Jpn J Clin Oncol 2007;37(1)44–48
doi:10.1093/jjco/hyl116

Prospective Study of Positron Emission Tomography for Evaluation of the Activity of Lapatinib, a Dual Inhibitor of the ErbB1 and ErbB2 Tyrosine Kinases, in Patients with Advanced Tumors

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Received June 26, 2006; accepted August 24, 2006; published online October 23, 2006

Background: To evaluate the role of FDG-PET in assessing anti-tumor efficacy of molecular targeted drugs, we prospectively performed FDG-PET and CT for response evaluation in patients treated with lapatinib, a dual inhibitor of ErbB1 and ErbB2 tyrosine kinases.
Methods: Lapatinib was given orally once a day at doses ranging from 1200 to 1800 mg in a phase I study. CT and FDG-PET were performed before treatment, and at 1, 2 and 3 months after the initiation of the treatment and every 2 months thereafter.
Results: A total of 29 FDG-PET examinations were performed in eight patients with various solid tumors and the metabolic activity in the tumor was evaluated as SUVmax. The best responses, as assessed by CT, were as follows; one partial response, four stable disease and three disease progression. The partial response was observed in a patient with trastuzumab-resistant breast cancer, whose SUVmax was decreased by 60% from baseline. In all of the four patients whose best response was stable disease, the SUVmax was decreased by 6–42% one month after the start of treatment. Prolonged stable disease (10 months) was observed in a patient with colon cancer, whose SUVmax was decreased by 42%. In the patient group with disease progression, SUVmax was increased in two out of three patients.
Conclusions: FDG-PET detected decreases in the metabolic activity of the tumors in patients who experienced clinical benefits on treatment with lapatinib. Thus, FDG-PET may be useful for the evaluation of molecular targeted drugs, such as lapatinib.

Key words: FDG-PET – lapatinib – phase I – pharmacodynamics – biomarker

INTRODUCTION

Recently, many molecular targeted drugs that act as cytostatic, rather than cytotoxic, agents have been developed. It is expected that they may slow or stop the growth of tumors, without causing existing tumors to shrink. Furthermore, their toxicities are expected to be mild. Therefore, toxicity and decrease in tumor size may not be used as endpoints in phase I and phase II studies, respectively and new endpoints are necessary for the clinical trial of molecular targeted drugs.

Positron emission tomography with the glucose analog fluorine-18 fluorodeoxyglucose (FDG-PET) allows the noninvasive serial measurements of glucose metabolism in tumors. In oncology, FDG-PET was first used for the diagnosis and staging of tumors. FDG uptake is closely related to the number and proliferative capacity of viable tumor cells (1,2). Therefore, treatment-induced changes resulting in tumor cell death or growth arrest leads to a reduction in FDG uptake. It has been reported that FDG-PET may be useful for the evaluation of anti-cancer treatments using cytotoxic chemotherapy (3–7). These data suggest that FDG-PET may offer a surrogate marker for clinical benefit in traditional chemotherapy. If molecular targeted drugs also inhibit the proliferation of cancer cells, reduction of FDG uptake by tumors should also occur after treatment with molecular targeted drugs. Therefore, FDG-PET can be expected to be a surrogate marker for the action of cytostatic molecular targeted drugs as well.

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Lapatinib is a new drug that inhibits the epidermal growth factor receptor tyrosine kinases ErbB1 and ErbB2. By inhibiting signals from these receptors, lapatinib blocks several downstream pathways involved in cell proliferation, invasion and apoptosis, such as ERK-1/2 and AKT, respectively. Phase I trials have been conducted in the USA (8), but the maximum tolerated dose was not determined because lapatinib was generally well tolerated. Biological activities, including partial responses in patients with trastuzumab-resistant breast cancer and disease stabilization of a variety of carcinomas, were reported. A phase I clinical trial has been conducted in patients with solid tumors in Japan (9). To evaluate the efficacy of lapatinib by FDG-PET and to correlate the results of FDG-PET with response evaluation by CT, FDG-PET was prospectively performed in a subsidiary study. This communication is therefore a report of the FDG-PET study conducted in association with a phase I study of lapatinib, details of which will be reported separately.

PATIENTS AND METHODS

Patients and Treatment

This phase I study was conducted in two institutions, Kinki University Hospital and the National Cancer Center Hospital East. Lapatinib was administered orally once daily until patients had disease progression or unacceptable toxicities. Six patients per dose were treated at 900, 1200, 1600 or 1800 mg/day. At the National Cancer Center Hospital East, three patients per group received 1200, 1600 or 1800 mg/day. Of these nine patients, eight were enrolled in the FDG-PET study. The protocols of the phase I study and the FDG-PET study were approved by the Institutional Review Board of the National Cancer Center. Written informed consent was obtained from each patient.

Evaluation of Tumor Responses

At study entry, up to three representative lesions were selected for tumor evaluation. The sum of the largest diameter of each of these lesions was assessed with CT and the maximum standardised uptake values (SUVmax), which is the maximum pixel value within the region of interest, of the same lesions were recorded with FDG-PET. CT and FDG-PET were performed before treatment, and at 1, 2 and 3 months after the initiation of the treatment and every 2 months thereafter. Responses by CT were classified according to the response evaluation criteria in solid tumors (RECIST). Treatment discontinuation owing to disease progression was based on CT findings according to the protocol of the phase I study. The results of the PET analysis were not taken into account for this purpose.

Time to progression was defined as the time from first dose of lapatinib to the earliest documentation of progression, death from any cause, or withdrawal from the trial for any reason.

FDG-PET was performed using a GE-Advanced scanner (General Electric Medical Systems, Milwaukee, WI, USA) with an axial field of view of 15 cm and a slice thickness of 4.75 mm. The SUVmax is known to be affected by several factors, including plasma glucose levels, time from FDG injection to measurement and body weight. Therefore, all patients fasted for at least 6 h before FDG-PET scanning and plasma glucose level was measured just before the FDG injection. Exactly 60 min after intravenous injection of 259–310 MBq FDG, an attenuation-corrected whole body scan was acquired in seven bed positions (5-min emission and 1-min transmission).

RESULTS

A total of 29 FDG-PET examinations were performed in eight patients whose characteristics are listed in Table 1. All patients had prior chemotherapy and four patients with non-small cell lung cancer had failed gefitinib treatment.

Time from FDG injection to the start of PET scanning was exactly 60 min in 28 examinations and 59 min on one occasion. Plasma glucose levels were always below 120 mg/dl (median, 97 mg/dl; range, 77–116). Little change in body weight of individual patients was observed during the course of the study.

The median number of days between pretreatment FDG-PET and treatment initiation was 4 (range, 1–12) days. In 93% of examinations, CT and FDG-PET were performed within 7 days; the median number of days between CT and FDG-PET examination was 1 (range, 0–21 days).

The best responses, as assessed by CT, were as follows; one partial response, four stable disease and three disease progression. Figure 1 shows the time course of the SUVmax and tumor responses in each patient.

The single partial response was observed in a patient with trastuzumab-resistant breast cancer (Her2, 3+; ER/PgR, negative) receiving 1600 mg/day, whose SUVmax was decreased by 60% from baseline one month after the start of treatment when a partial response was documented by CT; thereafter, SUVmax began to increase again 2 months before progression was documented by CT (Fig. 2A, B).

In all four patients whose best response was stable disease, the SUVmax was decreased by 6–42% 1 month after the start of treatment. In a patient with colon cancer with prolonged stable disease (10 months), the SUVmax was decreased by 42% at the first post-treatment evaluation and maintained thereafter for 9 months. The SUVmax also began to increase 1 month earlier than the documentation of disease progression by CT (Fig. 3A, B).

In the patient group with disease progression, the best SUVmax response ranged from +5% to −42%. SUVmax was increased by 4–5% in two out of three patients with CT-assessed progressive disease (Fig. 1). In a patient whose

Table 1. Patient characteristics and response to lapatinib

No.	Dose (mg)	Age (years)	Sex	Tumor type	P.S.*	No. of prior regimens of chemotherapy	Response to lapatinib	TTP† days
1	1200	49	F	NSCLC‡	1	4	SD	103
2	1200	61	M	Sarcoma	1	1	PD	20
3	1200	50	M	CRC§	0	2	PD	48
4	1600	55	F	Breast cancer	0	3	PR	132
5	1600	61	M	NSCLC‡	1	3	SD	98
6	1600	65	M	CRC§	0	2	SD	335
7	1800	53	M	NSCLC‡	1	4	PD	34
8	1800	37	F	NSCLC‡	0	3	SD	110¶

F, female; M, male.
*Performance status.
†Time to progression.
‡Non-small-cell lung cancer.
§Colorectal cancer.
¶Withdrawn from study without progression.

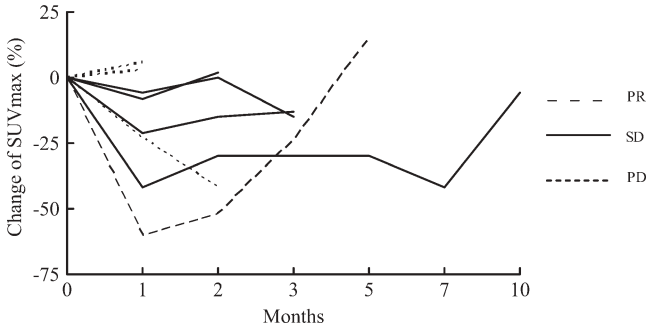

Figure 1. The time course of the SUVmax and tumor responses in eight patients.

SUVmax was decreased in spite of disease progression documented by CT, the selected targeted lesions were stable disease assessed by CT, but a new lesion appeared 2 months after the start of treatment.

DISCUSSION

Molecular targeted drugs aim at tumor growth stabilization rather than tumor shrinkage and no major volume changes are expected. In addition, the mechanism of action of some of these agents may be such that higher doses beyond a certain level may offer no additional benefit. With traditional cytotoxic drugs, increasing doses lead to increasing efficacy; thus, the recommended dose of cytotoxic agents has been routinely determined on the basis of toxicities in phase I studies. However, for molecular targeted drugs, the appropriate approach to determine recommended doses for further clinical trials has not yet been established, because toxicities of these drugs are not necessarily considered to correlate with their anti-tumor activity (10). Similarly, conventional

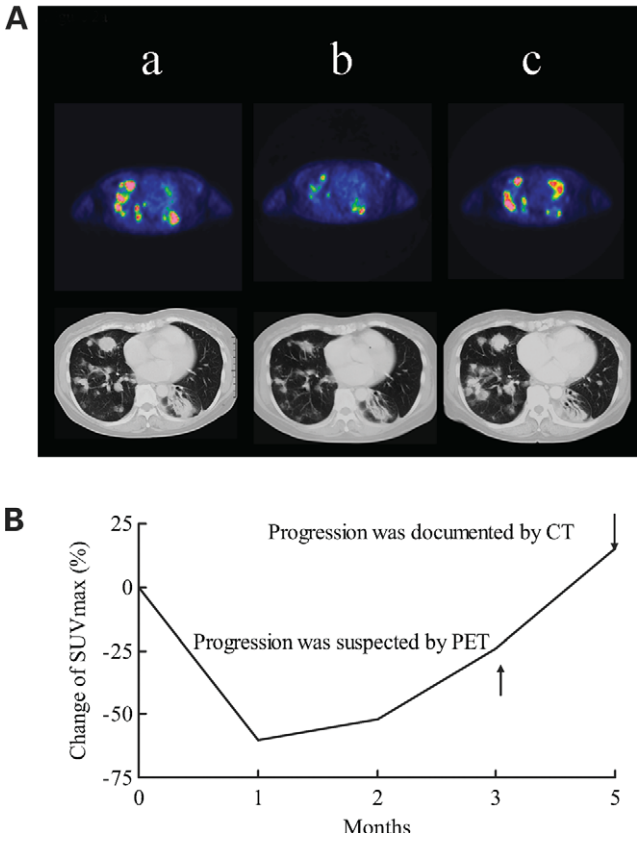

Figure 2. (A) Comparison of FDG-PET and CT with trastuzumab-resistant breast cancer with lung metastases. Partial response was documented by CT. a, before the treatment; b, the major reduction in FDG uptake and objective tumor response was observed after 1 month of treatment; c, disease progression was confirmed by CT after 5 months of treatment. (B) The time course of the SUVmax and tumor response in a patient with breast cancer with partial response was documented by CT. The SUVmax was decreased by 60% from baseline after 1 month of treatment. The SUVmax began to increase 2 months before progression was documented by CT.

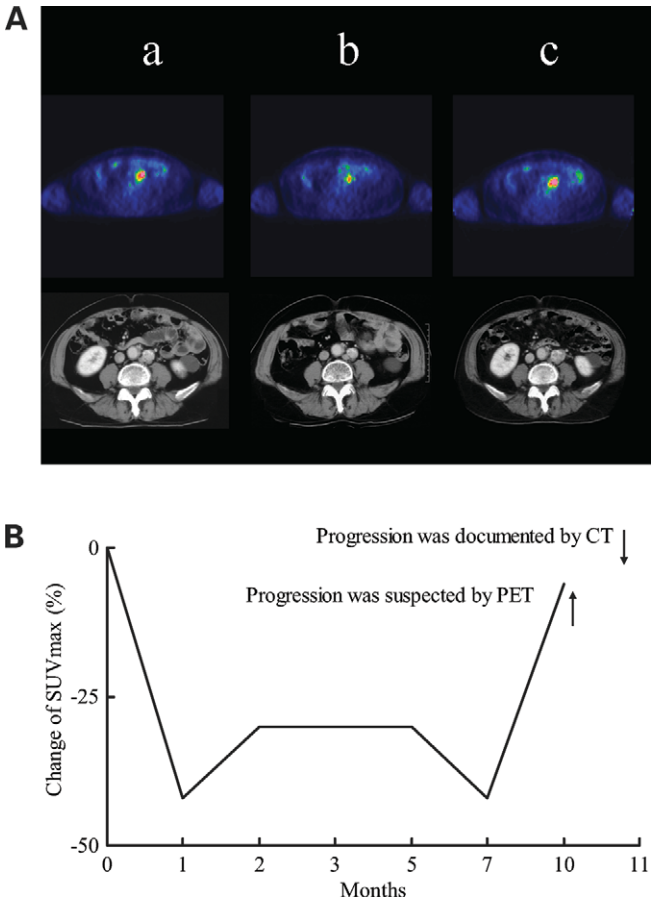

Figure 3. (A) Comparison of FDG-PET and CT with colorectal cancer with para-aortic lymph node metastases. Prolonged stable disease was documented by CT. a, before the treatment; b, the major reduction in FDG uptake was observed after 1 month of treatment, but no volume change was observed by CT; c, progression in FDG uptake was observed after 10 months of treatment, but no major volume change was observed by CT. (B) The time course of the SUVmax and tumor response in a patient with colorectal cancer with prolonged stable disease. The SUVmax was decreased by 42% from baseline after 1 month treatment, and maintained thereafter for 9 months. The SUVmax also began to increase 1 month earlier than the documentation of disease progression by CT.

strategies to evaluate anti-tumor activity in phase II studies may not be useful for molecular targeted drugs, because these agents may not cause a reduction in tumor size. The following approaches have been used to determine the appropriate dose of molecular targeted drugs for further clinical trials: (i) pharmacokinetic data in patients have been compared with the results of preclinical studies; (ii) changes in the targeted molecules in tumors or surrogate tissues have been evaluated; and (iii) the maintenance of stable disease has been suggested to be a marker of activity in the development of these new agents (11). However, thus far none of these parameters has been established as an endpoint for phase I studies.

In successful clinical trials of molecular targeted drugs such as trastuzumab (12), rituximab (13), imatinib (14), gefitinib (15), erlotinib (16) and sorafenib (17), tumor shrinkage was in fact observed. However, the relatively low response rates to these compounds may not fully explain the increased progression-free or overall survival observed in phase III studies. Furthermore, as discussed above, other molecular targeted drugs may not cause tumor shrinkage but induce tumor growth inhibition with mild toxicities. It is difficult to evaluate anti-tumor activity of these agents in phase II studies by the methodology established for cytotoxic drugs. The clinical value of any new agent must be documented in randomized phase III studies. If phase III trials were to be conducted without any preliminary evidence of efficacy, available patients and financial resources would be insufficient to test all new cytostatic agents under clinical evaluation. Therefore, other surrogate markers for response assessment are required in the clinical development of molecular targeted drugs to permit more efficient evaluation of cancer treatment. With such an approach, the most promising agents could be moved forward quickly, with less effective agents rapidly identified and discarded. FDG-PET is expected to be a surrogate marker for the action of cytostatic molecular targeted drugs.

A correlation between treatment efficacy and glucose metabolism in patients has been reported for imatinib therapy. FDG-PET could be used as an early and sensitive method to evaluate the response of gastrointestinal stromal tumors to imatinib mesylate treatment (18). FDG-PET data obtained 8 days after imatinib treatment correlated with symptom control as well as progression-free survival. It was also reported that micro-PET imaging with FDG could be used for monitoring the effect of PKI-166, another dual inhibitor of ErbB1 and ErbB2, in preclinical studies (19). The mechanism of action of PKI-166 is similar to lapatinib, which is also a dual inhibitor of ErbB1 and ErbB2.

The results of our study concurred with the findings of previous studies. The effect of lapatinib was evaluated by FDG-PET in eight patients, and clinical benefits of treatment, such as partial response and prolonged stable disease, were observed in the two patients with the greatest decrease in the SUVmax. The SUVmax was minimally or moderately decreased by treatment in all four patients whose best response was stable disease. The SUVmax was increased in two out of three patients with disease progression detected by CT. In the other patient with disease progression documented by CT, the SUVmax was decreased. In this case a new lesion appeared while the selected targeted lesions were stable. This may be due to the heterogeneity within different lesions of the same cancer.

At the present time, there are no standard criteria for evaluation by FDG-PET, although recommendations were published in 1999 by the European Organization for Research and Treatment of Cancer (EORTC) (7). In the EORTC recommendations, progressive metabolic disease is classified as an increase in standard uptake value greater than 25%, and partial metabolic response as a decrease in standard uptake value greater than 25% after more than one treatment cycle. SUVmax is influenced by factors such as

the time from FDG injection to measurement, plasma glucose level, body weight and partial volume effect (20). It was reported that the variability of FDG uptake as assessed by SUVmax without treatment is less than 20% (21). Therefore, it was proposed that a significant change in SUVmax for the evaluation of anti-tumor activity of chemotherapeutic agents should be above the 25% threshold (22). In the present study, SUVmax decreased by more than 25% in four patients, two of whom experienced significant clinical benefit, while the other two had stable disease and disease progression.

The usefulness of FDG-PET in evaluating the anti-tumor activity of lapatinib is suggested by the results of the present investigation. However, this was a small exploratory study, and its confirmation awaits the results of larger studies. Further studies should be conducted in conjunction with phase II or phase III trials in which patients with the same tumor types are treated in a uniform way. Moreover, it will be necessary to show that the response evaluated by FDG-PET is predictive of a clinical endpoint, such as survival.

In conclusion, FDG-PET may be useful for the evaluation of molecular targeted drugs, such as lapatinib. However, this will need further validation in phase II or phase III studies in patients with the same types of tumors.

Conflict of interest statement

None declared.

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