

Osteoblastic Changes During Non-Small Cell Lung Cancer (NSCLC) Treatment: How to Distinguish between Objective Response and Progressive Disease

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Short Communication

Recently, we published an article reporting an example of the potential misinterpretation in the evaluation of osteoblastic changes during tyrosine-kinase inhibitor treatment in metastatic ALK-rearranged non-small cell lung cancer (NSCLC) [1].

Bone metastases are common in disseminated NSCLC, occurring in approximately 30% to 40% of patients [2]. In the majority of cases, they present an osteolytic imaging pattern, even though osteoblastic or mixed-type patterns have also been reported in nearly 8% of cases [3,4]. Generally, in the assessment of objective response to anticancer agents, bone metastases are classified as non-target lesions and therefore “not evaluable” for response. However, according to the revised Response Evaluation Criteria in Solid Tumors guideline (RECIST version 1.1) [5], the appearance of new non-target lesions, including lytic or osteoblastic bone metastases, is a criterion for defining progressive disease. Sometimes, the evaluation of bone lesion response may be challenging and misinterpreted.

A caveat regarding the correct evaluation and interpretation of osteoblastic changes during treatment, usually referred to as “osteoblastic flare” or “osteoblastic reaction/response”, has been raised. In our opinion, these two terms, however, refer to two completely different conditions which need to be clearly distinguished.

Osteoblastic flare is a more appropriate term to describe a transient tumor progression, as indicated by worsening of symptoms, circulating tumor or bone biomarkers and functional imaging techniques (such as positron emission tomography and bone scintigraphy), precluding to a subsequent improvement. This paradoxical phenomenon seems to be related to an increased osteoblastic activity as result of early mechanisms of repair around the bone lesion [6]. In the last years, positron emission tomography (18F-FDG PET/CT) has replaced bone scintigraphy for the detection of bone metastases due to its higher sensitivity (85%) and specificity (99%) and to the concurrent acquisition of low-dose-CT images that provide an anatomical and possible bone structural characterization of increased tracer uptake sites [7].

Furthermore, in presence of osteoblastic reaction, bone scintigraphy might be inadequate to assess response during anticancer treatments as it could persistently show osteoblastic activity, irrespective of tumor control [8]. In NSCLC, different case series on transient increased bone 18F-FDG uptake during chemotherapy [9,10] indicating initial response to anticancer treatment rather than a treatment failure, have been reported. Similar findings have also been described with 18F-FDG-PET/CT [11] and 99mTc-Bone Scintigraphy during EGFR TKIs (Table 1) [12,13].

	No. of pts (%)	Histology	Therapy	Best response	First evidence of BF (weeks)	Imaging
Lemieux et al. [10]	2/33 (6)	LCC ADC	CTX	PR PR	13 6.3	BS BS
Chao et al. [13]	7/33 (21.2)	ADC (5) NSCLC NOS (2)	Gefitinib	PR	4.8 (4.1-11.0)	BS
Krupitskay et al. [9]	4	ADC	Beva + CTX	SD (2) PR (2)	6 (6.0-9.0)	18F-FDG-PET
Hashisako et al. [12]	1	ADC	Gefitinib	PR	4	BS

LCC: large cell carcinoma; ADC: Adenocarcinoma; CTX: Chemotherapy; PR: Partial Response; BS: Bone Scintigraphy; NSCLC NOS: Non-Small Cell Lung Cancer Not Otherwise Specified; Beva: Bevacizumab; SD: stable disease; 18F-FDG-PET/CT: 18 Fluorine-fluorodeoxyglucose-positron emission tomography

Table 1: Studies on Bone Flare (BF) during any treatment in NSCLC.

On the contrary, osteoblastic reaction/response consists in the appearance of either new osteoblastic lesions or of a sclerotic component within or around lytic lesions at CT imaging. These

radiological patterns, in the absence of other signs of progressive disease, should probably not be regarded as disease progression, but rather as healing of already established lytic metastases, as described in

prostate [14], breast [15] and small cell lung cancer (SCLC) [16,17]. Osteoblastic reactions have also been reported during epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment. In EGFR-addicted NSCLC population treated with targeted therapy, osteoblastic reaction reached prevalence higher than 20% [18]. Patients with osteosclerotic changes during EGFR TKI therapy showed good objective response both in primary and other metastatic sites [18,19]. Finally, these morphological changes after EGFR TKI could be

significantly related to an improved survival ($p < 0.01$) (Table 2) [20]. In oncogene-addicted NSCLC, the different tumor response patterns of bone metastases during EGFR TKI therapy may be related either to a direct cytotoxic effect on tumor cells or to an indirect effect on bone lesions by acting on bone tumor niche and its microenvironment, through anti-angiogenic mechanisms and the inhibition of osteoclasts recruitment [21].

Author	No. of pts (%)	Histology	Therapy	Best Response	First evidence of OR (weeks)	Imaging
Bersanelli et al. [18]	10/43 (23)	ADC (39) Others (4)	Erlotinib (12) Gefitinib (5)	PR (7) SD (2) PD (1)	4.3-17.4	CT
Pluquet et al. [19]	17/36 (36)	ADC (32) Others (4)	Erlotinib (12) Gefitinib (5)	PR/SD (12) PD (5)	NR	CT
Yamashita et al. [20]	11/41 (27)	ADC	Gefitinib	PR	9 (3.0-28.4)	CT
Lind et al. [22]	3	ADC	Erlotinib	PR	10 (6-13.04)	CT
Ansén et al. [23]	3	ADC	Erlotinib (2) Gefitinib (1)	PR	8 (7-13.04)	CT

ADC: Adenocarcinoma; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; CT: Computed Tomography

Table 2: Studies on osteoblastic reaction (or) during EGFR-TKI treatment in NSCLC.

In our opinion this phenomenon represents an underestimated condition of bone metastases response, particularly in highly chemosensitive tumors and in oncogene-addicted ones. In clinical practice, a misinterpretation of these morphological or functional bone changes could lead to erroneously discontinue an effective treatment and finally have a negative impact on patients' clinical outcome. To avoid this mistake, we believe that both a correct evaluation of patients' clinical condition and computed tomography imaging is crucial. In presence of a clinical benefit and tumor response in extra-skeletal sites, an apparent worsening of bone imaging at standard CT scan should not lead to modify the current treatment strategy. In these circumstances, integrating 18F-FDG-PET/CT with standard imaging could improve the evaluation of bone metastatic disease and help in distinguishing bone flare from bone reaction/response and bone progressive disease.

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