Osteoblastic Reaction in Non-small Cell Lung Carcinoma and its Association to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Response and Prolonged Survival

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Introduction: The aim of this study was to describe the characteristics and epidermal growth factor receptor (EGFR) mutational status of patients with non-small cell lung cancer (NSCLC) with osteoblastic reactions diagnosed before or during treatment with EGFR tyrosine kinase inhibitors (TKIs).

Methods: Retrospective study including patients with 36 NSCLC with at least one site of osteoblastic reaction at the time of diagnosis or during treatment with EGFR-TKI.

Results: The rate of patients with mutated EGFR tumors with osteoblastic reactions before or after EGFR-TKI treatment was similar. Median progression-free survival (PFS) for the entire group was more than 9 months and median survival was more than 12 months. There was no statistically significant difference in survival between patients with osteoblastic reactions before initiation of TKI and those diagnosed during TKI treatment. Patients with extraosseous metastases when treated with TKI had the lowest survival ($P < 0.0001$).

Conclusions: In patients with NSCLC treated with TKI, initial or development of an osteoblastic reaction seems to be related to a more favorable outcome. In patients with osteoblastic reactions, tumors present with clinical and biologic characteristics of better survival and response to TKI. The occurrence of osteoblastic reactions during treatment with TKI, while primary tumor and metastases are stable or in response, should not be considered as disease progression.

Key Words: EGFR mutations, Bone metastasis, Lung cancer, Tyrosine kinase inhibitors, Osteoblastic reaction.

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Bone metastases are a frequent complication of non-small cell lung cancer (NSCLC), occurring in up to 30 to 40% of patients during the progression of NSCLC. They have been characterized as osteolytic or osteoblastic. This classification actually represents two extremes of a continuum in which deregulation of the normal bone remodeling process occurs and patients can have both osteolytic and osteoblastic metastasis or mixed lesions. Generally in NSCLC, metastases are osteolytic, and there have only been very rare reports of osteoblastic reactions during chemotherapy for lung cancers, particularly in small cell carcinomas.[1,2]

A phenomenon, called osteoblastic flare, is a temporary increase in tracer uptake associated with therapy response of bone metastases that were previously undetected and is a healing response to effective cytostatic chemotherapy. It has

also been widely documented in breast and prostate cancer, but only very rarely in NSCLC.[3] The osteoblastic reaction is the radiographic equivalent of osteoblastic flare and is defined as the appearance of new osteoblastic bone lesions while disease response is observed at other tumor sites. It has also been described in breast and prostate cancer.[4,5] Indeed, a retrospective study in 24 patients with newly diagnosed small cell lung cancer and bone metastases indicated that osteoblastic reaction as a healing reaction seems to occur in most patients with small cell lung cancer and bone metastases and therefore should not be misinterpreted as progressive disease.[2] Detection of new osteoblastic bone metastases must be differentiated from a healing reaction due to response to chemotherapy, radiation therapy, or alternatively to effects related to drugs, e.g biphosphonates.

Molecular targeted therapies, such as the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are widely used in the treatment of metastatic NSCLC. They provide a different mechanism of action from chemotherapy and can be much more specific in their approach to cancer treatment by identifying subsets of patients who will derive the most benefit. Erlotinib and gefitinib are reversible TKIs of EGFR (EGFR-TKIs) that have demonstrated efficacy in the second- and third-line treatment of metastatic NSCLC[6] compared with placebo and are therapeutically equivalent to docetaxel with better clinical safety.[7,8] It has been observed that never smokers or former smokers, Asians and, to a lesser extent, women, as well as patients with adenocarcinoma are more likely to respond to EGFR-TKI treatment.[9–11] These clinical characteristics are highly associated with the presence of amplified and/or mutated exons 18 through 21 of the EGFR gene, making the tumor cells extremely sensitive to EGFR-TKI.[12–14]

It also appears that certain types of metastases respond particularly well to EGFR-TKI, particularly in the case of carcinomatous meningitis.[15] It has recently been suggested that the presence of an osteoblastic reaction is also associated with a significant response to EGFR-TKI[16] and that bone condensation may increase or even appear within osteolytic lesions over time (Figure 1*A*, *B*). In these observations, the osteoblastic reactions were either present before receiving TKI and increased during treatment or appeared during treatment in areas considered to be free of metastases.

The mechanism of the onset of this osteoblastic reaction is not fully understood; the action of the TKI can be considered as either having a direct therapeutic effect on the metastasis for which progression is thus impeded or stopped[17] or as having an effect on the osteoblasts and osteoblasts.[18] The prognostic significance of these bone condensations needs defining and, in particular, the significance of an osteoblastic reaction appearing during treatment in bone segments considered free of metastases.

The purpose of this retrospective study was to describe the characteristics of patients who presented an osteoblastic reaction, at the time of NSCLC diagnosis or during treatment with EGFR-TKI. We also intended to investigate the tumor EGFR mutational status, the progression of the original tumor, bone metastases, and any other metastases, during the course of the EGFR-TKI treatment.

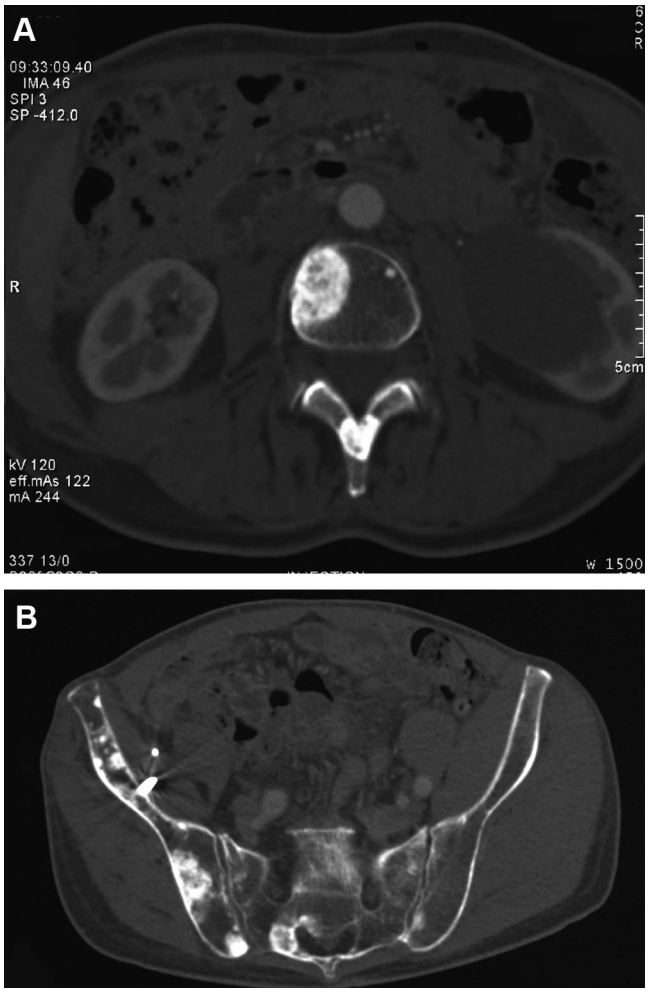

FIGURE 1. *A,* Osteoblastic response of a lumbar vertebra diagnosed before treatment. *B,* Pelvic osteoblastic response diagnosed during treatment with TKI.

MATERIALS AND METHODS

This retrospective study included 36 patients with histologically/cytologically proven NSCLC and presenting at least one site of osteoblastic reaction at the time of diagnosis, at the start of, or during treatment with an EGFR-TKI (erlotinib or gefitinib). The EGFR-TKI treatment had to have been evaluated at least once by medical imaging (computed tomography, bone scintigraphy, and magnetic resonance imaging) and followed-up until death or until the assessment date of August 1, 2008.

All files were reviewed by the same investigator (E.P.), and the information was collected on a standardized collection sheet. Clinical characteristics included age, gender, ethnicity, smoking history (nonsmoker = less than 100 cigarettes in their lifetime; former smoker = no smoking for over a year; and smoker), histologic type, tumor, node, metastasis stage at initial diagnosis, number and type of metastasis at

initiation of EGFR-TKI, type of bone metastasis (single or multiple, condensing bone, or mixed). Osteoblastic reactions were grouped according to the time of diagnosis (known before treatment with TKI or appearing during treatment with TKI). Therapeutic characteristics included number of lines of treatment, type of TKI, cutaneous tolerance, administration of bisphosphonates before or after initiation of TKI. Tumor evolution with treatment based on best response evaluated according to RECIST criteria,[19] time to progression and date of death. On available tissues, tests for EGFR mutations (exons 19 and 21) and K-*ras* were performed using DNA sequencing in four centers (Strasbourg, Grenoble, Caen, Paris), that had harmonized their analysis methods by applying a quality assurance procedure.

Statistical Analyses

Analyses comparing categorical variables were carried out using Fisher exact test tests. Analyses comparing continuous variables were carried out using *t* tests. Survival was calculated from the date of the first dose of TKI until progression (for PFS) or death (for overall survival); event-free individuals were censored. Survival of the different groups was compared using the log-rank test.

Multivariate analysis using the Cox model assessed the impact of the following variables on overall survival: smoking habit, gender, histology and the presence or increase/onset of an osteoblastic reaction in patients for whom extraosseous tumor metastases were responding or stable.

RESULTS

The clinical, therapeutic, and biologic characteristics of the 36 patients included in this retrospective study are presented in Table 1. Twenty-one (58.3%) patients were women and 32 (88.9%) had an adenocarcinoma. The other histologic subtypes were large-cell carcinoma (two patients), squamous cell carcinoma, and pleomorphic carcinoma (one patient each). Thirty-one patients were treated with erlotinib and five patients with gefitinib (Table 1). Four patients received a first-line treatment when participating in a clinical, 13 received a second-line treatment, and the 16 others a third-line treatment or beyond.

Thirteen patients were treated with bisphosphonates before the initiation of TKI. Calcemia before initiation of treatment was known in 22 patients with a median value of 2.32 micromoles (range 2.04–2.60); no patients had hypercalcemia.

Biopsies embedded in paraffin were available for 30 patients (Table 1). Testing for mutations showed that 13 of 25 patients (54%) presented with an EGFR mutation including exon 19 (9 of 25 patients), exon 21 (4 of 24 patients), and K-*ras* mutation (1 of 23 patient). The proportion of patients with an EGFR mutation was similar in patients presenting with condensing bone lesions before or after initiation of EGFR-TKI.

On the basis of the RECIST criteria, 14 (38.9%) patients were assessed as responders or stable to treatment with TKI and 22 (61.1%) patients in progression. However, among these 22 patients, only five had a well-documented progression other than bone metastases (lung and liver, three patients each and one patient had a nodular metastasis). In the 17 other patients, the progression involved onset of an osteoblastic reaction in 11 patients and an increase in number or spreading of already known osteoblastic reactions in six patients.

The median treatment duration was 287 days (range 48–1092) for all patients. There was no difference in the duration of TKI treatment in patients with osteoblastic reactions before treatment start and those with osteoblastic reactions detected during treatment. Treatment was still in progress in seven patients (19.4%) at the assessment date. Treatment with TKI was discontinued in 29 patients for the following reasons: disease progression (26 patients), adverse events (two patients, grade 4 asthenia and grade 4 respiratory disease), and death from concomitant disease (one patient).

Median PFS for the entire group was 300 days (~9.8 months) Table 2. At the assessment date, nine patients were alive and 27 were deceased (25 deaths related to the disease and two due to concomitant disease). With a median follow-up period of 868 days, the median survival of the entire group was 408 days (~13.4 months) with a survival rate at 1 and 2 years of 52 and 26%, respectively. Overall survival and PFS curves evaluating the impact of the response to TKI with or without an osteoblastic reaction are presented in Figure 2*A*, *B*. There was no statistically significant difference in PFS or overall survival between the group of patients presenting with an osteoblastic reaction before initiation of TKI and those for whom the osteoblastic reaction appeared during the treatment with TKI. Patients who presented with progression of extraosseous metastases while treated with TKI had poorer PFS than patients presenting with an osteoblastic reaction before initiation of TKI ($p < 0.0001$) or during treatment ($p < 0.0001$). Also, patients with progression of extraosseous metastases while treated with TKI had poorer overall survival than patients with an osteoblastic reaction before initiation of TKI ($p = 0.009$) and during treatment ($p = 0.009$).

Among the other parameters studied in single variable analysis, previous smoking habit ($p = 0.0003$) and performance status ($p = 0.006$) were associated with a better survival. The other factors including histology, gender, rash, or EGFR mutations had no impact on survival. Smoking also had an impact on PFS ($p = 0.005$).

A multivariate analysis using the Cox model is presented in Table 3. The size of the cohort and the strong predominance of women patients and adenocarcinoma probably explain the lack of significance of statistical test that could not demonstrate an impact of these two parameters on survival.

DISCUSSION

If RECIST criteria are strictly applied to patients with new lesions exclusively in the form of osteoblastic reactions, should the diagnosis be progression and lead to a modification of the treatment administered? Indeed, the appearance of an osteoblastic reaction during an active antitumor treatment can complicate the definition of best overall response using RECIST criteria. In this retrospective study, we have analyzed 36 cases of patients with NSCLC presenting with osteoblastic reactions either before treatment with TKI or

TABLE 1. Patients and Disease Characteristics Based on Whether or Not an Osteoblastic Reaction is Present at the Time of TKI Administration

	Osteoblastic Reaction Initially Present, $n = 23$ (%)	Osteoblastic Reaction During TKI Treatment, $n = 13$ (%)	p
Age (mean, range)	61 (27–80)	60 (36–76)	NS
Gender			
Males	10 (43.5)	5 (38.5)	NS
Females	13 (56.5)	8 (61.5)	
Asian origin	0	1 (7.7)	NS
Smoker			
Active	1 (4.3)	2 (15.4)	NS
Former	9 (39.1)	3 (23)	
Never	13 (56.5)	8 (61.5)	
Stage			
IIIA/B	6 (26)	6 (46.1)	NS
IV	17 (73.9)	7 (53.8)	
Histology			
Adenocarcinomas	21 (91.3)	11 (84.6)	NS
Other	2 (8.7)	2 (15.4)	
Performance status			
0	3 (13)	1 (7.7)	
1	9 (39.1)	3 (23)	NS
2	9 (39.1)	7 (53.8)	
3	2 (8.7)	2 (15.4)	
Metastasis			
Solitary	0	2 (15.4)	NS
Multiple	23 (100)	11 (84.6)	
Multiple bone	20 (86.9)	6 (46.1)	
Mutation			
Exon 19 deletion	5 (14 analyses)	4 (11 analyses)	
Exon 21 mutation	3 (14 analyses)	1 (10 analyses)	NS
K-*ras* mutations	0 (14 analyses)	1 (10 analyses)	
Treatment with Erlotinib	20 (86.9)	11 (84.6)	NS
Treatment with Gefitinib	3 (13)	2 (15.4)	
Line of treatment			
1st	3 (13)	1 (7.7)	
2nd	6 (26)	7 (53.8)	NS
3rd	13 (56.1)	3 (23)	
4th	1 (4.3)	2 (15.4)	
Treatment duration (d, mean, median, range)	381, 267, 48–1017	350, 308, 56–1092	NS
Rash grade ≥2	10 (43.5)	6 (46.1)	NS
Use of bisphosphonates			
Before TKI	11 (47.8)	2 (15.4)	0.03
During TKI	7 (30.4)	2 (15.4)	
No	11 (47.8)	11* (84.6)	

NS, not significant; TKI, tyrosine kinase inhibitor. * $P = 0.03$.

during treatment with TKI. The progression of the primary tumor and its metastases during TKI treatment was studied. In most patients, osteoblastic reactions were considered as bone metastases, they were multiple and associated with extraosseous metastases. Most patients (70%) had not received bisphosphonates before initiation of TKI.

In this cohort, we found a vast predominance of nonsmoker or never smoker patients (91.6%), adenocarcinomas (89%), and finally, women patients were found more frequently than is usually observed in NSCLC (58%). There was no difference between patients with documented osteoblastic reaction before or after treatment with TKI (Table 1). EGFR Mutations were observed in approximately 50% of the patients with 9 (36%) deletions of exon 19 and 4 (16.7%) mutations of exon 21; K-*ras* mutations were observed in 4% of the patients.

These clinical and biologic characteristics are very different from those observed in pivotal studies with TKIs. In

TABLE 2. Response and Survival Characteristics of the Cohort Studied Based on Whether or Not an Osteoblastic Reaction is Present at the Time of Prescription of TKI

	Osteoblastic Metastasis Initially Present (n = 23)	Bone Metastasis Becoming Osteoblastic During TKI Treatment (n = 13)
PR, SD/progression (excluding bone lesions)	20/3	11/2
PR, SD/progression (including bone lesions)	14/9	0/13
Median progression-free survival	252 d	342 d
Median survival	450 d	350 d
2-yr survival	31%	13.5%

TKI, tyrosine kinase inhibitor; PR, partial response; SD, stable disease.

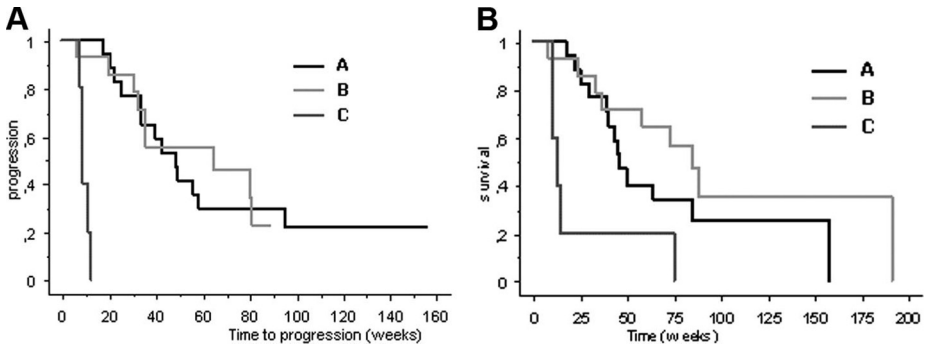

FIGURE 2. *A*, Analysis of progression-free survival based on the effect of TKI. A, Response or stable with increase or onset of osteoblastic reaction (17 patients); B, response or stable with stable osteoblastic reaction (14 patients); C, progression of extraosseous sites (five patients) (overall log rank $p < 0.0001$, A versus B $p = 0.87$, A versus C $p < 0.0001$, B versus C $p < 0.0001$). *B*, Analysis of overall survival based on the effect of TKI. A, response or stable with increase or onset of osteoblastic reaction (17 patients); B, response or stable with stable osteoblastic reaction (14 patients); C, progression of extraosseous sites (five patients) (overall log rank *p*, 0.002; A versus B *p*, 0.2; A versus C *p*, 0.009; B versus C *p*, 0.009).

TABLE 3. Analysis Using the Cox Model, Integrating Standard Prognostic Parameters with the Presence of Stable or Increased Osteoblastic Reaction in the Absence of Progression on Extraosseous Metastases

Parameter	HRs (95% CI; p Values)
Never or former smoker	0.13 (0.02–0.71; 0.01)
Adenocarcinoma histology	1.5 (0.32–6.8; 0.6)
Female	0.47 (0.2–1.2; 0.12)
Osteoblastic reaction increased	0.29 (0.09–0.89; 0.03)
Stable osteoblastic reaction	0.13 (0.03–0.47; 0.002)

HR, hazard ratio; CI, confidence interval.

the National Cancer Institute of Canada Clinical Trials Group, randomized, phase III, BR21 study, assessing 150 mg daily of single-agent erlotinib in patients with locally advanced or metastatic NSCLC after failure of at least one previous chemotherapy regimen, there were 35.5% women, 50.4% adenocarcinomas, and a majority of smokers.[7] Similarly, in the INTEREST study, a randomized phase III trial assessing gefitinib versus docetaxel in previously treated NSCLC, there were 36.4% women, 56.2% adenocarcinomas, and 79.8% smokers.[8]

In study BR21, KRAS was mutated in 15% of the patients and EGFR was mutated in 18% of the patients, whereas in the INTEREST study, EGFR mutations were observed in 14% of patients and K-*ras* in 17% of the patients.

The response rate is much higher than that usually observed when bone metastases are not taken into account,[7,8] and the median survival for the entire group was greater than 12 months, which is longer than that usually reported with TKIs (6.7 months in the BR21 study and 8.4 months in the INTEREST study). The PFS differences are even more important, because the median was greater than 9 months in this study compared with 2.2 months in the BR21 and INTEREST studies.

Patients who presented with progression of extraosseous metastases when treated with TKI had poorer survival than the others ($p < 0.0001$). There was no statistically significant difference in survival between patients with osteoblastic reactions before initiation of TKI and during the treatment with TKI. Furthermore, there was no difference in survival between those who were responders or stable when treated with TKI and those who presented with an onset of osteoblastic reaction or for whom osteoblastic reactions increased in size or number. In both univariate and multivariate analysis, these patients had better survival.

In conclusion, in patients with NSCLC treated with TKI, the initial presence or development of an osteoblastic reaction seems to be related to a more favorable outcome compared with patients with extraosseous metastasis. In pa-

tients with an osteoblastic reaction (before or during treatment), the tumors present with clinical and biologic characteristics of a response to TKI as well as better survival. Thus, the occurrence of an osteoblastic reaction during treatment with TKI, although extraosseous metastases are stable or in response, should not be considered as disease progression.

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