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Original Article

Clinical research on chemotherapy in combination with LMWH treatment of advanced lung cancer patients

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Abstract: To provide new option for advanced lung cancer treatments by discussing and trying to use prognostic significance of uPA and uPAR as monitor and verification of chemotherapy combined with low molecular weight heparin (LMWH) treatment in advanced lung cancer. 76 cases were collected (51 males and 25 females). Pathology is confirmed by transbronchial biopsy, sputum biopsy from percutaneous lung puncture or pleural fluid exfoliative cells. The treatment group (33 cases) only received chemotherapy. Meanwhile, experimental group (33 cases) receives chemotherapy as well as abdominal subcutaneous injection of low molecular weight heparin (LMWH) for 14 days. While in the control group (10 cases), only the supportive therapy was given. After receiving chemotherapy in patients with advanced lung cancer, serum expression of uPAR was significantly reduced. Before chemotherapy high levels of uPAR often prompts bad prognosis in patients with advanced lung cancer, which increased survival time was significantly lower than the uPAR-free patients. Meanwhile, We found that small doses of a short course of low molecular weight heparin calcium on extended the survival time of patients with lung cancer in this group, the median survival time was 73 days in the experimental group, significantly higher than the treatment group of 55 days, which was similar to the control group of 54 days. Changes of serum levels of uPAR in patients before and after chemotherapy demonstrate that uPAR can be used as advanced lung cancer chemotherapy curative effect and new indicator of prognosis. Excluded under the influence of confounding factors, low molecular weight heparin calcium in the treatment still has a significant effect on survival time, our study suggests that low molecular weight heparin anticoagulant therapy may increase lung cancer survival, provide a new direction for the treatment of lung cancer and worthy of further study.

Keywords: Chemotherapy, uPAR, uPA, low-molecular-weight heparin

Introduction

Vein thrombosis embolism syndrome (VTE) is common complication happened among lung cancer. The occurrence rate of it is 4-10%. Especially in advanced lung cancer patients with prethrombotic state, chemotherapy will aggravate hypercoagulable state and the activation of blood coagulation that occurs in the cancer patient makes cancer cells attach, invade and transfer easily which may also influence the biology of the tumor so as to create a poorer outcome for the chemotherapy [1]. Former researches demonstrate that low molecular weight heparin can prevent thrombosis complications effectively, reduce the mortality of patients and decrease costs spent on the medical nursing and treatments [2]. Meanwhile, chemotherapy as the main method to treat patients with advance lung cancer can also promote tumor cell releasing cell toxicities, such as free oxygen radicals. They may injury vascular endothelial, reduce natural anticoagulant blood barrier and increase the risk of VTE [3]. At present, the effect of low molecular weight heparin (LMWH) in the prevention of VTE among patients with advanced lung cancer undergoing chemotherapy is not clear and safety of using low molecular weight heparin (LMWH) on advanced lung cancer patients has not been studies yet. In this study, to discuss efficacy and safety of chemotherapy in combination with low molecular weight heparin (LMWH) treatment of advanced lung cancer patients in survival rate, prevention of VTE, body indexes in two groups (treatment group and experimental group) such

as the incidence rate of VTE, hemorrhage are observed and compared.

Plasminogen activator (PA) can be divided into two types: urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA) [4]. They all have capacity to transfer hydrolyzed plasminogen into plasmin. The difference between tPA and uPA is that tPA is highly affinitive with fibrin and plays a very important role in dissolving the thrombus and maintaining the balance between blood coagulation and fibrinolysis; uPA mostly will function during the process of tissue remodeling, cell immigration, fertilization as well as tumor metastasis. Urokinase-type plasminogen activator system, mainly composed of uPA, its receptor (urokinase-type plasminogen activator receptor, uPAR), substrate molecular (such as plasminogen), and inhibitor (plasminogen activator inhibitor type 1 and 2, PAI-1, PAI-2), is a key enzyme system to transfer mediated cells via degrading extracellular matrix under physiological or pathological condition. Meanwhile, hydrolysis of extracellular matrix is one of main steps included in invasion and metastasis of tumor cells requiring the involvement a series of proteases [5]. The process uPA involved in makes it a good candidate to prognose the tumor metastasis or evaluating the outcome of chemotherapy.

In addition to direct degradation of extracellular matrix, fibrinolytic enzymes can also activate metalloproteinase which is capable to join the extracellular proteolysis. uPA is the initiator of fibrinolytic enzyme secreted by tumor cells. Its functions involve interaction, modulation and regulation of uPAR and PAI.

The relevant of lung cancer prognosis and uPA, uPAR PAI-1 cannot be neglected. Research [6] reveals that in brain glioma, expression of uPA, uPAR is associated with a malignant glioma, higher the astrocytoma malignant degree is higher degree of expression. In benign meningioma, low expression can be detected and expression is not seen in normal brain tissue. uPAR staining is locating in glioma cells and endothelial cells. The expression levels of uPA and uPAR was negatively correlated with patient survival time. uPA is also associated with the prognosis of soft tissue sarcomas: elevated levels of uPA is often associated with malignancy of cells increased DNA aneuploidy, tumor necrosis and associated local recurrence and metastasis. Based on former report, uPA and PAI-1 have great value for evaluating prognosis as well: the level of uPA and survival time showed significant negative correlation and PAI-1 had no correlation in reported cases. Besides, in these cases, uPAR is negatively correlated with the survival time of patients. In this paper, by discussing and trying to use prognostic significance of uPA and uPAR as monitor and verification of chemotherapy combined with low molecular weight heparin (LMWH) treatment in advanced lung cancer, the study may provide new option for advanced lung cancer treatments.

Materials and methods

Materials

Collected inpatients clinical data from January 2013 to December 2014 after obtaining informed consent and approval from our institution's review board committee. 76 patients with advanced lung cancer were diagnosed by pathology or have found distant metastases without pathological diagnosis. Clinical diagnostic criteria: (1) For non-small cell lung cancer (NSCLC) cases, TNM staging of T3-T4 are required; for small cell lung cancer cases, extensive stage are required. (2) ECOG score is 3 or 4. (3) Patients didn't receive any treatment such as chemotherapy or targeted 3 months before experiment, only received supportive care. The histological grading and TNM classification of the patients' cases were performed according to the recommendations of the International Union Against Cancer. Exclusion criteria: (1) Patients have medical history that affect 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 × 109/L. (3) Preadmission hemoptysis. (4) In critical condition, with unstable vital signs or clinical expected survival time less than 15 days.

76 cases were collected: 51 males with the age range from 60-85 and average age of 72.35 ± 6.02; 25 females with the age range from 65-85 and average age of 77.90 ± 3.89. The pathology report showed that 51 cases of non-small cell lung cancer, small cell lung cancer in 15 cases, and no clear pathology in 10 cases. ECOG score 3 points in 48 cases and 4 in 28.

All patients underwent routine blood, liver and kidney function check, tumor markers, blood gas analysis, DIC exam and had complete history, physical examination, complete blood cell count with differential, serum biochemistry, computed tomography (CT) scan of the chest and upper abdomen, and electrocardiogram, obtained at baseline, PET-CT was done in some of the patients. After clinical staging, patients were randomly divided into control group and study group based on their ECOG score. The clinic data of two groups (gender, age, lesion location and pathological results) are comparable and not statistically significant ($P > 0.05$).

Treatment

Pathology is confirmed by transbronchial biopsy, tumor cells in sputum, biopsy from percutaneous lung puncture or pleural fluid exfoliative cells. In the control group (10 cases), the supportive therapy was given alone. While the treatment group only received a course of chemotherapy treatment [7]. Meanwhile, experimental group receives one course of chemotherapy as well as abdominal subcutaneous injection of low molecular weight heparin (LMWH) (Dalteparin sodium also known as Fragmin, produced by Vetter Pharma-Fertigung GmbH) for 14 days. The dose: if weight is greater than 50 kg, 4000 U and two times per day; if weight is less than 50 kg, 5000 U and once a day. All the patients were followed up to death with exact time of death, among which 60 died in our hospital, the rest were informed by the phone call with exact time of death.

uPA and uPAR test

Use enzyme linked immunosorbent assay (ELISA) method to test uPA and uPAR level in patients with advanced lung cancer before and after chemotherapy in treatment and experimental groups. Meanwhile, uPA and uPAR level were examined in the control group at baseline. ELISA assay kits were purchased from the R&D company (United States). The test procedure is based on the kit instructions strictly.

Response and toxicity criteria

During the study, use of any other anticoagulants or fibrinolytic drugs is forbidden, but use of antiplatelet agents and nonsteroidal anti-inflammatory drugs is allowed.

Toxicity criteria: (1) 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). (2) Another adverse reaction is any clinical related bleeding occurred in the first day of drug injection or not later than the third day after stop injecting. If hemorrhage occurred in important organ (cranial, vertebral tube, eyes, peritoneal, joint, pericardium or intramuscular syndrome), reduced hemoglobin levels 20 g/L or more, or leaded to infusing of 2 or more units of whole blood or red blood cell suspension, the bleeding will be defined as bleeding. (3) Thrombocytopenia: platelet less than 100 × 109/L. (4) The clinical stages for deep venous thrombosis: acute stage, occur less than 7 days after onset; subacute stage, onset between eighth and thirtieth day; chronic stage, onset after thirtieth day.

Currently, most of the literature is according to the standards of efficacy of deep venous thrombosis: (1) Healing: clinical symptoms and signs disappear, B-type ultrasound and other imaging studies show blood vessel recanalized totally. (2) Valid: clinical symptoms disappeared or decreased, B-type ultrasound and other imaging studies show blood vessel recanalized partially. (3) Invalid: no mitigating or aggravating clinical symptoms and signs appear, and B-type ultrasound imaging showed blood vessels do not change or blood clots increase. In this study, we use the following criteria to evaluate the outcome of treatment on patients with advanced lung cancer: CR: complete remission, PR: partial response, SD: stable disease, PD: disease progression.

After using low molecular weight heparin (LMWH) for two weeks, use of chest CT scan to check and evaluate effect, including disease control rate (DC=CR+PR+SD), objective has efficiency (RR=CR+PR) and total survival period OS (from the study began to death of time).

Statistical analysis

The statistical analysis was performed using SPSS software, version 17.0 (IBM SPSS Inc., Chicago, IL, USA) and Graphpad Prism, version 6.0. The data were evaluated statistically using an independent sample t-test when a simple comparison between two groups was required. Meanwhile, χ^2 tests were used to establish the

statistical significance of differences in the expression rate. Log-Rank test were used to determine whether the uPA expression was a potential prognostic factor for survival in this patient group.

Results

Clinical feature distribution between three groups

In the experimental group, 23 males and 10 females with the average age of 76.33 ± 5.66; the average age in treatment group is 76.01 ± 6.32, including 22 males and 11 females; while in the control group, 6 males and 4 females with the average age of 75.83 ± 5.87. ECOG scores in experimental group are 3 points in 20 cases and 4 points in 13 cases, in treatment group, there are 21 cases with 3 points and 12 cases with 4 points, there was 7 cases with 3 points and 3 cases with 4 points in control group. In the experimental group, non-small cell lung cancer in 22 cases and small cell lung cancer in 7 cases, undiagnosed lung cancer in 4 cases. In the treatment group, non-small-cell lung cancer in 23 cases, 6 cases of small cell lung cancer, undiagnosed lung cancer in 4 cases. While in the control group, non-small-cell lung cancer in 6 cases, 2 cases of small cell lung cancer, undiagnosed lung cancer in 2 cases. The distribution of clinical characteristics between the three groups showed no significant differences (P > 0.05).

Comparison of survival time

The median survival time was 73 days in the experimental group with average survival time of 81.0 ± 27.7, whereas the median survival time of 55 days in the treatment group with average survival time of 65.9 ± 26.5, which was similar to the control group of 54 days (57.8 ± 22.3). IT had significant differences in survival rates between the experimental and treatment groups (P=0.027), the experimental group of survival time longer than control group. However, there was no significant difference between the treatment and control groups (P=0.386).

Disease control rate in the experimental and treatment groups

After using low molecular weight heparin (LMWH) for two weeks in experimental group, similarly, at the same time point in the treatment group, use of chest CT scan to check and evaluate effect. There was no CR case in both groups, disease control rate in experimental group was 48.5% (16/33), while it was 24.2% (8/33) in the treatment group. Between the two groups showed significant difference (P=0.041).

Adverse reactions

In the process of the treatment, one patient in experimental group have small amount of blood in the sputum. After CT scan and B-type ultrasound checking, considered it unrelated to treatment and continue the injection till the end of study. During this process, the amount of hemoptysis didn't increase. After treatment, seven cases showed small amount of hemoptysis but during follow-up, no fatal hemoptysis occurred and patients in experimental group show any sign of platelets decrease related to low molecular weight heparin (LMWH). At the same time, in the experimental group, there was a case of venous thrombosis in the lower limbs which recanalized partially by itself.

In the treatment group, eight cases showed small amount of VTE during treatment, one case died because of fatal pulmonary embolism and a small amount of hemoptysis was found in one case. There are significant differences between the two groups in the number of VTE (P=0.031), but no significant differences in hemoptysis (P=0.059).

uPA and uPAR Levels before and after chemotherapy

There was 18 cases (54.5%) with uPA level decreased in experimental group, while it was 9 in treatment group with the ratio of 27.2%. Patients with decreased uPA level had a significantly difference in the two groups (P=0.042). On the other hand, the patients with uPAR decreased in the experimental and treatment groups were 16 and 8 respectively, it also had a significantly difference (P=0.022).

Compared with past researches found, variety type of tumor cell show uPA and uPAR expression increased, which suggested that inhibition of the activity may reduce tumor cells invasion and metastasis risk [8, 9]. Our results show that after receiving chemotherapy in patients with advanced lung cancer, serum expression

Table 1. The correlated data of the two groups

	Experimental group n=33	Treatment group n=33		
Average survival time	81.0 ± 27.7	65.9 ± 26.5	t=2.263	P=0.027
Disease control rate	48.5% (16/33)	24.2% (8/33)	χ^2=4.190	P=0.041
VTE rate	3.0% (1/33)	24.2% (8/33)	χ^2=4.632	P=0.031
Hemoptysis rate	21.2% (7/33)	3.0% (1/33)	χ^2=3.556	P=0.059
uPA decreased cases	54.5% (18/33)	27.2% (9/33)	χ^2=4.140	P=0.042
uPAR decreased cases	48.5 (16/33)	24.2% (8/33)	χ^2=4.190	P=0.041

P Values < 0.05 were considered to be significant. VTE, Vein thrombosis embolism syndrome; uPA, Urokinase-type plasminogen activator; uPAR, Urokinase-type plasminogen activator receptor.

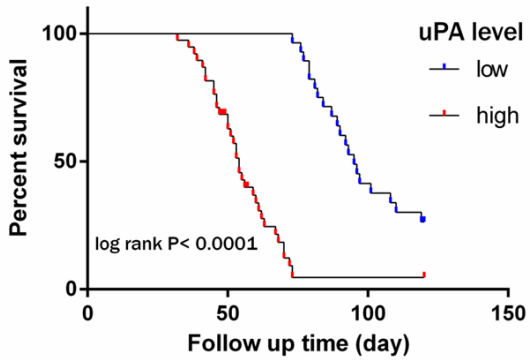

Figure 1. 120-days survival rate of patients with different expression levels of uPA. Low and high levels of uPA (log-rank test, P < 0.001).

of uPAR was significantly reduced in some patients, especially in the experimental group. Before chemotherapy high levels of uPAR often prompts bad prognosis in patients with advanced lung cancer, which increased survival time was significantly lower than the uPAR-free patients. Sensitive to chemotherapy in patients with advanced lung cancer, serum uPA and uPAR after chemotherapy reduced more significantly than resistance. Changes of serum levels of uPA and uPAR in patients before and after chemotherapy demonstrate that uPA and uPAR could be used as advanced lung cancer chemotherapy curative effect and new indicators of prognosis.

Effect of LMWH in cancer treatment

We found that small doses of a short course of low molecular weight heparin calcium on extended the survival time of patients with lung cancer in this group, the median survival time was 73 days in the experimental group, significantly higher than the treatment group of 55 days and the control group of 54 days.

Excluded the influence of confounding factors, low molecular weight heparin calcium in the treatment still has a significant effect on survival time in experimental group than the treatment and control groups, no significant increased risk of bleeding. Our study suggests that low molecular weight heparin calcium in the treatment of advanced lung cancer survival time may have a prolonged effect. But a multicenter study and large-scale clinical trials are needed to verify. Overall, our study suggests that low molecular weight heparin anticoagulant therapy may increase lung cancer survival, provide a new direction for the treatment of lung cancer and worthy of further study (**Table 1**).

Associations between uPA levels and survival

The 66 included patients in the treatment and experimental groups were divided into two groups based on uPA expression (mean uPA AOD, 0.035 ± 0.007). Kaplan-Meier estimates of survival for patients with different uPA levels are analyzed. The survival rates of patients with negative expression or decreased uPA levels (AOD ≤ 0.035) were significantly higher than the survival rates of patients with positve expression or high uPA levels (AOD > 0.035, P < 0.05). Patients with high uPA levels had a significantly poorer prognosis (**Figure 1**).

Associations between uPAR levels and survival

The 66 included patients were divided into two groups based on uPAR expression (mean uPAR OD, 0.032 ± 0.027). Kaplan-Meier estimates of survival for patients with different uPAR levels are analyzed. The survival rates of patients with negative expression or decreased uPA levels (AOD ≤ 0.032) were significantly higher than the survival rates of patients with positve expression or elevated uPAR levels (AOD > 0.032, P < 0.05). Patients with high uPAR levels had a significantly poorer prognosis (**Figure 2**).

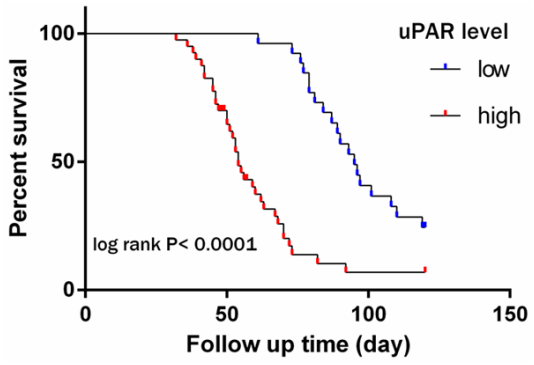

Figure 2. 120-days survival rate of patients with different expression levels of uPAR. Low and high levels of uPAR (log-rank test, P < 0.001).

Discussion

Lung cancer is a high incidence malignant tumor with features of fast growth and early transfer. Patients with advanced lung cancer always show complicated blood coagulation, and change of fiber dissolved function. Meanwhile these functions are conducive to the formation of new cancer cells. Along with the formation of cancer ties, the injured cancer cells escape mechanical or immune system will block capillaries and injury vascular endothelial, and make cancer cells easy to adhesion, invasion and transfer [10]. In clinical conventional treatment, the integrated treatment of chemotherapy in combination with other treatments is still the mainly recommended treatment. However, due to the death of cancer cells and toxins on near organizations, chemotherapy may activate and accelerate blood coagulation, then end up with activating the clotting process, intensifying coagulation and fibrinolysis disorders. Along with the development of medicine and study of malignant tumor [11], people are getting more knowledge about the interaction between blood coagulation in the advanced malignant tumor and fibrinolytic mechanism behind it. Anticoagulant and the application of related drugs may provide new ways for adjuvant therapy for advanced lung cancer.

Clinical development and applications of LMWH

There is evidence from large-scale clinical trials to suggest that VTE is a more aggressive disease in the cancer patient compared with the non-cancer patient. In a study of over 23,000 patients undergoing major surgery who were randomized to receive either low-dose UFH or low molecular weight heparin (LMWH) for perioperative thromboprophylaxis, the mortality rate was 3.1% in cancer patients compared with 0.7% in non-cancer patients (P=0.001) [12]. What was striking was that the rate of autopsy-proven PE (pulmonary embolism) was 0.31% in cancer patients compared with 0.09% in non-cancer patients (P < 0.001), despite the use of standard pharmacological thromboprophylaxis.

Further evidence that thrombosis may be a particularly aggressive disease in the cancer patient comes from analysis of data from of the Cortes study in which patients with acute DVT were randomized to receive either UFH or low molecular weight heparin (LMWH) for initial treatment of DVT [13]. There was a greater derangement of coagulation parameters, at initial presentation, in cancer patients compared with non-cancer patients. In particular there were marked elevations in circulating levels of prothrombin fragments, D Dimer and of activated Factor XII [14]. Patients with cancer presented with significantly higher Marder scores than their non-cancer counterparts and had significantly more proximal DVT than non-cancer patients presenting with DVT.

The potential benefits of low molecular weight heparin (LMWH) therapy may differ in different cancer populations. From the retrospective analyses of DVT treatment studies where cancer patients had an underlying thrombosis and where there was a very early and impressive reduction in mortality associated with a short administration of low molecular weight heparin (LMWH) [15], one might hypothesis that low molecular weight heparin (LMWH) acts by being an effective antithrombotic agent, reducing the incidence of fatal, but often silent, PE. On the other hand, under circumstances where cancer patients without existing thrombosis have received the low molecular weight heparin (LMWH) dalteparin and where a longer-term survival benefit has been suggested, the mechanism is more likely to be due to an effect of dalteparin on tumour biology.

A number of potential explanations have been proposed for the interesting survival observations seen in patients with malignant disease

receiving low molecular weight heparin (LMWH) therapy. Amongst these is the prevention of fatal thromboembolic events associated with active low molecular weight heparin (LMWH) therapy. However, the benefits of exposure to low molecular weight heparin (LMWH) appeared to continue beyond active exposure, indicating that some of the benefit must be independent of preventing fatal thromboembolic events. Coagulation proteases have been shown to play an important role in tumor biology. Low molecular weight heparin (LMWH), through potentiation of antithrombin, neutralized activated factor X and activated factor II thrombin, thus preventing their interaction with tumor expressed protease receptors. The impact of coagulation proteases has been seen in enhancing tumor growth invasion metastasis and angiogenesis. A further explanation for these potential benefits is associated with the direct cellular effects of heparin like molecules which have been shown to inhibit angiogenesis [16] and to enhance apoptosis in experimental tumor models [17]. A further explanation is neutralization of tumor heparinase activity through exposure to heparin-like molecules. Heparinase plays an important role in remodeling of the extracellular matrix, and its overexpression is associated with a more aggressive phenotype.

Previous studies prove that coagulation abnormality has relatively high incidence rate in advanced cancer. More than 90% metastatic cases and 50% cases without metastasis tumor are reported with coagulation dysfunction in patients, especially in patients with advanced lung cancer and gastrointestinal tumors [18]. Disorder of coagulation and fibrinolysis system are related with growth, invasion and migration of tumor cells, anticoagulant treatment can inhibit invasion of tumor cells, and can extended survival time of patients when combine with chemotherapy [19]. At this stage, some researches [20, 21] show that chemotherapy in combination of low molecular weight heparin (LMWH) cannot enhance the outcome of chemotherapy, elongate survival time or reduce the by-effect of chemotherapy significantly, but can obviously improve the dysfunction of blood coagulation and reduce the rate of patients' thrombosis complications before and after chemotherapy. As for the optimal dose, using time and course, clinical application has not reached to a conclusion. According to a series of systematic review and Meta-analysis, a conclusion can be drawn: among patients with cancer, anticoagulation in combination with specific anti-tumor treatment can elongate the survival time of patients. Compared with warfarin, low molecular weight heparin (LMWH) has better performance in elongating patients' survival time. Meanwhile, low molecular weight heparin (LMWH) are relatively safer than Vitamin K antagonists [22]. However, not all the patients can be benefit from low molecular weight heparin (LMWH), for example, some patients with small cell lung cancer and pancreatic cancer are easy to show thrombosis than other cancers such as knot rectal cancer and breast cancer due to their high sensitivities in specific organization [23]. More importantly, prothrombotic mechanisms are a promoting way to guarantee the success of cloning and are seen as a sign of early cancer and recurrence.

Potential mechanism of effect from uPA and uPAR on poor prognosis

Human physiological response accompanied by changes of cytokine expression levels. Cytokines are important medium of information transmission between tissues and organs, are the regulators of the body's immune system in tumor development and metastasis, also play an important role in the process. Therefore, cytokines can be used monitor the severity of and effectiveness of predictors. Previous studies have shown that chronic inflammatory stimuli for the risk factors of lung cancer, and induce various changes in cytokine levels in patients with advanced lung cancer. Study [24] confirmed that cytokine expression levels are related with disease states and changes of survival such as IL-2 levels are associated with decreased survival rates in patients with advanced lung cancer. In recent years, with detailed research [25] on the molecular level, new factors are found such as IL17A, produced by Th17, can be induced by TGFIL-6 IL-21 and IL-23, can regulate the growth of lung cancer. Clarifying the role of cytokines in tumor mechanism has become the focus of current research [26]. In the early study [27], scholars went through cell factors with antibody chip detecting the ILTGFTNFVEGF serum in patients with advanced lung cancer, 120 species cell factors were filtered and cell factors with significantly different expression are filtered out. Among these factors with diagnosis value in advanced lung can-

cer, uPAR and uPA were found relating to the tumor infiltration and the mechanism for tumor cells is: tumor cells can produce the uPA preferment and are activated by combining with the specific receptors on the surface of the tumor cell. After activation, uPA will positively catalyze the formation of plasmin from plasminogen causing degradation of the extracellular matrix to promote invasion of tumor cells to normal tissue. Langkilde [28] found that serum uPAR can be used as an independent prognostic factor in respiratory cancer. And in inflammatory and autoimmune diseases, mortality rate of increased uPAR is relatively high.

Conclusion

We think that our results are more informative than other studies, not only because we analyzed the greatest number of patients, but because of the character of the studies. Most of them were nonrandomized prospective studies, which were pharmacogenomic in character.

We found that small doses of a short course of low molecular weight heparin calcium on extended the survival time of patients with lung cancer in this group, the median survival time was 73 days in the experimental group, significantly higher than the treatment group of 55 days, which was similar to the control group of 54 days.

Excluded under the influence of confounding factors, low molecular weight heparin calcium in the treatment still has a significant effect on survival time, treatment group than in the control group, the relative risk of death was 0.30 of low-molecular-weight heparin calcium in the treatment of safety, no significant increased risk of bleeding. Our study suggests that low molecular weight heparin calcium in the treatment of advanced lung cancer survival time may have a prolonged effect. But our study of a multicenter study, large-scale clinical trials are needed to verify overall, our study suggests that low molecular weight heparin anticoagulant therapy may increase lung cancer survival, provide a new direction for the treatment of lung cancer and worthy of further study.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

LMWH, Low molecular weight heparin; uPAR, Urokinase-type plasminogen activator receptor; uPA, Urokinase-type plasminogen activator; VTE, Vein thrombosis embolism syndrome; PA, Plasminogen activator; tPA, Tissue-type plasminogen activator; PAI-1, Plasminogen activator inhibitor type 1; PAI-2, Plasminogen activator inhibitor type 2; NSCLC, Non-small Cell Lung Cancer; ECOG, Eastern Cooperative Oncology Group; CT, Computed tomography; ELISA, Enzyme linked immuno-sorbent assay; CR, Complete remission; PR, Partial response; SD, Stable disease; PD, Disease progression; OS, Overall Survival; PE, pulmonary embolism; AOD, average optical density; DVT, Deep venous thrombosis; IL-2, Interleukin-2; IL17A, Interleukin-17A; Th17, T helper cell 17.

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