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ORIGINAL ARTICLE

Safety and efficacy of multi-kinase inhibitor plus endostar treatment in patients with metastatic renal cell carcinoma and pleural effusion

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Abstract

Objective The aim of this study was to evaluate the safety and efficacy of multi-kinase inhibitor plus endostar treatment in patients with metastatic renal cell carcinoma (mRCC) and pleural effusion.

Methods A total of 10 patients with mRCC (8 clear-cell RCCs, 1 papillary RCC, 1 chromophobe RCC) with pleural effusion from January 2014 to October 2015 were recruited. Four patients received sorafenib (400 mg, twice daily), while six received sunitinib (50 mg, once daily; 2 weeks on and 1 week off). All patients received multi-kinase inhibitor plus pleural cavity perfusion of endostar (15 mg on days 1–4 for 1 or 2 weeks).

Results The response rate of pleural effusion was 70%. Adverse reactions were limited and mild.

Conclusion The regimen of multi-kinase inhibitor plus pleural cavity perfusion of endostar was both effective and safe for the treatment of patients with mRCC with pleural effusion, and may control local symptoms.

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Key word: renal cell carcinoma; pleural effusion; multi-kinase inhibitor; endostar

Multi-kinase inhibitors are the main treatment option for patients with metastatic renal cell carcinoma (mRCC), and the survival benefits are well established [1]. However, patients with mRCC and malignant pleural effusion have poor quality of life, short life expectancy, and a limited range of treatment options, and the efficacy and safety of these treatments are unsatisfactory [2]. To improve the control rate of pleural effusion and the quality of life of affected patients, we carried out a study to evaluate the safety and efficacy of multi-kinase inhibitor plus endostar treatment in patients with mRCC and pleural effusion.

Materials and methods

Clinical data

From January 2014 to October 2015, 10 patients with mRCC and pleural effusion were recruited, including 6 men and 4 women with a median age of 55 years (range 35–71 years). According to the World Health Organization (WHO) renal tumors pathology classification, there were 8 cases of renal clear-cell carcinoma (clear-cell RCCs), 1 of papillary RCC, and 1 of chromophobe RCC. Radiographic examination confirmed pleural effusion. After the occurrence of pleural effusion, 10 patients continued to receive multi-kinase inhibitor therapy. Among them, 4 patients received sorafenib (as first-line treatment), 6 patients received sunitinib (2 were second-line treatment with pleural effusion after sunitinib treatment failed, and 4 as first-line treatment). The metastatic sites included the lungs (8 cases), lymph nodes (5 cases), bone (3 cases), liver (3 cases), and adrenal gland (2 cases). The Eastern Cooperative Oncology Group (ECOG) scores of patients before treatment were 0 (1 case), 1 (1 case), and 2 points (8 cases). The Memorial Sloan-Kettering Cancer Center (MSKCC) risk scores of mRCC were as follows: 1 case of low-risk, 4 cases of middle-risk, and 5 cases of high risk (Table 1).

Treatment programs and evaluation methods

After the diagnosis of pleural effusion, relevant examinations were conducted (including liver and kidney function, blood routine, four indices of blood coagulation, cardiac color ultrasound, electrocardiogram,

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Table 1 Clinical features of 10 patients (*n*)

Clinical features	Cases
Age (years)	55 (35–71)
Male: female	6:4
ECOG score	
0	1
1	1
2	8
MSKCC risk classification	
0	1
1–2	4
≥ 3	5
Metastatic sites	
Lung	8
Lymph node	5
Bone	3
Liver	3
Adrenal gland	2
Treatment	
Sorafenib therapy	4
Sunitinib therapy	6
First-line treatment	8
Second-line treatment	2

and myocardial enzyme tests). Patients were informed of the potential benefits and risks associated with the treatment, and signed consent forms. The drainage tube (10F) was guided by ultrasonic guidance for the patients, and the pleural effusion was fully drained. Four patients received sorafenib (400 mg, twice daily); 6 patients received sunitinib (50 mg, once daily; 2 weeks on and 1 week off). All patients received multi-kinase inhibitor plus pleural cavity perfusion of endostar (15 mg on days 1–4 for 1 or 2 weeks).

The recent objective effects of pleural effusion were evaluated according to WHO standards as follows. Complete response (CR) indicated that the effusion quantity completely disappeared for more than 4 weeks, while partial response (PR) indicated that the effusion quantity had reduced by > 50%. Stable disease (SD) indicated that the effusion quantity had reduced by < 50% or increased by < 25%, while progressive disease (PD) indicated that the effusion quantity was increased by > 25%. The objective response rate was defined as CR + PR. We observed the remissions of patients with cough, shortness of breath, chest pain, and other symptoms associated with pleural effusion, and the treatment-related adverse reactions.

Results

The curative effects were evaluated after 4 weeks of treatment. The response rate of pleural effusion was 70% (7/10). One patient achieved CR and 6 achieved PR, while 3 exhibited SD and 1 exhibited PD. Adverse reactions were limited and mild. One patient had transient cardiac arrhythmia, which was relieved after treatment.

Discussion

Patients with mRCC rarely exhibit malignant pleural effusion simultaneously, and related reports and treatment experiences are limited. Malignant pleural effusion is mostly caused by tumor metastasis to the pleura, and the quality of life of patients with pleural effusion is poor. Patients often experience chest tightness, cough, shortness of breath, and dyspnea, and pleural effusion often causes pulmonary distention and respiratory failure. The median survival time is 6 months.

The administration of pleural hardeners, including talcum powder, is a classic method for the treatment of pleural effusion. The hardener causes aseptic inflammatory reactions and fibroin deposition in the pleural cavity, causing adhesion of the inner chest wall and the visceral pleura, resulting in the reduction or disappearance of the pleural cavity, thus achieving the therapeutic purpose [3]. However, pleural metastasis of tumors can increase the activity of pleural fibrin, often causing pleurodesis failure. In addition, medical talcum powder is unavailable for production and sale for pleural fixation. Ordinary sterilized talcum powder can cause severe chest pain after use, and may infrequently cause respiratory distress syndrome and even endanger life. Pleural cavity injection of cytotoxic drugs such as cisplatin can treat the tumor itself and may reduce the effusion. However, evidence-based medicine is still lacking. In addition, RCC exhibits low sensitivity to cytotoxic drugs [4].

With the development of molecular biology, the related genes and abnormal signaling pathways of RCC are revealed. It is currently believed that the continuous abnormal activation of signaling pathways represented by the von Hippel-Lindau (VHL)–hypoxia inducible factor (HIF)–vascular endothelial growth factor (VEGF) pathway is closely related to RCC [5]. Targeted drugs, including multi-kinase inhibitors, have been widely used clinically to benefit patients with mRCC [6]. VEGF is currently one of the most powerful pro-angiogenesis factors, which can participate in each pathway of angiogenesis directly or indirectly, and is also a key medium to regulate the development of malignant serous cavity effusion [7] . The VHL-HIF-VEGF pathway is activated in RCC, and the expression of VEGF in tumor tissue and serous cavity effusion is increased. Inhibiting the expression of VEGF and its receptors may reduce the generation of malignant serous effusion [8]. Matrix metalloproteinases (MMPs) can degrade the various protein compositions in the extracellular matrix (ECM), destroy the biological

barrier, promote tumor invasion and metastasis, promote tumor angiogenesis, increase the vascular permeability of tumors, and are closely related to the occurrence and development of malignant serous cavity effusion.

Endostatins are recombinant human vascular endostatins, which have been independently developed by Chinese researchers, and have been approved to treat advanced non-small cell lung cancer. Endostar can block VEGF-induced VEGF 2 expression and phosphorylation in vascular endothelial cells, and inhibit the activity of multiple protein kinases downstream of the VEGF receptor (VEGFR) signaling pathway [9] . Simultaneously, endostar can also downregulate the expression of MMP2/9 [10]. Treatment with VEGF and MMPs may be an effective way to treat malignant serous cavity effusion. The combination of multi-kinase inhibitor plus endostar may reinforce local lesion control and treat metastasis throughout the body. The half-life of endostar is shorter, so we administered small intermittent doses of the medicine, and satisfactory effects were obtained. The incidence of adverse reactions of endostatin was low, mainly involving adverse cardiac reactions. No significant adverse reactions were observed in this group. The patients included one case of papillary RCC and one case of chromophobe RCC, all of which obtained PR. VHL gene mutations and high HIF expression are uncommon in papillary RCC, but the expression of VEGF and VEGFR-2 are still increased [11]. The hyperexpression of VEGF and VEGFR are also present in chromophobe RCC, suggesting that the VEGF-related pathway is activated in chromophobe RCC, which provides a theoretical basis for the combination of multi-kinase inhibitor plus endostar [12].

The regimen of multi-kinase inhibitor plus pleural cavity perfusion of endostar is both effective and safe for the treatment of patients with mRCC and pleural effusion, and may also control local symptoms. The method of optimizing the drug delivery model of endostar and the effect of combination therapy on the total survival of patients still needs to be confirmed by further large-scale randomized controlled studies.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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