Is ^{18}F-FDG PET/CT Useful for the Early Prediction of Histopathologic Response to Neoadjuvant Erlotinib in Patients with Non–Small Cell Lung Cancer?

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Early prediction of treatment response is of value in avoiding the unnecessary toxicity of ineffective treatment. The objective of this study was to prospectively evaluate the role of integrated ^{18}F-FDG PET/CT for the early identification of response to neoadjuvant erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor. **Methods:** From October 2006 to March 2009, 23 patients with non–small cell lung cancer eligible for surgical resection were evaluated for this study. Patients received preoperative erlotinib (150 mg) once daily for 3 wk. ^{18}F-FDG PET/CT was performed before and at 1 wk after the administration of erlotinib. Changes in tumor ^{18}F-FDG uptake during treatment were measured by standardized uptake values and assessed prospectively according to the criteria of the European Organization for Research and Treatment of Cancer. Patients with a decrease in standardized uptake values of 25% or more after 1 wk were classified as "metabolic responders." The metabolic response was compared with the pathologic response, obtained by histopathologic examination of the resected specimen. **Results:** Following the ^{18}F-FDG PET/CT criteria of the European Organization for Research and Treatment of Cancer, 6 patients (26%) had a partial response within 1 wk, 16 patients (70%) had stable disease, and 1 patient (4%) had progressive disease. The median percentage of necrosis in the early metabolic responder group was 70% (interquartile range, 30%–91%), and the median percentage of necrosis in the nonresponder group was 40% (interquartile range, 20%–50%; $P = 0.09$). The κ-agreement between the metabolic and pathologic responders was 0.55 ($P = 0.008$). **Conclusion:** The results of this study suggest that early during the course of epidermal growth factor receptor tyrosine kinase inhibitor therapy, ^{18}F-FDG PET/CT can predict response to erlotinib treatment in patients with non–small cell lung cancer.

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Despite a multidisciplinary approach in the treatment of non–small cell lung cancer (NSCLC), the survival rate of NSCLC patients has improved little over the last few years. The number of patients presenting with stage IV disease has increased (*1*). This increase is most likely a result of better staging, because metastatic disease is identified long before it causes clinical symptoms. An important tool that has improved oncologic staging is ^{18}F-FDG PET. In patients with NSCLC, ^{18}F-FDG PET has been recognized as an adequate staging tool (*2–4*), and several studies also suggest that the standardized uptake value (SUV) has a prognostic value in NSCLC (*5–7*). By integrating functional ^{18}F-FDG PET and CT data, both anatomic and metabolic information can be provided, which increases the diagnostic performance in NSCLC patients (*8,9*).

In the era of patient-tailored treatment, response monitoring is important so that unnecessary toxicity and costs of ineffective treatment can be avoided. In previous studies concerning chemotherapy in NSCLC, ^{18}F-FDG PET/CT has been shown to predict response early during the course of chemotherapy (*10–12*).

In the last decade, several molecular-targeted agents—for example, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) such as erlotinib and gefitinib—have emerged for treatment of NSCLC. However, research concerning early response monitoring with ^{18}F-FDG PET for these new agents is scarce. In a panel of cell lines, Su

et al. (*13*) studied whether tumor response to EGFR-TKI could be identified by measuring treatment-induced changes in glucose utilization by ^{18}F-FDG PET. They concluded that ^{18}F-FDG PET may be a valuable clinical predictor for response to EGFR-TKI early in the course of treatment. Sunaga et al. (*14*) monitored gefitinib treatment in five patients using ^{18}F-FDG PET and reported that a decrease in metabolic uptake within 2 d of initiation of treatment predicted response.

Currently, a Dutch multicenter phase II study of neoadjuvant erlotinib in operable patients with NSCLC is open for accrual. In the context of this study, we prospectively evaluated ^{18}F-FDG PET/CT in predicting response to neoadjuvant erlotinib early in the course of erlotinib therapy in patients with NSCLC.

MATERIALS AND METHODS

Patients

^{18}F-FDG PET/CT was performed as part of an open-label, noncomparative, 2-stage phase II study at 4 medical centers in The Netherlands (The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam; Kennemer Hospital, Haarlem; Haga Hospital, The Hague; and University Medical Centre, Maastricht). From October 2006 to March 2009, patients with operable stage I–III NSCLC were included in the trial to study the response to and toxicity of the EGFR-TKI erlotinib. Eligibility criteria included operable adult (≥18 y) patients with resectable NSCLC (i.e., clinical stages I–III NSCLC, cT1–cT3 N0–N1) (*1*). Staging procedures included contrast-enhanced CT and PET/CT scans and, in the case of mediastinal metabolic uptake or nodes greater than 1 cm in shortest diameter, additional endoscopic ultrasound-guided fine-needle aspiration cytology or mediastinoscopy.

Patients had to be fit for surgery, with an Eastern Cooperative Oncology Group performance status of 0 or 1, and not be pregnant or nursing. The study was approved by the institutional review boards. Written informed consent was obtained from all patients. The study protocol was in accordance with the guidelines established by the World Medical Association Declaration of Helsinki.

Neoadjuvant Erlotinib

Preoperative treatment comprised 1 tablet of 150 mg of erlotinib daily for 3 wk. Surgical resection involved a radical resection of the tumor, preferably by lobectomy and regional lymph node dissection. The protocol allowed the use of erlotinib as adjuvant therapy, when the treating physician considered this to be in the best interest of the patient.

^{18}F-FDG PET/CT Acquisition

A baseline ^{18}F-FDG PET/CT scan was obtained during routine staging in all patients. The baseline scan had to be acquired within 1 mo before the start of neoadjuvant erlotinib treatment. For early monitoring, ^{18}F-FDG PET/CT was planned within 7 d after the initiation of erlotinib therapy. In this study, a Gemini TF (Philips) PET/CT scanner was used. ^{18}F-FDG was administered in doses of 180–240 MBq. Patients fasted for 6 h before imaging. Diabetes mellitus was regulated in advance, with plasma glucose less than 10 mmol/L. The interval between ^{18}F-FDG administration and scanning was 60 ± 10 min. Low-dose CT images (40 mAs, 5-mm slices) were acquired without intravenous contrast.

PET/CT, low-dose CT, and PET images were displayed using an OsiriX Digital Imaging and Communications in Medicine viewer in a Unix-based operating system (Mac OS X, Power G5; Apple) and evaluated with 2-dimensional orthogonal reslicing.

Interpretation and Analyses of ^{18}F-FDG PET/CT Data

A nuclear physician who was unaware of other patient data evaluated the acquired images semiquantitatively. ^{18}F-FDG tumor uptake was quantified using the maximum SUV (SUV_{max}), which was defined as the maximum tumor concentration of ^{18}F-FDG divided by the injected dose and corrected for the body weight of the patient. To establish the SUV_{max}, the maximum ^{18}F-FDG uptake within the volume of the primary tumor on the PET image was determined. This region was manually drawn. Metabolic tumor response was assessed according to the SUV measurement criteria of the European Organization for Research and Treatment of Cancer (EORTC) (*15*). On the basis of these criteria, metabolic response was defined as a decrease of at least 25% in SUV_{max}.

Pathology Analyses

Evaluation of the resection specimens for determination of pathologic response was 2-fold. In addition to the amount of residual vital tumor, morphologic signs of therapy-induced regression such as tumor necrosis, foam-cell reaction, giant-cell reaction, inflammation, and fibrotic alterations were also determined (*16*). Of the formalin-fixed resection samples, areas with macroscopic tumor tissue were paraffin-embedded, and serial sections were stained with hematoxylin and eosin. Tumor regression was scored as "pathologic response" if more than 50% necrosis was present with morphologic signs of therapy-induced regression or "no response" when either 0%–50% necrosis or necrosis that could not be attributed to the therapy effect was seen. If more than 90% necrosis was present in the resected specimen, tumor regression was defined as near-complete pathologic response. One pathologist evaluated all the resection specimens and was unaware of other patient data.

Statistical Analyses

Statistical analyses were performed to correlate the amount of necrosis in the specimen to the change in SUV_{max}. Percentage necrosis and SUV_{max} are presented as median and 25th and 75th percentiles, respectively, and interquartile ranges (IQRs). The Wilcoxon rank sum test with continuity correction was used to analyze differences between responders and nonresponders. The κ-value was used to describe correlation between the responders and pathologic results. P values less than 0.05 were considered statistically significant.

RESULTS

The study population included 23 patients (8 men [35%] and 15 women). The mean age was 63 y (range, 46–76 y). Clinical characteristics of the study population are shown in Table 1. For 23 of the 33 patients enrolled in the ongoing phase II trial, ^{18}F-FDG PET/CT at baseline and ^{18}F-FDG PET/CT within 7 d of initiation of treatment were available. The median time between these 2 scans was 21 d; the median time between the start of erlotinib therapy and follow-up ^{18}F-FDG PET/CT was 6 d (IQR, 3–7).

^{18}F-FDG PET/CT

The median SUV_{max} at baseline ^{18}F-FDG PET/CT was 11.0 (IQR, 7.2–15.7). The median SUV_{max} after 1 wk of

TABLE 1. Clinical Characteristics of Study Population

Variable	*n*	%
Sex		
Male	8	35
Female	15	65
Histology		
Adenocarcinoma	17	73
Other	6	26
Clinical stage		
IA	6	26%
IB	9	39%
IIA	2	9%
IIB	4	17%
IIIA	2	9%
Size of primary tumor (cm)		
1.0–2.0	5	22
2.1–3.0	7	30
3.1–5.0	6	26
>5.0	5	22
Smoking status		
Current	8	35
Former	11	48
Never	4	17
EGFR mutation status		
Yes	4	17
No	18	78
Unknown	1	4

Mean age of patients was 63 y (range, 46–76 y).

erlotinib therapy was 9.3 (IQR, 5.5–13.1). According to the EORTC criteria, 6 patients (26%) had a partial response within 1 wk (Fig. 1), 16 patients (70%) had stable disease, and 1 patient (4%) had progressive disease. The median relative difference in SUV_{max} between the baseline scan and the scan within 1 wk of therapy was −10% (IQR, −30% to +9%) (Fig. 2).

Association of ^{18}F-FDG PET/CT with Pathologic Results

The median percentage of necrosis in the resection specimens of treated patients was 40% (IQR, 20%–60%). In patients classified as "metabolic responders" (an SUV_{max} decrease by more than 25% [IQR, −100% to −25%]), the median percentage necrosis in the metabolic responder group was 70% (IQR, 30%–91%). The median percentage necrosis in metabolic nonresponders was 40% (IQR, 20%–50%), with a *P* value of 0.09 (Wilcoxon rank sum). The κ-agreement between the metabolic and pathologic responders was 0.55 ($P = 0.008$). Figure 2 shows the relation of change in tumor metabolic uptake and the percentage of necrosis in the resection specimen. Only 3 patients with metabolic response according to EORTC criteria had an EGFR mutation (all deletions in exon 19); other responders comprised cases of no mutation.

DISCUSSION

In this phase II trial of neoadjuvant erlotinib in NSCLC patients, 6 of 23 patients (26%) showed metabolic response

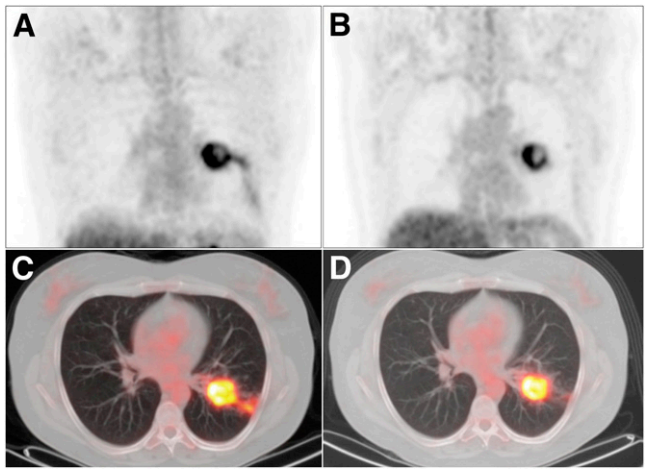

FIGURE 1. Coronal ^{18}F-FDG PET images of patient with carcinoma of left lung. Maximum-intensity-projection images before (A) treatment with erlotinib, showing reduction in uptake (ΔSUV_{max}, −57%), and increase in necrosis of primary tumor after 7 d (B) of treatment with erlotinib. This early effect is also observed on transversal PET/CT fusion images before (C) and after 7 d (D) of erlotinib. After erlotinib treatment, patient was operated on; resected specimen contained 80% necrosis.

within 1 wk of treatment. When a cutoff value of 25% decrease in SUV_{max} was used (PET EORTC criteria), early metabolic response corresponded to pathologic tumor regression in the resection specimen in most patients. To our knowledge, this is the first study on early response monitoring of EGFR-TKI therapy as measured by ^{18}F-FDG PET/CT.

The use of neoadjuvant therapy has several clinical advantages. First, it allows for the assessment of biologic

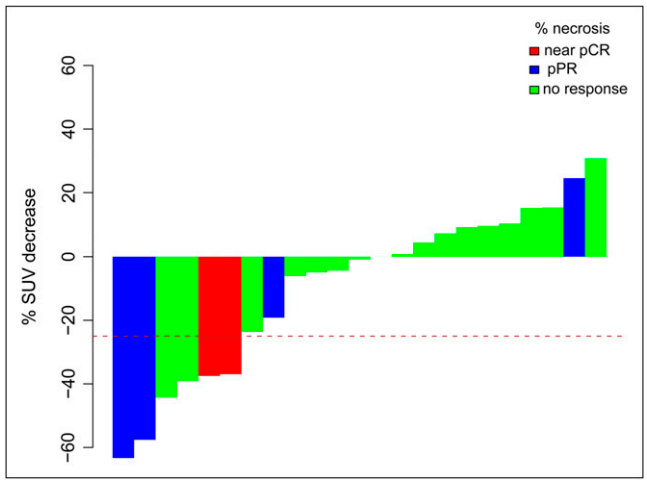

FIGURE 2. Percentage change in SUV_{max} on ^{18}F-FDG PET/CT scan within 1 wk of neoadjuvant erlotinib treatment in relation to pathologic response. pCR = pathologic complete response; pPR = pathologic partial response.

response in vivo. Second, after a favorable response to neoadjuvant therapy, the agent can be administered for a longer period or used as an adjuvant treatment. Third, the administration of preoperative treatment may improve the resectability of locally advanced disease. For all 3 applications, however, early and reliable evaluation of response is necessary. Only then can unnecessary side effects and costs be prevented in the case of no response or progression of disease.

Preoperative chemotherapy for NSCLC has been extensively investigated, but its role in patient management remains controversial. Although responses to several courses of neoadjuvant chemotherapy have been observed in up to 49% of the patients, no randomized trials have shown improvement in survival by preoperative chemotherapy as compared with surgery alone (*17,18*). ^{18}F-FDG PET was reported to predict response to chemotherapy (*10–12*). Hoekstra et al. (*10*) performed ^{18}F-FDG PET in 47 patients with stage IIIa NSCLC who received induction chemotherapy. They concluded that it was feasible to predict response after 1 cycle of chemotherapy. Decoster et al. (*12*) showed in 31 patients with locally advanced NSCLC that a complete response on ^{18}F-FDG PET was a more powerful predictor for survival than response on CT. Furthermore, Lee et al. (*11*) concluded that ^{18}F-FDG PET/CT after 1 cycle of chemotherapy could predict progressive disease earlier that CT evaluation. Dooms et al. (*19*) created a restaging strategy after induction chemotherapy for stage IIIa NSCLC patients, combining morphometric analysis of mediastinal lymph nodes and ^{18}F-FDG PET response monitoring in the primary tumor, allowing for more individualized treatment.

Erlotinib is able to induce swift responses in selected NSCLC patients and prolongs survival when given as a second-line treatment in advanced disease (*20,21*). However, in many patients no objective response is achieved (*22*). Several studies have reported that lung tumors carrying EGFR mutations are more sensitive to erlotinib, with significantly better treatment response. However, it may be difficult to obtain material for EGFR mutation analysis, and patients with EGFR mutations do not exclusively respond to EGFR treatment. Evaluation by PET after a short trial of treatment would be an interesting alternative or additional tool for treatment selection based on mutation status. Several phase II studies with preoperative EGFR-TKIs are ongoing, but studies that have evaluated ^{18}F-FDG PET for response monitoring in EGFR-TKI treatment are limited in quality and quantity.

Using ^{18}F-FDG PET and ^{18}F-3′-fluoro-3′-deoxy-L-thymidine (^{18}F-FLT) PET, Su et al. (*13*) investigated in cell lines whether tumors responding to EGFR-TKIs could be identified by monitoring glucose use. Uptake of ^{18}F-FDG reflected immediate cellular response to EGFR-TKI treatment. In contrast to the rapid decrease of ^{18}F-FDG uptake, ^{18}F-FLT PET showed no major changes. Su et al. (*13*) concluded that ^{18}F-FDG PET may be able to predict response to EGFR-TKI early in the course of treatment. Ullrich et al. (*23*) also studied the potential of ^{18}F-FDG and ^{18}F-FLT PET to detect response to EGFR inhibitors in a mouse model of EGFR-dependent lung cancer. They reported, in contrast to Su et al. (*13*), that ^{18}F-FLT PET was able to identify response to EGFR treatment more accurately than ^{18}F-FDG PET. The only patient-based report is that of Sunaga et al. (*14*), in which only 5 patients were included. ^{18}F-FDG PET results were studied in patients with unresectable stage III/IV NSCLC or recurrent disease after surgery, who received EGFR-TKI therapy. Although the data suggested a possible value of ^{18}F-FDG PET in response prediction, these results need to be confirmed by other studies.

CONCLUSION

In the prospective setting of a phase II trial, this study suggests that early during the course of EGFR-TKI therapy for NSCLC, ^{18}F-FDG PET/CT can identify response in most patients. Even though our study was relatively small, the results are promising and consistent with the results of preclinical studies. Further data in larger groups of patients are required to determine the optimal timing of response evaluation and the relevance of cutoff values of response parameters.

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