

# Sorafenib improves the postoperative effect of early stage renal cell carcinoma

TAIYANG LIU, JIE LI, XIUHUA WEN, ZHANG HUI and GUI QI

Department of Urology, Zhumadian Central Hospital, Zhumadian, Henan 463000, P.R. China

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**Abstract.** Sorafenib was examined to determine whether it improves postoperative effects during early stage renal cell carcinoma (RCC). A total of 133 patients with early renal clear cell carcinoma (T1-2N0M0) with surgical indications were continuously selected. The patients were divided into 3 groups according to different treatments, including the surgery alone group (40 cases), surgery combined with cytokine group (45 cases) and surgery combined with sorafenib group (48 cases), to make a comparison of their clinical effects. The surgery combined with sorafenib group significantly reduced the recurrence rate and increased the survival rate ( $P<0.05$ ). Its median survival period was  $>30$  months and the other 2 groups were 27 months ( $P<0.05$ ). In the subsequent 3 months patients were followed up and it was found that the creatinine levels were significantly elevated and hemoglobin levels were significantly decreased. The sorafenib group had significantly lower creatinine levels and higher hemoglobin levels than the other 2 groups ( $P<0.05$ ). In the 3-month follow-up, vascular endothelial growth factor (VEGF) levels were significantly reduced and tumor necrosis factor (TNF)- $\alpha$  levels were elevated, although the sorafenib group had significantly decreased VEGF levels and a higher TNF- $\alpha$  level than the other 2 groups ( $P<0.05$ ). The adverse reaction rate was significantly lower than that of the surgery combined with cytokines group ( $P<0.05$ ). In conclusion, sorafenib improves the early RCC postoperative survival rate and prolongs the survival time while reducing the recurrence rate. It does not increase adverse reactions, and improves renal function, by decreasing the level of VEGF, and improving the level of TNF- $\alpha$ .

## Introduction

Sorafenib (or nexavar), is an oral multi-kinase inhibitor that inhibits tumor signal transduction in multi-targets and blocks tumor cell proliferation, differentiation and migration (?). It also exerts the effect of inhibiting angiogenesis and inducing apoptosis (1). Sorafenib is an effective molecular-targeted drug in advanced renal cell carcinoma (RCC) and hepatocellular carcinoma (2).

Targeted therapy restricts medicine or the therapeutic effect to specific target cells, tissues or organs. This therapy is obviously superior to traditional radiotherapy and chemotherapy, with fewer adverse effects in advanced malignant tumors (3). It can also improve treatment results and prolong the survival period in advanced differentiated thyroid, lung, gastric, pancreatic and ovarian cancer (4). However, although there has been a focus on advanced tumor, to the best of our knowledge, few studies have been conducted on early-stage resectable tumor (5).

The aim of the present study was to examine whether sorafenib was capable of improving the postoperative effect of resectable tumor in RCC through an analysis of a small sample and a clinical control study at the Zhumadian Central Hospital (Henan, China), to provide a valuable reference for clinical treatment.

## Patients and methods

**Patients.** A total of 133 patients diagnosed with renal clear cell carcinoma at the Zhumadian Central Hospital from June, 2013 to June, 2015 were selected consecutively. The inclusion criteria for the present study were: T1-2N0M0 period in American Joint Committee on Cancer staging of RCCs, no secondary tumor in kidney or kidney stones, patients having completed surgical removal of the tumor and cytokines or sorafenib therapies, no participation in other clinical trials, good compliance and complete clinical data. The exclusion criteria for the study were: impaired kidney function, high level (doubled more than normal) of serum creatinine and urea nitrogen, hemoglobin  $<100$  g/l; history of renal trauma, isolated kidney, solitary kidney, renal tuberculosis; serious hypertension and poor diabetes control, and disease of cardiovascular combined with cerebrovascular, liver function damage, and other underlying diseases intolerable of surgery.

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*Correspondence to:* Dr Taiyang Liu, Department of Urology, Zhumadian Central Hospital, 747 Zhonghua Road, Zhumadian, Henan 463000, P.R. China  
E-mail: hsd337887uky@163.com

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Informed consent was obtained from patients and their families. The ethics committee at the Zhumadian Central Hospital approved the study protocol. The patients were divided into the surgery alone group (40 cases), surgery combined with cytokine group (45 cases) and surgery combined with sorafenib group (48 cases) according to the different treatments. The surgery alone group included 25 men and 15 women, aged 46-68 years with an average age of  $57.5 \pm 10.3$  years; tumor numbers were 1-3 with  $1.6 \pm 0.5$  on average; 32 cases of unilateral and 8 of bilateral; and maximum tumor diameters were 2-7.5 cm with  $4.8 \pm 1.9$  cm on average. The surgery combined with cytokines group included 28 men and 17 women, aged 43-69 years with an average age of  $56.2 \pm 11.4$  years; tumor numbers were 1-3 with  $1.4 \pm 0.6$  on average; 36 cases of unilateral and 9 of bilateral; and maximum tumor diameters were 2.5-8.0 cm with  $4.9 \pm 1.6$  cm on average. The surgery combined with sorafenib group included 29 men and 19 women, aged 44-72 years with an average age of  $59.3 \pm 14.2$  years; tumor numbers were 1-3 with  $1.7 \pm 0.8$  on average; 39 cases of unilateral and 9 of bilateral; and maximum diameters of the tumor were 2.5-8.5 cm with  $5 \pm 1.7$  cm on average. Differences of gender, age, tumor number, location and diameter in the 3 groups had no statistical significance ( $P > 0.05$ ).

**Treatment methods.** The operative methods included radical resection and nephron sparing surgery, and open and laparoscopic surgery, which were carried out according to the standard of medical procedures performed by one surgical and nursing team. There was no statistically significance in the different surgeries of the 3 groups ( $P > 0.05$ ). In the cytokine group, interleukin (IL)-2 was selected for an intravenous injection of 72,000 IU/kg·8 h, used for 5 days followed with 2 days of break, for a total of  $\leq 4$ -12 weeks. In the sorafenib group, sorafenib was injected at 400 mg each time, twice a day, for a total of 4-12 weeks. Any adverse reactions led to drugs being withdrawn.

**Observation index.** The follow-up was continued to January, 2016 and the 2 groups were followed-up 6-30 months; average of 20 months. Recurrence rates, survival rates, serum creatinine, hemoglobin levels, the levels of serum vascular endothelial growth factor (VEGF) and tumor necrosis factor (TNF)- $\alpha$ , and drug adverse reaction rates of the 2 groups were compared as per the commonly used chemotherapy drug toxicity standard CTC 3.0 version. Serum creatinine and hemoglobin levels were detected using conventional biochemical assay, and VEGF and TNF- $\alpha$  were detected using ELISA. Kits were purchased from R&D Systems, Inc. (Minneapolis, MN, USA) and used as per the manufacturer's instructions.

**Statistical analysis.** SPSS 20.0 (IBM SPSS, Armonk, NY, USA) was used for data analysis and processing. Quantitative data were presented as mean  $\pm$  standard deviation and groups were compared with single factor analysis of ANOVA. Qualitative data were expressed as cases number or percentage, and groups were compared using the  $\chi^2$  test. Survival time was compared using the Kaplan-Meier method (log-rank test).  $P < 0.05$  was considered to indicate a statistically significant difference.

Table I. Tumor recurrence and survival rates [cases no. (%)].

Group	Cases	Recurrence rate	Survival rate
Surgery	40	11 (27.5)	31 (77.5)
Surgery combined with cytokines	45	11 (24.4)	38 (84.4)
Surgery combined with sorafenib	48	4 (8.3)	46 (95.8)
$\chi^2$		6.133	6.504
P-value		0.047	0.039

## Results

**Comparison of recurrence rate and survival rate.** The Kaplan-Meier method was used to determine the recurrence and survival rates of different treatments. The results revealed that the surgery combined with sorafenib group had a significantly lower recurrence and higher survival rates (Fig. 1) ( $P < 0.05$ ). The median survival period in the sorafenib group was  $> 30$  months while that in the other 2 groups was 27 months, with a significant statistical difference ( $\chi^2 = 6.214$ ,  $P = 0.045$ ) (Table I).

**Comparison of serum creatinine and hemoglobin levels.** Differences of preoperative serum creatinine and hemoglobin levels were not statistically significant ( $P > 0.05$ ). In 3 months of follow-up, creatinine levels were significantly elevated while hemoglobin levels were significantly decreased. The sorafenib group had decreased creatinine and higher hemoglobin levels than those in the other 2 groups ( $P < 0.05$ ) (Table II).

**Comparison of VEGF and TNF- $\alpha$ .** Differences of preoperative VEGF and TNF- $\alpha$  levels were not statistically significant ( $P > 0.05$ ). In the 3 months of follow-up, VEGF levels were reduced but TNF- $\alpha$  levels were increased. The sorafenib group had significantly lower VEGF and higher TNF- $\alpha$  levels than those in other 2 groups ( $P < 0.05$ ) (Table III).

**Comparison of the incidence of adverse reactions.** The surgery combined with cytokine group had 6 cases of severe abdominal pain and diarrhea, 4 cases of headache, 5 cases of multiple organ dysfunction (such as myocardial ischemia, hypotension, respiratory difficulties, liver and kidney dysfunction, thrombocytopenia, anemia and mental disorders), with a total incidence of 33.3%. The surgery combined with sorafenib group had 3 cases of severe hand or foot skin reaction, 2 cases of hypertension, 1 case of diarrhea, 1 case of fatigue and loss of appetite, with a total incidence of 33.3%, which was significantly lower than those in the cytokine group ( $\chi^2 = 4.521$ ,  $P = 0.033$ ).

## Discussion

VEGF and platelet-derived growth factor is the most important regulatory factor for the promotion of angiogenesis. Sorafenib inhibits tyrosine kinase receptor activity contributing to angiogenesis and tumor development, thus blocking the formation of tumor angiogenesis and cuts off

Table II. Comparison of serum creatinine and hemoglobin level.

Group	Preoperative creatinine, $\mu\text{mol/l}$	Creatinine in 3 months	Preoperative hemoglobin, g/l	Hemoglobin in 3 months
Surgery alone	82.5 $\pm$ 26.3	243.6 $\pm$ 43.2	105.3 $\pm$ 13.2	92.4 $\pm$ 12.8
Surgery combined with cytokines	84.3 $\pm$ 24.7	225.7 $\pm$ 46.9	103.4 $\pm$ 14.6	93.5 $\pm$ 13.2
Surgery combined with sorafenib	85.2 $\pm$ 22.5	163.4 $\pm$ 35.2	102.8 $\pm$ 13.8	96.6 $\pm$ 12.7
F	0.321	5.624	0.632	5.128
P-value	0.465	0.037	0.597	0.044

Table III. Comparison of VEGF and TNF- $\alpha$  (pg/ml).

Group	Preoperative VEGF	VEGF in 3 months	Preoperative TNF- $\alpha$	TNF- $\alpha$ in 3 months
Surgery alone	326.4 $\pm$ 52.6	159.9 $\pm$ 32.6	265.4 $\pm$ 46.2	342.5 $\pm$ 65.4
Surgery combined with cytokines	331.5 $\pm$ 54.2	136.4 $\pm$ 33.4	246.7 $\pm$ 47.8	367.8 $\pm$ 69.3
Surgery combined with sorafenib	329.8 $\pm$ 51.3	79.6 $\pm$ 25.8	253.2 $\pm$ 46.3	532.9 $\pm$ 72.5
F	0.258	5.352	0.825	5.764
P-value	0.137	0.039	0.634	0.035

VEGF, vascular endothelial growth factor; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

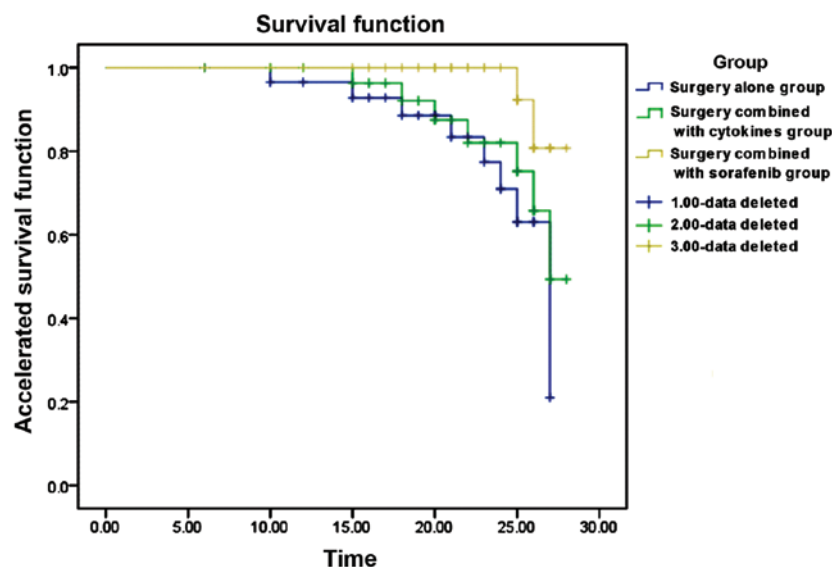


Figure 1. Survival curve by Kaplan-Meier method.

the supply of nutrients to tumor cells and therefore inhibits tumor cell growth indirectly (6). Sorafenib suppresses the Ras/Raf/MEK/ERK signaling pathway, which directly inhibits tumor cell proliferation (7). Sorafenib also suppresses cytokines, such as FLT-3 and C-KIT, which contribute to tumor cell evolution and proliferation, thus directly inhibiting tumor cell proliferation (8). Sorafenib induces tumor cells into the apoptotic process directly (9).

Phase II clinical studies conducted by Kondo *et al* (10) and phase III clinical trials from Mori *et al* (11) confirmed

that sorafenib may improve the therapeutic effect of advanced RCC and increase median progression-free survival. The multicenter and non-control open clinical study (II T) on advanced RCC in China also confirmed the safety and effect of sorafenib. Therefore, sorafenib was the first targeted drug used for RCC (12). The killing effect of G250-DC-CIK cells combined with sorafenib on RCC cells indicated that immune therapy combined with targeted drugs, not only had a direct inhibitory effect on tumor cells, but also killed tumor cells indirectly by regulating the immune system (13).

RCC in early stage has a high surgical resection rate, whereas 30% of the 3-year recurrence rate and 75% of the survival rate has a poor effect (14). In addition, renal carcinoma is not sensitive to radiotherapy and chemotherapy, which leads to treatment failure (15). Cytokine adjuvant therapy including IL-2 and interferon was confirmed not to improve the survival rate with more adverse drug reactions, which reduces patient quality of life (16). The study applied targeted therapy of sorafenib in early stage resectable RCC and found that the surgery alone group had a recurrence rate of 27.5% and survival rate of 77.5%, with no significant difference to the surgery combined with cytokine group. The surgery combined with sorafenib group had a significantly lower recurrence rate (8.3%) and higher survival rate (95.8%), prolonging the median survival time (>30 months, >27 months) with slight impaired renal function, which may be due to the biological activity on inhibition of tumor (17). VEGF levels were significantly lower whereas TNF- $\alpha$  levels were higher. It was suggested that sorafenib exhibited the mechanism of inhibiting tumor growth for early stage RCC, which had a guiding significance to increase the application scope of sorafenib (18). The incidence of adverse drug reactions decreased significantly, with a range of 1-2, and may be alleviated after symptomatic treatment, without drug withdrawal. However, the applying dose and pathway of cytokines, applying time of cytokines and sorafenib may affect study results (19,20). The innovation point of the present study is that the application of sorafenib in early stage RCC also has great therapeutic effect and leads to novel ideas regarding targeted therapy.

In summary, sorafenib can improve the postoperative survival rate of early stage RCC. It prolongs survival time and reduces the recurrence rate without increasing adverse reactions. Sorafenib improves renal function and decreases the level of VEGF and elevates the level of TNF- $\alpha$ .

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