RESEARCH ARTICLE

Comparison of Vinorelbine, Ifosfamide and Cisplatin (NIP) and Etoposide and Cisplatin (EP) for Treatment of Advanced Combined Small Cell Lung Cancer (cSCLC) Patients: A Retrospective Study

Jie Luo[1], Feng-Ying Wu[1], Ai-Wu Li[1], Di Zheng[1], Jin-Ming Liu[2]*

Abstract

Objective: To compare efficacy and safety profile of vinorelbine, ifosfamide and cisplatin (NIP) with etoposide and cisplatin (EP) in the treatment of advanced combined small cell lung cancer (c-SCLC). Methods: From January 2006 to December 2010, 176 patients with advanced c-SCLC were enrolled. The primary endpoint was overall survival (OS) and the secondary endpoints were progression free survival (PFS), response rate (RR) and toxicity. Results: Overall RR was 30.0% in the NIP and 38.5% in the EP group; there was no significant difference (P=0.236). The PFS in the EP group was little longer than that of NIP group, with 6.5 months for EP and 6.0 months for NIP group, but the difference was statistically non-significant (P=0.163). The median OS and one year survival rates were 10.4 months and 36.3% for NIP group, and 10.8 months and 49.0% for EP respectively, EP showing a survival benefit, although this was not statistically significant. Both groups well tolerated the adverse effects. The incidence of grade I-II leucopenia and alopecia in the NIP group was significantly higher than that of EP group (32.5% vs. 10.4% (P<0.001, 35.0% vs. 12.5%, P<0.001). Conclusion: the ORR, PFS and OS in NIP were slightly inferior to traditional regimen EP. The toxicity of NIP can be considered tolerable. The usage of three drugs combination in the treatment of mixed SCLC remains uncertain. Nevertheless, the results need to be further confirmed by large, prospective clinical trials.

Keywords: Lung neoplasms - carcinoma - small cell - combined chemotherapy - regimen

Asian Pacific J Cancer Prev, **13 (9)**, 4703-4706

Introduction

Combined small cell lung carcinoma (CSCLC) is defined as small cell carcinoma combined with an additional component consisting of any non–small cell histologic type, including adeno-carcinoma, squamous cell carcinoma (SCC), and large cell neuroendocrine carcinoma (LCNEC). Approximately 30% of small cell lung carcinomas (SCLCs) show A non–small cell lung carcinoma (NSCLC) component and clinical characteristics of CSCLC do not differ significantly from those in patients with pure SCLC (Adelstein et al., 1986; Mangum et al., 1989; Nicholson et al., 2002). Though, the overall survival (OS) in these two groups is similar, response to chemotherapy in early series was poorer among patients with CSCLC (Radice et al., 1982). The CSCLCs are currently considered a subset of SCLC by the WHO, although biologic evidence to support this classification scheme is lacking, and the validity of the current practice remains to be confirmed (Travis et al., 2004). In advanced NSCLC patients, the combination of vinorelbine plus ifosfamide and cisplatin has demonstrated a high response rate and has improved one-year survival in phase II trials. Several studies (Baldini et al., 1996; Souquet et al., 1996; Barone et al., 1998; Rey et al., 1998; Tan Eh et al., 1999; Montalar et al., 2011) have reported response rates ranging from 41% to 66%, median survival from 9.8 to 14 months and one-year survival from 47% to 60%. In our hospital, we have been using vinorelbine-ifosfamide-cisplatin (NIP) combination chemotherapy for the treatment of cSCLC for many years. In the present study, we retrospectively analyzed the patients' data and compared the efficacy and toxicity of NIP with the traditional regimen EP (etoposide and cisplatin) in the treatment of cSCLC.

Materials and Methods

Patients' Eligibility

This was a retrospective analysis. The entire patient's data were collected from the Shanghai Pulmonary Hospital Lung Cancer Patients' Data Bank. The data included the performance status, chemotherapy regimens, response evaluation and toxicity of each lung cancer patient in detail. From January 2006 to December 2010, a total of 176 eligible cases were accrued into this study. Eligibility

*[1]Department of Oncology, [2]Department of Respiratory, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China *For correspondence: jinmingliu_sh@hotmail.com*

criteria included: histological or cytological proven cSCLC; no prior chemotherapy, radiotherapy or surgery; age: 18-80 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1; measurable disease in the chest CT; two or more cycles of NIP or EP have been given; adequate organ function. The intervals of follow-up time were 3 months until patients die. The final follow-up time was September 1st 2011.

Treatment Assignment

The treatment schedule NIP consisted of vinorelbine 25 mg/m^2 on day-1 and day-8, ifosfamide 1.2 mg/m^2 infused with mesna for uroprotection on days 1 through 3 and cisplatin 25 mg/m^2 days 1 through 3. The schedule EP consisted of etoposide 100mg/m^2 on days 1 through 3, cisplatin 25 mg/m^2 days 1 through 3. Mesna was administrated intravenously just before, 4 h and 8 h after ifosfamide infusion. The cisplatin was administrated with hydration and forced diuresis. Treatment was preceded by parenteral administration of antiemetics consisting of 5-HT3 receptor antagonists. The cycles were repeated every 21 days. The response to the treatment was assessed after two cycles. Each case received at most 6 cycles of NIP or EP. The chest radiotherapy was conducted after 2 cycles of chemotherapy for those needed chest radiotherapy. After completion of the treatment, the patients were followed-up every 3 months until disease progression. The second-line regimens of irronotecan or docetaxol and so on were administrated after the disease was progressed.

Response Evaluation

The primary endpoint was OS, and secondary endpoints were PFS, ORR and toxicity. Tumor response was evaluated according to WHO evaluation criteria, including complete response (CR), partial response (PR), stable disease (SD) and progressed disease (PD). The CR and PR were classified as ORR. The OS was defined as the length of time from the start of treatment to patient death or final follow-up. The PFS was defined as the length of time from the start of medication to disease progression or patient's death caused by any reasons. The toxicity and adverse events (AEs) were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events, NCICTC 2.0.

Statistical Analysis

Statistical analysis was conducted using the SPSS 17.0; percentage, x±s, median, and 95%CI, χ^2 analyses was used to comparing percentage between two groups. The PFS and OS were estimated using the Kaplan-Meier method. P<0.05 represents statistical difference.

Results

Patients Characteristics

Out of 176 eligible patients, 80 patients received NIP with a median chemotherapy cycle of 3.03 (2-6 cycles), and 96 patients received EP with a median chemotherapy cycle of 3.99 (2-6 cycles). Majority of the patients were males in both the groups. Most of the patients were staged as phase III-IV and there was no significant difference for the percentage of patients in each phase (P=0.232). Seventeen (21.3%) patients in the NIP group and 20 (20.8%) patients in the EP group received chest radiotherapy. Overall, 15 (18.8%) patients in the NIP arm and 16 (16.7%) patients in the EP arm were found with brain metastasis at the time of diagnosis. The difference was not significant (P=0.964 and 0.718 respectively) (Table 1).

Table 1. Characteristics of Patients in Two Groups [n (%)]

	NIP group(n=80)	EP group (n=96)	P value
Gender			0.514
Male	71(88.8%)	82(85.4%)	
Female	9(11.2%)	14(14.6%)	
Median age	59(26~79)	63.5(43~80)	
Pathology			0.017
Squa + SCLC	30(37.5%)	21(21.9%)	
Adeno + SCLC	2(2.5%)	0(0%)	
Combined SCLC	48(60%)	75(78.1%)	
Stage			0.232
Phase I	2(2.5%)	5(5.2%)	
Phase II	2(2.5%)	0(0%)	
Phase III	29(36.2%)	42(43.8%)	
Phase IV	47(58.8%)	49(51%)	
Chest radiotherapy	17(21.3%)	20(20.8%)	0.946
Brain radiotherapy	15(18.8%)	16(16.7%)	0.718

Table 2. Comparison of Response Between Two Groups [n (%)]

	NIP group(n=80)	EP group(n=96)	P value
PR	24(30%)	37(38.5%)	0.236
SD	43(53.8%)	50(52.1%)	0.825
PD	13(16.2%)	9(9.4%)	0.17
PR+SD	67(83.8%)	87(90.6%)	0.17

Response Rate

All patients were eligible for assessment of their response to the treatment. There was no statistical difference in ORR and DCR between two groups. The ORR was 30.0% in NIP group, whereas 38.5% in EP group (P=0.236; Table 2). The DCR (CR+PR+SD) was 83.8% (67/80) in NIP group and 90.6% (87/96) in EP group (P=0.170).

PFS and OS

In NIP group, 10 patients were alive, the PFS data and OS data were not available in six (5+1 respectively) patients. While in EP group, 21 patients were alive, the PFS data and OS data were not available in eight patients (7+1 respectively). The median PFS was six months for NIP arm and 6.5 months for EP arm separately. The EP arm seems to have little longer PFS than NIP arm, but it failed to reach statistical significance (P=0.163, 95%CI: 5.655-6.745) (Figure 1). Moreover, EP arm seems to have slightly longer median OS (10.8 months vs. 10.4 months, P=0.935, 95%CI: 9.180-12.020) and one-year survival rate than NIP arm (49% vs. 36.3%, P=0.090, OR=0.593, 95%CI: 0.323-1.087). The stratified analysis indicated that there was no statistical difference between the groups in median PFS and median OS for those patients without

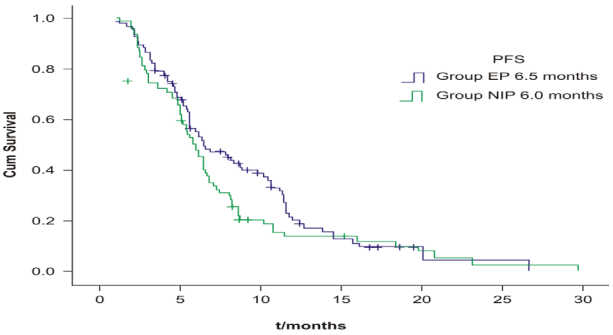

Figure 1. Kaplan-Meier Estimates of Time to Progression for 2 Groups

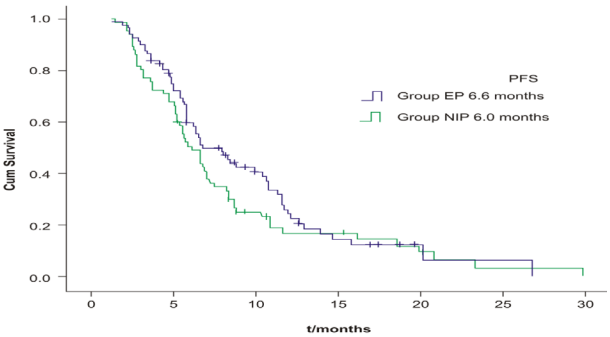

Figure 3. Kaplan-Meier Analysis of Time to Progression in Patients' Without Brain Metastasis

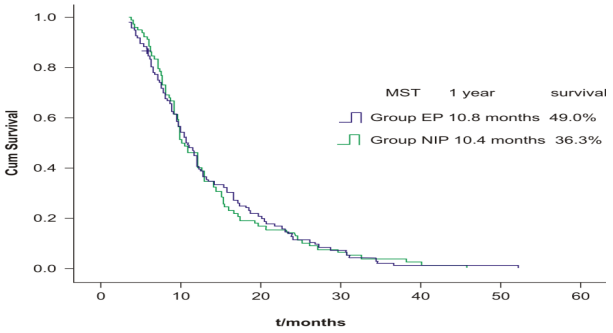

Figure 2. Kaplan-Meier Estimates of Overall Survival for 2 Groups

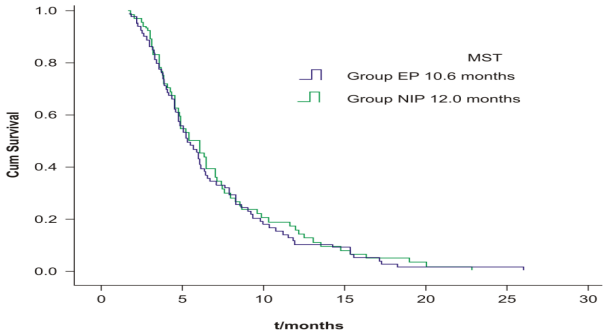

Figure 4. Kaplan-Meier Analysis of Overall Survival in Patients Without Brain Metastasis

Table 3. Comparison of NCI-CTC I/II Adverse Effects Between Two Groups [n (%)]

Adverse effects(I/II)	NIP group(n=80)	EP group (n=96)	Odds ratio	95%CI	P value
Leucopenia	26(32.5%)	10(10.4%)	4.141	1.852-9.260	<0.001
Thrombocytopenia	6(7.5%)	4(4.2%)	1.865	0.507-6.854	0.342
Anemia	3(3.8%)	1(1.0%)	3.701	0.377-36.297	0.23
Nausea, Vomiting	7(8.8%)	21(21.9%)	0.342	0.137-0.854	0.018
Liver malfunction	6(7.5%)	4(4.2%)	1.865	0.507-6.854	0.342
Kidney malfunction	1(1.3%)	1(1.0%)	1.203	0.074-19.536	0.897
Alopecia	28(35.0%)	12(12.5%)	3.769	1.764-8.056	<0.001
Nervous system damage	1(1.3%)	1(1.0%)	1.203	0.074-19.536	0.897
Diarrhea	2(2.5%)	1(1.0%)	2.436	0.217-27.368	0.457

Table 4. Comparison of NCI-CTC III/IV Adverse Effects Between Two Groups [n (%)]

Adverse effects(I/II)	NIP group(n=80)	EP group (n=96)	Odds ratio	95%CI	P value
Leucopenia	18(22.5%)	15(15.6%)	1.568	0.733-3.355	0.245
Thrombocytopenia	6(7.5%)	4(4.2%)	1.865	0.507-6.854	0.342
Anemia	7(8.8%)	5(5.2%)	1.745	0.532-5.727	0.353
Nausea, vomiting	14(17.5%)	12(12.5%)	1.485	0.644-3.425	0.236
Liver malfunction	4(5.0%)	3(3.1%)	1.632	0.354-7.515	0.526
Kidney malfunction	3(3.8%)	2(2.1%)	1.831	0.298-11.238	0 .5 0 8

brain metastasis. The median PFS was 6.0 months for NIP arm (65 cases) and 6.6 months for EP arm (P=0.239, 95%CI: 5.761-7.239) (Figure 3). The median OS was 12 months for NIP arm and 10.6 months for EP arm (P=0.687, 95%CI: 9.186-12.214) (Figure 4).

Toxicities/ Adverse Events

Both the groups were included with AEs: leucopenia, thrombocytopenia, anemia, nausea, vomiting, liver malfunction, kidney malfunction, alopecia etc. (Table 3 and Table 4). The incidence of grade I-II leucopenia and alopecia is significantly higher for NIP arm than EP arm (32.5% vs. 10.4%, OR=4.141, 95%CI: 1.852-9.260, P<0.001; 35.0% vs. 12.5%, OR=3.769, 95%CI: 1.764-8.056, P<0.001). For other AEs, there was no significant difference was found between the groups.

Discussion

With the advances in the diagnosis of lung cancer, the frequency of cSCLC has been raising in recent years. The combination of etoposide plus cisplatin has been considered as traditional first line treatment for SCLC. And in our hospital, NIP has widely been used for the treatment of cSCLC. To further explore which chemotherapy regimen is much more optimal for cSCLC, we compared the efficacy and toxicity of NIP with EP in the treatment of cSCLC by retrospective analysis.

In our study, a large proportion of patients were male, which was 88% and 85.4% for NIP and EP arm

respectively. Most male patients were smokers, suggesting cSCLC association with heavy smoking (Travis et al., 2004). The ORR was 30.0% and 38.5% for NIP and EP arm respectively. The ORR for EP arm seems to be higher than that of NIP arm, but it failed to reach significance (P=0.236). In our study, the ORR for NIP was lower than the previous report; it may be because of the difference in pathology among those study groups. Furthermore, there was no obvious difference for DCR between two arms: with 83.8% for NIP arm and 90.6% for EP arm individually (P=0.170). The PFS,OS and one-year survival rate for EP arm was slightly longer than that of NIP arm (6.5 vs. 6.0 months, P=0.163 for PFS; 10.8 vs. 10.4 months, P=0.935 for OS; 49.0% vs. 36.3%, P=0.090 for one-year survival respectively), but it failed to reach statistical difference.

The outcome of the analysis has been similar to (Souquet PJ et al., 2002) study. In this prospective trial NP was compared with NIP in 259 metastatic advanced NSCLC; ORR represents 34.6% in NP arm and 35.7% in NIP arm (P=0.85), median OS and one-year survival rates were 10.0 months and 38.4% for NP arm, and 8.2 months and 33.7% for NIP arm, respectively. The grade III-IV toxicities for NP and NIP were: neutropenia (20.3% vs. 9.0%), anemia (4.1% vs. 5.0%), nausea and vomiting (22.2% vs. 19.4%) and alopecia (5.6% vs. 29.8%). The NP arm led to greater survival benefit and less toxicities when compared with NIP.

Song et al. (2003) studied the efficacy of NIP as salvage chemotherapy in 44 advanced NSCLC patients. The results showed that the ORR was 27.3% (95%CI: 14.1-40.5), median response duration was 4.1 months (1.3-13 months), median PFS was 2.9 months (0.7-15.3 months), the main toxicity was grade III-IV neutropenia (3.6%) and anemia (0.7%). However, the PFS in the study was remarkably shorter than other studies; the reason may be that NIP was used as a salvage treatment in this study.

Gottfried et al. (2003) studied the usage of NIP as induction and adjuvant treatment in 156 locally advanced NSCLC. In this study, 65% of patients were with stage IIIA, 28% IIB, and 7% IIIB. After three cycles of induction in 143 assessable patients, 53.8% of patients showed PR and 3.5% showed CR. Grade III-IV neutropenia were found in 3% of patients, grade III-IV anemia in 4%, grade III nausea and vomiting in 11%, grade III anorexia in 6.5%, grade III-IV infection in 6.5%, grade III asthenia in 10% and grade III alopecia in 25.5%. After neoadjuvant chemotherapy with NIP, 107 patients underwent operation with complete resection in 74%, and downstaging after surgery was 29% (N2 to N0).

In our analysis, the toxicity in two arms was acceptable. The incidence of grade I-II leucopenia and alopecia are higher for NIP arm than EP arm (32.5% vs. 10.4%, P<0.001; 35.0% vs. 12.5%, P<0.001), while other adverse effects were similar in both groups.

In conclusion, the ORR, PFS and OS for NIP are slightly inferior to traditional regimen EP but the difference was not significant. The toxicity of NIP could be tolerable. The usage of three drugs combination in the treatment of mixed SCLC remains uncertain. Nevertheless, the results need to be further confirmed by large, prospective clinical trials.

References

Adelstein DJ, Tomashefski JF, Jr, Snow NJ, et al (1986). Mixed small cell and non–small cell lung cancer. *Chest*, **89**, 699-704.

Baldini E, Tibaldi C, Chella A, et al (1996). Phase II study of Vinorelbine/ ifosfamide/Cisplatin for the treatment of advanced non-small cell lung cancer. *Ann Oncol*, **7**, 747-9.

Barone C, Corsi DC, Pozzo C, et al (2000). Vinorelbine and alternating Cisplatin and ifosfamide in the treatment of non-small cell lung cancer. *Oncology*, **58**, 25-30.

Gottfried M, Ramlau R, Krzakowski M, et al (2008). Cisplatin-based three drugs combination (NIP) as induction and adjuvant treatment in locally advanced non-small cell lung cancer: final results. *J Thorac Oncol*, **3**, 152-7.

Mangum MD, Greco FA, Hainsworth JD, et al (1989). Combined small-cell and non–small-cell lung cancer. *J Clin Oncol*, **7**, 607-12.

Montalar J, Morales S, Maestu I, et al (2001). Vinorelbine, ifosfamide and Cisplatin as first-line treatment in patients with inoperable non-small cell lung cancer. *Lung Cancer*, **34**, 305-11.

Nicholson SA, Beasley MB, Brambilla E, et al (2002). Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. *Am J Surg Pathol*, **26**, 1184-97.

Radice PA, Matthews MJ, Ihde DC, et al (1982). The clinical behavior of "mixed" small cell/large cell bronchogenic carcinoma compared to "pure" small cell subtypes. *Cancer*, **50**, 2894-902.

Rey F, Astoul P, Marqueste L, et al (1998). Cisplatin, ifosfamide and Vinorelbine combination chemotherapy in stage III–IV non-small cell lung cancer—a phase II study. *Am J Oncol*, **21**, 518-22.

Souquet PJ, Fournel P, Bohas CH, et al (1996). Cisplatin and ifosfamide with various doses of Vinorelbine (Navelbine®) in advanced non-small cell lung cancer. *Semin Oncol*, **23**, 8-10.

Souquet PJ, Tan EH, Rodrigues Pereira J, et al (2002). GLOB-1: a prospective randomised clinical phase III trial comparing Vinorelbine - Cisplatin with Vinorelbine – Ifosfamide - Cisplatin in metastatic non-small-cell lung cancer patients. *Ann Oncol*, **13**, 1853-61.

Tan EH, Ang PT, Wee J, et al (1999). Vinorelbine, Ifosfamide and Cisplatin in advanced non-small cell lung cancer. *Acta Oncol*, **38**, 619-22.

Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC (2004). Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. World Health Organization Classification of Tumours. IARC Press, France.

Song SY, Kim WS, Kim K, et al (2003). Vinorelbine, Ifosfamide, ND Cisplatin Combination as Salvage Chemotherapy in advanced Non-small cell lung cancer. *Jpn J Clin Oncol*, **33**, 509-13.