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Gemcitabine plus conventional-dose epirubicin versus gemcitabine plus cisplatin as first-line chemotherapy for stage IIIB/IV non-small cell lung carcinoma—A randomized phase II trial

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Topoisomerase IIα (TopoIIα)

Summary
Background: Epirubicin was effective for the treatment of non-small cell lung carcinoma (NSCLC). This study compared the efficacy and safety of gemcitabine plus conventional-dose epirubicin (GE) with gemcitabine—cisplatin (GC) as first-line chemotherapy for stage IIIB/IV NSCLC and evaluated the predictive value of nuclear expression of excision repair cross-complementing group 1 (ERCC1) and topoisomerase IIα (TopoIIα) on treatment outcome.
Patients and methods: Patients were randomized to GE (gemcitabine, 1000 mg/m^2 on days 1, 8, and 15 and epirubicin, 70 mg/m^2 on day 15) or GC (gemcitabine, 1000 mg/m^2 on days 1, 8, and 15 and cisplatin, 80 mg/m^2 on day 15). Treatment cycles were repeated every 4 weeks. Immunohistochemical study of ERCC1 and TopoIIα was done for patients with available tumor specimens.
Results: The response rate was 31.0% (95% CI 16.4—45.5%) for GC ($n = 41$) and 37.2.0% (95% CI 22.2—52.3%) for GE ($n = 39$). No significant differences in median time-to-treatment-failure (TTF) (GC, 6.1 months; GE, 6.2 months) or overall survival (GC, 13.2 months; GE, 21.5 months) were found between the two arms. Grade 3/4 neutropenia and febrile neutropenia were more

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common in GE. However, delay of protocol treatment due to leukopenia was similar between the two arms. Patients with expression of both ERCC1 and TopoIIα had a significantly shorter TTF (median 2.4 months, 95% CI 0.7—4.1 months) than other patients (median 8.8 months, 95% CI 5.8—11.8 months) ($p = 0.04$).
Conclusion: GE regimen is effective and well-tolerated for NSCLC patients. Expression of both ERCC1 and TopoIIα may be associated with poor response to chemotherapy.

1. Introduction

Platinum-based chemotherapeutic regimens were considered the standard treatment for patients with inoperable, stage IIIB/IV non-small cell lung carcinoma (NSCLC) who have good performance status [1]. However, many patients were reluctant to receive platinum-based chemotherapy because of its significant toxicity, including nausea/vomiting, nephrotoxicity and neurotoxicity. During the 1990s the third-generation chemotherapeutic agents, including the taxanes, gemcitabine, and vinorelbine, have shown promising anti-cancer activity in NSCLC. Combinations of these new agents have been demonstrated similar efficacy but improved toxicity profiles compared with platinum-based regimens in randomized clinical trials for NSCLC [2]. Results from these trials led to the updated recommendation in the American Society of Clinical Oncology guidelines, stating that non-platinum-containing chemotherapy regimens may be used as alternatives to platinum-based regimens in the first line [3].

Despite the promising activity and favorable therapeutic index, combinations of two-third-generation chemotherapeutic agents are usually much more expensive than platinum-based regimens. Incorporation with less expensive, older-generation agents that are active for NSCLC with third-generation agents may produce comparable clinical efficacy at lower cost. For example, high-dose (more than 90 mg/m^2 per cycle) epirubicin has been considered an active treatment for NSCLC. The objective response rate of high-dose epirubicin reported in previous phase II trials for NSCLC was around 19—36%, but myelosuppression and cardiac toxicity may be significant with high-dose epirubicin use [4—7]. Although the objective response rate of conventional-dose epirubicin (60—90 mg/m^2 per cycle) was generally lower [8,9], these lower dose of epirubicin may allow safer combination with other third-generation agents. We recently reported that epirubicin 70 mg/m^2 plus paclitaxel, 175 mg/m^2 every 3 weeks produced partial response in 17 of 38 patients with stage IIIB/IV NSCLC (response rate 44.7%), and the median overall survival was 11.9 months [10]. The above data suggest that conventional-dose epirubicin may be effective in NSCLC treatment.

Gemcitabine appeared to be a good partner with epirubicin for the treatment of NSCLC. In vitro studies suggested synergistic anti-proliferative effects between gemcitabine and anthracyclines [11,12]. Combination of gemcitabine and epirubicin, in various doses and schedules, has been tested in patients with breast, pancreatic, ovarian, and urothelial cancers. Promising effects and acceptable toxicity were found [13—16]. The myelosuppression associated with gemcitabine is mild to moderate and there was no other overlapping toxicity with epirubicin. Therefore, gemcitabine and epirubicin should be an effective non-platinum-based regimen for NSCLC, but the optimal dosage of epirubicin should be better defined.

Recent studies have focused on identification of potential biomarkers to predict response to chemotherapy for NSCLC patients [17]. The excision repair cross-complementing group 1 (ERCC1) protein, which plays an important role in the repair of platinum-induced DNA damage, has been demonstrated to have predictive value for NSCLC patients who received platinum-based adjuvant chemotherapy [18]. Adjuvant chemotherapy significantly prolongs the lives of patients whose tumors were negative for ERCC1 expression. Biomarkers to predict response to other chemotherapeutic agents have also been extensively studied. For example, in patients with operable breast cancer, over-expression of topoisomerase IIα (TopoIIα) in tumor cells indicates superior disease-free and overall survival after anthracyclines-containing adjuvant therapy [19,20]. Whether TopoIIα expression can help predict response to anthracycline treatment for NSCLC remains unknown.

The primary objective of this study is to explore the efficacy of gemcitabine plus conventional-dose epirubicin, in terms objective tumor response, time-to-treatment-failure and overall survival, for patients with stage IIIB/IV NSCLC. Because patient selection can significantly influence the outcome to be evaluated and change in supportive care makes comparison with historical data questionable, a randomized phase II design was used and patients in the control arm received gemicitabine plus cisplatin chemotherapy. Immunohistochemical study for nuclear expression of ERCC1 and TopoIIα was done in patients with available tumor samples to explore the predictive value of these markers on treatment outcome.

2. Patients and methods

2.1. Eligibility of the patients

The study protocol was approved by the Ethical Committee of National Taiwan University Hospital. To be eligible for this study, the patients must have histological or cytological diagnosis of non-small cell lung cancer that was inoperable and not treatable by definitive radiotherapy (stage IIIB or IV by AJCC staging) [21]. The patients must be 18 years of age or older and cannot have previous cytotoxic chemotherapy. The patients must have acceptable performance status (0—2 on the Zubrod scale) and organ function reserves (white blood cell count $\geq$3500/mm^3, neutrophils $\geq$1500/mm^3, platelets $\geq$100,000/mm^3, hemoglobin $\geq$10 g/dL, serum alanine transaminase and aspartate transaminase less than five times of upper limit of normal range (ULN), serum bilirubin less than 1.5 times of ULN, and serum creatinine less