PET/CT, the last one performed in September 2013, confirmed that the patient was still in metabolic complete remission without having developed serious adverse events. Given the side-effects and the absence of metabolically active bone metastases in locations at risk of fracture, zoledronic acid was discontinued. The patient is continuing his planned hemodialysis treatment.

Discussion

Gefitinib metabolism is hepatic, mainly via the cytochrome P450 isoenzyme CYP3A4, while renal elimination accounts for less than 4% of the administered dose (4). The safety of administration of gefitinib at a full dose of 250 mg daily in elderly patients with chronic renal failure and advanced or metastatic NSCLC has been reported (10). These patients, however, were not undergoing hemodialysis. As far as we are aware, the first and only article on the use of gefitinib in patients on hemodialysis was written by Shinagawa et al. in 2007 (7). The patient described did not have a complete metabolic response to treatment.

To our knowledge, this is the first report where a patient undergoing hemodialysis has achieved a complete metabolic response in bone metastases. From CT images of PET, we also noticed that the bone lesions became osteoblastic. This confirms the efficacy of treatment, with normalization of the mineral component of bone tissue. This clinical data again confirms that apparently the pharmacokinetics of gefitinib was not radically-altered by hemodialysis. In fact, the patient did not have an increase in the expected side-effects. He achieved a rapid (less than three months) and prolonged complete response (more than 30 months) to treatment. Although at present there are still insufficient data on the use of gefitinib in patients with chronic renal failure, its administration should be considered the optimal therapeutic choice for patients harboring EGFR activating gene mutation. We also wanted to emphasize the fact that, as previously published (11-13), gefitinib appears to have especially good results on bone metastases. It has been hypothesized that the EGFR system regulates osteoblast activity and, therefore, bone resorption (14, 15).

Gefitinib is able to significantly inhibit the ability of bone marrow stromal cells to produce osteoclastogenic factors, such as macrophage colony-stimulating factor and receptor activator of NF-κB ligand (16). Another mechanism could be involved, since neo-angiogenesis is essential for the formation of bone metastases. In fact, the ability of anti-EGFR agents to inhibit the formation of bone metastases was correlated with the induction of apoptosis in EGFR expressing endothelial cells (17, 18).
Finally, this case report has shown that bone biopsy can be used as a source of tumor tissue in order to perform the molecular analysis of EGFR mutations (which is not widely accepted), knowing, however, that this is not the most suitable tissue, for this purpose. We have previously shown that CTX and amino-terminal pro-peptide of type I collagen measurement can be useful in monitoring patients with NSCLC during follow-up (19).

**Conclusion**

Gefitinib can be safely administered to patients with NSCLC undergoing hemodialysis due to chronic renal failure and its use can obtain a very good response in bone metastases in those with activating EGFR mutation.

**References**


