RESEARCH ARTICLE

Post-operative Treatment with Cisplatin and Vinorelbine in Chinese Patients with Non-small Cell Lung Cancer: A Clinical Prospective Analysis of 451 Patients

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Abstract

Purpose: To determine the efficacy of post-operative chemotherapy with cisplatin plus vinorelbine (NP) in Chinese patients with non-small cell lung cancer (NSCLC). Methods: A total of 451 patients with NSCLCs at stages I, II, and IIIA after surgical resection were treated with cisplatin plus vinorelbine for 4 cycles or volunteers observed between January 2002 and November 2004 and were followed for five years. The therapeutic efficacy was evaluated with reference to overall survival (OS) and disease-free survival (DFS), and adverse effects were also recorded. Potential factors affecting the lengths of OS and DFS were analyzed by multivariate analysis. Results: Most patients (86.7%) completed at least 4 cycles of treatment. Patients with chemotherapy survived significantly longer than those in the observation group (p<0.001). The absolute improvements in the 2 and 5-year OS were 3.8% [hazard ratio (HR) =0.674, 95% confidence interval (CI): 0.554-0.820, P<0.0001] and 13.0% (HR=0.732, 95% CI: 0.579-0.926, P=0.009), respectively. The improvement at 4-year DFS was 2.1% (HR=0.327, 95% CI: 0.214-0.500, P<0.0001). Stratification analysis revealed that older age, histological type, pathological degree, but not the gender and smoking status, are independent factors affecting the length of survival in this population. Many patients (63.3%) had grade 1-III tolerable adverse effects, and there was no treatment-related death. Conclusions: Post-operative chemotherapy with NP regimen is effective and tolerable in Chinese patients with NSCLC.

Keywords: Non-small cell lung cancer - cisplatin - vinorelbine - survival

Asian Pacific J Cancer Prev, **13 (9)**, 4505-4510

Introduction

Lung cancer is a leading cause of cancer mortality in the world (Jemal et al., 2006), and majority of lung cancer patients have non-small cell lung cancer (NSCLC). Patients with NSCLC have a 5-year survival rate of less than 15% (Jemal et al., 2007; Hu et al., 2010). Currently, surgical resection of tumor tissue remains the primary strategy for the treatment of patients with NSCLC at stage I, II, and IIIA. However, the long-term survival of patients with NSCLC who undergo surgery alone is still not satisfactory. Approximately one-third of patients relapses within a short period post surgery and die (Hotta et al., 2004). Therefore, optimal adjuvant chemotherapy may be necessary for prolonging the survival of patients with NSCLC.

In recent years, a number of high-level evidence-based clinical trials have shown that adjuvant chemotherapy with cisplatin and vinorelbine (NP) program can be used for the treatment of various types of cancer (Cella et al., 2010; Devleena et al., 2010; Pouessel et al., 2010; Gao et al., 2011; Shamseddine et al., 2011; Chen et al., 2012), but the efficacy of NP regiment is still controversial in the world. A meta-analysis reveals a small benefit of adjuvant chemotherapy for patients with NSCLC after resection of the tumor, however, other randomized clinical trials show contradictory results. Data from the ALPI (Adjuvant Lung Project Italy) and BLT (Big Lung Trial) trials show that chemotherapy has no beneficial for the overall response rate and survival of patients with NSCLC at stage I-IIIA after follow-up for more than 5 years (Scagliotti et al., 2003; Waller et al., 2004). On the other hand, platinum-based chemotherapy is effective for patients with NSCLC in American and European countries. The IALT (International Adjuvant Lung Trial) shows that platinum-based chemotherapy for patients with NSCLC improves a 5-year survival rate by 4.1% (Arriagada et al., 2004), but there is no significant benefit after follow-up for 90 months (Arriagada et al., 2010). The CALGB 9633 trial results in a similar finding (Strauss et al., 2008). Furthermore, the ANITA (Adjuvant Navelbine International Trialist Association) and JBR-10 (National Cancer Institute of Canada Clinical Trial Group) trials also confirm the survival benefit of adjuvant cisplatin-vinorelbine chemotherapy in patients with NSCLC at I-IIIA even after follow-up for 9.3 years (Winton et

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al., 2005; Douillard et al., 2006; Butts et al., 2010). In addition, the LACE (Lung Adjuvant Cisplatin Evaluation) collaborative group and ISA (Italian Survey on adjuvant treatment trial) independently confirm that the effect of NP treatment was significantly better than that of platinum-based combination (Pignon et al., 2008; Douillard et al., 2010; Banna et al., 2011). Interestingly, chemotherapy with uracil-tegafur, an alternative of cisplatin-based adjuvant therapy, also improves the survival rate in Japanese patients with NSCLC (Imaizumi et al., 2005; Nakagawa et al., 2006). Apparently, different ethnic populations of patients with NSCLC have varying responses to cisplatin-based adjuvant therapy. Currently, there are few clinical studies of the adjuvant chemotherapy for Chinese patients with NSCLC, particularly in a larger population. China is a developing country and the incidence of NSCLC in China is increasing. As a result, there are so many patients with NSCLC and many of them tend to be aging. Hence, the efficacy and safety of adjuvant chemotherapy with NP regimen need to be carefully evaluated.

This prospective clinical trial is aimed at evaluating the efficacy and safety of chemotherapy with the NP regimen for Chinese patients with NSCLC at stage I-IIIA following surgical resection of the tumors.

Materials and Methods

Patients

Patients with NSCLC at stage I, II, or IIIA who had received surgical resection of the tumors at the Department of Cardiothoracic Surgery, the Second Military Medical University, and the Department of Oncology, the Third People's Hospital Affiliated to School of Medicine, Shanghai Jiao-Tong University, were recruited from January 2002 to November 2004. Individual patients with NSCLC were diagnosed, according to histological examination, and their tumors were staged, according to the 2002 classification of the International Union against Cancer (UICC). The inclusion criteria included individual patients, who received surgical resection of the tumor and were marginally free of disease, had no prior history of cytotoxic chemotherapy or hormonal therapy, with Eastern Cooperative Oncology Group performance status scale (ECOG PS) =0 and adequate hematological, hepatic, and renal functions. The exclusion criteria included those with adjuvant chemotherapy, a history of coronary heart disease, diabetes, metabolic syndrome and other major systemic diseases, and those who was difficult to follow-up. Written informed consent was obtained form individual patients, and the experimental protocol was approved by the Ethics Committee of the Third People's Hospital.

Treatment

Individual patients were randomized, based on their willingness, and treated with adjuvant chemotherapy of cisplatin and vinorelbine (NP) regimen, or participated into the observation group without any antitumor therapy following surgery. This open-choice design was to determine whether postoperative chemotherapy conferred a survival benefit. The primary endpoints were the overall survival (from the date of surgery to the date of death or last follow-up) and disease-free survival (from the date of surgery to the date of locoregional or distant recurrence or tumor-related death). The second endpoint was chemotherapy-related adverse effects. Most patients in the chemotherapy group were treated with 80 mg/m^2 cisplation on day 1 and 30 mg/m^2 vinorelbine on day 1 and 8 of each cycle beginning within 40 days after surgery, and followed by an interval of 20 days. All of the patients received at least 2 cycles of postoperative treatment. Their chemotherapy profile, ECG, and complete blood counts were obtained prior to each new cycle of chemotherapy. In addition, patients were treated human granulocyte colony stimulating factor (G-CSF), dexamethasone, and cimetidine during chemotherapy. Both groups of patients were followed up every 3 months during the first 2 years after radical surgery and then every 6 months until death or last follow-up. Both groups received the same assessments of age, gender, smoking habit, histological type, clinicopathological stage, chemotherapy status, recurrence, and metastasis during follow-up visits.

Statistical analysis

Data are expressed as the numbers of cases and percentage. The difference between groups was determined by X^2 and fisher exact tests. The survival of individual groups of patients was estimated using the Kaplan-Meier method (Kaplan, 1958) and determined by the Log-rank test. The potential association between adjuvant chemotherapy treatment and survival outcomes was analyzed using multivariable Cox proportional hazards regression model following univariate analysis and 95% confident interval (CI). The statistical difference was analyzed using SPSS software version 15.0 (Chicago, IL, USA). A two-tail P value <0.05 was considerated statistically significant.

Results

Patients

A total 451 patients were recruited, and 225 patients received chemotherapy while 226 patients received no chemotherapy. These patients had a median age of 57 years (range 38~83 y), and 72.6% of them were male. Their demographic and clinical characteristics are summarized in Table 1. There was no significant difference in any of the measurementss between the patients with chemotherapy and those without chemotherapy. Of the 430 patients, the percentage of patients with squamous cell carcinoma (195 cases, 45.35%) or adenocarcinoma (223 cases, 51.86%) was significantly higher than that of those with adenosquamous carcinoma (12 cases, 2.79%). A similar pattern of the distribution of different types of NSCLC was observed in both groups of patients.

Most patients in the post-operative chemotherapy group received at least 4 cycles of chemotherapy with cisplatin and vinorelbine within 40 days post operation (Table 2). Those patients received chemotherapy for an average of 4.8 cycles (range 1 to 8.4). Due to personal reasons, untolerated adverse effect or disease progression, there were 14 patients with less than 4 cycles of chemotherapy

Table 1. Characteristics of the Patients

Parameter	Observation		Chemotherapy		Total	
	No.	%*	No.	%	No.	%
Patients	212	49.3	218	50.7	430	100.0
Lost to follow-up		14		7		21
Age (years)						
Median		58		55		57
Range		38~82		38~83		38~83
Sex						
Male	158	74.5	154	70.6	312	72.6
Female	54	25.5	64	29.4	118	27.4
TNM Stage**						
I A	63	29.7	79	36.2	142	33.0
I B	16	7.5	14	6.4	30	7.0
II A	47	22.2	55	25.2	102	23.7
II B	27	12.7	19	8.7	46	10.7
III A	59	27.8	51	23.4	110	25.6
Type of Surgery						
Pneumonectomy	115	54.2	111	50.9	226	52.6
Lobectomy/Other	97	45.8	107	49.1	204	47.4
Histology						
Squamous carcinoma	99	46.7	96	44.0	195	45.3
Ademocarcinama	107	50.5	116	53.2	223	51.9
Adenosquamous	6	2.8	6	2.8	12	2.8

*Because of rounding, percentages may not total 100; **TNM was staged, according to the International Union Against Cancer (UICC) 2002 TNM Classification of Malignant Tumors, 6th

Table 2. Chemotherapy Compliance

Parameter	Percentage (n)
Patients with chemotherapy for 4 cycles	86.7 (189)
Patients with chemotherapy for < 4 cycles	
< 3 cycles	2.3 (5)
< 4 cycles	4.1 (9)
Chemotherapy 40 days after surgery	
Individual requests	0.5 (1)
Disease progression	0.9 (2)
Reasons for treatment termination	
Patient refusal	1.8 (4)
Severe adverse events	1.4 (3)
Disease progression	2.3 (5)

and 12 patients with early termination of chemotherapy. In addition, a few patients delayed receiving chemotherapy. These patients were followed for five years, and 21 out of 451 patients were lost to follow-up. The median follow-up period was 46 months (range 3 to 72).

Efficacy and outcome of adjuvant therapy

During the follow-up period, there were 210 patients with NSCLC-related death and 130 (61.32%) patients in the observation group died. The death rate of patients in the observation group was significantly higher than that in the chemotherapy group of patients (80 cases, 36.7%, p<0.05). Furthermore, there were 67 patients with the relapse or metastasis of cancers. The recurrent rate in the observation group of patients (36 cases, 53.7%) was slightly higher than that in the chemotherapy group (31 cases, 46.3%). The majority of patients with NSCLC metastasized into the brain in both groups of patients (11 cases, 35.5% in the chemotherapy group vs. 15 cases, 41.7% in the observation group). Similar numbers of patients had locoregional relapse. Patients with chemotherapy showed a significantly longer period of OS and DFS (p<0.01 for both, Figure 1). Patients with chemotherapy had a

Table 3. Univariate Analysis of Survival Time of Patients with NSCLC

Characteristics	No.	Median survival time (month)	HR	95%CI	P-value
Gender					
Male	312	46	-		
Female	118	45	0.966	0.781-1.194	0.748
Age(years)					
≥55	255	41	-		
<55	175	60	0.589	0.485-0.715	<0.0001
Histology					
Squamous carcinoma	195	62	-		
Adenocarcinoma	223	42	0.925	0.763-1.121	0.426
Adenosquamous	12	32	2.315	1.282-4.179	0.005
TNM Stage					
I	172	62	-		
II	148	42	0.238	0.185-0.306	<0.0001
III A	110	32	0.451	0.350-0.581	<0.0001
Postoperative chemotherapy					
No	212	41	-		
Yes	218	53	0.672	0.554-0.814	<0.0001
Smoking status					
Yes	250	45	-		
No	180	48	0.862	0.711-1.046	0.132

HR, Hazard ratio; CI, Confidence interval; TNM, Tumor-node-metastasis; Two-sided was used to estimate P values

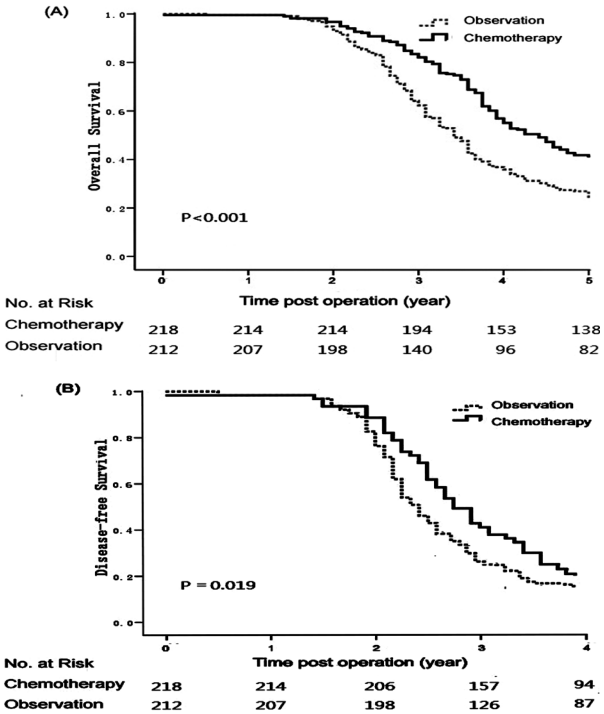

Figure 1. Stratification Analysis of the Survival of Patents. The survival curves of different groups of patients were established by the Kaplan-Meier method and the difference in the OS and DFS rates between the patients with post-operative chemotherapy and those in the observation group was analyzed by the log rank analysis. (A) The overall survival of patients; (B): The disease-free survival of patients. The numbers indicate the case numbers at each time point after surgery

median OS period of 53 months and DFS period of 39 months, which were significantly longer than that in the observation group (41 and 34 months, respectively, p<0.001, Figure 1). The absolute improvement in 2 and 5-year OS were 3.8% (HR =0.674, 95% CI: 0.554-0.820, P<0.0001) and 13.0% (HR=0.732, 95% CI: 0.579-0.926, P=0.009), respectively. The absolute improvement in

Table 4. Multivariable Analysis of Overall and Disease-free Survival

Variable	Overall survival		Disease-free survival	
	HR (95%CI)	P-value	HR(95%CI)	P-value
Age, 5-y intervals	0.504(0.411 to 0.618)	<0.0001	0.459(0.278 to 0.757)	0.002
Histology*		0.001		0.609
Ad vs. S	0.808(0.665 to 0.983)	0.033	1.106(0.757 to 1.618)	0.602
O vs. S	2.197(1.212 to 3.982)	0.009	1.564(0.610 to 4.012)	0.352
TNM Stage		<0.0001		<0.0001
II versus I	3.144(2.302 to 4.295)	<0.0001	2.957(1.563 to 5.595)	0.001
III versus I	9.561(6.721 to 13.602)	<0.0001	7.961(3.918 to 16.175)	<0.0001
Postoperative Chem.	2.122(1.597 to 2.818)	<0.0001	0.608(0.386 to 0.956)	0.031

*Ad, Adenocarcinoma; S, Squamous carcinoma; O, Other types of NSCLC

Table 5. The Main Toxicity of Chemotherapy

	Grade I	Grade II	Grade III	Grade IV	%
Neutropenia	29	41	7	0	35.3
Thrombocytopenia	103	22	12	0	62.8
Anemia	87	42	0	0	59.2
Nausea/vomiting	132	0	0	0	60.6
Phlebitis	29	3	11	0	19.7

Data shown are the numbers of cases

4-year DFS was 2.1% (HR=0.327, 95% CI: 0.214-0.500, P<0.0001).

Stratification analysis

Stratification analysis of all patients revealed that the survival lengths of patients were significantly associated with their age, the type of NSCLC, and its pathological stage, but not with gender and smoking status in this population. Indeed, patients at <55 years of age, with squamous carcinoma at stage I, had a significantly longer period of survival than those older, with adenosquamous NSCLC at stage II or IIIA (Table 3). Further analysis of patients with chemotherapy indicated that the survival lengths of patients with chemotherapy were associated with their age and the pathological stages. Patients with chemotherapy at <55 years of age survived significantly longer than those at ≥55 years of age (HR0.612, 95% CI: 0.543-0.706, p<0.0001) and patients with NSCLC at TNM I also surviced longer than those with tumors at TNM II (HR: 0.226, 95% CI 0.177-0.304, p<0.0001) or TNM IIIA (HR: 0.318, 95% CI: 0.261-0.416, p=0.002). Finally, multivariable Cox proportional hazards analysis revealed that an older age, histological type of NSCLC (adenocarcinoma or other types of NSCLC), the degrees of pathological stages, and the lack of postoperative chemotherapy were associated with a significantly shorter OS period (Table 4). However, the histological type of NSCLC appeared not to be significantly associated with the lengths of DFS in this population. Therefore, the patient's age, histological type, stage, and NP chemotherapy were independent prognostic factors for the lengths of OS in patients with NSCLC following resection of tumor.

Toxicity of Chemotherapy

During treatment with NP regimen, 49.5% of patients had grade II of toxicity and 13.8 percent had grade III toxic effects (Table 5). There was no patient with grade IV of toxicity. Of note, three patients failed to tolerate to grade II-III of toxicity and early terminated chemotherapy. There was no evidence of any cumulative hematological toxicity. Nausea/vomiting were the most frequent (60.6 percent) adverse effect, but displayed at grade I and did not affect the continual chemotherapy. There were no severe allergic reaction and no toxicity-related death. Hence, the NP regimen is tolerable in most patients.

Discussion

In this study, we prospectively assessed the effect of post-operative chemotherapy with the NP regimen on the OS and DFS in Chinese patients with NSCLC following radical surgery of the tumor. We found that patients with chemotherapy had a median OS of 51 months and DFS of 46 months, which were significantly longer than those in the observation group. As a result, post-operative chemotherapy with the NP regimen had an absolute benefit of 3.8% at 2 years and 13.0% at 5 years. Our findings are in agreement with the previous large-scale studies, such as IALT, JBR10, ANITA, LACE, and MRC meta-analysis (Vale et al., 2012). The positive advantage reported in our study also related to higher chemotherapy compliance and more stringent inclusion criteria. The majority of patients received at least 4 cycles of the NP regimen and had a median number of 4.8 cycles (range 1 to 8.4), which was greater than in the previous trials (Arriagada et al., 2004; Butts et al., 2010). In addition, the positive outcome may stem from a restrict criteria for enrolling patients. Indeed, this study excluded many patients with coronary heart disease, diabetes, metabolic syndrome, and other major systemic diseases. Therefore, our data support the notion that post-operative chemotherapy with the NP regimen following radical surgery can prolong the survival of some Chinese patients with NSCLC.

Previous studies have shown that many factors can affect the efficacy and outcome of post-operative chemotherapy with the NP regimen (Früh et al., 2008). We stratified the patients and found that patients with NSCLC at <55 years of age, with squamous carcinoma at stage I, survived significantly longer than those at older age, with adenocarcinoma or stage II or IIIA. However, the lengths of OS and DFS were not associated with the gender and status of smoking in those patients. Multivariate analysis revealed that the patient's age, histological type, stage and NP chemotherapy were independent prognostic factors for the lengths of OS in patients with NSCLC following resection of tumor. Our data were similar to a previous

report (Bennouna et al., 2011) and suggested that patients with younger age with squamous carcinoma or lower stage of adenocarcinoma should be encouraged for post-operative chemotherapy with the NP regimen.

During the follow-up period, we observed that 38.8% of the patients had NSCLC metastasis in the brain. These data were similar to that in previous reports (Scagliotti et al., 2003). Given that the lungs have sufficient blood supply, it is possible that the remaining cancer cells, such as cancer stem cells, and/or the reforming cancer cells migrate through the blood vessels into the brain. Hence, it is important to understand the molecular mechanisms by which NSCLC cells migrate into the brain. Possibly, new prophylactic treatment may be valuable for the prevention and inhibition of NSCLC metastasis to prolong the survival of patients with NSCLC following the surgery of the tumor.

Cytotoxic drugs usually have severe adverse effects in humans. In this study, we found that post-operative chemotherapy with the NP regimen only caused mild side effects in patients with NSCLC. Although the toxicity of the NP program was tolerable we should not ignore them. Recent studies have shown that combination of adjuvant chemotherapy with some medicines, such as Shenfu (Long et al., 2011), Astragalus (Guo et al., 2011), and some biological agents can reduce adjuvant chemotherapy-related adverse effects (Voortman et al., 2010; Andrews et al., 2011; Quoix et al., 2011; Klastersky et al., 2012). We are interested in further investigating whether post-operative chemotherapy with the NP regimen, together with these medicines can reduce the adverse effects and prolong the survival and life-quality of patients with NSCLC.

In conclusion, this analysis showed favorable effects of post-operative chemotherapy with the NP regimen on prolonging the survival of Chinese patients with NSCLC following surgical resection of the tumor. We found that the age of patients and the histological type and stage of tumor were independent prognostic factors of the efficacy of post-operative chemotherapy with the NP regimen in Chinese patients with NSCLC following surgical resection the tumor. Patients with the NP regimen only had mild and tolerable adverse effects. We recognized that our study had limitations of small sample size, nature of a non-double blinded manner, and lack of early intervention of recurrent and metastasized tumors. Although our findings support that post-operative chemotherapy with the NP regimen is beneficial for patients with NSCLC following surgical resection of the tumor, further studies of combination of this regimen with other medical strategies to prevent the recurrence and metastasis of NSCLC are warranted.

Acknowledgements

The author(s) declare that they have no competing interests. This research is supported by the Shanghai Education Committee Foundation grant (No. 08YZ47) and Shanghai Science and Technology Committee Foundation grant (No. 10JC1409200).

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