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Perfusion Parametric Map in Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Therapy in Patients with Non-Small Cell Lung Cancer: A Feasibility Study

2012년 2월
의학 석사 학위 논문

비소세포폐암환자에서
표피성장인자수용체-티로신ки나아제억제제 치료 후
관류영상 : 예비연구

Perfusion Parametric Map in Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Therapy in Patients with Non-Small Cell Lung Cancer : A Feasibility Study

2012년 2월

지도교수 김원홍

이 논문을 석사학위 논문으로 제출함
이 논문을 이주원의 석사학위논문으로 인정함.

2012 년 2 월

주심
석사
부심
위원
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ABSTRACT

Purpose
To quantify the anti-angiogenic effect of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) by mapping perfusion parameters on a voxel-by-voxel basis using dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) in patients with non-small cell lung cancer (NSCLC).

Materials and methods
Five patients were prospectively enrolled, satisfying the following criteria: 1) patients with pathologically-proven recurrent or metastatic NSCLC; 2) patients with primary masses of more than 3 cm along the longest diameter; and 3) patients with EGFR mutations or at least 2 of the following factors, adenocarcinoma, female, or never-smokers. Patients were treated with gefitinib or erlotinib and the start of chemotherapy was denoted Day 0 (D0). DCE-MRI was performed at Day-1 (D-1), Day+7 (D+7), and Day+28 (D+28). Perfusion parameters were calculated using extended Kety model. Dynamic curve pattern was analyzed with time-concentration curve for the lung cancer region. Longitudinal changes of anti-angiogenic effect were quantified on a voxel-by-voxel basis and compared to Response Evaluation Criteria in Solid Tumors (RECIST) results.
Results

Two patients showed partial response and three patients showed stable disease by RECIST at the 28th day of follow-up after EGFR-TKI treatment. The $K_{\text{trans}}$ (volume transfer constant) and $v_e$ (volume of extravascular extracellular space per unit volume of tissue) in the lung cancer showed a significant decrease at D+28 ($P = .04$ and <.00, respectively). On the 7th day of follow-up after EGFR-TKI treatment, at least 3 out of 5 patients showed a decrease of over 30% in the perfusion parameters of $K_{\text{trans}}$, EA (enhancement amplitude), and MS (maximum slope), while not a single patient exhibited decreases of more than 30% along the longest diameter based on RECIST.

Conclusion

We quantified perfusion parameters from DCE-MRI and described the voxel-based response map for the lung cancers. Perfusion parameters can be an early non-invasive imaging biomarker for the response evaluation of target agent treatment in NSCLC.

KEY WORDS

Dynamic contrast enhanced magnetic resonance imaging
Epidermal growth factor receptor tyrosine kinase inhibitors
Lung cancer
Perfusion parameters
Response evaluation
Tumor angiogenesis
INTRODUCTION

Tumor angiogenesis is one of the most important biomarkers in cancers. Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) gives functional information on tumor angiogenesis and may reflect hemodynamic changes during treatment [1, 2]. Several techniques have been tested to characterize tumor angiogenesis by analyzing signal intensity-time or attenuation-time curve with semi-quantitative parameters including peak enhancement, wash out, maximum slope, and time-to-peak [3-5]. However, these semi-quantitative parameters are limited to quantify the physiologic changes of tumor angiogenesis like increased permeability, lack of differentiation between venule and arteriole, and abundant extravascular space in cancerous tissue. Relatively complicated pharmacokinetic modeling is needed to quantify these physiologic characteristics and begin their evaluation in oncologic practice [6].

Angiogenic factors from tumor cells can trigger the vascular endothelial cells into a rapid growth phase and their receptors and intracellular reactions are relevant targets for cancer therapy. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI), such as gefitinib or erlotinib, are well-known target agents for novel treatment of non-small cell lung cancer (NSCLC). Epidermal growth factor receptors (EGFR) are involved in tumor growth in many steps including cellular proliferation, angiogenesis, metastasis, and inhibition of apoptosis [7, 8]. EGFR signaling up-regulates
the expression of multiple angiogenic factors and indirectly regulates angiogenesis by increasing the synthesis and release of proangiogenic factors from tumor cells [9]. EGFR-TKI therapy has showed dramatic responses in subsets of NSCLC patients. Clinical trials have demonstrated better responses to EGFR-TKI in association with somatic mutations in EGFR [10-12] and with the following clinical characteristics: adenocarcinoma, no history of smoking, female sex, and Asian ethnicity [13-15]. However, there remains a great deal of variation in predicting the responsiveness to EGFR-TKI therapy due to many factors, including primary or acquired resistance caused by additional mutations in the EGFR gene or KRAS mutation [16, 17]. Therefore, non-invasive, repeatable, and early predictive parameters benefit NSCLC patients by helping to determine a suitable treatment regimen, a practice revolutionized by the emergence of personalized therapy.

Although Response Evaluation Criteria in Solid Tumors (RECIST) is a well established method for monitoring response in solid tumors, it cannot sufficiently measure change in anti-angiogenic effects before it is reflected in tumor volume [18, 19]. DCE-MRI is considered to measure tumor angiogenesis quantitatively by the perfusion parameters of a diffusible tracer, gadolinium chelates [6, 20], and may generate parameters which respond earlier than changes in tumor size. DCE-MRI has been tested as a novel biomarker in assessing anti-angiogenic effects in several kinds of tumors,
including renal cell carcinoma, pancreatic cancer, and hepatic metastasis from colorectal cancer [21-23]; however it has not been tested in NSCLC. The purpose of this study is to prospectively quantify the anti-angiogenic effect of EGFR-TKI on a voxel-by-voxel basis using perfusion parameters from DCE-MRI in patients with NSCLC and comparing its efficacy to that of the RECIST criteria.

METHODS

This study was approved by the institutional review board and all patients were given written informed consents.

PATIENT SELECTION

Figure 1 is a diagram showing patient selection. Patients with pathologically-proven recurrent or metastatic NSCLC, at more than 3 cm along longest diameter, were assessed for EGFR-TKI therapy. The criteria for EGFR-TKI therapy were either the presence of somatic mutation of EGFR or more than 2 among the following requirements: 1) adenocarcinoma, 2) female sex, or 3) no history of smoking. Exclusion criteria included the following: abnormal renal function and contraindications for MRI (claustrophobia, cardiac pacemaker, etc). Five patients were recruited between September 2009 and March 2010 and they were treated with gefitinib (Iressa®; AstraZeneca Pharmaceuticals, Wilmington, DE, United States) at a dose of 250 mg/day orally on a 4-week schedule or
erlotinib (Tarceva®; Genentech, Inc., CA, United States or Hoffmann-LaRoche Ltd, Basel, Switzerland) at a dose of 150 mg/day orally on 4-week schedule. All patients who agreed to participate in this study underwent a baseline DCE-MRI at Day-1(D-1). D0 denotes the starting date of chemotherapy. Follow-up DCE-MRI scans were scheduled at D+7 and D+28. The window period is ± 2 days.

**DCE-MRI Acquisition**

DCE-MRI was performed with a 3-Tesla MRI system (Achieva; Philips Medical Systems) equipped with a gradient system capable of ensuring maximum gradient amplitude of 80 mT/m, a rise time of 0.2 milliseconds, and a slew rate of 200 T/m/s. A sensitivity-encoding cardiac coil (SENSE, Philips Medical Systems) with a six-coil element was used for DCE-MRI covering the entire thorax.

The acquisition protocols are shown in Table 1. Transverse T2-weighted images with a multishot (MSH) spectral presaturation inversion recovery (SPIR) sequence were obtained for evaluation of the anatomy and the location of measurable disease. T1 mapping was done by multiple acquisition using T1-weighted 3D spoiled gradient-recalled echo (SPGR) sequence of the thorax with different flip angles (5°, 15°, and 35°). DCE-MRI of the lung parenchyma was optimized with the following acquisition parameters: TR (repetition time), 5.6 msec ; TE (echo time), 1.47 msec; flip
angle, 35°; rectangular field of view, 350 x 448 mm; voxel size, 3 x 3 mm; reconstructed voxel size, 1.75 x 1.74 mm; reconstructed matrix, 256 x 256; coronal orientation. The slab thickness was 100 mm, and the slab was divided into 10 partitions to produce 10 images with 10 mm in section thickness. To increase acquisition speed, a sensitivity-encoding factor of 2 was applied in the phase-encoding direction. The temporal resolution was 3.0 seconds covering the whole thorax on coronal plane and a total of 60 dynamic scans were obtained. The entire DCE-MRI acquisition lasted up to 3 minutes imaging every 3 seconds. The patients were asked to breathe in as shallow a manner as possible during the MRI scanning. Gadolinium chelate (Dotarem; Guerbet, Aulnay-sous-Bois, France) was administered at a dose of 0.2 mL per kilogram of body weight by means of a power injector (Medrad, PA, USA) at a rate of 4 mL/sec, followed by administration of 20 mLs of normal saline in order to flush the tubing.

All MR image data were directly interfaced to our PACS (picture archiving and communicating system) (Pathspeed or Centricity 2.0, GE Healthcare), which displayed all image data on 4 monitors (1,536 x 2,048 image matrices, 8-bit viewable gray-scale, 60-ft-lambert luminescence). Dynamic enhanced images were viewed on these monitors.

**Data Analyses**

Concentration of contrast agent was estimated from MR signal intensity
by computing the difference in longitudinal relaxation rate: 

\[ C(t) = \frac{1}{T_1(t)} - \frac{1}{T_{10}} \cdot r_1, \]

where \( T_{10} \) is pre-contrast T1 value and \( T_1(t) \) is post-contrast T1 value, and \( r_1 \) denotes the longitudinal relaxivity (4.5 s\(^{-1}\)mM\(^{-1}\) for blood) [24]. The \( T_{10} \) value of each voxel was computed using the variable flip angle method [25]. The general equation for signal intensity values (S) at a given flip angle is 

\[ S = S_0 \left[ \sin \alpha \left( 1 - \exp\left( -\frac{TR}{T_{10}} \right) \right) / (1 - \cos \alpha \exp\left( -\frac{TR}{T_{10}} \right)) \right], \]

where TR is the repetition time, \( \alpha \) is the flip angle, and \( S_0 \) is the equilibrium longitudinal magnetization. The \( S_0 \) and \( T_{10} \) parameter were estimated by a linear least-squares method using three sets of SPGR sequences with different flip angles (5°, 15°, and 35°). Following estimation of \( T_{10} \) from the precontrast images, postcontrast \( T_1(t) \) can be estimated as 

\[ 1/T_1(t) = -\ln \left\{ \frac{1 - (S_{post} / S_{pre}) \left[ 1 - \exp\left( -\frac{TR}{T_{10}} \right) \right]}{\exp(1)} \right\} / TR. \]

DCE-MRI for lung tumors was analyzed using semi-quantitative and quantitative methods: the sigmoid fitting method for time-concentration curve pattern analysis and the pharmacokinetic modeling method.

For semi-quantitative analysis, a sigmoid equation was used [26]: 

\[ C(t) = A / \left[ 1 + \left( B / t \right)^C \right], \]

where \( C(t) \) is the time-concentration curve averaged across all voxels within the region-of-interests (ROIs) of the lung tumor, \( A \) is the asymptotic enhancement amplitude (EA), and \( B \) is time of half rising (\( T_{1/2max} \)). Maximal slope (MS) was estimated as the first derivative
of the above equation at $T_{\text{max}}$ time point (Figure 2).

For quantitative analysis, the extended Kety two-compartment model was used [6]:

$$C_t(t) = K^{\text{trans}} C_p(t) \otimes \exp(-K^{\text{trans}} t / v_e) + v_p C_p(t),$$

where $C_t$ is the concentration of contrast agent in the observed tissue, $C_p$ is the concentration in blood plasma, $v_p$ is the fractional blood plasma volume per unit volume of tissue, $K^{\text{trans}}$ is the volume transfer constant, and $v_e$ is the fractional extravascular extracellular space (EES) per unit volume of tissue. The $k_{ep}$, flux rate constant between EES and blood plasma was calculated as $K^{\text{trans}} / v_e$.

The arterial input function (AIF) was determined semi-automatically by selecting an area within the pulmonary trunk or right ventricle among several candidates showing homogeneous Kendall’s coefficients for time-concentration curves. The AIF at D-1 MRI was used as a baseline AIF and applied for analyzing data at D+7 and D+28 for each patient.

**Response Assessment**

The longest diameters of the measurable diseases were measured using an electronic caliper of the PACS. The measurement of size was performed on the T2-weighted axial images. The one-dimensional diameters were assessed by the RECIST criteria [27]. If the sum of the diameters of target lesions showed a decrease of at least 30% on follow-up, it is considered as
partial response (PR). Progressive disease was defined as an increase of at least 20% in the sum of diameters on follow-up. Stable disease was considered as having neither shrinkage sufficient to qualify for PR nor an increase sufficient to qualify for PD on follow-up.

The longitudinal percentage change (% change) in each perfusion parameter was evaluated at D+7 and D+28. Increases in \( T_{\text{2max}} \) and decreases in EA, MS, \( K_{\text{trans}} \), \( v_e \) and \( k_{\text{ep}} \), were considered anti-angiogenic effects.

**Statistical Analysis**

For the analysis of time-concentration curves after EGFR-TKIs therapy, the difference in EA, MS, and \( T_{\text{2max}} \) between days was compared using the Wilcoxon signed rank test with Bonferroni’s correction.

Voxel-by-voxel data of \( K_{\text{trans}} \), \( v_e \) and \( k_{\text{ep}} \) within a subject were selected at each 5\textsuperscript{th} percentile level from minimum to maximum and each patient had 20 representative values of perfusion parameters at D-1, D+7 and D+28. The difference of pixel data distribution between days was evaluated using the Kolmogorov-Smirnov with Bonferroni’s correction.

A \( P \)-value < .05 indicated a statistical significance. Statistical analyses were performed using SAS (version 9.13, Cary, NC, USA).

**RESULTS**
Patients’ Characteristics

All five patients (four men and one woman; median age, 53 years; age range, 46 – 65 years) underwent EGFR-TKIs therapy and DCE-MRI. The histological subtype of all patients was adenocarcinoma. Four out of the five patients had EGFR mutations and the remaining one patient was a woman without a history of smoking. In terms of prior treatment: one patient had conventional chemotherapy and cyberknife surgery; one patient had 1st line chemotherapy; three patients had 1st line plus another chemotherapy.

Longitudinal Changes in Perfusion Parameters

Perfusion parameters were calculated for each voxel of the lung cancer region. The longitudinal changes in these parameters were demonstrated with color changes in the lung cancer region on color map images, lower scale colors showing on follow-up (Figure 3a). The values of perfusion parameters of each voxel in the lung cancer region were graphed quantitatively. Longitudinal parameter changes were demonstrated by changes in distribution of each voxel value of the whole lung cancer region. A bar graph of perfusion parameters depicts a shift toward the lower range of values on follow-up (Figure 3b). Longitudinal changes of curve patterns were also quantitatively evaluated by sigmoid fitting of time-concentration curve. These curves showed lower enhancement amplitude and maximum slope on follow-up (Figure 3c).
Perfusion parameter and curve pattern analysis suggested anti-angiogenic effects after chemotherapy by showing a decrease in $K_{\text{trans}}$, $v_e$, $k_{ep}$, EA, and MS and an increase in $T_{1/2}\text{max}$ (Table 2). The distribution of $K_{\text{trans}}$ and $v_e$ were significantly decreased at D+28 after EGFR-TKI treatment on voxel based analysis ($P = .04$ and <.00, respectively, Kolmogorov-Smirnov with Bonferroni’s correction) (Figure 4a-b). Concerning parameters from the curve pattern analysis, EA and MS were reduced and $T_{1/2}\text{max}$ was increased after the start of EGFR-TKI therapy, but the statistical significance of this finding was not proven (Table 2).

**Response Assessment**

Two patients showed partial response and three patients showed stable disease with RECIST on the 28th day of follow-up after EGFR-TKI treatment (Figure 5a). No patients met the criteria of partial response at the 7th day of follow-up after treatment according to the RECIST criteria. However, perfusion parameters showed more than 30% $v_e$ decrease in two patients, more than 30% $K_{\text{trans}}$ and EA decrease in three patients and all five patients showed a 30% decrease in MS on the 7th day of follow-up after treatment (Figure 5b-e). On the 7th day of follow-up after EGFR-TKI treatment, 3 out of 5 patients showed more than 30% change in at least 4 out of the 6 pharmacokinetic parameters.
DISCUSSION

The lung is known to be a difficult organ to image using MRI. Normal lungs produce little signal because they are filled with air. Inevitable motion artifact from the heart, great vessels, and lungs makes excessive noise in the field of view. Air-soft tissue interfaces are everywhere in the lung field, increasing susceptibility artifacts. Although all these unfavorable factors decrease the signal-to-noise ratio of lung MR imaging, there is definitely attractive benefits to lung imaging with MR. MR has no radiation exposure. This kind of advantage is maximized when it comes to perfusion imaging because tens of repeated phases are needed to cover the whole field of view with very short intervals for the fitting of the time-concentration curve for perfusion analysis. Lung cancer is one of the best candidates for obtaining advantage from perfusion analysis, where characterization of tumor angiogenesis can be done with quantitative parameters and the change of tumor angiogenesis may be followed after treatment without the hazard of radiation. But, the feasibility of perfusion MR for lung cancer must be tested first. Our study demonstrated the anti-angiogenic effects of EGFR-TKIs for lung cancer in five patients. Perfusion parameters were quantified on a pixel-by-pixel basis for the whole lung cancer region with DCE-MRI and the longitudinal changes in perfusion parameters were compared with size changes from RECIST.

Perfusion parameters based on two-compartment model are believed to
be a better indirect biomarker for the evaluation of tumor angiogenesis. There have been efforts to understand the characteristic dynamic enhancement pattern of lung cancer using helical dynamic CT and MRI [3, 5, 28, 29]. But, these curve pattern analysis only demonstrated the amount of contrast media that remained in the whole tumor including intravascular and extravascular extracellular spaces. On the other hand, two-compartment model such as the extended Kety model put an emphasis on permeability between plasma and the extravascular extracellular space, which shows more striking differences when comparing tumor angiogenesis and physiologic angiogenesis. These perfusion parameters were quantified in terms of $K^\text{trans}$, $v_e$, and $k_{ep}$ in our study. Quantification was possible through the process of T1 mapping [25], which generate tissue-specific T1 values instead of using signal intensities, which are relative values in MRI.

Although EGFR-TKIs do not have direct anti-angiogenic effect [3, 5, 28, 29], they are known to have many indirect effects in diminishing angiogenesis. Our results demonstrated early and large percentage changes in perfusion parameters and in curve pattern parameters, which preceded changes in tumor size after EGFR-TKI treatment. This may suggested early anti-angiogenic effects of EGFR-TKIs decreasing permeability and EES volume in the lung cancer on treatment before shrinkage in the tumor volume. Perfusion parameters may be early and objective biomarkers for response evaluation in patients treated with anti-
angiogenic drugs.

There are a few limitations to our study. First, the number of patients was small since this was a feasibility study. Second, the correlation between perfusion parameters and long-term clinical outcome was not investigated. Third, patients who had tumors less than 3 cm were excluded from this study in order to measure a decrease in perfusion parameters and volume on follow-up image.

In conclusion, perfusion parameters from DCE-MRI can be quantified in patients with lung cancer. Quantitative biomarkers from DCE-MRI may play a role as objective parameters for tumor angiogenesis and early indicators for response evaluation of target agent treatment in NSCLC.
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18


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## TABLES

**Table 1. Parameters for MRI Sequences**

<table>
<thead>
<tr>
<th>Acquisition parameters</th>
<th>(unit)</th>
<th>T2WI</th>
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<td>MSH SPIR sequence</td>
<td>3D SPGR sequence</td>
<td>3D SPGR sequence</td>
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<td>Repetition time/echo time</td>
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<td>breath hold</td>
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Note. – MRI = magnetic resonance imaging, MSH = multishot, SPIR = spectral presaturation with inversion recovery, SPGR = spoiled gradient-recalled echo
Table 2. Longitudinal Changes of Perfusion Parameters

<table>
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<td>$K_{\text{trans}}$</td>
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<td>$T_{\frac{1}{2}}^{\text{max}}$</td>
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Note. – D = day (D0, starting day of chemotherapy), $K_{\text{trans}}$ = volume transfer constant, $v_e$ = fractional extravascular extracellular space (EES) per unit volume of tissue, $k_{\text{ep}}$ = flux rate constant between EES and blood plasma was calculated as $K_{\text{trans}}$ / $v_e$, EA = enhancement amplitude, $T_{\frac{1}{2}}^{\text{max}}$ = time of
half rising, MS = maximal slope, * = Two-sided P values were calculated using Kolmogorov-Smirnov test with Bonferroni’s correction. † = Two-sided P values were calculated using Wilcoxon signed rank test.
**FIGURE AND LEGENDS**

**Figure 1.** Flow diagram demonstrates patient selection algorithm.

Note. – NSCLC = non-small cell lung cancer, EGFR = epidermal growth factor receptor, DCE-MRI = dynamic contrast enhanced magnetic resonance imaging.
Figure 2. Time-concentration curve fitted to a sigmoid curve.
a) A series of images showing the changes in $K_{\text{trans}}$, $V_e$, and $K_{\text{ep}}$ over time (D-1, D+7, D+28).

b) A histogram showing the number of pixels for $K_{\text{trans}}$ across different timepoints (D-1, D+7, D+28).
Figure 3. Longitudinal changes of perfusion parameters in a 46-year-old male patient with adenocarcinoma in the left upper lobe. The patient had an EGFR mutation and was treated with gefitinib. (a) Color maps visualize the decrease of $K_{\text{trans}}$, $v_e$ and $k_{\text{ep}}$ in the lung cancer (arrows) by showing color changes from red toward blue. (b) Histogram demonstrates the voxel values of $K_{\text{trans}}$ of the whole tumor at each time point. The distribution of $K_{\text{trans}}$ shifts to the left, showing a decrease in $K_{\text{trans}}$ value after chemotherapy. (c) The pattern of time-concentration curves change after chemotherapy with interval decrease in EA and MS, especially between baseline and D+7.

Note. – $K_{\text{trans}}$ = volume transfer constant, $v_e$ = fractional extravascular extracellular space (EES) per unit volume of tissue, $k_{\text{ep}}$ = flux rate constant between EES and blood plasma was calculated as $K_{\text{trans}} / v_e$. 
Figure 4. Changes in the following perfusion parameters: (a) $K_{\text{trans}}$ and (b) $v_e$. Changes between D-1 and D+28 show significant drop ($P < .05$ Kolmogorov-Smirnov test with Bonferroni’s correction).
Figure 5. Graphs show longitudinal % change of (a) tumor size, (b) $K_{\text{trans}}$, (c) $v_e$, (d) EA and (e) MS. No patients show partial response at D+7 in tumor size using RECIST criteria. However, three out of five patients have a decrease in $K_{\text{trans}}$ of more than 30% and two out of five patients had decreases in $v_e$ of more than 30% at D+7. Also, three of five patients had a decrease in EA of more than 30%, and all patients demonstrated decrease in MS of more than 30% at D+7.