Plasma and Pleural Fluid Pharmacokinetics of Erlotinib and its Active Metabolite OSI-420 in Patients With Non–Small-Cell Lung Cancer With Pleural Effusion

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Abstract

Background: Erlotinib is orally active and selectively inhibits the tyrosine kinase activity of the epidermal growth factor receptor. The pleural space penetration and exposure of erlotinib is poorly understood. Thus, we investigated the pharmacokinetics (PK) of erlotinib and its active metabolite OSI-420 in non–small-cell lung cancer (NSCLC) of malignant pleural effusion (MPE). **Patients and Methods:** We analyzed the PK of erlotinib and OSI-420 on days 1 and 8 after beginning erlotinib therapy in 9 patients with MPE. Their concentrations were determined by high-performance liquid chromatography with ultraviolet detection. Blood samples were obtained five times per day: before administration, and 2, 4, 8, and 24 hours after administration. Pleural effusions were obtained once per day, 2 hours after administration on day 1, and before administration on day 8. The exceptions were cases 2 and 4, which had pleural effusions obtained just before drug administration, and 2, 4, 8, and 24 hours after administration. **Results:** The mean percentage of penetration from plasma to pleural effusion for erlotinib was 18% on day 1 and 112% on day 8, while these values for OSI-420 were 9.5% on day 1 and 131% on day 8. The area under the drug concentration-time curve of pleural fluid for erlotinib was 28,406 ng-hr/mL for case 2 and 45,906 ng-hr/mL for case 4. **Conclusions:** There seems to be a significant accumulation of both erlotinib and OSI-420 in MPE with repeated dosing. Although larger studies will be necessary to determine the true impact of erlotinib MPE accumulation on plasma PK and safety, erlotinib can be administered safely to patients with MPE with respect to efficacy and side effects.

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Introduction

Understanding the signal-transduction pathways that facilitate neoplastic transformation and progression has led to the development of molecularly targeted anticancer agents. Epidermal growth factor receptor (EGFR) is a tyrosine kinase of the ErbB family that regulates signaling pathways for cellular proliferation and survival. Targeting EGFR as a means of anticancer therapy has been proposed on the basis of its ubiquitous expression in solid human tumors.[1] Inhibiting kinase activation with small molecule drugs has proven to be an effective approach in the treatment of malignant tumors,[2-4] and EGFR-tyrosine-kinase inhibitors have been approved for the therapy of non–small-cell lung cancer (NSCLC).

Erlotinib hydrochloride, formerly known as OSI-774, is an orally administered EGFR and ErbB2 inhibitor. In the United States, it has

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Table 1 Clinical Characteristics of the Patients

Case	Age (y)	Sex	PS	Histology	EGFR Gene	Stage	Smoking Status	Previous Treatment
1	74	M	2	Sq	Wild type	cT4N2M0	Current	Two chemotherapies
2	85	M	1	NSCLC	L858R/T790M	cT4N2M0	Never	Gefitinib
3	75	M	0	Ad	Wild type	cT4N3M0	Never	Chemo-radiotherapy
4	78	F	3	NSCLC	NE	cT4N2M0	Never	No
5	65	F	1	Ad	NE	cT4N2M1	Never	Two chemotherapies
6	82	F	2	NSCLC	Wild type	cT4N2M1	Never	Chemotherapy
7	85	F	3	Ad	L858R	cT4N0M1	Never	Gefitinib
8	60	F	0	Ad	Wild type	cT4N2M0	Current	Two chemotherapies
9	63	M	2	Sq	Wild type	cT2N2M0	Ex	No

Abbreviations: M = male; F = female; PS = performance status; Sq = squamous cell carcinoma; NSCLC = non–small-cell lung carcinoma; Ad = adenocarcinoma; EGFR = epidermal growth factor receptor; NE = not evaluated; Never = never a smoker; Ex = ex-smoker.

been approved for use in patients with locally advanced or metastatic NSCLC or pancreatic cancer.[4,5] Compared to a placebo, erlotinib improved survival for patients with previously treated advanced NSCLC in a randomized phase III trial.[4] Moreover, the use of erlotinib has been reported for patients with advanced NSCLC in the elderly or poor performance status (PS).[6-9]

In patients with malignant pleural effusion (MPE), treatment of carcinomatous pleurisy by adhering the pleuras via antitumor agents and pleura-stimulating substances is thought to prolong survival and improve quality of life. Physiologic third space created by pleural effusions provides a reservoir for some drugs, such as Methotrexate, and thereby contribute to delayed excretion, delayed drug elimination, and serious toxicity.[10,11] So there seems to be clinical importance to evaluate the drug accumulation in pleural effusions. Although the pharmacokinetics (PK) of erlotinib in healthy volunteers and adult patients with cancer have been well characterized,[12-15] very little is known about pleural space penetration and exposure to this drug. These are critical issues in the treatment of patients with advanced NSCLC with MPE.

To confirm the safety of erlotinib administration in patients with MPE, in this study, we performed extensive plasma and pleural effusion PK studies of erlotinib and its active metabolite OSI-420 in 9 patients for the first time.

Patients and Methods

Patients

Nine patients with advanced NSCLC diagnosed between June 2009 and December 2009 at Kyoto University Hospital were enrolled in this study. The clinical characteristics of all patients are summarized in Table 1. All patients were Japanese, and comprised of 4 men and 5 women, with a median age of 75 years (range, 60-85 years) and were treated with 150 mg erlotinib daily. Enrolled patients had either adenocarcinoma (4 of 9), unspecified NSCLC (3 of 9), or squamous cell carcinoma (2 of 9). Seven patients were nonsmokers and other patients were former or current smokers. The Eastern Cooperative Oncology Group PS was 2-3 for 5 patients and 0-1 for 4 patients. Five patients had been treated with at least one regimen of chemotherapy, 2 patients had received gefitinib therapy, and 2 patients received erlotinib therapy as the first-line regimen. All patients had MPE. Case 2 had EGFR gene mutations: a single-point mutation in exon 21, L858R, and an acquired mutation in exon 20, T790M. Case 7 had an L858R EGFR gene mutation. Cases 4 and 5 did not have their mutations evaluated. Cases 2 and 7 were previously treated with gefitinib. Cases 4 and 9 were administered erlotinib as an initial treatment because of poor PS.

Methods

Before analysis, written informed consent was obtained from all patients. The study was approved by the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine. Standard Response Evaluation Criteria in Solid Tumors (version 1.1) were used for response evaluation.[16] The evaluation of pleural effusion was conducted with chest X-ray on day 1 and day 8. For cases 2 and 4, the evaluation of pleural effusion was conducted with the amount of daily effusion from a chest drainage tube. We performed PK analysis of erlotinib and OSI-420 on days 1 and 8 after starting administration of erlotinib. Plasma or MPE samples were centrifuged at 3000g for 10 minutes and stored at 4°C. Drug concentrations were determined by high-performance liquid chromatography with ultraviolet detection as previously reported.[17] The specificity of the method was evaluated using blank human plasma and MPE samples from different donors. Blood samples were obtained 5 times each day: just before administration (C0), and then 2 (C2), 4 (C4), 8 (C8), and 24 hours (C24) after administration. Pleural effusions were obtained 2 hours after administration (C2) on day 1 and before administration (C0) on day 8. The exceptions were cases 2 and 4 from whom pleural effusions were obtained just before administration (C0), and then 2 (C2), 4 (C4), 8 (C8), and 24 hours (C24) after administration. The definition of a percent penetration is the ratio between plasma C0 on day 1 and day 8 and C0 of MPE on day 1 and day 8. The reason why we chose 2 hours after drug dosing on day 1 to draw the MPE sample is because this was when they expected Cmax in plasma. However, from patients 2 and 4, it is clear the times to peak level in plasma and MPE are different, which was an unexpected finding.