A Phase II Clinical Trial of Celecoxib Combined with Platinum-Based Regimen as First-Line Chemotherapy for Advanced Non-Small Cell Lung Cancer Patients with Cyclooxygenase-2 Positive Expression

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ABSTRACT

Objective: To evaluate the efficacy and safety of celecoxib plus platinum-doublet as first-line chemotherapy in treatment of advanced non-small cell lung cancer (NSCLC), and to determine the subgroup benefiting from celecoxib combined therapy by molecular analysis.

Methods: A total of 44 treatment-naive patients of advanced NSCLC with positive cyclooxygenase-2 (COX-2) expression confirmed by immunohistochmical (IHC) staining were designed to receive celecoxib plus platinum-doublet chemotherapy (cisplatin plus gemcitabine, novelbine or docetaxol) from February 2005 to May 2007. On 5−7 day before chemotherapy, 400 mg celecoxib was administered twice a day orally until obvious evidence of disease progression or tolerable toxicity was found. Adverse events were recorded according to NCI-CTC criteria. The primary endpoint was overall survival (OS). The secondary endpoints included progression-free survival (PFS), 1-year survival rate, response rate (RR) and safety. Additionally, we detected epithelial growth factor receptor (EGFR) status including EGFR gene amplification by real-time PCR and gene mutations by DHPLC followed by sequencing.

Results: The response rate was 45% (20/44), and the disease control rate (DCR) was 59% (26/44). The median progression-free survival time and median survival time were 6 m and 18 m, respectively. The 1-year survival rate was 68%. Chemotherapy cycle numbers and best response were found to be the predictive factors for PFS by COX model analysis ($P=0.023$ and $P=0.000$, respectively). No factor was found to affect OS. The most common toxicities included neutropenia and nausea/vomit. EGFR gene amplification was an independent prognostic factor influencing OS ($P=0.0002$). Patients with EGFR mutations (exon 21) had a tendency of disease progression ($P=0.041$).

Conclusion: Encouraging activities of celecoxib combined with platinum-doublet chemotherapy were demonstrated in treatment-naive patients with advanced NSCLC, with good tolerances. For COX-2 IHC positive patients, positive EGFR amplification and mutation might be related to poor clinical outcomes.

Key words: Cyclooxygenase-2; Epithelial growth factor receptor; Non-small-cell lung cancer

INTRODUCTION

Lung cancer is one of the most common human malignancies and also the leading cause of cancer-related death in the world. Non-small cell lung cancer (NSCLC) constitutes about 85% of all lung cancers[1], and multiple genetic and epigenetic changes are involved in the development and progression of NSCLC[2]. Since 1990s, platinum
combined with newly third-generation agents, such as gemcitabine and taxanes, has become the most common first-line chemotherapy regimens[3, 4] and some prolonged survival benefits for patients with advanced NSCLC were obtained. However, the benefits of these regimens were limited to median survival time of 8−11 m and 1-year survival rate of 20%−46%[5]. So new agents and combined therapies were under investigation. Based on the molecular pathogenetic knowledges of NSCLC, it is possible to provide specific anticancer therapies, such as therapy targeting the protein COX for NSCLC patients.

Cyclooxygenase has two isoforms, COX-1 and COX-2, encoded by different genes. COX-1 is constitutively expressed in most tissues and appears to be responsible for the production of prostaglandins, mediating normal physiologic functions such as maintaining gastric mucosa and regulating renal blood flow. In contrast, COX-2 which is normally undetectable in most tissues, may contribute to tumorigenesis and malignant phenotypes of tumor cells through inhibiting apoptosis, increasing angiogenesis and invasiveness, and modulating inflammation and immunosuppression[6, 7]. A number of studies have demonstrated that COX-2 is highly expressed in many solid malignancies such as colon cancer[8], prostate cancer[9], and breast cancer[10] as well as NSCLC[11]. COX-2 overexpression was considered as a marker of poor prognosis, especially for lung cancer patients[11, 12]. Some preclinical studies have provided evidences of the efficacy of COX-2 inhibition in suppressing tumor development[13, 14]. Based on these preclinical researches, the safety and synergistic effects of celecoxib combined with standard chemotherapeutic regimens have been confirmed by some phase I trials in lung cancer cell lines and patients with NSCLC[15−17]. One recent report by Francis et al.[18] demonstrated that celecoxib plus docetaxel could slow disease progression compared with single-agent docetaxel as second-line therapy.

Due to the anticancer activity of COX-2 inhibitors confirmed by accumulated preclinical and clinical studies, it is reasonable to investigate the efficacy of the combination regimen of celecoxib plus currently standard platinum-based chemotherapy as the first-line treatment for patients with advanced NSCLC. Therefore, we initiated a phase II clinical trial to evaluate the effects of these combination strategies in treatment-naive patients with advanced NSCLC and positive COX-2 confirmed by immunohistochemistry. Moreover, on the basis of the cross-talk between COX-2 and EGFR, we also detected the EGFR status including protein expression, amplification and mutations in the patients who had samples, in order to find the prevalent groups benefiting from celecoxib.

**PATIENTS AND METHODS**

**Patients**

From February 2005 to May 2007, 44 patients with advanced NSCLC without any chemotherapy were enrolled in this phase II trial. Stage IIIB or IV tumors were confirmed in all patients, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of grade II or less. The adequate hematological parameters were shown as follows: blood routine test (leukocyte count ≥3.5×10^9/L, absolute neutrophil count ≥2.0×10^9/L, platelet count ≥100×10^9/L); serum creatinine level ≤2.0 mg/dL; total bilirubin ≤institutional upper limit of normal (ULN); aspartate transaminase and/or alanine transaminase ≤1.5×ULN; alkaline phosphatase <5×UNL.

**Treatment Plan**

Within 7 d in the beginning of the study, all patients received a complete medical history and physical examination, documentation of performance status, biochemical testing and electrocardiography. Additionally a chest spiral CT scan, an abdominal spiral CT scan, brain MRI/CT and systemic bone ECT were performed within 3 weeks prior to enrollment. Measurable lesions were defined as 10 mm or larger. All other lesions were defined as unmeasurable disease, including small lesions (less than 10 mm) and truly unmeasurable lesions (eg., bone lesions, pleural/pericardial effusion, and/or abdominal masses). Patients were ineligible if they had received any prior chemotherapy regimens, concomitant use of