

Osteoblastic Response in Patients with Non-small Cell Lung Cancer with Activating EGFR Mutations and Bone Metastases during Treatment with EGFR Kinase Inhibitors

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Frequently, treatment of patients with non-small cell lung cancer with tyrosine kinase inhibitors is stopped because of new or progressive bone metastases. Osteoblastic response is considered a healing reaction during effective systemic therapy, defined by osteoblastic demarcation of preexisting or “new” bone lesions, whereas disease response can be identified in other tumor locations.¹ In this study, we describe three patients with non-small cell lung cancer harboring sensitizing epidermal growth factor receptor (EGFR) mutations with osteoblastic responses during disease control by tyrosine kinase inhibitor treatment.

PATIENT 1

This 47-year-old woman, former smoker, was diagnosed with stage IV adenocarcinoma (EGFR exon19 del) of the lung with pulmonary, hepatic, and osseous metas-

tases. After five cycles of platinum-containing chemotherapy plus radiotherapy (right shoulder, thoracic spine, and both femurs), progressive hepatic and osseous metastasis occurred. Gefitinib was started, and 8 weeks later, computed tomography (CT) confirmed a partial response in lung and liver. Simultaneously, progressive demarcation of a preexisting osteoblastic lesion in the left iliac bone could be identified as possible sign of response (Figures 1A, B). Six months later, when progressive disease was diagnosed in lung, liver, and axillary lymph nodes, the lesion in the left iliac bone showed less sclerosis and more lytic areas (Figures 1B, C).

PATIENT 2

This 62-year-old woman with a 4 pack-year history of smoking presented with stage IV adenocarcinoma (EGFR exon19 del) of the lung involving the middle lobe, the sixth cervical vertebra, and the left ilium. Bisphosphonate therapy was started. After chemotherapy with carboplatin/gemcitabine (progressive disease) and docetaxel/vinorelbine (stable disease), erlotinib was started because of bone marrow toxicity. Seven weeks later, a significant reduction of the primary tumor, the lymphangiosis, and pleural effusion was observed. Accordingly, progressive demarcation of an osteoblastic lesion in vertebral body Th10 (Figures 2A, B) could be detected as a possible sign of response.

PATIENT 3

This 59-year-old woman, never smoker, with stage IB adenocarcinoma (EGFR exon19 del) of the lung underwent a lobectomy of the right lower lobe (R0 resection). Nine months later, she suffered from a relapse involving lung, mediastinum, and bone. Bisphosphonate therapy and chemotherapy were started. After failure of carboplatin/etoposide plus radiotherapy (mediastinum, vertebral bodies Th4–Th7) as well as gemcitabine/docetaxel, treatment with erlotinib was started. CT 6 weeks

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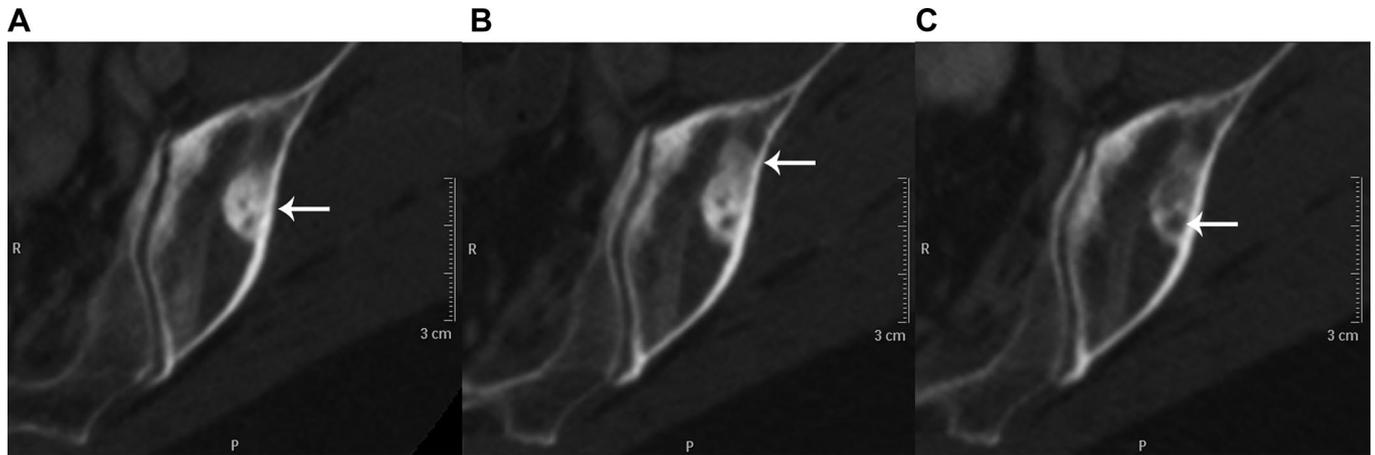


FIGURE 1. A, Baseline computed tomography (CT) before therapy with gefitinib shows an osteoblastic metastasis in the left iliac bone (arrow). B, Restaging CT 8 weeks after initiation of gefitinib therapy demonstrates progressive demarcation of the preexisting osteoblastic lesion in the left iliac bone (arrow). C, CT 6 months later at progression illustrates increased osteolysis in the former blastic area (arrow) compared with the baseline CT, shown in A, paralleling the overall tumor progression.

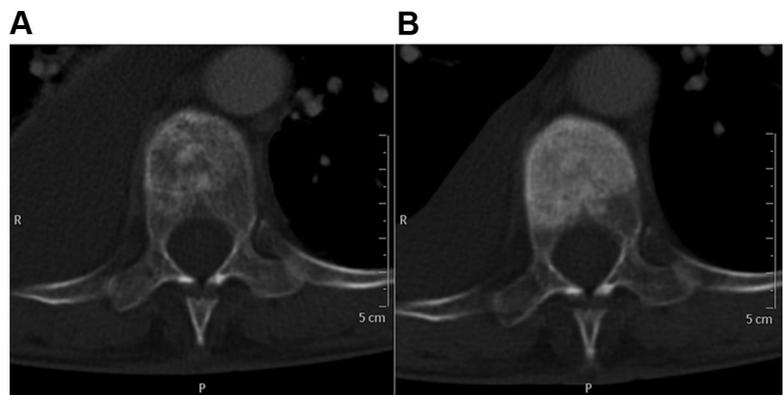


FIGURE 2. A, Baseline computed tomography before treatment with erlotinib shows an osteoblastic lesion in Th10. B, Corresponding to the clinical benefit after 7 weeks of erlotinib therapy, healing reaction of the osteoblastic lesion in Th10 is shown. The size of the lesion is not necessarily increased, but sclerosis is markedly amplified.

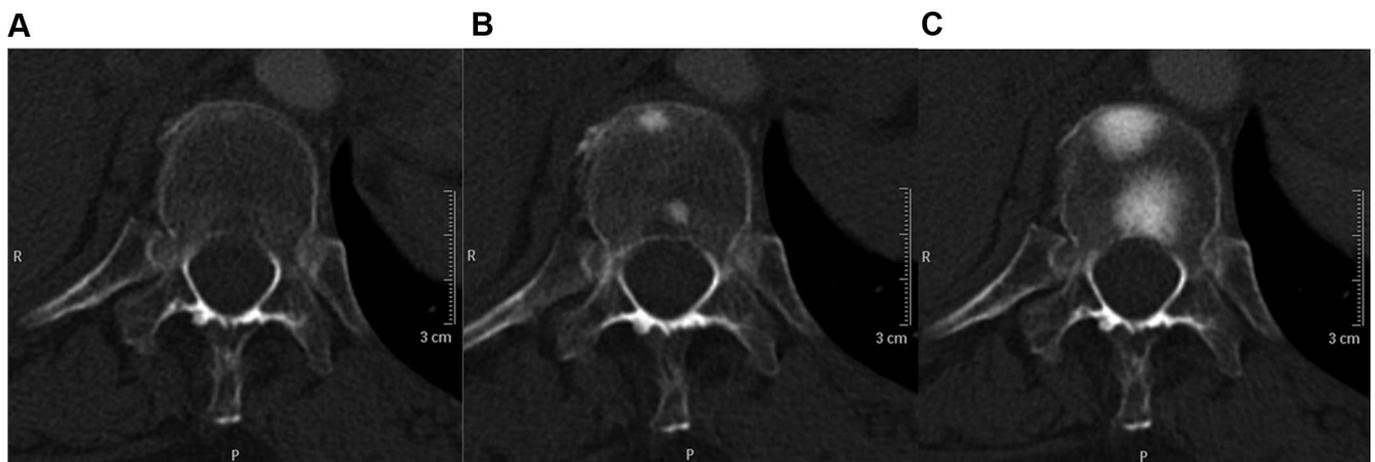


FIGURE 3. A, Baseline computed tomography before start of erlotinib therapy shows an insignificant vertebra Th11. B, “New” osteoblastic lesions in Th11 are shown in comparison with the baseline imaging 3 months after partial response to tyrosine kinase inhibitor treatment had been documented while the patient had still stable disease. C, At overall progression 5 months later, an enlargement of the osteoblastic lesions in Th11 could be identified. Note the blurry edges of the osteoblastic lesions at this time point.

later revealed a partial response along with unchanged bone metastases. Follow-up CT performed 3 months later confirmed stable disease and showed new osteoblastic lesions in Th11 (Figures 3A, B) possibly indicating a delayed response to erlotinib in these locations. The next follow-up 5 months later documented progressive disease in the lung and enlargement of the osteoblastic lesions in Th11, which appeared with more blurry edges at this time point (Figure 3C).

This report demonstrates that the time course of osteoblastic response can vary considerably between patients and that assessment of bone metastasis based on formal radiologic criteria alone is not recommended. Instead, the radiologic interpretation of metastatic bone disease should always include the full clinical picture to avoid discontinuation of an

actually effective treatment especially when disease control in other tumor locations can be identified.

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