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Assessing the Effectiveness of Montelukast Sodium in Managing Pulmonary Infections in Lung Cancer Patients

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Abstract: *Objective:* To investigate the efficacy of montelukast sodium in the treatment of lung cancer patients with pulmonary infections. *Methods:* A total of 330 patients diagnosed with lung cancer and pulmonary infection, who were admitted to the First Affiliated Hospital of Xi'an Medical University from 2020 to 2022, were selected as research subjects. They were randomly divided into two groups: a control group receiving conventional treatment and an observation group receiving conventional treatment combined with montelukast sodium. Each group consisted of 165 cases. The time required for clinical symptom improvement, the resolution of lung infection signs, and the levels of serum inflammatory factors before and after treatment were compared between the two groups. *Results:* The observation group exhibited significantly faster improvement in clinical symptoms compared to the control group ($P < 0.001$). ELISA assays were conducted to detect the expression levels of IL-1β, IL-6, IL-8, and TNF-α in the serum of both groups at 1 week and 2 weeks into the treatment. The results indicated that, as the treatment progressed, the observation group displayed significantly lower levels of the four serum inflammatory factors compared to the control group ($P < 0.001$). *Conclusion:* Montelukast sodium demonstrates efficacy in the treatment of patients with lung cancer complicated by pulmonary infections. These findings suggest its potential for further verification and clinical application.

Keywords: Lung cancer; Pulmonary infections; Montelukast sodium; Clinical symptoms; Inflammatory factors

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1. Introduction

Lung cancer stands as a prevalent malignancy within the respiratory system. Factors such as smoking, air pollution, occupational exposure, a history of chronic obstructive pulmonary disease (COPD), and family medical history have contributed to a continuous increase in lung cancer incidence year by year [1]. Clinical case data statistics reveal a rising trend in the occurrence of lung infections among lung cancer patients in recent years. It is well-known that infections typically trigger a prominent inflammatory response within the body, leading to the release of various serum inflammatory factors. These, in turn, cause damage to the vascular endothelium and exacerbate the patient's condition.

The advent of emerging targeted therapies and immunotherapy has substantially improved the overall survival of lung cancer patients. However, a significant number of patients eventually experience relapse and develop drug resistance. In this context, researchers have been increasingly uncovering new anti-tumor properties in some older medications. Montelukast sodium, for instance, has demonstrated notable anti-tumor effects in prostate cancer and colon cancer [2,3]. Nevertheless, there is limited research pertaining to its effect on lung cancer.

Therefore, this study endeavors to explore the potential of montelukast sodium in treating patients afflicted with both lung cancer and pulmonary infections. By examining the levels of serum inflammatory factors, this study aims to gain insights into its therapeutic efficacy. This research may offer a novel avenue for the treatment of patients dealing with the dual challenges of lung cancer and pulmonary infections.

2. Materials and methods

2.1. General information

A total of 330 patients diagnosed with lung cancer and concurrent pulmonary infections, who were admitted to the First Affiliated Hospital of Xi'an Medical University between 2020 to 2022, were chosen as the study subjects. These patients were randomly divided into two groups: an observation group and a control group, each comprising 165 cases. The observation group consisted of 92 males and 73 females, with ages ranging from 45 to 90 years old and an average age of 65.03 ± 0.52 years. The control group consisted of 85 males and 80 females, with ages ranging from 39 to 82 years old and an average age of 62.05 ± 0.08 years. General information of the patients are shown in **Table 1**.

Patients in both groups had one or more underlying conditions, primarily including hypertension, COPD, diabetes, and coronary heart disease, among others. There was no statistically significant difference between the two groups regarding lung cancer staging and type ($P > 0.05$). Additionally, all patient data were reviewed and approved by the hospital's ethics committee.

Inclusion criteria encompassed:

(1) Compliance with the diagnostic criteria for lung cancer as defined by the 8th edition of the "International TNM Staging Criteria for Lung Cancer" issued by the International Society for the Study of Lung Cancer in 2015 [4].
(2) Chest CT scans indicate lung lesions characterized by nodules, infiltrates, honeycombing, or reticular patterns, suggesting inflammatory changes.
(3) Clear indications of a lung infection through a combination of pulmonary function tests, blood tests, clinical symptoms, and physical signs.

Exclusion criteria included:

(1) Coexistence with other malignancies.
(2) Concomitant severe heart, liver, kidney, or other organ dysfunction.
(3) Presence of other primary infectious diseases or immune disorders.
(4) Use of targeted drugs or new immune preparations during the study.
(5) Inability to cooperate with clinical treatment or incomplete clinical data.

Table 1. Patients general information

General information	Observation group (n = 165)	Control group (n = 165)	χ^2 value	P value
Gender			0.587	0.44
Male	92	85		
Female	73	80		
Age (years)			1.673	0.196
< 60	59	48		
≥ 60	106	117		
Lung cancer staging			3.68	0.298
I	11	15		
II	32	28		
III	6 1	48		
IV	6 1	74		
Tumor type			8.373	0.38
Adenocarcinoma	6 7	52		
Squamous cell carcinoma	45	7 0		
Small cell lung cancer	30	24		
Other	23	19		

2.2. Research methods

The control group received conventional treatments such as standard chemotherapy, radiotherapy, and anti-infective treatment. The observation group received conventional treatments as well as montelukast sodium (Merck; trade name Singulair; National Drug Approval No. J20130047) at a dosage of 10 mg orally each night before bedtime. The treatment course for both groups extended over a period of 2 weeks.

2.3. Serum inflammatory factors assessment

After 1 and 2 weeks of treatment, 5 mL of fasting median cubital venous blood was collected from both patient groups and serum samples were extracted. Enzyme-linked immunosorbent assay (ELISA) was used to assess interleukins IL-1β, IL-6, and IL-8 levels in the serum as well as tumor necrosis factor-alpha (TNF-α) expression of the patients. The ELISA kit was procured from Beijing Jingmei Bioengineering Co, Ltd., and procedures were conducted following the kit instructions.

2.4. Statistical processing

Data analysis was performed using SPSS 21.0 software. Measurement data were expressed as mean ± standard deviation (SD). The *t*-test was used for comparisons between the two groups. Count data were expressed as %. The χ^2 test was used for intergroup comparisons. A P value of less than 0.05 was considered a statistically significant difference.

3. Results

3.1. Time for improvement of clinical symptoms

After 2 weeks of treatment, the time required for improvement in clinical symptoms and physical signs in

both patient groups was observed. Specifically, the resolution time of symptoms such as fever, cough and expectoration, asthma, and the presence of pulmonary rales was focused on. **Table 2** shows the time for improvement of clinical symptoms in both groups.

Table 2. Time for improvement of clinical symptoms in both patient groups (mean ± SD)

Group	*n*	Fever	Cough and expectoration	Asthma	Pulmonary rales
Observation group	165	3.28 ± 0.32	12.72 ± 4.05	4.46 ± 1.02	5.16 ± 1.41
Control group	165	4.36 ± 0.51	17.36 ± 4.64	5.12 ± 1.15	7.24 ± 1.48
t		23.042	9.752	5.515	13.071
P		< 0.001	< 0.001	< 0.001	< 0.001

3.2. Determination of serum inflammatory factor levels

Serum samples from both patient groups were collected, and the ELISA method was utilized to assess the levels of IL-1β, IL-6, IL-8, and TNF-α in the serum of both the observation group and the control group. Initially, all four serum inflammatory factors in both groups were maintained at elevated levels before treatment, with no statistical difference between them ($P > 0.05$). As the treatment progressed, the levels of these inflammatory factors in the serum of both groups exhibited significant reductions after 1 week and 2 weeks of treatment ($P < 0.001$). **Table 3** shows the comparison of serum inflammatory factor levels between the two groups before, 1-week, and 2-week after treatment.

Table 3. Comparison of serum inflammatory factor levels between the two patient groups (mean ± SD)

Index	Group	Before treatment	1-week after treatment	2-week after treatment
IL-1β (pg/mL)	Observation group	6.16 ± 0.55	3.34 ± 0.32	2.45 ± 0.21
	Control group	6.12 ± 0.58	4.28 ± 0.41	3.82 ± 0.35
	t	0.6248	23.2159	43.1147
	P	> 0.05	< 0.001	< 0.001
IL-6 (pg/mL)	Observation group	17.56 ± 1.60	10.06 ± 0.71	8.21 ± 0.22
	Control group	17.53 ± 1.64	12.15 ± 0.93	7.15 ± 0.43
	t	0.1682	82.0089	28.1897
	P	> 0.05	< 0.001	< 0.001
IL-8 (pg/mL)	Observation group	19.47 ± 3.08	8.63 ± 0.81	8.35 ± 0.62
	Control group	19.45 ± 2.93	15.25 ± 1.39	12.45 ± 0.79
	t	0.0604	52.8568	52.4430
	P	> 0.05	< 0.001	< 0.001
TNF-α (ng/mL)	Observation group	6.25 ± 0.71	2.27 ± 0.33	1.57 ± 0.24
	Control group	6.23 ± 0.69	4.16 ± 0.48	2.87 ± 0.39
	t	0.2595	41.6785	34.4658
	P	> 0.05	< 0.001	< 0.001

4. Discussion

Lung cancer ranks among the most prevalent clinical malignancies. Statistics from the American Cancer Society in 2022 revealed that lung cancer remains the leading cause of cancer-related fatalities, with a low 5-year survival rate of only 20% [5]. Due to environmental pollution and shifts in lifestyle, its incidence and mortality continue to rise yearly [6]. Recent data from the National Cancer Center indicates that, with an aging population, China's cancer incidence exceeds that of the United States, making lung cancer the most prevalent cancer and the foremost cause of cancer-related death in China [7]. Owing to the subtle early symptoms of the disease, most patients are already grappling with pulmonary infections upon diagnosis. Combined with factors such as resistance to radiotherapy and chemotherapy, patient outcomes are often suboptimal, and the prognosis is grim [8-10]. The 5-year survival rate for patients remains dishearteningly low. Discovering novel treatments is an imperative trend in the management of malignant tumors, including lung cancer.

Montelukast sodium, marketed under the trade name Singulair, serves as a leukotriene receptor antagonist with a distinct inhibitory impact on cysteinyl leukotriene receptors (CYSLTRs). It suppresses the release of crucial inflammatory factors in various cells, including mast cells and eosinophils [11]. This drug has been widely used to prevent and treat asthma-related conditions, as it relaxes bronchial smooth muscle and diminishes airway hyperresponsiveness [12-13]. Recent years have unveiled the potential of montelukast sodium in tumor treatment. Tsai *et al*. found that administering montelukast sodium to mice with lung cancer significantly delayed tumor growth, inhibited lung cancer cell proliferation and colony formation, and induced lung cancer cell apoptosis [14]. By limiting hypoxia-inducible factor 1-alpha (HIF-1α) protein translation, montelukast sodium demonstrates tumor-suppressing effects, leading to the belief that it may serve as a novel treatment for prostate cancer [2]. In the realm of lung cancer research, it was discovered that montelukast sodium can inhibit the expression of cysteinyl leukotriene receptor 1 (CYSLTR1) in lung cancer cells and prevent lung cancer cell migration [6]. Bellamkonda *et al*. demonstrated that montelukast sodium can impede tumor cell growth in a nude mouse model of colon cancer. Additionally, *in vitro* studies showcased its ability to inhibit tumor cell proliferation, and adhesion, and induce cell cycle arrest and apoptosis in a dose-dependent manner [3]. As of now, there is a dearth of reports on the effectiveness of montelukast sodium in lung cancer treatment in China. This study observed that, after the administration of oral montelukast sodium treatment to the observation group, compared to patients not receiving montelukast sodium, their symptoms demonstrated significant improvement ($P < 0.001$), suggesting that montelukast sodium may play a clinical role in the treatment of lung cancer patients dealing with concurrent pulmonary infections.

Serum inflammatory factors serve as objective indicators for identifying and diagnosing infectious diseases while also playing a role in the onset and progression of pulmonary infections [15]. Research has indicated that IL-6, TNF-α, IL-1β, and others exhibited significant elevation in patients with pulmonary infections [16]. IL-1β, a pleiotropic cytokine, serves as a key mediator in immune response regulation and inflammation. Recent studies have highlighted IL-1β's involvement in tumorigenesis, angiogenesis, tumor invasion, and tumor metastasis, influencing the tumor microenvironment and affecting drug responsiveness through various pathways [17]. IL-6, a multifunctional cytokine, also acts as an inflammatory chemokine. Elevated IL-6 concentrations have been linked to immune response suppression, vascular endothelial cell damage, and lung injury [18]. Initially considered a factor in inflammation, IL-8 has progressively been associated with cancer initiation. An increasing amount of research found that certain chemotherapy drugs combined with radiotherapy can reduce IL-8 expression in tumors [19]. TNF-α, produced by activated macrophages and various tumor cells, functions as a pro-inflammatory factor with multiple biological roles. It serves as a crucial factor in cell activation, differentiation, proliferation, and apoptosis signaling, with TNF-α protein secreted by macrophages and tumor

cells potentially accelerating tumor progression through autocrine mechanisms [20].

The influence of these serum inflammatory factors underscores their close association with tumor development and lung infections. There have been no reports domestically and internationally on serum inflammatory factor levels in patients with lung cancer complicated by pulmonary infections who have undergone montelukast sodium treatment. This study results indicate that, prior to administering montelukast sodium to the observation group, serum expression levels of IL-8, IL-1β, IL-6, and TNF-α were essentially identical to those in the control group, with no statistical difference ($P > 0.05$). However, following 1 and 2 weeks of montelukast sodium treatment in the observation group, serum inflammatory factor levels were assessed, revealing that the observation group exhibited significantly lower levels compared to the control group ($P < 0.001$). These findings indicate that montelukast sodium may reduce the expression of IL-8, IL-1β, IL-6, and TNF-α in the serum of patients with pulmonary infections. Li and colleagues have reported that serum levels of IL-1β, IL-6, and TNF-α gradually rise in patients with stage I-IV lung cancer [21]. While this study has yet to establish a refined link between lung cancer stages and inflammatory factor levels, the treatment course has led to the conclusion that serum inflammatory factor levels in the observation group substantially decreased over time following montelukast sodium application. Some scholars believe that lung cancer patients with pulmonary infections experience an inflammatory stress state, which impacts immune function, triggers immune system activation, and raises the risk of lung infection [22-24]. This study further illustrates that, while effectively managing pulmonary infections, attention to tumor treatment should not be disregarded. Montelukast sodium may offer effective treatment for lung cancer accompanied by pulmonary infections.

In conclusion, this study demonstrates that, following treatment with montelukast sodium in patients with lung cancer and concurrent pulmonary infections, clinical symptoms such as cough, fever, asthma, and signs of pulmonary rales were significantly improved. Moreover, serum pro-inflammatory factors TNF-α, IL-8, IL-1β, and IL-6 exhibited marked decreases. These findings underscore the importance of evaluating patient conditions and enhancing treatment effectiveness, particularly when addressing pulmonary infections in these patients, by considering symptoms, signs, and the body's inflammatory stress state.

Disclosure statement

The authors declare no conflict of interest.

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