RESEARCH ARTICLE

Etoposide-Cisplatin Alternating with Vinorelbine-Cisplatin Versus Etoposide-Cisplatin Alone in Patients with Extensive Disease Combined with Small Cell Lung Cancer

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Abstract

Background: The aim of this study was to evaluate the efficacy of alternating etoposide-cisplatin and vinorelbine-cisplatin (EP-NP) compared with an etoposide-cisplatin (EP) regimen for advanced combined small cell carcinomas. Materials and Methods: Histologically confirmed combined small cell carcinoma patients who met the inclusion criteria were randomly assigned (1:1) into either the EP-NP setting (group A) or the EP setting (group B). The primary endpoint was progression-free survival in patients who received at least one dose of treatment. Results: Eighty-two patients entered into this trial, 42 in group A and 40 in group B. The objective response rates in group A and group B were 42.9% and 32.5%, respectively (p=0.334). Survival analysis showed that median progression-free survival was 6.1 months in group A, which was significantly longer than the 4.1 months in group B (p=0.041). However, as to overall survival, no significant difference was found between the two groups (11.0 *vs* 10.1 months in groups A and B, respectively, p=0.545). No unexpected side effects were observed in either group. Conclusions: The EP-NP regimen for combined small cell carcinomas prolonged progression-free survival compared with the EP regimen. Further clinical investigations are warranted.

Keywords: Combined small cell lung cancer - chemotherapy - efficacy - etoposide-cisplatin - vinorelbine-cisplatin

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Introduction

Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are two completely different classes of pulmonary malignancies. SCLC is an extremely aggressive malignancy, with significantly shortened doubling time, higher growth fraction, and earlier onset of remote metastasis, is usually sensitive to chemotherapy with an objective response rate of 80-90% (Schiller et al., 2001; Simon et al., 2003; Stupp et al., 2004; Socinski et al., 2006; Jemal et al., 2010). There is an intersection between SCLC and NSCLC that the WHO/IASLC classification in 1999 defined combined small cell lung carcinomas (C-SCLC). Despite this classification, NSCLC components are frequently visible in SCLC tissue samples. Thus, C-SCLC has been specifically defined as a distinct subgroup of SCLC in cancer pathology according to the latest version of tumor classification (WHO, 2004). In detail, the diagnosis of C-SCLC relies on microscopical evidence that NSCLC components are more than 10% of the whole SCLC tumors (Fushimi et al., 1996). These NSCLC components may be large-cell neuroendocrine carcinoma, adenocarcinoma, or squamous cell carcinomas.

C-SCLC accounts for 2-28% of all SCLC cases (Adelstein et al., 1986; Mangum et al., 1989; Nicholson et al., 2002). Currently, the literal documentations for C-SCLC are rare with sporadic case reports (Hsiao et al., 2006). Therefore, the optimal therapy for C-SCLC are still not been defined. The updated 2013 NCCN guidelines still recommend the classical chemo-combination for SCLC, etoposide and cisplatin (EP) regimen, for the first line therapy of C-SCLC (Weng et al., 2008; Wong et al., 2009). Luo et al. (2012) investigated the feasiblity of three drugs combination as the first line therapy for C-SCLC, and showed an inferior response rate, progression-free survival (PFS) and overall survival (OS) with more toxicity compared with EP regimen. Nowadays, heterogeneous and mixed responses are frequently phenomena we medical oncologist encountered (Bai et al., 2012). A potential strategy for this situation is to combine two different therapeutic settings, just like (Goldberg et al., 2013) continuous epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) together with chemotherapy in the acquired assistance of EGFR-TKIs

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in advanced NSCLC patients.

Since vinorelbine and cisplatin (NP) (Schiller et al., 2002) and EP (Hanna et al., 2006; Lara et al., 2009) are standard first line settings for NSCLC and SCLC respectively. The aim of this study was to evaluate the efficacy and the side effect of alternating chemotherapies with EP-NP regimen for extensive disease C-SCLC patients comparing with EP regimen alone.

Materials and Methods

Patients

Eligible patients were aged over 18 years and had histologically confirmed extensive C-SCLC. They also had measurable lesions which were assessed according to response evaluation criteria in solid tumors (RECIST version 1.0), an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2, and adequate haematological, biochemical and vital organ function. Patients were excluded from the study if they had uncontrolled brain metastases or had received previous systemic anticancer therapies. All patients were enrolled at Shanghai Pulmonary Hospital. All pathological specimens were reviewed by two experienced pathologists. The histopathological confirmation and the diagnosis were made according to World Health Organization (WHO) guidelines. Immunohistochemistry markers, such as cyto-keratin 7/8 (CK7/8), P63, and thyroid transcription factor-1 (TTF-1) were chosen to discriminate components of non-small cell lung cancer. Neuron specific enolase (NSE), and chromogranin (ChrA) were commonly used to recognize SCLC components (Kalhor et al., 2006; Bishop et al., 2010). This study was approved by the Institutional review board of Shanghai pulmonary hospital and the Informed Consent Forms (ICF) was signed by each eligible patient before the initiation of any trial related procedure.

Study design

Eligible patients were randomly assigned (1:1) into two groups. The stratification factors included gender (female *vs* male), ECOG PS (0 *vs* 1-2) and age (<65 *vs* ≥65 years old).

Group A were received alternating chemotherapy with EP at cycles 1, 3, and 5 and NP at cycles 2, 4, and 6, while patients in Group B received EP alone up to 6 cycles. Etoposide was administered at a dose of 100 mg/m^2 on days 1-3, cisplatin at 75 mg/m^2, divided into days 1-3, and vinorelbine at 25 mg/m^2 on days 1 and 8 (Faller and Pandit 2011). Chemotherapy was repeated every three weeks. Palliative radiation for brain/lung metastasis was allowed for patients with evidenced progressive disease. Additionally, administration of bisphosphonate was allowed if bone metastasis was confirmed.

Procedures

Tumor response was evaluated every two cycles according to the RECIST 1.0 criteria (Therasse et al. 2000). Adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria version 3.0. In case of Grade-4 hematological toxicity or Grade-3 non-hematological toxicity, the doses of chemo-agents were reduced to 75% of the original in subsequent cycles.

All patients were followed-up every 2 months by out-patient clinic visit, phone or mail. Chest CT scan and blood tumor markers were reviewed at local hospital or in our hospital for outpatient. During follow-up, information of survival, cancer recurrence or metastasis, and cause of death were obtained for further analysis. OS was defined as the interval from the commencement date to date of death. PFS was defined as the interval from date of randomization to date of documented progression per RECIST or death due to any cause.

Statistical analysis

The primary endpoint of this study was the PFS and the secondary endpoints were objective response rate (ORR), OS, and side effects. Cases without documented progression or death were censored during the last documented evaluation. Fisher's test was used to estimate the correlation among different variables between arms. Survival estimation was performed using the Kaplan-Meier method with log-rank test. Cox proportional hazards regression models were fitted to estimate hazard ratios (HR) in a multivariate analysis. Statistical analysis was performed using SPSS 15.0 software (SPSS Inc., Chicago). Two-sided p value<0.05 was considered statistically significant.

Results

Patient characteristics

From Jan 2008 to Aug 2011, a total of 82 patients who met the inclusion criteria were enrolled and randomized in this clinical trial, including 42 patients in Group A and 40 in Group B. 68 of them were histologically diagnosed by bronchoscopic biopsies, and the other 14 cases were diagnosed by CT-guided lung biopsies. The ECOG PS, smoking status, age and gender distribution were well balanced between the two groups and shown in Table 1.

All patients received at least one cycle of chemotherapy (median, 3 cycles; range, 1-6 cycles). The mean of chemotherapeutic cycles in Group A and Group B were

Table 1. The Baseline Characteristics in the Whole Population

Characteristics		Total (N=82)	Group A (N=42)	Group B (N=40)	p value
Median age (range)		61(42-81)	62(49-78)	59(42-81)	0.1
Gender	Male	75	38	37	1
	Female	7	4	3	
ECOP PS	0	12	7	5	0.59
	1-2	70	35	35	
Smoking status	Yes	54	31	23	0.12
	No	28	11	17	
Radiotherapy	Thoracic	22	10	12	0.87
	Cranial	6	4	2	
	No	54	28	26	
NSCLC components	Sq*	70	35	35	0.594
	Ad*	9	5	4	
	LC*	3	2	1	
Weight loss	≥5%	10	5	5	0.934
	<5%	72	37	35	

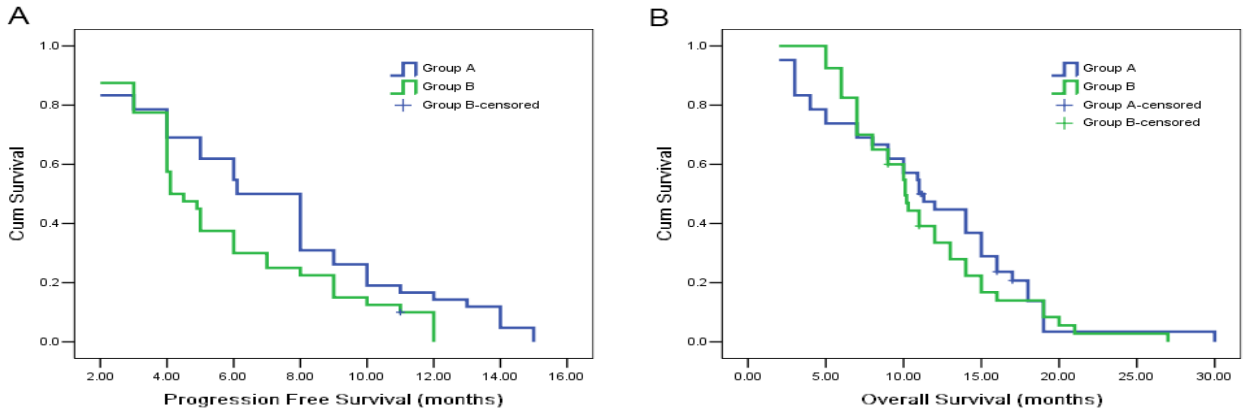

Figure 1. PFS and OS of EP-NP Regimen Compared with the EP Regimen. A) Etoposide-cisplatin and vinorelbine-cisplatin (EP-NP) regimen prolongs the progression-free survival (PFS) compared to that with the etoposide-cisplatin (EP) regimen (6.1 *vs* 4.1 months, *p*=0.041). **B)** The overall survivals (OS) were similar in both groups (11.0 *vs* 10.1 months, *p*=0.545).

Table 2. General Information of Toxicities

Toxicity	EP+NP (Group A)	EP (Group B)	*p* value
Anemia			NS
Grade I/II	2/0	0/1	
Leucopenia			NS
Grade I	8	9	
Grade II	4	5	
Grade III	7	6	
Grade IV	5	5	
Thrombocytopenia (Grade I)	2	8	0.017
Renal dysfunction	1	0	NS
Hepatic dysfunction	3	4	NS
Abdominal pain (Grade II)	1	0	NS

3.9±1.6 and 3.0±1.4, respectively. Thirty-six patients (48%) completed at least 4 cycles of treatment. Radiation was administered to 28 patients, among whom there were 4 cranial cases and 10 thoracic-radiation cases in Group A. Additionally, 14 patients received radiation in Group B, including 2 cranial radiotherapies and 12 thoracic radiotherapies.

Tumor response

Of the 82 patients available for response evaluation, 31 patients with partial response, 44 with stable disease, and 7 with progressive disease as their best tumor response. In Group A, 18 patients with PR and 19 patients with SD. Therefore, the ORR in Group A was 42.9%, which was numerically higher than 32.5% (13/40) in Group B (*p*=0.334).

Survival outcomes

Survival analyses were performed in all of the patients with a median follow-up period of 11 months (95% confidence interval [CI], 8.7-13.8). Among these patients, 1 (1.2%) was still not progress and 6 (7.3%) were still alive until the last follow-up data of March 08 2012.

Patients treated with EP alternating with NP regimen had significantly improved PFS when compared with patients treated with EP regimen (*p*=0.041, shown in Figure 1A). Median PFS for patients in group A and group B were 6.1 months (95%CI, 4.63 to 7.57 months) and 4.1 months (95%CI, 2.98 to 5.22 months), respectively. Multivariate Cox regression model also showed significant differences between the groups who received alternating regimen versus EP regimen (HR, 0.61; 95%CI, 0.38 to 0.96; *p*=0.034).

Patients treated with EP alternating with NP regimen had numerically longer OS when compared with patients treated with EP regimen (*p*=0.545, shown in Figure 1B). Median OS for patients in group A and group B were 11.0 months (95%CI, 8.56 to 13.44 months) and 10.1 months (95%CI, 8.80 to 11.39 months), respectively. Multivariate Cox regression model also showed no significant differences between the groups who received alternating regimen versus EP regimen (HR, 0.89; 95%CI, 0.55 to 1.44; *p*=0.627).

Side effects

Major toxicities included grade 3-4 hematological, such as leucopenia, neutropenia or thrombocytopenia. The severity and incidence of hematological toxicities were similar between the two study groups (see Table 2). Eleven (26.2%) cases in Group A developed grade 3-4 leucopenia and 10 (27.5%) cases in Group B (*p*=0.903) developed leucopenia. Grade 1 thrombopenia was more commonly seen in patients with EP treatment, which consisted of 8 cases in Group B and 2 cases in Group A, respectively. Most commonly seen non-hematological toxicities included moderate nausea, fatigue, and diarrhea. Ten patients developed transient renal or hepatic toxicity and eleven patients required dose reduction.

Discussion

This study was a phase II trial in which EP alternating with VP regimen was compared with EP alone in patients with C-SCLCs. We found that patients treated with alternating EP-NP regimen had a significantly longer PFS, numerically higher ORR and longer OS, apart from acceptable side effect (s).

C-SCLCs are neoplasms containing areas of small cell morphologic components with a discrete additional component (s) of NSCLC. The non-small cell component can be adenocarcinoma, SCC, LCNEC, or large cell carcinoma not otherwise classified. Individual tumors containing up to 4 different morphologic constituents

have been described (Adelstein et al., 1986). Although the exact proportion of SCLCs in multiphasic malignant lung tumors is uncertain, the estimations were have ranged from 2% to 28% (Adelstein et al., 1986; Mangum et al., 1989; Nicholson et al., 2002). The incidence of lung cancer is increasing rapidly in China which results in a considerable amount of patients with C-SCLCs. However, there was still few clinical studies, especially randomized clinical trials, focusing on the treatment of C-SCLC (Mangum et al., 1989; Hage et al., 1998; Murase et al., 2003; Murray et al., 2006). Therefore, the current NCCN guideline still recommends the same chemotherapy regimen for patients with C-SCLC as for those with SCLC.

Mixed-response to chemotherapy is frequently observed in clinical practice. Recent study (Bai et al., 2012) showed that the heterogeneity of inter-tumor or intra-tumor was the key reason for mixed-response. A good strategy to overcome mixed-response is to combine or intercalate two anti-cancer strategies, which has showed promising results in the treated patients with NSCLC (Goldberg et al., 2013; Zheng et al., 2013). As for C-SCLC, a combined treatment with 3 drugs or alternative 2 chemotherapy regimens, which is for both SCLC and NSCLC, might be feasible strategy to improve the prognosis of C-SCLC. However, Luo et al (Luo et al., 2012) investigated the feasibility of the combination of the 3 drugs as the first line chemotherapy for C-SCLC in a retrospective study and showed the triple-drugs regimen had not only a lower response rate and an poor PFS and OS but also a higher toxicity compared with EP regimen.

The present study is the first study comparing alternating EP-NP regimen with EP regimen as the first-line chemotherapy for C-SCLC patients. Our study showed that the alternating EP-NP regime (group A) had a significantly longer PFS than the EP regimen (group B) (6.1 *vs* 4.1 months, p=0.041). We also found that the ORR was numerically higher in the group A than in the group B (42.9% *vs* 32.5% p=0.334), the median survival of group A was also numerically longer than that of group B (11 *vs* 10.1 months, p= 0.545). The superior efficacy of alternating EP-NP regimen might be due to the different chemotherapy drugs which fully cover the NSCLC and SCLC components, resulting in killing tumor cells to a great extent and inhibiting the tumor growth in a short term. In addition, the severity and incidence of hematological toxicities were similar between two study groups (p=0.903) and the toxicities were acceptable in the study.

It is noteworthy that the ORR observed in this study for whole C-SCLC population was 37.8%, while the previous research had reported 60-80% for SCLCs and 30-40% for NSCLCs (Schneider 2008; Jemal et al., 2010). The median OS and the median PFS for patients with C-SCLC were 11.0 months and 6.1 months, respectively, which were similar to survival data of patients with NSCLC. On the contrary, Hage et al. (Hage et al., 1998; Babakoohi et al., 2013) found that C-SCLC was clinically similar to SCLC. Murase et al. hypothesized that the SCLC component originated from the squamous component in C-SCLCs (Murase et al., 2003). However, all of these studies were based on the observation of limited cases, further large scale studies are needed to learn more about the biological behaviors of C-SCLC.

In conclusion, the present study showed that alternating EP-NP regimen significantly prolonged PFS of patient with C-SCLC compared to EP regimen alone. In further, a larger population phase III trial should be conducted to confirm the findings in this study.

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