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The effects of Gualou Qumai Wan combined with Sunitinib on VEGFA, HIF1A, and renal function in advanced clear cell renal cell carcinoma

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Abstract

Objective: To study the efficacy of Gualou Qumai Wan (GQW) combined with Sunitinib in the treatment of advanced clear cell renal cell carcinoma (ccRCC) and its effects on vascular endothelial growth factor A (VEGFA), hypoxia inducible factor 1A (HIF1A), and renal function. **Method:** A retrospective analysis was conducted on 20 patients with advanced ccRCC treated with GQW combined with Sunitinib at Shouguang Hospital of Traditional Chinese Medicine from January 2021 to January 2023. Analyze the patient's quality of life, serum VEGFA and HIF1A levels, renal function indicators, T lymphocyte subgroup levels, traditional Chinese medicine (TCM) symptom scores, and clinical efficacy. **Result:** The total effective rate of clinical efficacy in patients after treatment was 70%; The serum levels of VEGFA and HIF1A in patients were lower than before treatment, and the difference was statistically significant (P<0.05); The levels of serum creatinine (Scr), blood urea nitrogen (BUN), and urinary albumin (ALB) in patients were lower than before treatment, and the differences were statistically significant (P<0.05). Before and after treatment, there was no statistically significant difference in the levels of T lymphocyte subgroup among patients (P>0.05). After treatment, the TCM symptom score and EORTC QoL–C30 score of the patients all decreased compared to before treatment, and the difference was statistically significant (P<0.01). **Conclusion:** The combination of GQW and Sunitinib has a significant therapeutic effect on advanced ccRCC, and can effectively improve the levels of VEGFA, HIF1A, and renal function.

1.   Introduction

Advanced clear cell renal cell carcinoma is a malignant tumor of the urinary system, accounting for a high proportion of kidney tumors. The high-risk age range is between 50 and 70 years old, which seriously affects the quality of life of patients.[1-2] The growth and metastasis of tumors depend on neovascularization, which can provide sufficient nutrition for tumor cells. Among them, VEGFA is a pro endothelial cell growth factor; The expression of HIF1A induced transcription factors is associated with increased distant metastasis and low survival rates in various tumor types. At present, immunotherapy is the main treatment for advanced ccRCC. Sunitinib is a small molecule targeted drug with multi-target tyrosine kinase inhibitory activity, which can inhibit various tyrosine kinase activities, inhibit tumor neovascularization and tumor cell proliferation, and is a first-line therapeutic drug in clinical practice. TCM believes that advanced ccRCC can be classified into categories such as "hematuria", "lower back pain", and "kidney accumulation" based on clinical symptoms. The disease is located in the kidney, and kidney deficiency is the core of the pathogenesis. TCM therapy can help patients with advanced ccRCC recover their body functions, alleviate symptoms, improve quality of life, and prolong survival. Therefore, this study observed the efficacy of GQW combined with Sunitinib in the treatment of advanced ccRCC, and analyzed its effects on VEGFA, HIF1A, and renal function. The summary report is as follows.

2.   Method

2.1   General information

Retrospective analysis of 20 patients with advanced ccRCC treated with GQW combined with Sunitinib at Shouguang Hospital of Traditional Chinese Medicine from January 2021 to January 2023. Among them, there are 12 males and 8 females, with a patient age of 18–70 years old and an average of (46.79±8.54) years old; Among them, there were 11 cases of left ccRCC and 9 cases of right ccRCC, with an average tumor length of (2.58±0.63) cm.

2.2   Inclusion criteria

(1) Pathological diagnosis of advanced ccRCC; (2) Expected survival time>3 months; (3) Age>18 years old; (4) The patient is unable to undergo surgery or cannot tolerate surgery due to other reasons; (5) Patients and their families were informed and agreed to this study.

2.3   Therapeutic method

All patients were treated with GQW combined with sunitinib, taking sunitinib 50 mg orally once a day for 4 weeks; Simultaneously taking GQW orally, the drug composition is as follows: Trichosanthis Radix 10g, Poria Cocos(Schw.) Wolf. 15g, Rhizoma Dioscoreae 15g, Aconiti Lateralis Radix Praeparata 10g, Dianthi Herba 5g, 1 dose/day, 300mL of water decoction juice, 150mL/time, twice a day, taken 30 minutes after breakfast and dinner,

continuously treated for 4 weeks, then stopped for 2 weeks. Patients maintained treatment until intolerable or the condition progressed.

2.4   Observation indicators

(1) The quality of life assessment scale (QoL–C30) for cancer patients was developed by the European Organization for Research and Treatment of Cancer (EORTC) to evaluate the quality of life of patients before and after treatment. (2) Serum VEGFA, HIF1A levels, renal function indicators, and T lymphocyte subgroup levels. (3) According to the relevant symptom scoring standards of the Guiding Principles for Clinical Research of New Chinese Medicines (Trial), the TCM symptom scoring system scores fatigue, abdominal distension, loss of appetite, lumbar acid, loose stools, lustreless face, limb heaviness, and tinnitus symptoms as 1, 2, 3, and 4 points, respectively, based on no, mild, moderate, and severe symptoms. The higher the score, the more severe the symptoms are. (4) Clinical efficacy. The evaluation criteria are: significant effect, lesion reduction 50%; Effective, lesion reduction by 30% to 49%; Invalid, there is no objective evidence of improvement in clinical practice. Total effective rate= (significant+effective)/total number of cases x 100%.

3.   Result

3.1   Clinical efficacy of patients

After treatment, the clinical efficacy of the patients was significantly improved in 5 cases (25%), effective in 9 cases (45%), and ineffective in 6 cases (30%), with a total effective rate of 70% (14/20).

3.2   Comparison of serum VEGFA and HIF1A levels before and after treatment in patients

After treatment, the serum levels of VEGFA and HIF1A in patients were lower than before treatment, and the differences were statistically significant ($P<0.05$), as shown in Table 1.

Table 1 Comparison of serum VEGFA and HIF1A levels before and after treatment in patients

Time	VEGFA/ng·mL^{-1}	HIF1A/ng·mL^{-1}
Before treatment	472.37±95.35	267.43±14.37
After treatment	277.65±75.43*	167.74±12.61*

Compared with before treatment, *$P<0.05$.

3.3   Comparison of T lymphocyte subgroup levels before and after treatment in patients

Before and after treatment, there was no statistically significant difference in the levels of T lymphocyte subgroup among patients ($P>0.05$), as shown in Table 2.

3.4   Comparison of renal function indicators before and after treatment in patients

After treatment, the levels of Scr, blood BUN, and urine ALB in patients were lower than before treatment, and the differences were statistically significant ($P<0.05$), as shown in Table 3.

Table 2 Comparison of T lymphocyte subgroup levels before and after treatment in patients

Time	CD3+/%	CD4+/%	CD3+/ CD4+
Before treatment	68.63±5.54	44.88±4.51	1.76±0.36
After treatment	66.61±5.42	45.43±4.24	1.77±0.35

Table 3 Comparison of renal function indicators before and after treatment in patients

Time	Scr/μmol·L^{-1}	Blood BUN/mmol·L^{-1}	Urine ALB/mg·L^{-1}
Before treatment	95.79±8.69	5.65±1.87	167.54±44.09
After treatment	67.07±7.17*	4.11±0.88*	87.25±22.65*

Compared with before treatment, *P<0.05.

3.5 Comparison of Traditional Chinese Medicine Symptom Scores before and after Treatment

Compared with before treatment, the TCM symptom score of patients decreased after treatment, and the difference was statistically significant (P<0.01), as shown in Table 4.

Table 4 Comparison of TCM Symptom Scores before and after Treatment

Time	Fatigue	Abdominal distension	Loss of appetite	Lumbar acid
Before treatment	3.56±0.61	2.63±0.64	2.67±0.62	3.32±0.69
After treatment	2.59±0.57*	2.05±0.47*	1.79±0.58*	2.39±0.57*

Time	Loose stool	Lustreless face	limb heaviness	Tinnitus	Total score
Before treatment	2.61±0.66	2.97±0.71	3.25±0.63	2.21±0.83	57.59±5.65
After treatment	2.17±0.51*	1.98±0.51*	2.27±0.52*	1.69±0.55*	43.79±3.76*

Compared with before treatment, *P<0.01.

3.6 Comparison of EORTC QoL-C30 scores before and after treatment

Compared with before treatment, the EORTC QoL-C30 score of patients decreased after treatment, and the difference was statistically significant (P<0.01), as shown in Table 5.

4. Discussion

Renal cell carcinoma is one of the most common malignant tumors in the urinary system, which is more common in males and accounts for 5% of all malignant tumors.[3] ccRCC is the most common and malignant type of RCC, with 25% to 30% of patients diagnosed with tumor metastasis, and a 5-year survival rate of only 12%.[4] Vascular endothelial growth factor receptor tyrosine kinase inhibitors are first-line targeted drugs for the treatment of advanced ccRCC, including pezopanib, sunitinib, cabozantinib, etc.[5] Anti angiogenic drugs can also effectively inhibit the proliferation of ccRCC tumor cells and have a significant effect on prolonging the survival of low-risk patients, but the drug has obvious side effects. [6-7]

Table 5 Comparison of EORTC QoL−C30 scores before and after treatment

Time	Effortless activity	Difficulty walking long distances	Difficulty walking short distances	Breathe hard
Before treatment	2.36±0.61	2.79±0.62	2.79±0.69	2.73±0.86
After treatment	2.01±0.42*	2.09±0.47*	2.14±0.39*	2.01±0.64*

Time	Frailty	Anorexia	Diarrhea	Fatigue	Total score
Before treatment	3.51±0.61	2.66±0.61	3.41±0.65	3.32±0.71	73.09±7.61
After treatment	2.59±0.55*	1.78±0.47*	2.41±0.55*	2.39±0.58*	55.07±6.21*

Compared with before treatment, *$P<0.01$.

The development of tumors in the kidneys and bladder is related to the long-term insufficient water supply in the kidneys and bladder, which leads to internal heat. Moreover, internal heat and water deficiency can cause damage to the kidneys and a decrease in metabolic function. The unmetabolized impurities and pathogenic heat create an environment for tumor growth. The foundation of GQW in the treatment of kidney yang deficiency with Aconiti Lateralis Radix Praeparata dispelling cold is to increase the vaporization function of the renal system and enhance transpiration; Using Rhizoma Dioscoreae and Trichosanthis Radix to nourish lung yin. At the same time, these two medicines can strengthen the descending function of the lungs, giving the kidneys strength from top to bottom, ensuring that the kidney qi is "inclusive" and the tumor does not spread, while also filling the body's essence. The purpose of Poria Cocos(Schw.) Wolf. is to remove excess turbid water and reduce the burden on the kidneys. The core difference of this prescription lies in the use of Dianthi Herba. Dianthi Herba is a bitter and cold medicine with functions of clearing heat, removing sewage, eliminating carbuncle, breaking blood, and detoxifying. It can effectively reduce the heat and turbidity of tumors, inhibit tumor growth, and is the finishing touch of this formula.

The results of this study showed that after the combination of GQW and sunitinib treatment, the Scr, blood BUN, and urine ALB levels of patients decreased compared to before treatment ($P<0.05$), while the TCM symptom score and EORTC QoL-C30 score decreased compared to before treatment, with statistical significance ($P<0.01$); The combination of GQW and sunitinib can improve renal function and quality of life in patients with advanced ccRCC. The possible reason for this may be that GQW relieves the immune suppression of tumor cells on immune cells, enhances the immune sensitivity of tumor cells, and enables immune cells to exert their anti-tumor immune effects again, killing tumor cells; Sunitinib has a dual effect of anti-tumor proliferation and anti-tumor angiogenesis, exerting inhibitory effects on tumor blood vessels, blocking the nutrients and blood required for tumor growth. The combination of the two drugs improves efficacy, thereby inhibiting the growth of renal clear cell carcinoma and improving patient prognosis.

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