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Original Article

Effect of prostaglandin E1 in patients with advanced lung cancer treated with chemotherapy

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Abstract: To examine potential VTE risk reducing effect of prostaglandin E1 (PGE1) as supplemental therapy in patients with advanced lung cancer treated by chemotherapy.68 patients were recruited in this study: 46 males with age range from 58-85 and the average age of 67.48 ± 6.06; 22 females with age range from 55-85 and the average age of 68.05 ± 7.72. All patients were randomly assigned into three groups. Patients in the therapy group (33 patients) only received chemotherapy. On the other hand, patients in experimental group (25 patients) received combination therapy with chemotherapy and intravenous injection of PGE1 (Alprostadil, produced by Beijing Tide Pharmaceutical company) for 14 days. While in the control group (10 patients), only the supportive therapy was given. All patients were followed up till the end of their lives, with the exact time of death recorded, among which 51 died in our hospital, the rest were informed by phone calls to confirm the exact time of death. The median survival time was 61 days in the experimental group, which was not statistically significant to those of control group (52.5 days, p=0.237) and therapy group (56 days, p=0.656). In the therapy group, 9 cases showed small amount of VTE during treatment, one patient died because of fatal pulmonary embolism. In experimental group, only 2 cases experienced non-fatal VTE. The main adverse reaction of PGE1 was nodular vasculitis in 3 cases which was well tolerated. Concomitant application of PGE1 with chemotherapy significantly reduced the risk of VTE in patients with advanced lung cancer while it did not extend the patients' survival time.

Keywords: Prostaglandin E1, advanced lung cancer, survival time

Introduction

Prostaglandins (PG) are unstable bioactive substances, to work by synthesis of arachidonic acid in reaction to external stimuli (such as soft tissue injuries) [1]. Depending on structure and function, prostaglandins are divided into several types with different or even conflicted functions. Aberrantly high level of PG was reported in breast and gynecological cancer, colon cancer, lung cancer and other types of malignancies [2]. In addition, prostaglandin E (PGE) levels were higher in patients with bone metastases than in those without metastasis [3]. And this aberrant high level of PGE was believed to facilitate bone metastases [4]. prostaglandin E1 (PGE1) and Prostaglandin B2 (PGB2) were not involved in cyclic adenosine monophosphate (cAMP) synthesis which can be interpreted as inhibition of cell proliferation, suggesting potential anti-tumor effects of PG [5].

Widely expressed in peripheral and coronary blood vessels, PGE1 leads to relaxation of smooth muscle, and inhibits platelet aggregation as well as atherosclerotic lipid plaque formation [6]. Also, PGE1 has significant anti-inflammatory and anti-oxidative stress effect [7]. Ishikawa found that PGE1 inhibits secretion of tumor necrosis factor (TNF) and interleukin-10 (IL-10) in mononuclear cells [8]. Fang discovered that PGE1 inhibits endothelial cell activated oxygen (reactive oxygen species, ROS), enhances endothelial nitric oxide synthase (eNOS) expression, and promotes NO release [9].

Vein thrombosis embolism syndrome (VTE) is a complication commonly seen in patients with lung cancer, especially in advanced lung cancer patients with prethrombotic state [10]. Furthermore, chemotherapy will aggravate hypercoagulable state and activation of blood coagu-

lation facilitates cancer cells attachment, invasion and transfer which may in turn influence biology of the tumor, resulting in a poorer outcome of chemotherapy [11]. Patients treated with long-term chemotherapy may experience small pulmonary artery spasms, increase in pulmonary vascular resistance, pulmonary hypertension and increase of right heart load, which may lead to right heart failure or heart failure [6, 12, 13]. Nowadays studies show that humoral factors such as prostaglandins play an important role in hypoxic pulmonary vasoconstriction [14]. There are two types of prostaglandins derivatives which are thromboxanes and prostacyclins. Among them, thromboxane A2 (TXA2) causes vasoconstriction, prostaglandin F2a (PGF2A) cable and vasodilation of prostacyclin (PGI2), alprostadil (PGE1) in two categories. Hypoxic pulmonary vasoconstriction largely depends on local vasoconstrictive substances and vasodilative substances [15]. In addition, hypoxia, hypercapnia, stimulation of aortic body and carotid body chemoreceptors, and sympathetic activity lead to increased catecholamine secretion, pulmonary vasoconstriction, and pulmonary arterial hypertension [16]. Chronic hypoxia can also generate secondary polycythemia, increase blood viscosity and hematocrit, increase platelet adhesion effect of microcirculation perfusion, leading to thrombosis in pulmonary circulation and coronary circulation, and potential heart failure [17].

PGE1 can dilate bronchial and artery vein blood vessels, and thus increase myocardial contractility [18]. By exciting mucosa of the respiratory tract, PGE1 receptor exerts its action directly on bronchial smooth muscle. PGE1 can decrease section of reacting substance and other inflammatory mediators, release inhibitory overactive sympathetic neurotransmitter, decrease airway hyper responsiveness during heart failure and bronchial dilation [19]. Therefore ventilation and hypoxia are improved. Furthermore, PGE1 dilates arteries and veins, reduces pre- and after- load of the heart and pulmonary artery pressure, enhances myocardial contractility and renal vascular expansion, and increases urine output [19]. Microcirculation and macrocirculation of the heart are improved with strong anti-platelet aggregation effect of PGE1. In this paper, we used PGE1 as supplemental therapy to examine its effect in patients treated with chemotherapy [20].

Materials and methods

Materials

Clinical data of inpatients were collected from January 2013 to December 2015. Protocol of the study was approved by review board committee of Tianjin first central hospital. Written informed consent was obtained from each patient. 68 patients with advanced lung cancer were diagnosed by pathological confirmation or by distant metastases without pathological diagnosis. Inclusion criteria: (1) for non-small cell lung cancer (NSCLC) cases, TNM staging of T_3-T_4 are required; for small cell lung cancer (SCLC) cases, extensive stage are required. (2) ECOG score is 3 or 4. (3) patients were not under chemotherapy or targeted therapy 3 months before enrollment, with only supportive care. The histological grading and TNM classification of the patients' cases were performed according to the recommendations of the International Union Against Cancer (2009). Exclusion criteria: (1) patients with medical history that affects blood coagulation (such as severe liver and kidney disease, thromboembolic disease, diabetes, surgery trauma and severe infections within 1 month, receiving anticoagulant and antifibrinolytic or haemostatic treatment within two weeks). (2) Platelet <100,000/l. (3) pre-existing hemoptysis. (4) Patients in critical condition, with unstable vital signs or clinical expected survival time less than 15 days.

68 cases were enrolled in this study: 46 males with the age range from 58-85 years old and average age of 72.35 ± 5.73 (years ± SD); 22 females with the age range from 55-85 years old and average age of 67.65 ± 5.90 (years ± SD). According to pathology reports, 43 cases were NSCLC, 13 cases were SCLC, and the rest 12 cases were with no clear pathological classification. ECOG scores were 3 points in 30 cases and 4 points in 38 cases. At baseline, all patients received a panel of tests including routine blood test, liver and kidney function tests, complete blood cell count with differential leukocyte count, serum biochemistry, tumor markers panel examination, blood gas analysis, DIC check; and received physical examination, bronchoscopy, computed tomography (CT) scan of the chest and upper abdomen, and electrocardiogram. After clinical staging confirmed, patients were randomly assigned into control

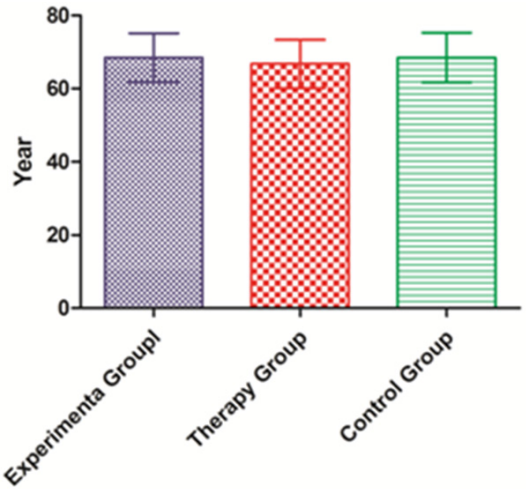

Figure 1. Age distribution of patients in all three groups. Age of patients in each group is comparable. Average age of patients in experiment group was 68.48 ± 6.64 (years ± SD); average age in therapy group was 66.79 ± 6.59 (years ± SD); average age in control group was 68.50 ± 6.77 (years ± SD).

group (10 cases), therapy group (33 cases) and experimental group (25 cases) based on their ECOG score by coin throwing random method. Clinic data of the three groups (gender, age, lesion location and pathological results) are comparable and not statistically significant.

Treatment

Pathology is confirmed by transbronchial biopsy, sputum biopsy from percutaneous lung puncture or pleural fluid exfoliative cells. The therapy group (33 cases) only received chemotherapy. Experimental group (25 cases) received chemotherapy combined with intravenous injection of PGE1 (Alprostadil, produced by Beijing Tide Pharmaceutical company) for 14 days. Supportive therapy was given to patients in the control group (10 cases). PGE1 was administered at the standard dosage recommended by medication instruction which is 10 ug in 10 ml 5% glucose or 0.9% NS once daily for 14 days. The exact time of death was recorded for each patient. 51 died in our hospital and their time of death was recorded by doctor. For the rest of patients, they were followed up once a week by phone and their time of death was confirmed by phone call to their close family members at home.

Response and toxicity criteria

Throughout the study, use of any other anticoagulants or fibrinolytic drugs is prohibited, but use of non-steroidal anti-inflammatory drugs is allowed.

VTE diagnostic criteria: VTE includes deep venous thrombosis of lower extremity, non-fatal pulmonary embolism or death-related venous thromboembolism (fatal pulmonary embolism and death of unknown causes).

The adverse reaction of PGE1 being observed in this study is any clinical related hemorrhage occurred starting from the first day of drug administration throughout the course of study to no later than 3rd day after the last administration. Hemorrhage is defined as any of the following conditions: (1) hemorrhage occurred in organs such as skull, vertebral tube, eyes, peritoneum, joint, pericardium, or intramuscle, (2) hemoglobin levels reduced to 20 g/L or less, or (3) infusion of 2 or more units of whole blood or red blood cell suspension.

The clinical stages of deep venous thrombosis: acute stage defined as occurrence less than 7 days after onset; sub-acute stage defined as between 9th and 13th day of onset; chronic stage defined as after 30th day of onset.

Statistical analysis

The statistical analysis was performed using SPSS software, version 19.0 (IBM SPSS Inc., Chicago, IL, USA). The data were evaluated statistically using an independent sample t-test when a simple comparison between two groups was required, analysis of variance (ANOVA) was used to compare the data in multiple groups, and least significant difference and Student-Newman-Keuls processes were used to compare the differences between each pair of groups. Finally, χ^2 tests were used to examine the statistical significance of differences in the expression rate.

Results

Demographic data of patients

Experiment group was consisted of 18 male patients and 7 female patients with the average age of 68.48 ± 6.64 (years ± SD); therapy group included 22 male patients and 11 female patients with the average age of 66.79 ± 6.59 (years ± SD); control group had 6 male patients and 4 female patients with the average age of 68.50 ± 6.77 (years ± SD) (**Figure 1**). ECOG scores were comparable among all three

Table 1. Demographic data of the three groups

	Experimental group n=25	Therapy group n=33	Control Group n=10	
Average Age	68.48 ± 6.64	66.79 ± 6.59	68.50 ± 6.77	P=0.32
ECOG				
3 point	11	15	4	P =0.43
4 point	14	18	6	P =0.26
Tumor Type				
NSCLC	18	21	4	P=0.33
SCLC	4	6	3	P=0.78
Undiagnosed	3	6	3	P =0.83

ECOG: Eastern Cooperative Oncology Group.

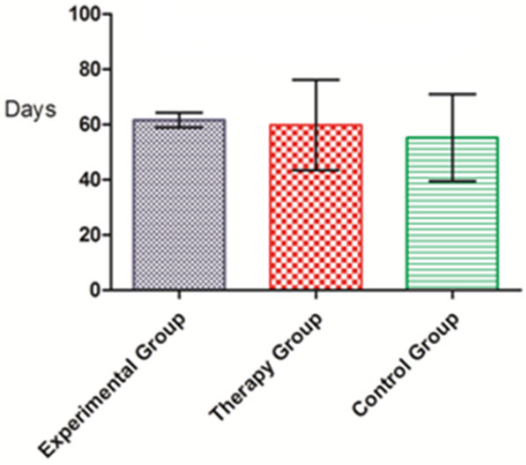

Figure 2. Survival time of all three groups. The average survival time was 61.6 ± 13.3 days in the experimental group. Average survival time was 59.8 ± 16.4 days in the therapy group. In control group, it was 55.3 ± 15.7 days. There was no significant differences between the experimental and therapy group (p=0.656).

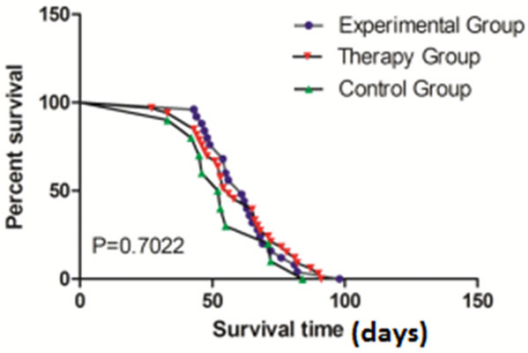

Figure 3. Survival curves of all three groups through the study.

groups, with 11 cases of 3 points and 14 cases of 4 points in experiment groups, 15 cases of 3 points and 18 cases of 4 points in therapy group, and 4 cases of 3 points and 6 cases of 4 point in control group. As to the disease type, the experiment group had 18 cases of NSCLC, 4 cases of SCLC, and 3 cases of undiagnosed lung cancer; the therapy group had 21 cases of NSCLC, 6 cases of SCLC, and 6 cases of undiagnosed lung cancer; the control group had 4 cases of NSCLC, 3 cases of SCLC, and 3 cases of undiagnosed lung cancer. The distribution of clinical characteristics among the three groups showed no significant differences (**Table 1**).

Comparison of survival time

The median survival time was 61 days in the experimental group with average survival time of 61.6 ± 13.3, whereas the median survival time was 56 days in the therapy group with average survival time of 59.8 ± 16.4, which was similar to that of the control group (52.5 days, 55.3 ± 15.7). There was no significant differences in survival time between the experimental and therapy group (p=0.656) (**Figures 2**, **3**).

VTE and adverse reactions

During PGE1 treatment, 3 patients in experimental group developed nodular vasculitis. In therapy group (n=33), 9 cases showed small amount of VTE during treatment with 1 patient died due to fatal pulmonary embolism. In the experimental group (n=25) only one patient experienced non-fatal VTE. On the other hand, in the control group, 3 patients developed VTE. The results showed that the incidence rate of VTE was significantly lower in the experimental group compared with the therapy group (**Tables 2**, **3**).

Discussion

Lung cancer is one of the most common malignant tumors in China, which is of great harm to people's health condition and life expectancy due to its high incidence rate and high mortality rate [21]. Chemotherapy is a common treatment for advanced lung cancer. However, although chemotherapy kills tumor cells, it also causes damage to normal cells [22]. For example, anticancer medicine has strong inhibitory

Table 2. The VTE and adverse reactions of experimental and therapy group

	Experimental group n=25	Therapy group n=33		
VTE rate	4.0% (1/25)	27.3% (9/33)	χ^2=3.89	P=0.049
Adverse reaction (nodular vasculitis)	12.0 (3/25)	0.0% (0/33)	χ^2=2.09	P=0.148

VTE: Vein thrombosis embolism syndrome.

Table 3. The VTE and adverse reactions of experimental and control group

	Experimental group n=25	Control group n=10		
VTE rate	4.0% (1/25)	30.0% (3/10)	χ^2=2.55	P=0.061
Adverse reactions (nodular vasculitis)	12.0 (3/25)	0.0% (0/10)	χ^2=0.23	P=0.542

VTE: Vein thrombosis embolism syndrome.

effect on bone marrow and leads to reduced levels of granulocyte and platelet [23]. Thrombosis formation is easier in cancer patients than in healthy people due to their hypercoagulable state and thrombin produced by tumor cell membrane [24]. Patients with advanced lung cancer usually have disorder of coagulation; therefore they are more likely to develop VTE with chemotherapy treatment [25] . In this study, it was found that administration of PGE1 concurrently with chemotherapy significantly decreased the incidence rate of VTE and reduced the risk of fatal embolism. In terms of survival time, the present study showed that the survival time of patients treated with chemotherapy alone was not significantly different from that of the supportive treatment group [26]. And there was no significant difference in the mean survival time among all three groups, which is different from previous reports where it was shown that chemotherapy combined with anticoagulant can prolong survival time of patients [27]. The possible reason may be that the sample sizes of this study were too small to show statistical differences.

It had been more than 10 years since the first report claiming that PGE may be beneficial in the treatment of ischaemic peripheral vascular disease [28]. PGE1 administered intra-arterially increased calf blood flow at doses between 1 and 10 ng/kg/min [29]. However, therapeutic benefit has been controversial for PGE administered intravenously. PGE1 administered intravenously at a dose of 10 ug per day was reported to produce clinical benefit for patients with advanced lung cancer [30]. However, a large double-blind controlled trial of PGE1 showed no beneficial effect in patients suffering from ulcers secondary to advanced lung cancer. The healing rate in PGE1 treated group was not higher than that of the placebo group which was approximately 50%.

Our study showed that PGE1 significantly reduced the incidence of VTE during chemotherapy in patients with advanced lung cancer. The underlying mechanisms could be that PGE1 can enhance fiber dissolution activity, reduce pathological changes during ischemic injury, and promote the VTE thrombolysis. The beneficial effects may be related to the multiple biological activities of PGE1. ①The effects on coagulation and fibrinolytic system: activation of platelet prostaglandin receptor by PGE1 inhibits the release of TXA2. Therefore the TXA2 induced strong release and aggregation of platelet was inhibited and vasoconstrictive effect of platelet was reduced. This could contribute to the prevention of VTE, especially in the hypercoagulation and microvascular occlusion state of patients with advanced lung cancer under chemotherapy. Previous investigations showed that PGE1 can enhance local thrombolytic infusion effect of thrombolytic drugs (tPA, urokinase, streptokinase), which was seen in animal models of porcine coronary artery thrombosis, rabbits inferior vena cava thrombus and jugular vein thrombosis and in vitro thrombus model [31]. Moreover, PGE1 can inhibit the activity of plasminogen activator inhibitor -1 (PA-1) in vivo. In addition, PGE1 has a direct protective effect on vascular endothelial cells, which is beneficial to the production of tPA by endothelial cells and the enhancement of local fibrinolytic activity. ②The effects of PGE1 on impaired microcirculation: PGE1 is a powerful vasodilator by relaxing vascular smooth muscle for the whole body. The application of PGE1 in patients with advanced lung cancer, especially in those under chemotherapy, facilitates the establishment of collateral circulation

and improves local microcirculation, thus preventing the pathological process of ischemic injury. Moreover, PGE1 can inhibit platelet aggregation, reduce blood viscosity, reduce the aggregation of red blood cells and improve its deformability, thereby improving the perfusion and repair of damaged tissue [32, 33]. Aside from its beneficial effect on prevention and treatment of VTE, the only adverse reaction of PGE1 is vasculitis which is mild and well tolerated. Taken together, the application of PGE1 has significant benefits to patients with advanced lung cancer.

Conclusion

In this study, we discovered that PGE1 significantly reduced the incidence rate of VTE in patients with advanced lung cancer. However we did not find significant effect on overall survival time of patients among all three groups. Therefore, it is still uncertain whether PGE1 administration could lead to therapeutic improvement in patients treated by chemotherapy. Further study needs to be carried out to test other infusion regimes with different doses and even different routes of administration.

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Disclosure of conflict of interest

None.

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