A Phase III Randomized Trial of Gemcitabine–Oxaliplatin versus Carboplatin–Paclitaxel as First-Line Therapy in Patients with Advanced Non-small Cell Lung Cancer

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Purpose: This phase III study compared the efficacy and tolerability of gemcitabine and oxaliplatin (GEMOX) with paclitaxel and carboplatin (PCb) in chemotherapy-naive patients with stage IIIB/IV non-small cell lung cancer.

Patients and Methods: Patients aged 18 years or older were randomized to PCb (paclitaxel 225 mg/m^2 followed by carboplatin area under the curve = 6 on day 1 every 3 weeks) or GEMOX (gemcitabine 1,000 mg/m^2 on days 1 and 8 followed by oxaliplatin 130 mg/m^2 on day 1 every 3 weeks) for up to six cycles. The primary end point was progression-free survival (PFS), with tumor response rate, overall survival (OS), and quality of life as secondary end points.

Results: The study was terminated after 383 patients had been randomized (371 received treatment) as the incidence of adverse events had exceeded the protocol-specified safety threshold (≥20% in either arm). No formal statistical comparisons were conducted. Median PFS was 4.44 months and 4.67 months in the GEMOX and PCb groups, respectively. Objective response rates (complete or partial) were 15.2% and 22.4% in the GEMOX and PCb arms, respectively. Median OS was 9.90 months (GEMOX) and 9.24 months (PCb); post hoc analyses showed median OS in patients aged 70 years or older to be similar to those younger than 70 years. PFS was similar in both groups of patients with adenocarcinoma histology, although OS favored the GEMOX group. Quality of life was improved from baseline in both groups. Toxicity profiles were comparable between the groups.

Conclusion: PFS, OS, and objective response rates with GEMOX were similar to PCb. Nevertheless, toxicities limit the adoption of this regimen for routine use in advanced non-small cell lung cancer.

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Platinum-containing combinations are standard therapy for advanced non-small cell lung cancer (NSCLC), achieving significant reductions in overall mortality and disease progression compared with nonplatinum regimens.[1] The most commonly used regimen for the treatment of advanced NSCLC in the United States is the combination of paclitaxel and carboplatin (PCb), the efficacy of which has been established in randomized phase III studies.[2–6] On the basis of efficacy and toxicity results from the Eastern Cooperative Oncology Group (ECOG) study 1594 comparing four chemotherapy regimens in patients with stage IIIb or IV NSCLC, PCb was recommended by the authors as the reference regimen for future trials.[5]

Oxaliplatin is a platinum compound with a similar mechanism of action to cisplatin. In vitro data suggested that the mechanisms of action of oxaliplatin and gemcitabine may be synergistic.[7] In a phase II study in patients with metastatic NSCLC, the combination of gemcitabine and oxaliplatin (GEMOX) demonstrated a favorable side-effect profile and an overall response rate (RR) of 31%, with a median overall survival (OS) of 11.3 months.[8] A number of GEMOX dosing regimens have been studied in NSCLC. From a phase I/II trial conducted by a consortium of centers in the United States, the recommended dose regimen was gemcitabine 1000 mg/m^2 on days 1 and 8 and oxaliplatin 130 mg/m^2 on day 1, every 3 weeks.[9] This schedule was chosen for this study.

This study was conducted to determine the relative efficacy, safety, and clinical benefit of GEMOX compared with PCb as first-line therapy for patients with stage IIIB/IV NSCLC. The primary end point was progression-free survival (PFS); secondary end points were tumor RR, time to treatment failure (TTF), OS, safety, and quality of life (QoL).

METHODS

Patient Eligibility

Enrolled patients were aged 18 years or older with histologically confirmed, newly diagnosed, untreated, stage

IIIB or IV NSCLC, ≥1 measurable (unidimensional) lesion with diameter ≥20 mm using conventional computed tomography (CT) or magnetic resonance imaging, or ≥10 mm using spiral CT, and an ECOG performance status of 0 or 1. Other inclusion criteria included no history of an acute cardiac or central nervous system event within 6 months of study entry; no current congestive heart failure or unstable coronary artery disease; adequate hematologic, hepatic, and renal function tests; negative pregnancy test in women; and no peripheral neuropathy of grade more than 1. Exclusion criteria included symptomatic brain metastases; history of hypersensitivity to any of the four study drugs; receipt of concurrent immunotherapy; serious uncontrolled medical or psychiatric illness; and history of other malignancy within the last 5 years (except for squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, or superficial transitional cell carcinoma of the bladder). The study protocol was approved by the institutional review boards before patient enrollment. All patients provided written informed consent.

Treatment Plan

Patients were randomly assigned to receive GEMOX (gemcitabine 1000 mg/m^2 over 30 minutes on days 1 and 8 followed by oxaliplatin 130 mg/m^2 over 2 hours on day 1, every 3 weeks) or PCb (paclitaxel 225 mg/m^2 over 3 hours on day 1 followed by carboplatin area under the curve = 6 over 30–60 minutes on day 1, every 3 weeks). Treatment was planned for a maximum of six cycles unless discontinued because of disease progression, unacceptable toxicity, physician or patient decision, pregnancy, requirement for palliative radiotherapy, or death. Patients treated with oxaliplatin could receive 5-HT$_3$ receptor antagonists, with or without dexamethasone, whereas patients treated with paclitaxel could receive dexamethasone and H$_1$ and H$_2$ receptor antagonists before infusion. Supportive care, including bisphosphonates and prophylaxis for neurotoxicity, was also permitted.

A single-dose reduction was permitted for each drug based on worst toxicity for any organ system during the previous cycle. Further dose reductions required discontinuation. For nonhematologic toxicity of grade ≤2, the drug doses of both regimens were delayed until toxicity had declined to grade ≤1. For grade 3 nonhematologic toxicity, all study drugs were given at their reduced doses (gemcitabine 750 mg/m^2; oxaliplatin 100 mg/m^2; paclitaxel 175 mg/m^2; and carboplatin area under the curve = 5). Patients experiencing grade 4 nonhematologic toxicity were withdrawn from the study. In the case of persistent grade 2 neurologic toxicity or grade 3 toxicity lasting for more than 7 days, dose reductions were introduced for oxaliplatin, paclitaxel, and carboplatin. In the event of grade 4 neurologic toxicity, or grade 3/4 acute hypersensitivity or anaphylactic reactions, the patient was withdrawn. In the case of febrile neutropenia on day 1, all study drugs were given at their reduced doses. On the first occurrence of thrombocytopenia, only gemcitabine and carboplatin doses were reduced. On the second occurrence of thrombocytopenia, only oxaliplatin and paclitaxel doses were reduced. When the absolute neutrophil count was in the range 500 to 999 cells/μL, gemcitabine was delayed until absolute neutrophil count ≥1000 cells/μL and was then given at its reduced dose.

Assessment of Efficacy and Safety

Tumor response was evaluated after cycles 2 and 4 using RECIST criteria.[10] Tumor assessment was performed by CT scan (RECIST) after cycles 2 and 4, and after cycle 6 for patients who had a response at cycle 4. To be assigned the status of a partial response (PR) or complete response (CR), tumor measurements had to be confirmed ≥4 weeks after criteria for the response were first met. Toxicities were graded before each treatment cycle according to National Cancer Institute Common Toxicity Criteria for adverse events (AEs) (Version 3.0).

A QoL Functional Assessment of Cancer Therapy-Lung questionnaire was completed after every cycle. This questionnaire is divided into physical, social/family, emotional, and functional well-being subdomains and includes a lung cancer subscale (symptoms, cognitive function, and regret of smoking). The Trial Outcome Index (TOI) was calculated as the sum of the physical, functional, and lung cancer subscales. Reductions in TOI indicate improvements in QoL.

Statistical Analysis

Assuming a recruitment duration of 22 months and that the last accrued subject would be followed for 8 months, a hazard ratio (HR) of 1.3, and median PFS for subjects on PCb of 3.1 months, a sample size of 480 patients (240 in each group) was sufficient to provide 80% power to detect the difference between two treatments using a two-sided test with a type I error of ≤5%.

PFS was defined as time from date of randomization to date of first observation of progression or death due to any cause. TTF was defined as time from randomization to time the patient was removed from the study for any of the following events: withdrawal due to AEs; progressive disease (PD) or insufficient therapeutic response; failure to return; treatment refusal/lack of cooperation/withdrawal of consent; new treatment started; or death.

OS and PFS were estimated using the Kaplan-Meier method. Nevertheless, no formal statistical analyses were conducted to compare the two treatment groups with respect to the primary end point because the early termination did not allow for sufficient enrollment to adequately power the study.

In post hoc analyses, OS and PFS were assessed in patients according to age (<70 years versus ≥70 years) and tumor histology (adenocarcinoma versus squamous).

The intent-to-treat (ITT) population comprised all subjects who were randomized, regardless of whether they received any study drug or therapy different from that to which they were randomized. The safety population consisted of all subjects who received ≥1 dose of any of the study drugs.

Two interim analyses were planned: after 154 and 308 subjects had documented PD, respectively. If, at the time of interim analysis, ≥20% of patients in either treatment group had discontinued study therapy due to unacceptable toxicity, the study would be terminated.