Thai Female Non-Smoker with Recurrent Lung Adenocarcinoma Who has Dramatic and Prolonged Response to Gefitinib for Over One Year

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A 53-year old non-smoking Thai female was diagnosed with metastatic non-small cell lung cancer to bone. The initial biopsy from the bone lesion showed metastatic adenocarcinoma. She achieved partial response after treatments with radiation therapy to the bones, followed by 6 cycles of combination chemotherapy. About 4 months later, recurrence of the pulmonary and osseous disease was apparent. She has ECOG performance status of 3. Gefitinib 250 mg/day was administered until disease progression for about 14 months. After 6 weeks on this therapy, she had dramatic improvement of all symptoms including her performance status and had nearly complete resolution of all pulmonary lesions. Tolerability was good, with only mild fatigue. The overall survival was 28 months. This illustrates that gefitinib could produce significant clinical benefits in selected Thai patients even with poor performance status. This result is consistent with previous reports that the clinical characteristics of female, non-smoker and adenocarcinoma histology seem to predict response to gefitinib.

Keywords: Non-small cell lung cancer, Gefitinib

Lung cancer is the leading cause of cancer death worldwide with Non-Small Cell Lung Cancer (NSCLC) accounting for 80% of these cases. The majority of patients present with locally advanced stage or metastatic disease. Although there have been advances in the treatment of lung cancer, outcomes for locally advanced and metastatic cases are still poor. The current standard of care for these patients is systemic chemotherapy with a two-drug combination regimen that includes a platinum agent with response rates ranging from 17% to 28% and median survival times ranging from 7.4 to 8.5 months\(^1\). Although systemic chemotherapy reduces the rate of death attributable to lung cancer compared with best supportive care without chemotherapy, disease progression is inevitable. Patients who failed first-line therapy may benefit from second-line therapy using docetaxel, with a response rate of 7.1% and median survival 7 months\(^2\). However, toxicities associated with chemotherapy may interfere with the ability of some patients with advanced NSCLC to receive the standard first-line or second-line therapy. Such patients include the elderly, patients with poor performance status, and patients with comorbidities. It is therefore crucial to investigate the novel agents in the treatment of these deadly diseases.

Case Report

A 53-year old Thai female with a no smoking history presented with left femur and pelvic bone pain for 3 weeks. The radiograph revealed multiple areas of osteolytic lesions involving the pelvic bone and left femur. She underwent biopsy and internal fixation of the left femoral neck. The biopsy from the bone lesion showed metastatic adenocarcinoma. The CT scan of the chest and the abdomen revealed a 3 x 4 cms right lung mass, matted hilar lymph nodes adjacent to the mass and numerous small pulmonary nodules in both lungs. She was diagnosed with stage IV non-small cell lung cancer and received palliative radiation therapy initially to the left femur and iliac bone, followed by 6

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cycles of combination chemotherapy consisting of paclitaxel and carboplatin. She achieved partial response by the end of these treatments. About 4 months later, recurrence of the pulmonary and osseous disease was apparent. The patient suffered from severe dyspnea, dry cough, bone pain and had ECOG performance status of 3. Gefitinib 250 mg/day was administered until disease progression for about 14 months. After 6 weeks on this therapy, she had dramatic improvement of all symptoms including her performance status and had nearly complete resolution of all pulmonary lesions. As the result of therapy, the patient gained appetite and weights and returned to fully ambulating without assistance for over a year. Tolerability was good, with only mild fatigue. The patient died from progressive disease after discontinuation of gefitinib for 1 month. The overall survival was 28 months.

Discussion
Recent understanding of molecular oncology leading to the design of the molecularly targeted therapies aim to inhibit specific pathways and key molecules implicated in tumor growth and progression while sparing normal cells. Several therapies which target signal transduction pathways involved in angiogenesis, metastasis, and apoptosis, are in clinical development to treat lung cancer. Among these targeted therapies are the oral, small-molecule epidermal growth factor receptor-tyrosine kinase (EGFR-TK) inhibitors gefitinib which had undergone studies to treat lung cancer. Gefitinib [4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline] (‘Iressa”, ZD1839) is a novel low-molecular-weight (447-kDa) quinazoline derivative. It selectively inhibits EGFR-tyrosine kinase by competing with adenosine triphosphate for its binding site on the intracellular domain of the receptor, thereby inhibiting the phosphorylation and activation of tyrosine kinase. The proposed mechanisms of action include blockade of EGFR downstream signal transduction pathways, cell cycle arrest, inhibition of angiogenesis and metastasis, and augmentation of the antitumor effects of chemotherapy and radiotherapy\(^{(9)}\). This agent has been validated preclinically as a new treatment approach for NSCLC and has shown single-agent activity against advanced, chemorefractory NSCLC in clinical trials.

In its initial dose finding phase 1 studies, gefitinib was active against non-small-cell lung cancer across a broad range of doses up to daily oral dose of 1,000 mg. Diarrhea was identified as dose-limiting toxicities at daily oral doses of gefitinib at 700 and 1,000 mg. Skin toxicities including a pustular rash, dryness and pruritus also commonly occurred\(^{(4)}\). Based on these data, the two doses selected for phase II study were 250 mg and 500 mg, as 250 mg was higher than the lowest dose at which objective tumor regression were seen, and 500 mg was the highest dose that was well tolerated when administered chronically. The subsequent 2 large randomized phase 2 trials, reported response rates of 9 to 19 percent with the use of doses of 250 or 500 mg per day. Another 30 percent or more of patients had stable disease. Many patients reported symptomatic improvement. Occasional patients had dramatic, long-lasting responses. In both trials, tumor response and improvement in disease related symptoms were nearly identical between two dosages. However, adverse effects were dose-related, and the 250-mg dose had a favorable therapeutic index\(^{(10)}\).

Based on these study results, gefitinib at 250 mg/day has been approved by the regulatory authorities in many countries for use in patients with recurrent or refractory non-small cell lung cancer to standard chemotherapy. During this period, for countries including Thailand where this drug was not available in the year 2003, there is the gefitinib (Iressa\(^{TM}\)) Expanded Access program (EAP) from the manufacturing of this drug; AstraZenaca Pharmaceuticals which enables patients to receive gefitinib on a compassionate-use basis. Eligibility criteria to obtain gefitinib (Iressa\(^{TM}\)) in this program are patients with recurrent or refractory non-small cell lung cancer who are ineligible for clinical trials or have no other treatment options available. The patient in this report received gefitinib via this program in July 2003 when she suffered from symptomatic recurrent disease (Fig. 1). After 6 weeks on therapy, she had a dramatic symptomatic improvement of cough, dyspnea, bone pain, performance status and had nearly complete resolution of all pulmonary lesions (Fig. 2). She tolerated well to this medication extremely without requiring dose interruption throughout the course of therapy for about 14 months. The patient died from progressive lung cancer (Fig. 3) after discontinuation of gefitinib for 1 month.

Previous pivotal trials of gefitinib demonstrated that the majority of lung cancer patients do not respond to therapy and have no survival or symptom benefit while occasional patients had dramatic, long-lasting responses as seen in the presented patient. Identification of those patients who are most likely to respond to EGFR-TK inhibitor gefitinib is crucial. Cumulative multivariate analysis from several studies...
showed pretreatment clinical factors that can predict gefitinib sensitivity are history of never smoking cigarettes, presence of adenocarcinoma with bronchioalveolar features, female sex and born in eastern Asia\(^5\)-\(^7\). While type of prior chemotherapy, number of prior chemotherapy regimens and presence or intensity of EGFR staining in pathologic specimens determined by immunohistochemistry, do not predict sensitivity to gefitinib. Based on this data, the response rate and median survival for patients with all 3 pretreatment clinical characteristics (i.e. never smoked cigarettes, presence of adenocarcinoma with bronchioalveolar features in pathologic specimens, female sex) similar to the patient in the present report could predict to be as high as 56% and 14 months respectively. The calculated response rates and median survival for patients with none of these factors present treated with gefitinib are only 3% and 3 months respectively\(^8\).

In the most recent reports, several groups of investigators have shown that mutations in the tyrosine kinase domain of EGFR as assessed by DNA sequencing are associated with sensitivity of NSCLC to gefitinib\(^9\)-\(^11\). Deletions or substitution of amino acid in exons 18,19 and 21 of EGFR were found in about 80% of tumors sensitive to gefitinib, but in none of the tumors with no response. In untreated NSCLC, such mutations have been found in about 10% of specimens examined, with higher frequency observed in Japanese patients compared to Caucasian and in never smokers.
with adenocarcinoma. However, these mutation analysis of EGFR are currently not available for routine testing in the study hospital.

In conclusion, Gefitinib provides dramatic benefit in symptoms improvement and survival for selected patients with recurrent NSCLC. How these patients can be best selected will be the focus of a future study. Seemingly, several clinical characteristics including female, never smoked cigarettes and individuals whose tumors have adenocarcinoma with any features of bronchoalveolar carcinoma as illustrated in this case and the presence of EGFR mutation could identify patients who are more likely to benefit from gefitinib.

References
ผู้ป่วยหญิงไทยไม่สูบบุหรี่เป็นโรคมะเร็งปอด adenocarcinoma ที่กลับเป็นซ้ำตอบสนองต่อการรักษาด้วย Gefitinib อย่างรวดเร็วและยาวนานกว่าหนึ่งปี: รายงานผู้ป่วย 1 ราย

ชัยยุทธ เจริญธรรม

ผู้ป่วยหญิงไทยอายุ 53 ปี ไม่มีประวัติสูบบุหรี่ได้รับการวินิจฉัยว่าเป็นมะเร็งปอดชนิด adenocarcinoma ที่กลับเป็นซ้ำและตอบสนองต่อการรักษาด้วย gefitinib อย่างรวดเร็วและยาวนานกว่าหนึ่งปี. ผู้ป่วยนี้มี performance status เท่ากับ 3 และมีระยะเวลารอดชีวิตจากโรคมะเร็งเป็นเวลา 28 เดือน รายงานนี้แสดงให้เห็นว่าการรักษาด้วย gefitinib สามารถตอบสนองต่อการรักษาของผู้ป่วยได้ดีและผู้ป่วยมีระยะเวลารอดชีวิตจากโรคมะเร็งเป็นเวลา 28 เดือน.

การป้องกันการกลับเป็นซ้ำของมะเร็งปอดชนิด adenocarcinoma สามารถทำได้ด้วยการรักษาด้วย gefitinib อย่างรวดเร็วและยาวนาน.

ผู้ป่วยหญิงไทยที่ไม่สูบบุหรี่ ไม่ได้โรคประจำตัวที่ซับซ้อน และไม่มีประวัติอาการที่ทำให้ป้องกันการกลับเป็นซ้ำของโรคมะเร็งปอด adenocarcinoma ได้良好的ได้รับการรักษาด้วย gefitinib อย่างรวดเร็วและยาวนานกว่าหนึ่งปี.