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Original Article

Clinical observation on combined treatment of isosorbide mononitrate with vinorelbine and cisplatin in advanced non-small cell lung cancer

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Abstract: Objective: To investigate the efficacy and safety of isosorbide mononitrate plus vinorelbine and cisplatin for treating patients with advanced stage non-small-cell lung cancer (NSCLC). Methods: 110 patients with stage IIIB-IV NSCLC were randomly assigned to group A (57 cases) and group B (53 cases). Patients in group A were treated with vinorelbine (25 mg/m^2) on days 1 and 8, and cisplatin (25 mg/m^2) on day 2-4, with transdermally applying isosorbide mononitrate sustained release tables (40 mg, daily for 8 days). Patients in group B were treated with vinorelbine and cisplatin. Response to treatment was assessed by RECIST1.1 and adverse effect was assessed by NCI-CTC (3.0). Results: The response rate in group A (58.2%, 32/55 patients) was significantly higher than that in group B (30.8%, 16/52 patients; χ^2=8.120, *P*=0.004). Median TTP and median OS in group A were longer than those in group B (8.2 *v* 5.8 months, χ^2=10.684, *P*=0.001; 11.6 *v* 9.0 months, χ^2=11.231, *P*=0.001). Patients with squamous carcinoma showed better response to chemotherapy (RR=2.438, 95% *CI* 1.136-5.231, *P*=0.022). The difference of adverse effect was not significant between group A and B, except for headache. The rate of grade 1 to 2 headache in group A (34.5%; 19 of 55 patients) was significantly higher than that in group B (3.8%; 2 of 52 patients; *P<0*.001). Conclusion: Using of isosorbide mononitrate sustained release tables combined with vinorelbine and cisplatin may improve overall response, TTP and OS in patients with advanced stage NSCLC.

Keywords: Non-small cell lung cancer, vinorelbine, cisplatin, nitric oxide

Introduction

Lung cancer is one of the most common malignant tumors, which has greatly threatened human health. The non-small cell lung cancer (NSCLC) occupies about 80% of lung cancer. Most of the patients are with late stage when diagnosed, which results in the missing opportunities for operations and radiotherapy [1]. The third generation new drugs combine with radiotherapy of Platinum-based, which is the first-line chemotherapy for the late stage of NSCLC. The vinorelbine (NVB) is the third generation of vinblastine derivatives, which combines with cisplatin (DDP), also as the first-line therapy of NSCLC. A research showed that nitric oxide (NO) could reduce the drug resistance with using anti-cancer drugs and improve chemotherapeutic effect [2]. The isosorbide mononitrate sustained release tablets had been applied in treating cardiovascular disease safely and widely. It was as the stable donor of NO in this study (60 mg/d). We investigated on the radiotherapeutic effects of the combined treatment with NP (NVB + DDP) in NSCLC IIIb~IV.

Materials and methods

Entrance and exclusion criteria

The inclusion criteria were followed: ① the presence of a measurable disease was required; ② patients with a cytological or histological diagnosis as NSCLC, stage-IIIB or stage-IV; ③ a performance status (PS) of zero, one, or two scale according to the Eastern Cooperative Oncology Group (ECOG); ④ blood routine examination, liver and kidney function and cardiogram were all normal; ⑤ patients had not treatments with chemotherapy or radiotherapy before; ⑥ prediction of survival time was more than three months.

Table 1. Clinical features of 110 cases NSCLC

Clinical features	Experimental group	Control group	χ^2 value	*P* value
Gender				
Male	36	29	0.869	0.368
Female	21	24		
Age				
≤60	37	33	0.592	0.442
>60	20	20		
Clinical stage				
IIIB	20	16	0.814	0.367
IV	37	37		
Pathological types				
Squamous cell carcinoma	29	24	0.392	0.822
Adenocarcinoma	23	22		
Large cell carcinoma	5	7		
Histological grade				
High or moderate differentiation	31	25	0.014	0.906
Low differentiation	26	28		
ECOG behavior state score				
≤1	43	39	0.149	0.700
=2	14	14		

ECOG: Eastern Cooperative Oncology Group; NSCLC: Non-small cell lung cancer.

The exclusion criteria were followed: ① patients were with acute myocardial infarction and unstable angina within three months; ② patients were with serious organs dysfunction.

From July 2007 to February 2012, a total of 110 patients with advanced NSCLC were recruited for this study. The patients were assigned randomly to experimental group (A group, NP therapy + isosorbide mononitrate sustained release tablets, n=57), IX (n=37) and control group (B group, NP therapy, n=53). The protocol was approved by the Ethical Review Committees of Yantai Hill Hospital. Written informed consent or assent for participation was obtained from each patient.

Clinical features

Male (67 cases) and female (43 cases), age from 31 to 77 (average age of 58), were in this study, and with ratio of 1.4:1. The clinical features of experimental group (A group, 57 cases) and control group (B group, 53) was showed in **Table 1**.

Chemotherapy regimen

A group: NVB 25 mg/m^2, 1st and 8th day; DDP 25 mg/m^2, 2nd to 4th day; orally taking isosorbide mononitrate sustained release tablets (40 mg) once a day in the morning, 1st to 8th day, repeated every 3 weeks. B group: NVB 25 mg/m^2, 1st and 8th day; DDP 25 mg/m^2, 2nd to 4th day, repeated every 3 weeks. All patients received at least 2 cycles and most 4 cycles of treatment. The responses were evaluated after 2 cycles. If there were effective therapy, the patients would receive original therapy; if not, the therapy would be changed into others. Patients were under the supporting therapy when ECOG score was >2.

Efficacy evaluation

All patients were received the CT and MRI scan after 2 cycles of the chemotherapy, and those who were with target focus were evaluated by response evaluation criteria in solid tumors (RECIST) 1.1, including complete response (CR), partial response (PR), stable disease (SD) and progression disease (PD). Observation on the adverse reaction was accorded to NCI-CTC 3.0.

Observation indexes

Response rate (RR): the percentage of cases with CR + PR to all cases. Time to progression (TTP): the time from beginning treatment to cancer development. Overall survival (OS): the time from beginning treatment to death.

Statistical analysis

Statistical analysis was performed by using SPSS 16.0 software. The χ^2 analysis was used to compare the effective rate between the two groups. Kaplan-Meier analysis was used to calculate survival rate. Significant analysis of TTP and OS group was analyzed by Log-Rank method. All *P* values were based on a two-sided test of statistical significance. Differences at the level of P≤0.05 were considered statistically significant.

Results

107 cases were received at least 2 cycles of the chemotherapy. All the patients were con-

Table 2. Multiple regression analysis of chemotherapeutic efficacy of 107 cases NSCLC

Clinical characteristics	CR+PR n=48		SD+PD n=59		Regression analysis		
	Cases	Percentage (%)	Cases	Percentage (%)	*RR*	95% *CI*	*P* value
Gender							
Male	27	56	36	61	1		
Female	21	44	23	39	0.856	0.355-2.065	0.729
Age (year)							
≤60	30	62	38	64	1		
>60	18	38	21	36	0.905	0.354-2.313	0.835
Histological type							
Squamous cell carcinoma	28	58	25	42	1		
Adenocarcinoma	20	42	34	58	2.438	1.136-5.231	0.022
Large cell carcinoma							
Histological grade	18	38	16	27	1		
High or moderate differentiation	30	62	43	73	1.503	0.540-4.178	0.435
Low differentiation							
Squamous cell carcinoma	23	48	31	53	1		
Adenocarcinoma	25	52	28	47	1.085	0.441-2.669	0.860
ECOG behavior state score							
≤1	39	81	38	64	1		
=2	9	19	20	36	2.028	0.747-5.503	0.165
Isosorbide mononitrate sustained release tablets							
Yes	32	67	23	39	1		
No	16	33	36	61	5.769	2.146-15.515	0.001

NSCLC: Non-small cell lung cancer; ECOG: Eastern Cooperative Oncology Group.

ducted efficacy. The adverse reaction evaluations were performed in 110 cases. 3 cases (2 in group A, 1 in group B) withdrew for too early to be analyzed and being unable to tolerate adverse reactions. Another 107 cases were received 3 cycles of the chemotherapy meanly.

Short term response rate

The efficacy evaluation on 7 cases in the 107 patients was CR (6.5%), 5 cases in A group, 2 cases in B group; 41 cases were PR (38.3%), 27 cases in A group, 14 cases in B group; 34 cases were SD (31.8%), 14 cases in A group, 20 cases in B group; 25 cases were PD (23.4%), 9 cases in A group, 16 cases in B group. Response rate (RR) was 44.8% totally, 58.2% (32/55) in group A and 30.8% (16/52) in group B, separately. There was statistical significance between two groups (χ^2=8.120, *P*=0.004, *OR*=5.128, 95% *CI* 1.740-14.436).

By regression analysis, the efficacy of patients who were treated with isosorbide mononitrate sustained release tablets (RR=5.769, 95% CI 2.146~15.515, P=0.001) was better than those with squamous cell carcinoma (RR= 2.438, 95% CI 1.136~5.231, P=0.022) (**Table 2**).

Survival time

Until August 31th, 2011, the mean follow-up time was 17.8 months. 2 cases of the 107 failed to be followed with the lost rate was 1.9%. 16 patients did not appear during disease developing, and 27 cases were survival at the end of follow-up. Median time to progression (MTTP) of the 107 patients was 7.0 months (95% *CI* 6.133~7.867) totally, 8.2 months (95% *CI* 7.424~8.976) in group A and 5.8 months (95% *CI* 5.125~6.475) in group B. There was statistical significance between the two groups (χ^2=10.684, *P*=0.001, **Figure 1**). Median survival time (MOS) of the 107 patients was 9.4 months (95% *CI* 8.697~10.103) totally, 11.6 months (95% *CI* 11.041~12.159) in group A and 9.0 months (95% *CI* 8.241~9.759) in group B. There was statistical significance between the two groups (χ^2=11.231, *P*=0.001, **Figure 2**).

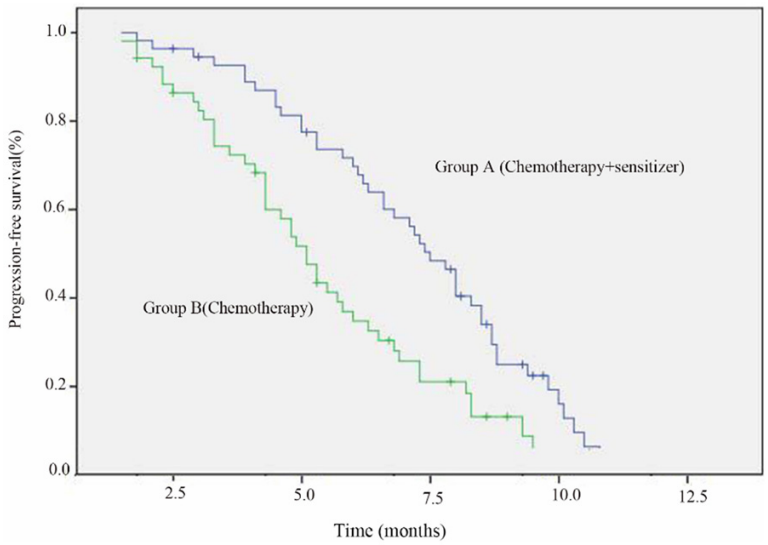

Figure 1. Progression-free survival curve of the 107 cases NSCLC. Progression-free survival (%).

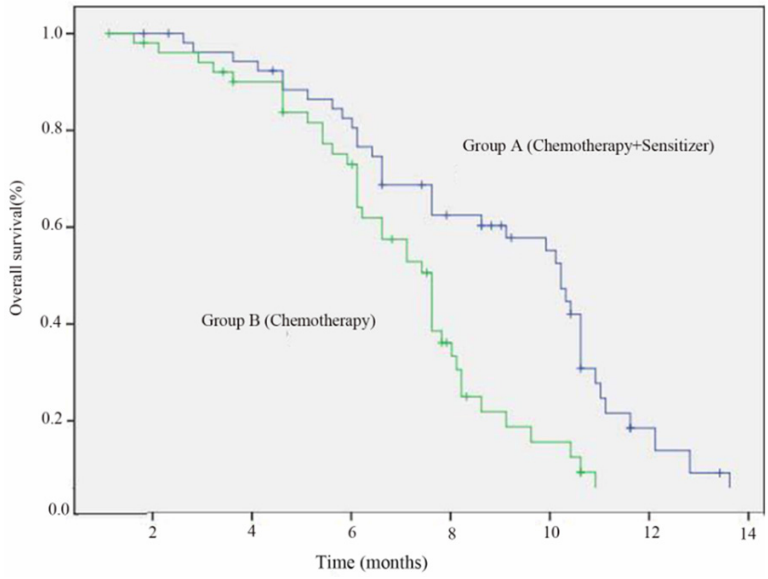

Figure 2. Survival curve of 107 cases NSCLC.

Adverse reaction

There was no statistical significance between A and B groups on hematological or gastrointestinal toxicity. But the incidence rate of I and II headache in A group was significantly higher than in B group (P<0.001, see **Table 3**).

Discussion

Lung cancer is one of the most common malignant tumors, which has greatly threatened human health. The population diagnosed as lung caner is 130 million nowadays. Death for lung cancer is about 11 million all over the world every year, which is with the highest mortality in malignant tumors [3]. At present, the therapy for advanced NSCLC is the comprehensive treatments with predominantly whole body chemotherapy. The third generation new drugs combine with radiotherapy of Platinum-based, which is the first-line chemotherapy for the late stage of NSCLC. However, the efficacy rate is only 30% to 40%, and the median survival time was 8 to 10 months, indicating the individual differences.

Compared with normal tissues, solid tumor is under hypoxia because the blood flow is relative deficiency. The latter has relationship with anti-tumor drug resistance. The hypoxia of solid tumor inner results in the accumulation of the hypoxia inducible factor-1α (HIF-1α), which could stimulate the expression of many target genes related to growth, metabolism and chemotherapy drug resistance. The tumor promoted the stable of HIF-1α under hypoxia, which indicated the inhibition of HIF-1α was with relationship to anti-tumor drug resistance [4]. NO can inhibit the accumulation and promotion of HIF-1α in the malignant tumor under hypoxia, as well as improve the sensitivity of tumor cells to chemotherapy [5]. On the other hand, promotion of the NO signal pathway could improve the effects of immune system for the tumors [6]. Additionally, NO was expected to promote the apoptosis of tumor cells and inhibit tumor growth and development [7]. A study showed that NO had a role in inhibiting the angiogenesis of tumor [8]. In 2006, Japanese researchers

Table 3. Adverse reactions of 107 cases NSCLC treated with chemotherapy

Adverse reaction	Experimental group					Control group					Mann-Whitney analysis
	0	I	II	III	IV	0	I	II	III	IV	*P* value
Leucopenia	21	15	13	5	1	19	13	11	7	2	0.616
Neutropenia	23	12	14	6	0	20	15	13	4	0	0.942
Thrombocytopenia	39	7	8	1	0	37	8	5	2	0	0.941
Erythropenia	35	10	7	3	0	32	8	11	1	0	0.789
Nausea	19	18	13	5	0	20	19	11	2	0	0.431
Vomiting	22	17	12	3	1	19	18	10	5	0	0.790
Hypotension	54	1	0	0	0	50	2	0	0	0	0.647
Headache	36	12	7	0	0	50	2	0	0	0	<0.001

NSCLC: Non-small cell lung cancer.

conducted a phase II clinical trial, and found that nitroglycerin was as the exogenous donor of NO. The treatment efficacy of two therapies was compared between nitroglycerin combined with platinum-based regimens chemotherapy and single chemotherapy. 120 patients with NSCLC of progressive stage enrolled. The result showed that the efficacy (72%:42%, *P*<0.001) and MTTC (327 d:185 d, *P*=0.006) of nitroglycerin group were all improved significantly [8].

The donors of NO were compounded with different structure that could release NO. Their chemical activities depended on oxidation state of relating nitrogen atom, which controlled the rate and grade of physiological transformation of NO. The ideal donor of NO could release NO spontaneously and steadily without cellular metabolism or development of drug resistance. The donors of NO were organic nitrate, mainly including nitroglycerin, isosorbide dinitrate and isosorbide mononitrate. They could release NO under hydrolysis of esterase in body. Organic nitrate was the common drug that could treat and prevent angina pectoris. Many studies had revealed that they could improve the sensitivity of the tumor to radiotherapy and chemotherapy, and inhibit the proliferation and prevent tumor migration to some degree.

The isosorbide mononitrate sustained release tablet was selected as the donor of NO in this study, and the clinical efficacy was observed. The patients with advanced NSCLC were treated with combination therapy. The isosorbide mononitrate sustained release tablet was absorbed completely by oral and without hepatic first pass effect. 30% of drugs released rapidly and 70% slowly for 17 h, which avoided the adverse reactions induced by peak serum levels of drugs. The combined therapy overcame the disadvantages and attained the stability of plasma concentration for long time. The results suggested that the RR of combination therapy with isosorbide mononitrate sustained release tablet was 58.2%, MTTP was 8.2 months, and MOS was 11.6 months, which were all significantly higher than single chemotherapy (30.8%, 7.0 and 9.0 months, *P* value 0.004, 0.001 and 0.001). The efficacy was better on squamous cell carcinoma (*RR*=2.438, 95% *CI* 1.136~5.231, *P*=0.022). The isosorbide mononitrate sustained release tablet group had no significant difference between two groups in hematological and gastrointestinal toxicity except headache, which was higher than chemotherapy (*P*<0.001). The results were the similar to the study of Japanese researchers.

The isosorbide mononitrate sustained release tablet was as donor of NO in this study, and the plasma concentration was more stable. It could improve the sensitivity of old patients with IIIb~IV NSCLC during chemotherapy, with safety, applying conveniently and higher efficacy on squamous cell carcinoma. However, due to the limited sample size, large double-blind randomized controlled trials were needed to confirm the result.

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Disclosure of conflict of interest

None.

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References

[1] Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, Dunant A, Torri V, Rosell R, Seymour L, Spiro SG, Rolland E, Fossati R, Aubert D, Ding K, Waller D and Le Chevalier T. Lung adjuvant cisplatin eva-luation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008; 26: 3552-3559.

[2] Hagen T, Taylor CT, Lam F and Moncada S. Redistribution of intracellular oxygen in hypoxia by nitric oxide: effect on HIF1alpha. Science 2003; 302: 1975-1978.

[3] Parkin DM, Bray F, Ferlay J and Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108.

[4] Raval RR, Lau KW, Tran MG, Sowter HM, Mandriota SJ, Li JL, Pugh CW, Maxwell PH, Harris AL and Ratcliffe PJ. Contrasting properties of hypoxia-inducible factor 1 (HIF-1) and HIF-2 in von Hippel-Lindau-associated renal cell carcinoma. Mol Cell Biol 2005; 25: 5675-5686.

[5] Yasuda H, Nakayama K, Watanabe M, Suzuki S, Fuji H, Okinaga S, Kanda A, Zayasu K, Sasaki T, Asada M, Suzuki T, Yoshida M, Yamanda S, Inoue D, Kaneta T, Kondo T, Takai Y, Sasaki H, Yanagihara K and Yamaya M. Nitroglycerin treatment may enhance chemosensitivity to docetaxel and carboplatin in patients with lung adenocarcinoma. Clin Cancer Res 2006; 12: 6748-6757.

[6] Siemens DR, Hu N, Sheikhi AK, Chung E, Frederiksen LJ and Pross H. Graham CH. Hypoxia increases tumor cell shedding of MHC class I chain-related molecule: role of nitric oxide. Cancer Res 2008; 68: 4746-4753.

[7] Frederiksen LJ, Sullivan R, Maxwell LR, Macdonald-Goodfellow SK, Adams MA, Bennett BM, Siemens DR and Graham CH. Chemosenstization of cancer in vitro and in vivo by nitric oxide signaling: Chemosenstization of cancer in vitro and in vivo by nitric oxide signaling. Clin Cancer Res 2007; 13: 2199-2206.

[8] Yasuda H, Yamaya M, Nakayama K, Sasaki T, Ebihara S, Kanda A, Asada M, Inoue D, Suzuki T, Okazaki T, Takahashi H, Yoshida M, Kaneta T, Ishizawa K,Yamanda S, Tomita N, Yamasaki M, Kikuchi A, Kubo H and Sasaki H. Randomized phase II trial comparing nitroglycerin plus vinorelbine and cisplatin with vinorelbine and cisplatin alone in previously untreated stage IIIB/IV non-small-cell lung cancer. J Clin Oncol 2006; 24: 688-694.