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Original Article

Efficacy and safety of nitroglycerin combined with chemotherapy in the elderly patients with advanced non-small cell lung cancer complicated with coronary heart disease

Zhen He[1*], Yufeng Wu[1*], Qian Sun[2], Mingzhi Zhang[3], Guangyin Wu[4], Xiaobing Chen[1], Chunyan Chen[5], Ruijie Li[2], Hong Tang[1], Lili Wang[1], Hongqiang Guo[1], Qiming Wang[1]

[1]Department of Oncology, Henan Cancer Hospital, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou 450008, China; [2]Department of Oncology, Henan Provincial Chest Hospital, Zhengzhou 450008, China; [3]Department of Oncology, The First Affliated Hospital of Zhengzhou University, Zhengzhou 450052, China; [4]Department of Radiotherapy, Henan Provincial People's Hospital, Zhengzhou 450003, China; [5]Department of Geriatrics, People's Hospital of Zhengzhou, Attached to Southern Medical University, Zhengzhou 450008, China. [*]Equal contributors.

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Abstract: Objective: To investigate the efficacy and safety of the treatment of nitroglycerin combined with docetaxel/carboplatin chemotherapy for elderly patients with advanced non-small cell lung cancer (NSCLC) complicated with coronary heart disease (CHD). Methods: 70 elderly patients (≥ 65 years) with NSCLC complicated with CHD were randomized into two groups (n=38 for the treatment group; n=32 for the control group). Patients in treatment group were received nitroglycerin combined with docetaxel/carboplatin chemotherapy, and the patients in control group were given docetaxel/carboplatin chemotherapy. The patients were immediately discontinued from the treatment once any unbearable symptom was occured. Results: Patient baseline characteristics had no significant difference between the two groups. Compared with control group, the tumor response rate and disease control rate in treatment group were significantly increased (25.00% *vs* 52.63% and 40.60% *vs* 65.80%, respectively, $P<0.05$). The median overall survival (OS) in the treatment group was 10.8 months, which were significantly longer than that 8.3 months of the control group ($P<0.05$). For the safety, the incidence rate of angina pectoris and myocardial infarction in the treatment group were significantly lower than that in the control group ($P<0.05$). Conclusion: Addition of nitroglycerin in docetaxel/carboplatin chemotherapy improves efficacy in the elderly patients with NSCLC complicated with CHD, and prolongs the OS and reduces the risk of CHD. The regimens can be considered as a safe and effective option for NSCLC patients with CHD in clinical practice.

Keywords: Nitroglycerin and chemotherapy in NSCLC patients with CHD

Introduction

With the arrival of the aging society in China, there is an increasing incidence of lung cancer in elderly people, in which non-small cell lung carcinoma (NSCLC) accounts for nearly 80%. 70%-80% of the patients with NSCLC have lost the best operative chance when they are finally diagnosed, or they can not tolerate the surgery because of the complications. Thus, a systemic chemotherapy targeting both cancer and comorbidity is needed [1]. Since many elder patients with NSCLC are usually complicated with coronary heart disease (CHD) or angina pectoris, whether they can stand for the chemotherapy and how to carry out the chemotherapy have been became the serious concerns and issues for clinicians. Cardiovascular disease and hypertension are the most frequent comorbidities, there is a high risk of myocardial infarction or angina attack during or after chemotherapy [2]. The aim of is to investigate the effect of the chemotherapy regimen carried out with nitroglycerin intravenous injection on efficacy and safety profiles, such as reduction angina pectoris or CHD, in aged patients.

Table 1. Baseline of the treatment group and the control group

Clinical data	Treatment group (n=38)	Control group (n=32)	χ^2	*P*
Gender				
Male	28 (73.7%)	22 (68.8%)	0.207	0.6489
Female	10 (26.3%)	10 (31.2%)		
Pathological types				
Squamous	20 (52.6%)	18 (56.3%)	2.852	0.7621
Adenomatous	14 (36.8%)	11 (34.4%)	0.050	0.8301
Adeno-squamous	4 (10.6%)	3 (9.3%)	0.030	0.8729
Comorbidity				
Hypertension	10 (26.3%)	7 (21.8%)	0.1863	0.6660
Diabetes mellitus	5 (13.2%)	4 (12.5%)	0.0140	0.9347
Cerebral infarction	3 (7.9%)	2 (6.3%)	0.0700	0.7901
Chronic bronchitis	8 (21.1%)	5 (15.6%)	0.3384	0.5608
Stages				
III	26 (68.4%)	24 (75%)	0.3684	0.5439
IV	12 (31.6%)	8 (25%)		

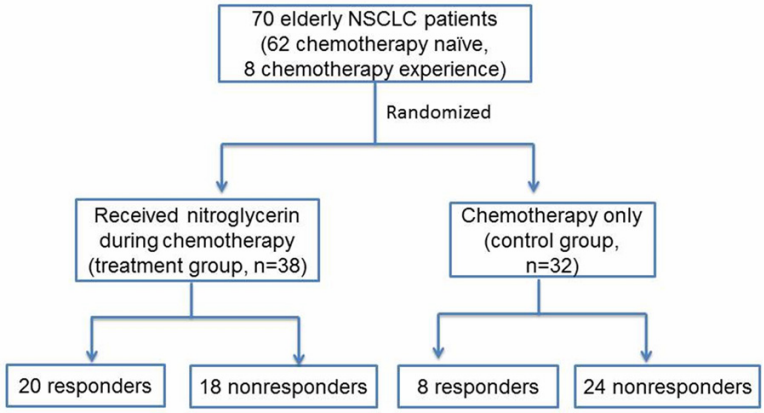

Figure 1. A total of 70 elderly patients with non-small cell lung cancer were randomized to chemotherapy with or without nitroglycerin and were observed to evaluate the effects of nitroglycerin on response to chemotherapy and safety profile.

Materials and methods

Subjects

Elder patients (≥ 65 years) with NSCLC complicated with CHD in our hospital from July 2012 to June 2015 were enrolled in this study. The patients were diagnosed as NSCLC stage III to IV by pulmonary spiral computed tomography (SCT), pathological examination and tumor node metastasis (TNM) staging. They were also diagnosed with chronic heart disease (CHD) by qualified physicians. Specific inclusion criteria included: 1) At least one measurable lesion (tumor size ≥ 10 mm, scanned by SCT or MRT); 2) Eastern Cooperative Oncology Group (ECOG) score 0-2; 3) expected survival longer than 3 months; 4) normality in blood routine, liver function and renal function; 5) without trauma; 6) diagnosed with ischemic heart disease by clinical nomenclature of the report of the Joint International Society and Federation of Cardiology/World Health Organization [3]; 7) without acute myocardial infarction in the latest 3 weeks; 8) a normal electrocorticography (ECG); 9) not contraindicative to nitroglycerin. The study complied with the Declaration of Helsinki. It was approved by the ethical review board; all patients signed an informed consent document before participation. Patients were 65 to 80 years old with a median age of 70.4 years. Among the 70 patients, 62 cases were newly diagnosed, 8 cases were previously diagnosed and had been undergone chemotherapy, but discontinued from chemotherapy due to the occurrence of angina pectoris. Patients were randomized into treatment group (n=38) and control group (n=32). Characteristics of the two groups were comparable and showed no significant difference (**Table 1**). Patient flow chart is described in **Figure 1**.

Experiment scheme

Patients in both groups were received chemotherapy with docetaxel and carboplatin. One day before chemotherapy, patients were received 16 mg/day dexamethasone by oral, so as to prevent allergic reaction and fluid retention. On the first day of the chemotherapy, 75 mg/m^2 docetaxel (Jiangsu Hengrui medicine co., LTD., China; National Medical License Number: H20020543, Specifications: 20 mg/

ramus) was dissolved in 150 mL 0.9% sodium chloride injection and was administrated by intravenous drip infusion. On the second day, carboplatin (Shandong Qilu Pharmaceutical Factory, China; National Medical License Number: H20020180, Specifications: 100 mg/ramus) was dissolved in 250 mL 5% glucose injection and was administrated by intravenous drip infusion. For the patients in the treatment group, 24 h continuous intravenous nitroglycerin via micro-pump was carried out from the start of the chemotherapy. Nitroglycerin (Beijing Yimin Pharmaceutical Co., Ltd., China) was diluted into 5% glucose or 0.9% sodium chloride in a ratio of 1:1. The dilution was injected intravenously with a starting speed of 20 μg/min. The injection speed was gradually increased and maintained at 50 μg/min. During the maintaining time, the injection speed was adjusted according to the blood pressure and the angina pectoris conditions [4]. Prior the chemotherapy, for patients with the diabetes in both groups, the blood glucose was managed within an appropriate range with oral hypoglycemic agents or subcutaneous insulin.

Evaluation of therapeutic effects

The response evaluation criteria in solid tumors (RECIST criteria) was used to evaluate tumor response as complete remission (CR), partial remission (PR), progressive disease (PD) and stable disease (SD) [5]. Overall response rate was calculated as the proportion of enrolled patients and tumor response-qualified patients who achieved a tumor response of PR or CR. Disease control rate was calculated as the proportion of enrolled patients and tumor response-qualified patients who achieved a tumor response of PR, CR or SD. Time to tumor progression (TTP) was defined as the time from the start of chemotherapy to the time of disease progression, and survival time (OS) refers to the time from the start of chemotherapy to death or to the last follow-up time. Last patient visited in this analysis was on 20th November, 2015. No patient was lost to follow-up in the study.

Observation of therapeutic effects and adverse events

Below tests were performed before and after each chemotherapy cycle: blood, urine and stool routine examination, liver and renal function, cardiac enzymes, troponin and ECG. ECG was continuously monitored during chemotherapy. After chemotherapy, blood route examination was carried out every 3 to 5 days. Before the first chemotherapy and at two weeks after the end of each chemotherapy cycle, SCT chest and abdominal imaging (ultrasound or SCT) were carried out to evaluate tumor response. In addition, color doppler ultrasound was used for the evaluation of cardiac function. Mitral E/A values, left ventricular fractional shortening (FS) and left ventricular ejection fraction (LVEF) were measured by conventional two-dimensional ultrasound. Early diastolic velocity (Ea), the late diastolic velocity (Aa) of mitral annulus and the ratio of Ea/Aa were recorded when the sampling section was placed at the septal mitral annulus at the standard four-chamber view, in a two-dimensional color TDI speed mode.

Statistical analysis

Numeration data were analyzed with Chi-square test. Time to progression and survival were analyzed using Kaplan-Meier method (survival difference was analysis using log-rank test univariate analysis). Measurement data with normal distribution were showed as mean ± standard deviation (SD). Results between two groups were compared using *t* test and $P< 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS software program v17.0 (Chicago, IL, USA).

Results

Chemotherapy exposure

For chemotherapy exposure, in the treatment group, 89.5% of the patients (34 out of 38 patients) received 4-6 cycles of chemotherapy, 5.3% (2 patients) received 3 cycles chemotherapy and 5.3% (2 patients) received 2 cycles chemotherapy. In the control group, 68.6% of the patients (22 out of 32 patients) received 4-6 cycles chemotherapy, 6.2% (2 patients) received 3 cycles chemotherapy, 9.4% (3 patients) received 2 cycles chemotherapy, and 15.6% (5 patients) received 1 cycle chemotherapy.

Tumor response

After chemotherapy, in the treatment group, there were 2 cases of CR, 18 cases of PR, 5

Table 2. Response rate between two groups

	Treatment group (n=38)	Control group (n=32)	χ^2	*P*
CR	2 (5.3%)	1 (3.1%)	0.190	0.6599
Response rate (CR+PR)	20 (52.6%)	8 (25.0%)	8.090	0.0045
Disease control rate (CR+PR+SD)	25 (65.8%)	13 (40.6%)	4.432	0.0353

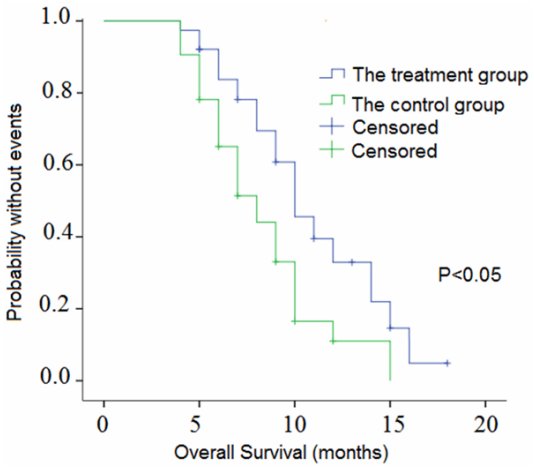

Figure 2. Survival curves of the treatment group and the control group.

cases of SD and 13 cases of PD. In the control group, there were one case of CR, 7 cases of PR, 5 cases of SD and 19 cases of PD. The overall response rates in the treatment group was 52.63% (20/38), which was significantly higher than that in the control group (25%, 8/32, *P*<0.05). Disease control rate in the treatment group was 65.8% (25/38), significantly higher than that in the control group (40.6%, *P*<0.05) (**Table 2**).

Survival analysis

Until to the last follow-up, the TTP in the treatment group (7.3 months) was remarkably longer than that in the control group (5.5 months, χ^2=9.035, *P*<0.05) and the median overall survival in the treatment group was 10.8 months, which was also longer than that in the control group (8.3 months, χ^2=7.146, *P*<0.05) (**Figure 2**). However, the long-term efficacy may need a further observation.

Safety evaluation

To evaluate safety of the chemotherapy with nitroglycerin, monitoring of adverse reactions focused on several aspects. For 34 and 22 patients from the treatment group and the control group, respectively, who received 4-6 cycles of chemotherapy, hematological toxicities occurrence rates were similar (35.3% and 27.3%). For the 38 and 32 patients from the treatment group and the control group, respectively, the occurrence rates of hypotension were similar between the two groups. However, there were significantly lower rates of angina pectoris, myocardial infarction, ECG change and myocardial enzymes change reported in the treatment group compared to the control group (*P*<0.01, <0.05, <0.01 and <0.01, respectively). 5.26% and 0% of the patients in the treatment group were discontinued from the treatment due to angina pectoris and myocardial infarction, respectively. However, there were of 31% and 15.6% of the patients in the control group were discontinued from the treatment due to angina pectoris and myocardial infarction, respectively. 21.1% of the patients from the treatment group were underwent clinically significant ECG changes, which was significantly lower than that in the control group (56.3%, *P*<0.05). The percentage of patients with abnormal serum creatine kinase in the treatment group (26.3%) was also lower than that of the control group (56.3%, *P*<0.05) (**Table 3**).

In addition, for patients who completed 4-6 cycles of chemotherapy, evaluation of the systolic and diastolic function was carried out before and after the chemotherapy. There was no statistical difference before and after the chemotherapy in the treatment group, while in the control group, a significant decrease in the heart function was observed after the chemotherapy (**Table 4**).

Discussion

Most patients suffer from metastasis when they were diagnosed as lung cancer, among which up to 75% patients were in advanced cases. The median age of newly diagnosed non-small cell lung cancer cases was 60 to 62 years, however, patients >65 years account for more than 50%, and patients >70 years account for 30% to 40% [6]. Elderly patients often com-

Table 3. The adverse reactions between the two groups

	Treatment group (n=38)	Control group (n=32)	χ^2	*P*
Hematological toxicities (III-IV)	12/34 (35.3%)	6/22 (27.3%)	0.39	0.5302
Angina pectoris	2 (5.3%)	10 (31.3%)	8.25	0.0041
Myocardial infarction	0 (0%)	5 (15.6%)	6.39	0.0114
ECG change	8 (21.1%)	18 (56.3%)	9.21	0.0024
Myocardial enzymes change	10 (26.3%)	18 (56.3%)	6.48	0.0109
Hypotension	10 (26.3%)	5 (15.6%)	1.18	0.2775
Overall adverse reaction	32	54		

Table 4. The cardiac function before and after the chemotherapy

Cardiac function	Treatment group (n=34/38)			Control group (n=22/32)		
	Before	After	*P*-value	Before	After	*P*-value
E/A	1.54±0.47	1.53±0.32	0.873	1.60±0.53	1.46±0.44	0.0271
FS (%)	37.20±5.10	35.80±5.10	0.651	38.10±4.80	37.10±4.50[b]	0.0326
LVEF (%)	65.20±5.60	64.70±6.00	0.357	65.70±3.50	61.40±3.80	0.0106
Ea/Aa	1.31±0.35	1.29±0.49	0.538	1.30±0.57	1.21±0.31	0.0135

Data are shown as mean ± SD.

plicate with other diseases, such as cerebrovascular disease, diabetes, hypertension and other diseases [7].

With the increasing age, the incidence of concomitant disease in elderly people is significantly increased. CHD has a high prevalence and accounts for 1/3-1/2 of the deaths in the United States. For the elderly patients with tumor complicated with CHD, the risks and benefits of the treatment should been balanced, and the concomitant diseases need to be treated properly. Therefore, a cooperation of multidisciplinary is needed. To date, various treatment strategies have been explored, no mature model is identified yet.

In the study, we took a treatment of chemotherapy (docetaxel/carboplatin) combined with continuous infusion of nitroglycerin for elderly patients with NSCLC complicated with CHD. Docetaxel/carboplatin is the first line care of NSCLC, and nitroglycerin is widely used for CHD. The overall response rates of 52.63% and a disease control rate of 65.8% were achieved, which were both significantly higher than those in the control group (25% and 40.6%, respectively). Our results are consistent with the work of Yasuda and colleagues [8, 9], who took nitroglycerin transdermal patch as a chemotherapeutic sensitizer and found that the response rate in the treatment group (72%; 43 of 60 patients) was significantly higher than that for patients in the control group (42%; 25 of 60 patients). Median TTP in treatment group was longer than that in the control group (327 v 185 days).

The mechanism underlying benefits of chemotherapy nitroglycerin may be elucidated from the following aspects. Firstly, patients with lung cancer are generally in a hypercoagulable state, which can be aggravated with metabolic wastes from the damaged tissue caused by chemotherapy. Therefore there are theoretical higher risks of myocardial infarction and other thrombotic events for patients with NSCLC. As the most common coronary dilatation drug, the main pharmacological effects of nitroglycerin is to relax vascular smooth muscle and cause arteriovenous vasodilation and peripheral venous dilation, so as to reduce the returned blood volume, decrease the cardiac preload and reduce the cardiac after load [10]. Especially, nitroglycerin has a relaxing effect for the cases that the blood supply is insufficient or the vascular smooth muscle in infarct region. Arteriovenous dilatation can result in reduction of myocardial oxygen consumption, and thereby reduce the risk of angina and myocardial infarction [11]. Nitroglycerin has shown effects of coronary blood vessels dilution and it could reduce occurrence of angina and myocardial infarction during the chemotherapy [12]. In the present study, the use of nitroglycerin in the treatment group effectively reduced the adverse effects of chemotherapy on systolic and diastolic function, which might be the cause of lower discontinuation rate of the treatment group. 89.47% of patients in the treatment group were underwent 4-6 cycles of chemotherapy, which was higher than that in the control group (68.75%). A thorough chemother-

apy is essential for disease control rate in cancer patients. In this study, our results shown that nitroglycerin significantly reduced angina pectoris.

Secondly, the hypoperfusion and the endothelial permeability are blocked in tumor tissue, which lead to poor drug delivery, thus the concentration of anticancer drugs such as taxol and carboplatin in tumor tissue is low. Nitric oxide released by nitroglycerin can activate guanylate cyclase and regulate the smooth muscle contraction, thereby dilate blood vessel. Thus, the blood perfusion of the blood vessel in tumor is increased. With the increasing of vascular permeability in tumor, delivery of oxygen and the local concentration of chemotherapeutic drugs are also increased [13-15]. Activation of guanylate cyclase in NO signaling pathway can lead to activation of downstream protein kinase G, and thereby results in a series of phosphorylation and other biological effects, and ultimately an inhibitory effect on tumor cell division, proliferation and metastasis [16].

Thirdly, as a NO donor, nitroglycerin inhibits the expression of HIF-1α and improves the oxygen load of tumor tissue, thus reduces the expression of VEGF and inhibits the tumor angiogenesis. Meanwhile, the downregulation of HIF-1 lead to inhibition of the transcriptional expression of P-gp, reverses of multiple drugs resistance and increases the sensitivity to chemotherapy [16-18]. Furthermore, other effects of nitroglycerin are to enhance the antitumor activity of cisplatin, activate P53 and promote the apoptosis of tumor cells [19, 20]. Using gene chip technology, nitroglycerin is demonstrated as down-regulator of most genes associated with angiogenesis including the encoding genes of matrix metalloproteinase-9, integrin αV and cell surface proteins [21]. These kinds of genes play an important role in the tumor cell ablation, invasion and metastasis [22].

In conclusion, our study demonstrates that continuous injection of nitroglycerin along with chemotherapy in elderly patients with NSCLC complicated with CHD significantly reduce adverse events, improve tolerance to chemotherapy and enhance response rate to chemotherapy. Nevertheless, the results may need the further validation by larger sample size and longer observation.

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Disclosure of conflict interest

None.

Address correspondence to: Qiming Wang, Department of Internal Medicine, Henan Cancer Hospital, No. 127, Dongming Road, Zhengzhou 450008, China. E-mail: wangqiming325@126.com

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