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Nedaplatin or Oxaliplatin Combined with Paclitaxel and Docetaxel as First-Line Treatment for Patients with Advanced Non-Small Cell Lung Cancer

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Both nedaplatin and oxaliplatin combined with paclitaxel or docetaxel have demonstrated potent activity in advanced non-small cell lung cancer (NSCLC) patients, but there is no study comparing the difference between these 2 chemotherapy regimens. The aim of this study was to evaluate and compare the efficacy and safety between the combination chemotherapy of nedaplatin or oxaliplatin plus paclitaxel and docetaxel in patients with advanced NSCLC.

Material/Methods: We retrospectively reviewed patients with stage III-IV unresectable NSCLC from 1 January 2010 to 31 December 2013 at Southwest Hospital. They all received nedaplatin (80 mg/m^2, nedaplatin group) or oxaliplatin (130 mg/m^2, oxaliplatin group) combined with paclitaxel (175 mg/m^2) or docetaxel (75 mg/m^2) as first-line treatment.

Results: There are 174 patients enrolled – 123 patients in the nedaplatin group and 51 patients in the oxaliplatin group. The objective response rates were 47.3% and 34.1% and the disease control rates were 87.5% and 79.5% in nedaplatin and oxaliplatin groups, respectively. The progression-free survival time was 10.4 months and 9.6 months (p=0.722) and the overall survival time was 18.5 months and 25.5 months in the nedaplatin and oxaliplatin groups, respectively (p=0.09). Total toxicity was greater in the oxaliplatin group (p=0.008), but there is no significant difference among ¾ grade adverse events between the 2 groups (P=0.595).

Conclusions: The effect of nedaplatin plus paclitaxel and docetaxel is the same as oxaliplatin plus paclitaxel and docetaxel, and the toxicity of nedaplatin is well tolerate as first-line treatment for patients with advanced NSCLC.

MeSH Keywords: Carcinoma, Non-Small-Cell Lung • Chemotherapy, Adjuvant • Paclitaxel • Platinum Compounds

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Background

Lung cancer is the leading cause of cancer-related deaths worldwide [1] and about 85% of these are non-small cell lung cancer (NSCLC). More than half of the patients with NSCLC present with advanced disease at the time of diagnoses, and systemic chemotherapy of platinum-based doublets is generally considered to be the standard first-line chemotherapy in those patients. However, choosing a specific platinum-based doublet remains controversial. Cisplatin- and carboplatin-based platinum chemotherapy have shown effectiveness in advanced NSCLC but caused severe toxicity.

Nedaplatin is a second-generation platinum derivative that provides activity against NSCLC. In a phase III study in patients with advanced NSCLC, the combination of nedaplatin and vindesine produced similar response rate and an overall survival rate to those of cisplatin and vindesine, but causes less nausea/vomiting and nephrotoxicity [2]. Paclitaxel and docetaxel are taxanes regarded as promising chemotherapy drugs in the treatment of various malignancies [3–5], especially as first-line therapy for advanced NSCLC based on phase III studies [6,7], and combination of nedaplatin plus taxanes has shown strong anticancer activity and is well tolerated by these patients. Two phase II studies of nedaplatin plus docetaxel in patients with advanced NSCLC also demonstrated promising object response rate of 50% and 53.2%, median progression-free survival (PFS) of 7.4 months and 5 months, respectively, and both had a median overall survival (OS) of 13 months [2,8]. In 2 studies, the combination chemotherapy of nedaplatin plus docetaxel showed a higher response rate of 66.7% and 62% for squamous cell lung cancer [8,9].

Oxaliplatin is a third-generation platinum derivative with demonstrated effectiveness in colorectal, ovarian, and pancreatic cancers, as well as in advanced NSCLC [10,11]. The combination of oxaliplatin and paclitaxel and docetaxel also showed a good clinical benefit in terms of response rate and OS. A phase II study of oxaliplatin and paclitaxel resulted in a favorable response rate of 34.2% and overall survival of 9.2 months [12], and another study using the chemotherapy of oxaliplatin plus docetaxel showed a response rate of 37%, and overall survival of 10.9 months [13]. Furthermore, oxaliplatin requires less hydration due to the low occurrence of nephropathy and vomiting associated with cisplatin, and causes less myelosuppression than carboplatin, making this agent as a desired therapy for frail patients with advanced cancer. Above all, combination chemotherapy of nedaplatin or oxaliplatin plus taxanes is effective and well tolerated in untreated advanced NSCLC patients.

Material and Methods

Eligibility

Patients with histologically or cytologically proven stage III/IV NSCLC from 1 January 2010 to 31 December 2013 at Southwest Hospital were enrolled in this study. All the patients received nedaplatin or oxaliplatin combine with paclitaxel and docetaxel as first-line treatment. All the eligible patients were over 20 years old; Karnofsky performance status (KPS) was greater than or equal to 70; the measurable lesion was measured according to the Response Evaluation Criteria in Solid Tumors (RECIST); with adequate bone marrow function (leukocyte count $\geq 4.0\times10^9$/L, absolute neutrophil count $\geq 2.0\times10^9$/L, platelet count $\geq 100\times10^9$/L, hemoglobin count ≥9.5 g/dl), and adequate other organ function (serum aspartate aminotransferase, serum alanine aminotransferase, serum creatinine concentration, serum total bilirubin and the alkaline phosphatase were normal).

Treatment

In the nedaplatin group, patients received nedaplatin 80 mg/m^2 reconstituted in 500 ml of physiological saline intravenously over a period of 1.5 h, along with paclitaxel (175 mg/m^2) or docetaxel (75 mg/m^2) reconstituted in 250 ml of physiological saline or 5% glucose solution intravenously over a period of 1 h on Day 1. In the oxaliplatin group, patients received oxaliplatin 130 mg/m^2 reconstituted in 500 ml of physiological saline intravenously over a period of 1 h, along with paclitaxel (175 mg/m^2)/ docetaxel (75 mg/m^2) reconstituted in 250 ml of physiological saline or 5% glucose solution intravenously over a period of 1 h on Day 1. All patients received paclitaxel and docetaxel premedication consisting of dexamethasone 8 mg orally twice a day for 3 days and Lansoprazole 30 mg intravenously 30 min prior to infusion. All patients received anti-emetic therapy 30 min prior to chemotherapy infusion with metoclopramide 10 mg or tropisetron 5 mg. The chemotherapy was repeated every 21 days for a maximum of 6 but at least 2 cycles. When patients had disease progression or uncontrolled advent events, we changed the chemotherapy regimen to include radiotherapy, targeted therapy, or symptomatic and supportive treatment.

Treatment evaluation

The primary endpoints of this study were objective response rate (ORR) and disease control rate (DCR), the secondary endpoints includes progression-free survival (PFS), overall survival (OS), and toxicity. We evaluated the tumor size and other organ metastases by computed tomography (CT) every 2 cycles and the function of bone marrow, liver, and kidney were assessed weekly or biweekly. Tumor response was assessed according to RECIST 1.1. Complete response (CR) was defined

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Table 1. Patient characteristics.

	Nedaplatin n (%)	Oxaliplatin n (%)	P value
N	123	51	
Sex			0.69
Male	93 (75.6)	40 (78.4)	
Female	30 (24.4)	11 (21.6)	
Age			0.715
Median (rear)	59	59	
<60	76 (61.8)	30 (58.8)	
≥60	47 (38.2)	21 (41.2)	
KPS			0.48
70–80	77 (62.6)	29 (56.9)	
90–100	46 (37.4)	22 (43.1)	
Histological subtype			0.404
Squamous cell	71 (57.7)	29 (56.9)	
Adenocarcinoma	48 (39.0)	22 (43.1)	
Adeno-squamous cell	4 (3.3)	0 (0.0)	
Stage			0.921
IIIA	27 (22.0)	10 (19.6)	
IIIB	37 (30.0)	15 (29.4)	
IV	59 (48.0)	26 (51.0)	

KPS – Karnofsky performance status.

as the complete clinical and radiographic disappearance of the tumor without the appearance of new lesions. Partial response (PR) was characterized as a reduction by at least 50% of the products of the longest diameters of all measurable lesions, no growth of other lesions, and no appearance of new lesions. Stable disease (SD) was defined as a decrease in the sum of the products of 2 perpendicular diameters of all measured lesions by <50% or an increase by <25% after a minimum of 2 cycles of therapy. Progressive disease (PD) was characterized as an increase in the product of the longest diameters of the measured lesion by ≥25% or the appearance of new lesions. Toxicity was graded according to World Health Organization (WHO) toxicity criteria.

Statistical analysis

ORR was defined as the sum of CR and PR rate. DCR was defined as the sum of ORR and SD rate. OS was defined as the time from the date of treatment to death, with living patients censored on the date of last follow-up. PFS was calculated from start of treatment until the date of objective disease progression or death. The estimations of OS and PFS were performed according to the Kaplan-Meier method, which was used to assess time-to-treat variables and the log-rank test was used to compare survival curves of treatment groups. ORR and DCR among demographic factor groups were compared using the chi-square test and p values of less than 0.05 were considered statistically significant.

Results

There are 174 patients in this study between 1 January 2010 and 31 December 2013, including 123 patients in the nedaplatin group and 51 patients in the oxaliplatin group. The characteristics of eligible patients are shown in Table1. There were more females than males in this study, the median ages are both were 59 years old, and most patients presented with

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Table 2. Objective response rate (ORR) and disease control rate (DCR).

	Nedaplatin n (%)	Oxaliplatin n (%)	P value
N	112	44	
CR	1 (0.9)	1 (2.3)	
PR	52 (46.4)	15 (34.1)	
SD	45 (40.2)	20 (45.5)	
PD	14 (12.5)	8 (18.2)	
ORR	53 (47.3)	15 (34.1)	0.134
DCR	98 (87.5)	35 (79.5)	0.208

CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; ORR – objective response rate; DCR – disease control disease; m – months.

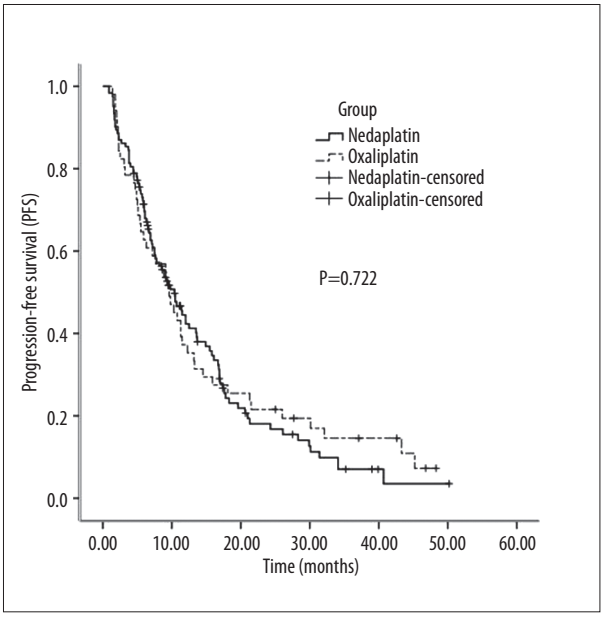

Figure 1. Progression-free survival (PFS) in nedaplatin and oxaliplatin group were 10.4 months and 9.6 months, respectively, P=0.722.

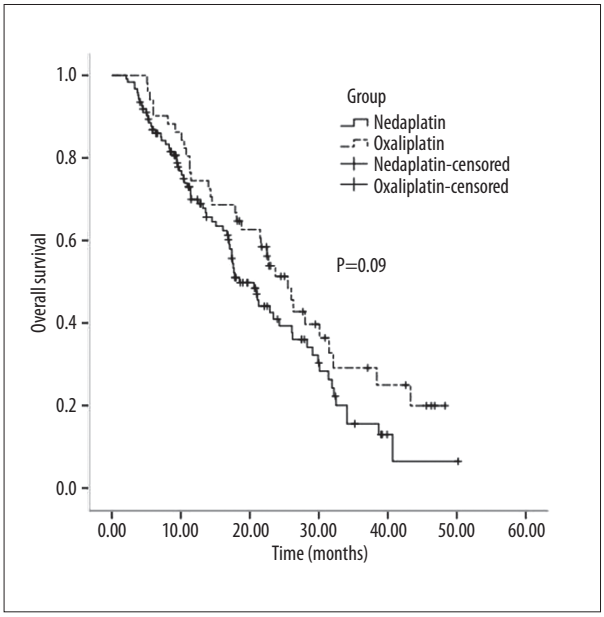

Figure 2. Overall survival (OS) in nedaplatin and oxaliplatin group were 18.5 months and 25.5 months, respectively, P=0.09.

squamous cell carcinoma and had stage IV disease, but there is no statistical differences in baseline characteristics between the 2 treatment groups.

Objective response rate

We evaluated 156 patients out of the 174 initially eligible patients (112 in the nedaplatin group and 44 in the oxaliplatin group) were evaluated for ORR and DCR (Table 2), and the other 18 patients were lost to follow-up when they finished the second treatment cycle. The objective response rate for the nedaplatin group and oxaliplatin group were 47.3% (95% CI, 38.2–56.6%) and 34.1% (95% CI, 21.3–48.9%), respectively. The combination chemotherapy of nedaplatin showed a higher response rate compared with oxaliplatin, although there was no significant difference between the 2 groups (P=0.134). The disease control rate for nedaplatin and oxaliplatin groups were 87.5% (95% CI, 80.4–92.7%) and 79.5% (95% CI, 65.8–89.5%), respectively, and there was no statistical difference between the 2 groups (P=0.208).

Survival

For all the patients enrolled, the PFS was 10.4 months and 9.6 months in nedaplatin and oxaliplatin groups, respectively, and

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Table 3. Toxicity.

	Nedaplatin n (%)	Oxaliplatin n (%)	P value
N	123	51	
Total toxicity	76 (61.8)	42 (82.4)	0.008
3/4 Grade toxicity	20 (16.3)	10 (19.6)	0.595
3/4 Grade hematologic	16 (13)	8 (15.7)	0.641
Neutropenia	11	8	
Thrombopenia	0	0	
Anaemia	4	0	
3/4 Grade Non-hematologic	5 (4.1)	2 (3.9)	0.965

there was no significant difference between the 2 groups (P=0.722) (Figure 1). The OS for the 2 groups were 18.5 months and 25.5 months, respectively, and there was still no statistical difference between nedaplatin and oxaliplatin groups (P=0.09) (Figure 2).

Toxicity

In all the eligible patients, the most common toxicities were anemia (38.5%), neutropenia (35.1%), and nausea and vomiting (35.1%), but the most frequent 3/4 grade toxicity was neutropenia, which accounted for 11.5%, and all 6 grade 4 adverse events happened in patients with neutropenia. The characteristics of toxicities in the 2 treatment groups are shown in Table 3. Oxaliplatin combined with paclitaxel and docetaxel was prone to more adverse events compare with the nedaplatin combination group, especially in total toxicity (p=0.008). There were no statistical differences among 3/4 grade adverse events (p=0.595), 3/4 grade hematologic (p=0.641), and non-hematologic (p=0.965) adverse events.

Discussion

This is the first report to compare the efficacy and safety of nedaplatin and oxaliplatin combination chemotherapy as first-line therapy for advanced NSCLC. Our study found that the combination chemotherapy of nedaplatin plus taxanes yield a higher objective response rate (47.3% *vs.* 34.1%), disease control rate (87.5% *vs.* 79.5%), PFS (10.4 m *vs.* 9.6 m), OS (18.5 m *vs.* 25.5 m), and less adverse events (61.8% *vs.* 82.4%) compared with the combination chemotherapy with oxaliplatin plus taxanes, but there were no statistical differences between the 2 groups except the adverse events.

At present, platinum-based doublet regimens are accepted as the standard of care for first-line therapy in the treatment of advanced or metastatic NSCLC, and taxanes, especially docetaxel plus platinum, are an effective treatment option. Fossella [7] showed that compared with docetaxel plus vinorelbine regimen, docetaxel plus platinum had a more favorable overall response (31.6% *vs.* 24.5%, p=0.029) and survival rate (p=0.044). Kubota [6] also reported that cisplatin combined with docetaxel showed a statistically significant survival benefit (ORR 37% *vs.* 21%, p<0.01; OS 11.3 *vs.* 9.6 months, p=0.014) over cisplatin combined with vindesine. Furthermore, paclitaxel plus cisplatin and carboplatin also resulted in a long overall survival (7.8 and 10.5 months, respectively) [14,15].

Originally, cisplatin- and carboplatin-based chemotherapy showed efficacy as first-line treatment for advanced NSCLC, and cisplatin and docetaxel seemed superior to oxaliplatin and docetaxel in terms of response rate (47% *vs.* 28%, p=0.118), but there were no significance differences in time to progression (6.3 *vs.* 4.9 months, P=0.111) and median overall survival (11.6 *vs.* 7.0 months, P=0.102) [16–18]. However, toxicity of chemotherapy drugs still needs attention, and some can cause fatal injury [19]. Cisplatin and docetaxel are associated with more severe leukopenia (44% *vs.* 14%), neutropenia (56% *vs.* 27%), and renal toxicity (56% *vs.* 11%) compared with oxaliplatin and docetaxel. In other randomized phase III studies of cisplatin-based chemotherapy, rates of grades 3–4 neutropenia, thrombocytopenia, and anemia were 24–76%, 7–36%, and 3–19%, respectively [20–22], Compared with those studies, the combination of nedaplatin plus docetaxel results in less hematologic toxicities [2,8], thus oxaliplatin and nedaplatin combined with taxanes appears to be a more feasible regimen for advanced NSCLC.

Our study found that the ORR in nedaplatin and oxaliplatin groups was 47.3% and 34.1%, respectively, which was similar to other reports, except for 1 study. The study by Radhakrishnan [23] used the combination chemotherapy of oxaliplatin and

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docetaxel and showed an overall response rate of 50%, median progression-free survival was 2.4 months, and median overall survival was 7.9 months. The high ORR reported in that study is due to chemotherapy administered at 2-week intervals, while we administered chemotherapy at 3-week intervals. The median age of our study patients was 59, while the median age in the Radhakrishnan study was 69, and the older age of patients might explain the lower PFS.

The subgroup analysis of the present study demonstrated some contrasting results in terms of the relationship between histological types and response rate. In the nedaplatin group, patients with squamous cell carcinoma tended to have a higher response rate compared with that of patients with non-squamous cell carcinoma (54% *vs.* 39%), in contrast, patients in the oxaliplatin group with squamous cell carcinoma had a lower response rate compared with that of patients with non-squamous cell carcinoma (21% *vs.* 50%). In addition, several studies reported that nedaplatin based combination chemotherapy could be a favorable regimen for patients with squamous cell carcinoma of lung cancer [24] but there are no related data about an oxaliplatin regimen, so more trials are required.

The PFS and OS in our study were higher than in other studies [2,8,9,12,13,23]. Among those studies, most of the enrolled patients were in stage IV, and the patients in stage IV accounted for more than 90% in each study. In our study, for 48% and 51% of patients were in stage IV in nedaplatin and oxaliplatin groups, respectively. Furthermore, the number of patients enrolled in our study was larger than in other studies, which may explain the higher PFS and OS in our study.

Conclusions

Both nedaplatin and oxaliplatin combined with taxanes were effective and well-tolerated as first-line chemotherapy for advanced NSCLC. Nedaplatin combination chemotherapy showed more favorable results and less toxicity, especially in patients with squamous cell carcinoma. Further prospective trials to compare the efficacy and safety of these 2 chemotherapy regimens are required.

Conflict of interest

The authors declare that they have no conflict of interest.

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