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ORIGINAL ARTICLE

Efficacy of sorafenib combined with radiofrequency ablation in renal cancer and its effects on immunity and inflammation in patients

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Summary

Purpose: *To explore the efficacy of sorafenib combined with radiofrequency ablation (RFA) in renal cancer and its effects on immunity and inflammation in patients.*

Methods: *A total of 132 patients with advanced renal cancer treated in our hospital from January 2016 to January 2018 were randomly divided into control group and observation group. The patients in the control group were treated with sorafenib, while those in the observation group underwent RFA based on the treatment in the control group. The efficacy, immune function and changes in inflammatory factors in patients were compared between the two groups after treatment.*

Results: *After treatment, the observation group had a significantly higher disease control rate ($p<0.05$), remarkably higher levels of cluster of differentiation 3$^+$ ($CD3^+$) and $CD4^+$, and a notably lower level of $CD8^+$ than the control group. The increases in tumor necrosis factor-a (TNF-a) and interferon-γ (IFN-γ) as well as the decreases in interleukin-6 (IL-6) and C-reactive protein (CRP) were evidently greater in the observation group than in the control group ($p<0.05$). Finally, there was a markedly higher Karnofsky performance status (KPS) score in the observation group than in the control group ($p<0.05$).*

Conclusions: *Sorafenib combined with RFA can significantly improve the therapeutic effect in renal cancer patients, with a high clinical therapeutic value, so it is worthy of clinical popularization and application.*

Key words: *sorafenib, radiofrequency ablation, renal cancer, immunity, inflammation*

Introduction

As the incidence of renal cancer is rising year by year in China, most patients with this malignancy do not receive clinical treatment until they reach advanced stages due to inconspicuous symptoms in early stage [1,2]. The treatments of renal cancer include medical treatment and surgical treatment, and multidisciplinary treatments such as minimally invasive surgery have been used lately [3,4].

Sorafenib, a multi-kinase inhibitor, is commonly administered at present, which can inhibit the mitogen-activated protein kinase (MAPK) signaling pathway, thereby suppressing the growth of tumor cells. Related clinical studies have demonstrated that sorafenib can improve the therapeutic effect on advanced renal cancer, but the desired efficacy of the drug used alone has not been obtained [5,6]. Currently, combination therapies are

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frequently adopted, including sorafenib combined with conventional agents like interleukin-2 (IL-2) [7]. The laparoscope-guided RFA is a relative new method for the clinical treatment of tumors, and can discover the potential lesions through imaging examinations such as B-ultrasound and CT, facilitating the removal of tumor lesions during the operation [8,9]. However, this technique is rarely studied in advanced renal cancer, and RFA combined with sorafenib has not been popularized yet. In the present study, therefore, patients with advanced renal cancer were treated with RFA combined with sorafenib, so as to explore the clinical therapeutic effect of the regimen.

Methods

Clinical data

A total of 132 patients with advanced renal cancer treated in our hospital from January 2016 to January 2018 were divided into the control group (n=66) and the observation group (n=66) using a random number table. There were no differences in the general clinical data between the two groups. All patients signed informed consent after being informed of the treatment methodology and scope. This study was approved by the Ethics Committee of our hospital.

Inclusion criteria: 1) Patients pathologically diagnosed with advanced renal cancer, with an average disease course of less than 6 months; 2) those with a Karnofsky performance status (KPS) score >60 and an expected survival time >3 months; and 3) those without serious dysfunction in the vital organs, such as the heart, liver and kidney.

Exclusion criteria: 1) Patients who had poor compliance or could not cooperate during treatment; 2) those who were treated with immunosuppressants or glucocorticoids; or 3) those allergic to the drug used in the study.

Methods

The patients in the control group were administered sorafenib per os (Bayer, Germany, 200 mg/tablet) twice a day (1 tablet per time). At the same time, IL-2 (Sigma, St. Louis, MO, USA, 1,000,000 U/pcs) was intravenously infused for 15 min, 5 days a week. On the basis of above treatments, the patients in the observation group were treated with RFA. Specifically, after anesthesia with subcutaneous lidocaine (10 g/L) and intravenous analgesia with ketamine (0.1-0.2 mg/kg), a 3 mm-long incision was made at the puncture site, and the radiofrequency needle was placed into the abdomen. Under the guidance of laparoscope, artificial pneumoperitoneum was created to expose the renal tumor, and the tip of the radiofrequency needle was positioned to the center of the tumor under ultrasonic guidance. Next, RFA was performed using a cool circulating pump and radiofrequency generator to kill tumor cells at 60°C. When the radiofrequency needle tip expanded, the transient high-level echo indicated the coagulation necrosis of tumor tissues. After the local tumor tissues were killed, the non-ablated tumor tissues were ablated subsequently using the radiofrequency needle until there was a uniform high-level echo in the tumor tissues. After that, the temperature of the tip was set to 90-100°C for 10 s before the radiofrequency needle was withdrawn, so as to carbonize the needle passage for hemostasis. During the RFA, the power and duration of RFA were adjusted according to the patient's tolerance. After the radiofrequency needle was withdrawn, the wound was pressed to stop bleeding and sutured under the laparoscope, and hemostatic and anti-infective drugs could be applied if necessary. The patients in both groups were followed up for 36 weeks.

Observation indexes

The therapeutic effect was evaluated as follows: Complete remission (CR): The lesions disappear for more than 4 weeks. Partial remission (PR): The product of the largest perpendicular diameters of single largest lesion

Table 1. Comparisons of general clinical data between the two groups of patients

Group	*n*	*Age (years)*	*Gender (male/female)*	*Pathological type*			
				Renal clear cell carcinoma n	*Collecting duct carcinoma n*	*Sarcomatoid carcinoma n*	*Mixed carcinoma n*
Control group	66	59.78±6.09	38/28	48	7	6	5
Observation group	66	60.11±6.32	36/30	52	7	4	3

Table 2. Comparison of therapeutic effect between the two groups of patients

Group	*CR n*	*PR n*	*SD n*	*PD n*	*Disease control rate (%)*
Control group	5	10	12	39	27 (40.9)
Observation group	10	22	19	15	51 (77.3)*

*p<0.05 *vs.* control group

decreases by more than 50% for 4 weeks. Stable disease (SD): The product of the largest perpendicular diameters of single largest lesion decreases by less than 50% or increases by less than 25%, and there are no new lesions. Progressive disease (PD): The tumor volume is expanded by more than 25%, and there are new lesions. The disease control rate= (CR + PR + SD) / total cases × 100%.

Determination of cluster of differentiation 3+ ($CD3^+$), $CD4^+$ and $CD8^+$: fasting venous blood was drawn from patients, added with the fluorescence-labeled monoclonal antibody (20:1) and placed at room temperature for 20 min. Then, the blood was added with the red blood cell lysis buffer for 10 min and washed with phosphate-buffered saline (PBS), followed by centrifugation and flow cytometry.

The content of immunoglobulin A (IgA), IgG and IgM in the serum was determined *via* scattering immunoturbidimetric assay (ELISH) kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China) in strict accordance with the manufacturers'instructions.

The content of interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), IL-4, IL-6 and C-reactive protein (CRP) in the serum was measured *via* enzyme-linked immunosorbent assay (ELISA) strictly according to the instructions of the kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

The quality of life was evaluated by means of the KPS score (0-100 points) involving normal activity, disease conditions and self-care ability. The higher score corresponded to the better physical condition and higher quality of life of patients.

Statistics

SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing and statistics. The measurement data was expressed as mean±SD and *t*-test was performed for evaluation of the difference between two groups. The enumeration data was expressed as case (n), and x^2 was performed for the difference between two groups. Survival curves were plotted according the Kaplan-Meier method and survival differences were detected using log-rank test. P<0.05 suggested that the difference was statistically significant.

Results

Comparisons of general clinical data between the two groups of patients

The general clinical data had no differences between the two groups (p>0.05) (Table 1).

Comparison of therapeutic effect between the two groups of patients

The disease control rate in the observation group (77.3%) was significantly higher than that in the control group (40.9%) (p<0.05) (Table 2).

Comparisons of peripheral blood lymphocyte subsets before and after treatment between the two groups of patients

There were no significant differences in the levels of $CD3^+$, $CD4^+$ and $CD8^+$ between the two groups before treatment. After treatment, however, the levels of $CD3^+$ and $CD4^+$ in the observation group were notably higher than those in the control group, while the level of $CD8^+$ was remarkably lower than that in the control group (p<0.05) (Table 3).

Table 3. Comparisons of peripheral blood lymphocyte subsets before and after treatment between the two groups of patients

Group	*$CD3^+$*		*$CD4^+$*		*$CD8^+$*	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*
Control group	56.09±6.09	59.78±6.45	30.89±3.78	37.67±4.09	25.78±2.89	20.89±2.67
Observation group	56.34±5.98	68.09±7.56*#	31.09±3.97	41.34±4.34*#	26.09±3.09	16.09±1.89*#

*p<0.05 *vs.* control group, #p<0.05 *vs.* before treatment

Table 4. Comparisons of levels of inflammatory factors before and after treatment between the two groups of patients

Group	*TNF-a (pg/mL)*		*IL-4 (pg/mL)*		*IL-6 (pg/mL)*		*CRP (μg/mL)*		*IFN-γ (pg/mL)*	
	Before treatment	*After treatment*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*	*Before treatment*	*After treatment*
Control group	109.34 ±10.89	112.78 ±12.09#	87.78 ±9.78	89.78 ±9.56	189.78 ±20.89	143.78 ±15.09#	16.78 ±2.09	14.09 ±1.98	243.78 ±22.78	280.89 ±29.78#
Observation group	110.98 ±11.89	163.67 ±17.78**#	88.98 ±7.89	89.98 ±9.23	190.78 ±19.78	98.89 ±10.09**#	15.89 ±1.78	8.78 ±1.09**#	249.09 ±25.78	335.78 ±33.78**#

#p<0.05 *vs.* before treatment, **p<0.01 *vs.* before treatment

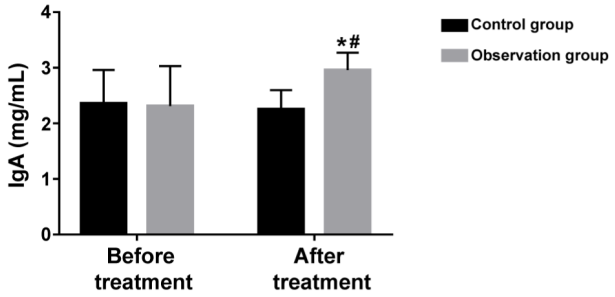

Figure 1. Comparison of IgA level before and after treatment between the two groups of patients (*Compared with before treatment, p<0.05; #Compared with control group, p<0.05).

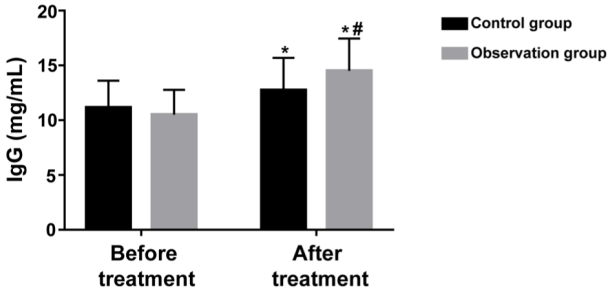

Figure 2. Comparison of IgG level before and after treatment between the two groups of patients (*Compared with before treatment, p<0.05; #Compared with control group, p<0.05).

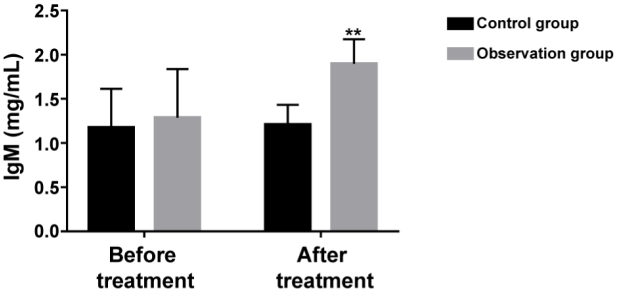

Figure 3. Comparison of IgM level before and after treatment between the two groups of patients (**Compared with before treatment, p<0.01).

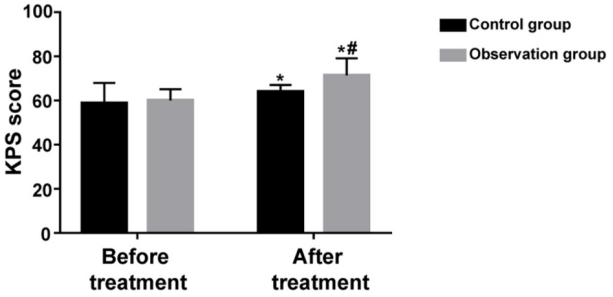

Figure 4. Comparison of KPS score before and after treatment between the two groups of patients (*Compared with before treatment, p<0.05; #Compared with control group, p<0.05).

Comparisons of levels of humoral immunity indexes before and after treatment between the two groups of patients

No differences were detected in the levels of IgA, IgG and IgM between the two groups before treatment. After treatment, the levels of IgA, IgG and IgM were obviously increased in the observation group, significantly higher than those in the control group (Figures 1-3).

Comparisons of levels of inflammatory factors before and after treatment between the two groups of patients

The differences in inflammatory factors TNF-α, IL-4, IL-6, CRP and IFN-γ were not significant between the two groups before treatment. After treatment, there were prominent changes in TNF-α, IL-6, CRP and IFN-γ in both groups. Moreover, the observation group exhibited evidently greater increase in the levels of TNF-α and IFN-γ as well as decrease in the levels of IL-6 and CRP than the control group (p<0.05) (Table 4).

Comparison of KPS score before and after treatment between the two groups of patients

The KPS score had no significant difference between the two groups before treatment (p>0.05), but it was remarkably increased in both groups after treatment, which was notably higher in the observation group than in the control group (p<0.05) (Figure 4).

Discussion

Renal cancer is a highly malignant tumor of the genitourinary system, which is pathologically characterized by extremely rapid progression and an extremely high mortality rate. Renal cancer was mainly treated with IL-2 and TNF-α previously, but the disease is relieved in only 10% of patients as it is not sensitive to such drugs, according to clinical studies [10,11]. In terms of surgical operation, radical nephrectomy and partial nephrectomy are performed for most cases of renal cancer, but their therapeutic effects are far from satisfactory because the majority of renal cancer patients are in advanced stage, accompanied with distant metastasis when diagnosed [12,13]. According to clinical reports, the 5-year survival rate of patients with advanced renal cancer is less than 10%, so the treatment of renal cancer has always been the focus in clinical research.

Renal cancer is mainly treated with drug therapy based on the therapeutic targets, including repression of the vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR) pathway and mTOR pathway, the former of which mainly aims to reduce the nutrition supply to tumor cells and inhibit the growth of new vessels at the tumor site, thereby restraining the tumor development. Sorafenib is a drug commonly

used to inhibit the VEGF/VEGFR pathway, whose major mechanism of action is to inhibit the RAF/MEK/ERK signaling pathway, suppress the VEGFR and platelet-derived growth factor receptor simultaneously, and inhibit the nutrition supply to tumor cells [14-16]. Clinical studies suggest that sorafenib possesses a better clinical therapeutic effect, but its monotherapy cannot significantly extend the long-term survival of patients, so it is often administered in combination with other drugs.

In laparoscopic RFA, the tumor cells are radically eliminated through tissue destruction at the lesion site. Endowed with higher puncture accuracy and resolution, such a technique is able to better determine the size and number of tumor lesions, which is beneficial to restraining the growth of tumor cells [17,18]. At present, the cool-tip RFA has been gradually applied in the treatment of malignant tumors. Tissue carbonization often occurs after traditional RFA due to excess temperature, which increases the impedance and prevents the transmission of energy to the surrounding tissues easily. In cool-tip RFA, however, the temperature of the needle tip can be controlled at about 20°C to avoid the carbonization of tissues around the electrode, so that the energy can be rapidly transmitted to the adjacent tissues, and the solidified lesion is further expanded.

As for patients with advanced renal cancer, the immune function will be destroyed, and the cellular immune function mediated by T lymphocytes will also be seriously affected. T lymphocytes can be classified into $CD3^+$, $CD4^+$ and $CD8^+$, among which $CD4^+$ has an anti-cancer effect and can promote the growth and differentiation of cytotoxic T lymphocytes, and $CD8^+$ is an inhibitory T cell involved in the suppression of immune response [19]. It has been found in clinical studies that the immune function declines and the immune activities are inhibited in cancer patients. B cells, important players in the immune function, primarily mediate the humoral immunity and have close correlations with the differentiation and release of IgA, IgG and IgM. In the present study, it was found that there were no significant differences in the levels of $CD3^+$, $CD4^+$ and $CD8^+$ between the two groups before treatment. After treatment, distinctly elevated levels of $CD3^+$ and $CD4^+$ and notably lowered level of $CD8^+$ were observed in the observation group compared with those in the control group ($p<0.05$). Besides, the levels of IgA, IgG and IgM in the observation group were remarkably higher than those in the control group, indicating that sorafenib combined with RFA can improve the immune function, regulate the growth of immune cells and increase the levels of immune cells. Moreover, the observation group exhibited an obviously higher disease control rate than the control group ($p<0.05$), suggesting that the combination therapy can improve the therapeutic effect on patients. RFA is capable of ablating the tumor tissues through a thermal effect produced by radio waves, which can reduce the wound infection and effectively improve the therapeutic effect on patients. Inflammatory response occurs in most cancer patients, leading to abnormal expressions of inflammatory factors *in vivo*, such as the excessively high or low levels of TNF-α, IL-6, CRP and INF-γ [20]. In the present study, the levels of TNF-α and INF-γ were remarkably higher, while those of IL-6 and CRP were prominently lower in the observation group than those in the control group ($p<0.05$) after treatment, suggesting that the combination therapy can enhance the anti-inflammatory ability and reduce the release of inflammatory factors in patients distinctly. In addition, the KPS score was raised notably in the observation group in comparison with that in the control group after treatment ($p<0.05$). It can be seen that the combination therapy can significantly improve the quality of life, shorten the treatment time, enhance the immunity and inhibit the expression of inflammatory factors, thereby strengthening the therapeutic effect and living ability of patients.

Conclusions

In conclusion, sorafenib combined with RFA can significantly enhance the therapeutic effect, improve the quality of life, improve the immune function and reduce the inflammation in patients with renal cancer, which leads to extremely excellent clinical therapeutic effects.

Conflict of interests

The authors declare no conflict of interests.

References

1. Wong E, Kapoor A. Epidemiology of prostate and kidney cancer in the Aboriginal population of Canada: A systematic review. Can Urol Assoc J 2017;11:E222-32.
2. Petrut B, Hogea M, Tat T, Buse M, Schitcu V, Sparchez Z. Literature review on the feasibility of laparoscopic partial nephrectomy for renal cancer during pregnancy: a propos of a case. J BUON 2018;23:872-6.

3. Yu SS, Quinn DI, Dorff TB. Clinical use of cabozantinib in the treatment of advanced kidney cancer: efficacy, safety, and patient selection. Onco Targets Ther 2016;9:5825-37.
4. Fragkoulis C, Papadopoulos G, Gkialas I, Ntoumas K. The role of tyrosine kinase inhibitors (TKIs) as adjuvant treatment for renal cancer. Where do we stand today? J BUON 2017;22:1608-10.
5. Niinivirta M, Enblad G, Edqvist PH, Ponten F, Dragomir A, Ullenhag GJ. Tumoral cubilin is a predictive marker for treatment of renal cancer patients with sunitinib and sorafenib. J Cancer Res Clin Oncol 2017;143:961-70.
6. Guo G, Cai W, Li H et al. Presurgical neoadjuvant targeted molecular therapy for kidney cancer with concomitant vena cava tumor embolus: A clinical study. Oncol Lett 2017;14:369-75.
7. Sidaway P. Kidney cancer: High-affinity Fc-gamma variants improve IL-2 responses. Nat Rev Urol 2017;14:9.
8. Gorin MA, Allaf ME. Kidney cancer: radiofrequency ablation of small renal masses--more work required. Nat Rev Urol 2012;9:297-8.
9. Gebauer B, Werk M, Lopez-Hanninen E, Felix R, Althaus P. Radiofrequency ablation in combination with embolization in metachronous recurrent renal cancer in solitary kidney after contralateral tumor nephrectomy. Cardiovasc Intervent Radiol 2007;30:644-9.
10. Fu JH, Yang S, Nan CJ et al. MiR-182 affects renal cancer cell proliferation, apoptosis, and invasion by regulating PI3K/AKT/mTOR signaling pathway. Eur Rev Med Pharmacol Sci 2018;22:351-7.
11. Chen YA, Li HN, Wang RC, Hung SW, Chiu KY. Malignant Glomus Tumor of the Kidney: A Case Report and Review of the Literature. Clin Genitourin Cancer 2017;15:e151-3.
12. Forbes CM, Rendon RA, Finelli A et al. Disease progression and kidney function after partial vs. radical nephrectomy for T1 renal cancer. Urol Oncol 2016;34:417-86.
13. Wang Z, Wang G, Xia Q et al. Partial nephrectomy vs. radical nephrectomy for renal tumors: A meta-analysis of renal function and cardiovascular outcomes. Urol Oncol 2016;34:511-33.
14. Roodhart JM, Langenberg MH, Witteveen E, Voest EE. The molecular basis of class side effects due to treatment with inhibitors of the VEGF/VEGFR pathway. Curr Clin Pharmacol 2008;3:132-43.
15. Yokoi K, Kobayashi A, Motoyama H et al. Survival pathway of cholangiocarcinoma via AKT/mTOR signaling to escape RAF/MEK/ERK pathway inhibition by sorafenib. Oncol Rep 2018;39:843-50.
16. Saidak Z, Giacobbi AS, Louandre C, Sauzay C, Mammeri Y, Galmiche A. Mathematical modelling unveils the essential role of cellular phosphatases in the inhibition of RAF-MEK-ERK signalling by sorafenib in hepatocellular carcinoma cells. Cancer Lett 2017;392:1-8.
17. Hildebrand P, Kleemann M, Roblick U, Mirow L, Birth M, Bruch HP. Laparoscopic radiofrequency ablation of unresectable hepatic malignancies: indication, limitation and results. Hepatogastroenterology 2007;54:2069-72.
18. Zhang X, Yan L, Li B et al. Comparison of laparoscopic radiofrequency ablation versus open resection in the treatment of symptomatic-enlarging hepatic hemangiomas: a prospective study. Surg Endosc 2016;30:756-63.
19. Xian P, Li Y, Zhou H, Luo H, Liu N, Dai JY. [Effect of Sunitinib therapy on immune function of patients with advanced renal cell carcinoma]. Zhonghua Wai Ke Za Zhi 2016;54:741-5.
20. de Vivar CA, Finke J, Bukowski R. The role of inflammation in kidney cancer. Adv Exp Med Biol 2014;816:197-234.