Original Article

Nedaplatin/Gemcitabine Versus Carboplatin/Gemcitabine in Treatment of Advanced Non-small Cell Lung Cancer: A Randomized Clinical Trial

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ABSTRACT

Objective: To evaluate the efficacy and safety of nedaplatin/gemcitabine (NG) and carboplatin/gemcitabine (CG) in the management of untreated advanced non-small cell lung cancer (NSCLC).

Methods: Sixty-two patients with previously untreated advanced NSCLC were recruited between June 2006 and November 2007. Subjects were randomly assigned to the NG arm (n=30) and the CG arm (n=32). Only patients (24 and 25 in the NG and CG arms, respectively) who completed ≥2 chemotherapy cycles were included in the data analysis. The primary outcome measure was the objective response rate (ORR). The secondary outcome measures included progression-free survival (PFS), overall survival (OS) and adverse events.

Results: There were no statistically significant differences in the efficacy measures (ORR, *P*=0.305; median PFS, *P*=0.198; median OS, *P*=0.961) or in the major adverse events (grade 3/4 neutropenia, *P*=0.666; grade 3/4 anemia, *P*=0.263; grade 3/4 thrombocytopenia, *P*=0.212) between the two treatment arms. However, there was a trend towards higher ORR (37.5% vs. 24.0%), longer PFS (6.0 vs. 5.0 months), and less adverse events in the NG arm.

Conclusion: NG regimen seems to be superior over CG regimen for advance NSCLS, but further investigation is needed to validate this superiority.

Key words: Non-small cell lung cancer; Chemotherapy; Nedaplatin; Carboplatin; Gemcitabine; Squamous cell carcinoma

INTRODUCTION

Non-small cell lung cancer (NSCLC) poses a significant health problem worldwide. At the early stage, NSCLC is potentially curable with surgical resection. However, in most cases, the disease has progressed to an advanced stage upon diagnosis[1]. For advanced NSCLC, platinum-based combination chemotherapy is the mainstay of the treatment[2-4].

Since the approval of cisplatin (the protypic platinum coordination compound) as a chemotherapeutic agent for testicular and ovarian cancers in the late 1970s, cisplatin-based combination chemotherapy has become the cornerstone of treatment of advanced NSCLC[5]. One of the major limitations with cisplatin is its severe and sometimes dose-limiting side effects, including but not limited to nausea/vomiting, renotoxicity and thrombocytopenia. As a result, many cisplatin derivatives have been developed, among which nedaplatin and carboplatin are of particular importance.

Nedaplatin is believed to have anti-tumor activities that are equivalent to cisplatin but with less toxicity[6,7]. Nedaplatin-based combination regimens have been evaluated in several clinical trials. In a phase I study of nedaplatin/gemcitabine (NG) that included both previously treated and untreated advanced NSCLC[8], nedaplatin was well tolerated (maximum tolerated dose up to 100 mg/m^2) and active; an overall response rate of 16.7% was observed; a median survival time of 9.1 months and a 1-year survival rate of 34.1% were achieved. In a phase II study of NG in patients with untreated NSCLC, a response rate of 30.3% [95%

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confidence interval (95% CI), 15.6%–48.7%] and a median survival time of 9.0 (range, 1–17) months were demonstrated[9]. Two additional phase II studies of nedaplatin in patients with NSCLC conducted in Japan achieved an objective response rate of 14.7% and 20.5%, respectively[10,11]. In a phase III study of previously untreated patients with NSCLC, a combination of nedaplatin and vindesine yielded response rate and overall survival rate similar to that obtained with cisplatin or vindesine alone[11]. Taken together, these studies suggest that nedaplatin-based combination chemotherapy may offer a promising and effective chemotherapeutic strategy for previously untreated advanced NSCLC.

Carboplatin-based combination regimens have also been evaluated. A phase III study showed that the overall response rate, median progression-free survival (mPFS), median overall survival (mOS) and 1-year survival rate were 27%–42%, 4.8–7.3 months, 7.9–11.6 months and 13%–40%, respectively, in patients with advanced NSCLC following the treatment with carboplatin/ gemcitabine (CG)[12]. An acceptable toxicity profile was demonstrated for CG in patients with advanced NSCLC[13].

NG has been demonstrated to be superior to CG in an animal model of NSCLC[14]. However, to our knowledge, NG and CG have not been evaluated head-to-head in human trials. This randomized clinical trial compared the efficacy and safety profile of NG and CG as chemotherapeutic regimens for patients with previously untreated advanced NSCLC.

MATERIALS AND METHODS

Ethical Considerations

The study was approved by the Institutional Ethics Committee of Guangdong General Hospital & Guangdong Academy of Medical Sciences and conducted in compliance with the Helsinki Declaration. Written informed consent was obtained from all study subjects.

Subject Recruitment

A total of 62 subjects were recruited between June 2006 and November 2007. The inclusion criteria included: 1) wet stage III B (including malignant pleural or/and pericardial effusion) or stage IV NSCLC as categorized based on the International Union Against Cancer (UICC) 1997 International System for Staging Lung Cancer[15] and confirmed by radiographic imaging, magnetic resonance imaging (MRI), computer tomography (CT) scan, and histological and cytological assessments; 2) no prior chemotherapy; 3) responsive lesions as assessed according to Response Evaluation Criteria in Solid Tumor (RECIST) version 1.0[16]; 4) East Cooperation Oncology Group (ECOG) score at 0–2; 5) estimated life expectance at ≥12 weeks; 6) adequate bone marrow reserve (white blood cell at 3,500–12,000/μl, neutrophil count ≥1,500/μl, platelet ≥100,000/μl, and hemoglobin ≥9.0 g/dl); 7) normal renal function (serum creatinine <1.5 mg/dl and creatinine clearance rate ≥50 ml/min); and 8) aspartate aminotransferase and alanine aminotransferase levels at or less than twice the upper limit of the normal range and no juandice. The exclusion criteria included: 1) metastasis to the brain; 2) active secondary malignancy; 3) evident infection; and 4) co-morbid severe heart diseases or other uncontrolled systemic disease.

Treatment Allocation and Regimens

Subjects were randomized to the NG (n=30) or CG (n=32) arm based on the last digit of the admission number (even: NG; odd: CG). The NG regimen consisted of nedaplatin [Jiangsu Aosaikang Pharmaceutical Co., Ltd; 80 mg/m^2, 60 min, d1, every 3 weeks (q3w)] and gemcitabine (1,250 mg/m^2, 30 min, d1, d8, q3w). The CG regimen included: carboplatin at area under the curve (AUC)=5, 20 min, d1, q3w; and gemcitabine 1,250 mg/m^2, 30 min, d1, d8, q3w. All chemotherapeutic agents were administration as an intravenous (iv) drip. No prophylactic granulocyte colony-stimulating factor and prophylactic antibiotics were used. Toxicity profile was evaluated based on the criteria set in the US National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTC) Version 3.0[17]. Whenever grade 4 toxicity developed, a dose reduction of 20% was applied. Patients requiring more than two dosage adjustments were withdrawn from the study. A rest period of up to 42 d was allowed between the cycles to minimize the therapy-related toxicities.

Outcome Assessment

Objective response was assessed every 2 cycles of the chemotherapy based on the criteria stated in RECIST 1.0[16]. Complete response (CR) was defined as disappearance of all target lesions, partial response (PR) as at least 30% decrease in the sum of diameters of target lesions relative to the baseline prior to the treatment, progressive disease (PD) as at least 20% increase in the sum of diameters of target lesions, relative to the smallest sum of diameters during the study or as the appearance of one or more new lesions, and stable disease (SD) as either insufficient shrinkage to qualify for PR or insufficient increase to qualify for PD. CR and PR were established based on at least 4-week response, and SD based on at least 6-week observations.

Patients with SD after 2 cycles underwent one or two additional treatment cycles. Those achieving PR or CR after 2 cycles continued the same regimen for additional 2–4 cycles. Those developing PD were