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ORIGINAL ARTICLE

Analysis of efficacy of sorafenib combined with vascular endothelial growth factor inhibitor Avastin in renal cell carcinoma

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Summary

Purpose: *The study was designed to investigate the short-term efficacy of sorafenib combined with vascular endothelial growth factor (VEGF) inhibitor Avastin in the treatment of renal cell carcinoma (RCC).*

Methods: *A total of 64 patients with RCC were selected as objects of study and randomly divided into 2 groups as control group (CG, n=32) and observation group (OG, n=32). Patients in the CG were treated with sorafenib tosylate alone, while those in the OG were treated with Avastin in combination with sorafenib. The changes in the levels of peripheral T lymphocyte subset, natural killer (NK) cells and VEGF, changes in the quality of life (QoL), short-term efficacy, and major clinical adverse reactions were compared between the groups before and after the treatment.*

Results: *The levels of cluster of differentiation CD3+, CD4+, CD4+/CD8+ and NK, and the QoL score in the OG after treatment were significantly increased compared with those in the OG before treatment and in the CG after treatment, while the level of CD8+ was significantly lower than that in the OG before treatment and in the CG after treatment, respectively ($p<0.05$). The level of VEGF in the OG 2 and 3 months after treatment was lower than in the OG before treatment and in the CG after treatment, respectively ($p<0.05$). In the OG, the effective control rate and 3-year survival rate were remarkably higher than those in the CG ($p<0.05$). Moreover, there was no statistically significant difference in the incidence rate of clinical adverse reactions between the two groups ($p>0.05$).*

Conclusion: *Sorafenib combined with Avastin can significantly improve the immune functions, reduce the expression level of VEGF, improve the QoL, prolong the survival time, and obtain satisfactory short-term efficacy in RCC patients, hence suggesting an important application value in RCC.*

Key words: *sorafenib, Avastin, renal cell cancer, immune function, vascular endothelial growth factor, short-term efficacy*

Introduction

Renal cell carcinoma (RCC) is derived from the renal parenchymal urinary tubular epithelial system, which is one of the common malignant tumors in clinical urology, accounting for about 2-3% in all malignant tumors and more than 80% of malignant renal tumors in adults. According to relevant statistical data, the clinical incidence rate of RCC has gradually increased in recent years, making it one of the factors threatening the people health [1,2]. There are no obvious symptoms in the early stage of RCC, so most patients are found with metastasis at the initial diagnosis, bringing about great difficulties in treatment.

Sorafenib is a novel multi-targeted, orally-administered, and small-molecule tyrosine kinase inhibitor (TKI), which acts as a molecular switch in

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the proliferation of oncoproteins through selectively targeting some receptors. Currently, sorafenib has been confirmed as one of the effective therapeutic drugs in a variety of cancers after phase II and III clinical trials in China and foreign countries [3,4]. Avastin is a novel anti-angiogenesis drug inhibiting the vascular endothelial growth factor (VEGF), hence can block the tumor blood flow, inhibit tumor spread, and enhance the chemotherapeutic efficacy [5]. In our study, the short-term efficacy of sorafenib combined with avastin in the treatment of RCC was explored.

Methods

General data

A total of 64 patients with RCC treated in our hospital from August 2015 to August 2017 were included in study. Inclusion criteria: 1) patients meeting the diagnostic criteria for RCC via clinical imaging along with pathological and laboratory examinations [6]; 2) advanced or metastatic RCC; 3) patients with an expected survival >3 months. Exclusion criteria: 1) patients with autoimmune diseases or severe coagulation disorders; 2) pregnant or lactating women; 3) patients with active infection; or 4) patients who were allergic to related drugs. This study was reviewed and approved by the Ethics Committee of Tianjin Medical University General Hospital, and patients or their families signed written informed consent.

Patients in the CG were treated with sorafenib alone, while those in the OG were administered avastin in combination with sorafenib. Sorafenib tosylate (Bayer Pharma AG, approval No.: H20160201, 200 mg*60 tablets/box) was given orally, in a fasted state, 400 mg twice a day (Bid). High-fat diet was prohibited within 2 h after drug administration. If severe toxic reactions occurred after drug administration, the drug dosage could be reduced by half or the treatment could be interrupted. The time of drug readministration was determined according to the patient improvement or relief of toxic reactions after dose modification.

Patients in the OG were treated with sorafenib in combination with bevacizumab-avastin (Roche & Genentech, Inc., Basel, Switzerland, NDC: 50242-060-01, 100 mg/4 mL). Bevacizumab was administered as a solution for intravenous infusion at an initial dose of 5 mg/kg once every 14 days. Before infusion, bevacizumab was diluted with 0.9% sodium chloride solution to 100 mL and infused once every 2 weeks for 90-120 min at the first time, and the infusion time was adjusted later according to the patient tolerance during the first infusion, with all subsequent infusions being administered over 30 min. Patients in both groups were treated for 3 courses in all (3 months per course), with 4 weeks interval between 2 courses.

Observation indexes

The levels of peripheral T lymphocyte subset, natural killer (NK) and VEGF, major clinical adverse reactions, and quality of life (QoL) were compared between the two groups before and after the treatment. The levels of peripheral T lymphocyte subset and NK were detected using the Attune NxT flow cytometer (Thermo Fisher, Waltham, MA, USA), the level of VEGF was detected via enzyme-linked immunosorbent assay (ELISA) using the ELISA kit (MSK, BIO), and QoL was evaluated using the QoL Questionnaire-Core 30 (QLQ-C30) [7], in which the body, role, emotional and social functions were scored, with the higher scores corresponding to better improvement in QoL.

Therapeutic evaluation

The short-term efficacy was evaluated according to the *Response Evaluation Criteria in Solid Tumors* [8], and it is divided into 4 parts as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). CR: After treatment the lesion disappears, there are no new lesions, and the serum tumor markers return to normal (maintained >1 month). PR: After treatment the maximum diameter of lesion declines by more than 30%, and the serum tumor markers return to normal (maintained >1 month). SD: After treatment the maximum diameter of lesion does not increase or it decreases by less than 30%. PD: The maximum diameter of lesion increases >20% or there are new lesions. Effective control rate = [(CR + PR + SD)/total cases] × 100%. Patients were followed up for 3 years and the survival in both groups was recorded.

Statistics

SPSS 19.00 (SPSS Inc., Chicago, IL, USA) was used for data analysis and processing. Measurement data in

Table 1. Comparison of baseline data between the groups

Item	*Observation group (n=32)*	*Control group (n=32)*	t/x^2	*p*
Male/female	21/11	20/12	0.019	0.890
Age (years)	30-69	29-68	-	-
Average age (years)	55.46±5.33	54.76±5.24	0.101	0.460
Pathologic type				
Clear cell carcinoma, n (%)	20 (28.00)	21 (27.12)	0.007	0.934
Papillary cell carcinoma, n (%)	5 (16.00)	4 (16.95)	0.046	0.831
Granular cell carcinoma, n (%)	7 (28.00)	7 (30.51)	0.053	0.818

line with normal distribution, such as peripheral T lymphocyte subsets, NK, VEGF, and QLQ-C30 score, were expressed as mean±standard deviation, and independent *t*-test was used for quantitative data analysis. Numerical data were expressed as percentages (%). Chi-square test was adopted for the comparisons of short-term efficacy and clinical adverse reactions between the two groups, and Kaplan-Meier analysis was performed for survival. P<0.05 suggested that the difference was statistically significant.

Results

Comparisons of changes in the levels of peripheral T lymphocyte subsets and NK between the two groups before and after the treatment

First, there were no statistically significant differences in clinical data between the two groups of patients (p>0.05) (Table 1). There were no statistically significant differences in the levels of CD3+, CD4+, CD8+, CD4+/CD8+ and NK between the groups before the treatment (p>0.05). In the CG, the levels of CD3+ and CD4 after treatment were significantly increased (p<0.05), while there were no changes in CD8+, CD4+/CD8+ and NK (p>0.05). The levels of CD3+, CD4+, CD4+/CD8+, and NK in the OG after treatment were significantly higher than those in the OG before treatment and in the CG after treatment, while the level of CD8+ was markedly lower than that in the OG before treatment and in the CG after treatment, respectively (p<0.05) (Table 2).

Comparison of changes in the VEGF level between the groups before and after treatment

There were no statistically significant differences in the VEGF level between the groups before and at 1 month after treatment (p>0.05), and its level significantly declined at 2 and 3 months after treatment (p<0.05). The levels of VEGF in the OG at 2 and 3 months after treatment were significantly lower than those in the CG (p<0.05) (Table 3).

Table 2. Comparison of the changes in the levels of peripheral T lymphocyte subsets and NK between the groups before and after treatment (mean±SD)

Group	*n*	*Time*	*CD3+ (%)*	*CD4+ (%)*	*CD8+ (%)*	*CD4+/CD8+*	*NK*
Control group	32	Before treatment	63.74±5.44	30.12±5.07	32.46±5.21	0.93±0.24	13.35±3.54
		After treatment	67.64±4.96	34.77±4.11	33.13±4.15	1.05±0.27	13.11±3.27
t/p within the group			3.765/<0.001	4.030/<0.001	0.569/0.571	1.879/0.065	0.282/0.779
Observation group	32	Before treatment	63.83±5.50	30.94±5.12	32.57±4.82	0.92±0.29	13.42±3.46
		After treatment	72.11±5.11	41.13±4.64	29.46±3.17	1.38±0.31	18.47±5.56
t/p within the group			9.253/<0.001	9.161/<0.001	3.049/0.003	6.129/<0.001	4.362<0.001
t/p between the groups after treatment			5.139/<0.001	5.804/<0.001	3.975/<0.001	4.541/<0.001	4.701<0.001

Table 3. Comparison of the changes in VEGF level between the groups before and after the treatment (mean±SD, pg/mL)

Group	*n*	*Before treatment*	*1 month after treatment*	*2 months after treatment*	*3 months after treatment*
Control group	32	330.53±35.47	317.88±33.59	301.57±29.33	278.42±23.18
Observation group	32	329.87±35.53	311.65±33.48	279.45±28.78	221.16±21.34
t		0.074	0.743	3.045	10.281
p		0.941	0.460	0.003	<0.001

Table 4. Comparison of QoL score between the groups before and after the treatment (mean±SD, points)

Group	*n*	*Time*	*Body function*	*Role function*	*Emotional function*	*Social function*
Control group	32	Before treatment	61.55±5.33	46.62±6.08	55.45±6.11	47.11±6.13
		After treatment	67.74±5.78	51.12±5.56	60.67±5.73	54.14±5.09
t/p within the group			4.454/<0.001	3.090/0.003	3.525/0.001	4.991/<0.001
Observation group	32	Before treatment	61.27±5.31	47.18±5.87	56.04±6.24	47.24±6.27
		After treatment	72.24±5.65	57.43±5.47	66.78±5.67	59.12±5.46
t/p within the group			8.003/<0.001	7.226/<0.001	7.206/<0.001	8. 083/<0.001
t/p between the two groups after treatment			3.149/0.003	4.576/<0.001	4.288/<0.001	3.774/<0.001

Table 5. Comparison of major clinical adverse reactions between the groups

Group	*n*	*Fever*	*Hemorrhage*	*Diarrhea*	*Nausea*	*Fatigue*	*Total incidence rate*
Control group	32	8 (25.00)	0 (0.00)	3 (9.38)	5 (15.63)	4 (12.50)	20 (62.50)
Observation group	32	5 (15.63)	3 (9.38)	3 (9.38)	4 (12.50)	2 (6.25)	17 (53.13)
x^2							0.577
p							0.448

Table 6. Comparison of short-term efficacy between the groups

Group	*n*	*CR*	*PR*	*SD*	*PD*	*Effective control rate*
Control group	32	0 (0.00)	10 (31.25)	7 (21.88)	15 (46.87)	17 (53.13)
Observation group	32	2 (6.25)	14 (43.75)	9 (28.13)	7 (21.88)	25 (78.12)
x^2						4.433
p						0.035

Table 7. Median survival time and survival rate in both groups

Group	*n*	*Mean survival time (months)*	*Survival rate, n (%)*		
			1 year	*2 years*	*3 years*
Control group	32	27.45±7.56	21 (65.63)	15 (46.88)	11 (34.38)
Observation group	32	42.35±7.21	28 (87.50)	24 (75.00)	20 (62.05)
x^2		7.635	3.135	4.201	3.516
p		<0.001	0.077	0.040	0.033

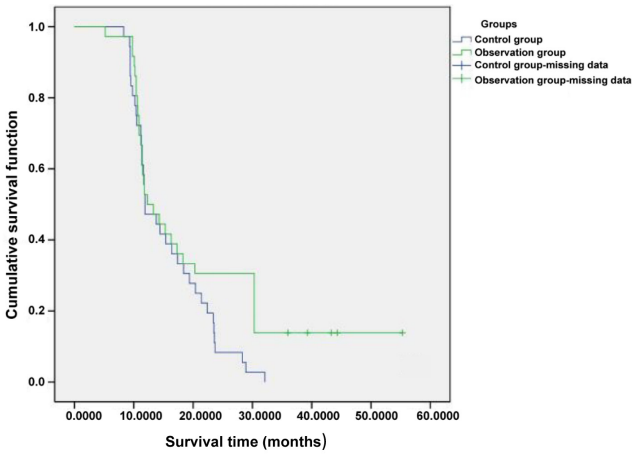

Figure 1. Kaplan-Meier survival in both groups (p<0.05).

Comparison of QoL score between the groups before and after the treatment

The scores of body, role, emotional and social function had no statistically significant differences between the groups before the treatment (p>0.05). After treatment the scores of body, role, emotional, and social function in both groups were significantly increased (p<0.05) and were remarkably higher in the OG than those in the CG (p<0.05) (Table 4).

Comparisons of major clinical adverse reactions between the groups

In the OG, there were 5 cases with fever, 3 cases with hemorrhage, 3 cases with diarrhea, 4 cases with nausea and 2 cases with fatigue, with total incidence rate of adverse reactions being 53.13% (17/32). In the CG, there were 8 cases with fever, 3 cases with diarrhea, 5 cases with nausea and 4 cases with fatigue, and no case of hemorrhage, with total incidence rate of adverse reactions being 62.50% (20/32). There was no statistically significant difference in the incidence rate of major clinical adverse reactions between the groups (p>0.05) (Table 5).

Comparison of short-term efficacy between the groups

The total effective control rate in the OG [78.12% (25/32)] was significantly higher than that in the CG [53.13% (17/32)] (p<0.05) (Table 6).

Comparison of survival rate between the groups

The 3-year follow-up showed that the median survival time in the OG was longer than that in the CG (p<0.05), with no significant difference in the 1-year survival rate between the groups (p>0.05). The 2- and 3-year survival rates in the OG were re-

markably higher than those in the CG ($p<0.05$) (Table 7). Moreover, the survival rate in both groups was analyzed via Kaplan-Meier analysis and the results revealed that the survival in the OG was significantly longer than that in the CG ($p<0.05$) (Figure 1).

Discussion

The clinical incidence rate of RCC ranks only second in urologic cancers following bladder cancer, with an increasing trend in recent years [9]. In terms of RCC subtypes, clear cell is the dominant type, accounting for approximately 85%, while other types such as papillary cell carcinoma and granular cell carcinoma account for about 15% [10]. At present, according to researches, the pathogenesis of RCC still remains unclear but is closely related to some factors including genetics, immunity, smoking, obesity, and hypertension [11,12]. With the ongoing advances in science and medical technology in recent years, the pathogenesis of RCC has been gradually understood, and its onset has close correlations with various cancers and tumor suppressor genes, among which the abnormal expression of von Hippel-Lindau (VHL) gene can lead to rapid activation and expansion of hypoxia-inducible factor, thus activating the overexpression of VEGF, transforming growth factor-α (TGF-α) and platelet derived growth factor-β (PDGF-β), and promoting the reproduction, migration, spread and survival of RCC cells [13]. Clinical studies have proved that the efficacy and safety of targeted therapy for VHL gene in RCC patients are much superior to those of IFN-α and IL-2 [14].

Sorafenib is a novel multi-targeted tyrosine kinase inhibitor, which not only directly blocks the RAF-MEK-ERK signaling pathway to inhibit the cancer cell growth through blocking the downstream effector of RAS protein but also blocks the tumor neovascularization through inhibiting the expressions of VEGF, c-KIT and PDGF, thus exerting an indirect antitumor effect [15]. In general, the utilization rate of sorafenib can be up to 40-50%, which, however, can be significantly reduced by the high-fat diet. To improve the clinical utilization rate, high-fat diet should therefore be avoided within 2 h after drug administration [16]. Currently, a large number of phase II and III clinical trials have been performed in China and foreign countries, and sorafenib has shown an obvious effect in prolonging the survival of patients, hence the mean survival time of patients has been prolonged by 2.5-8.0 months [17]. Avastin is a novel anti-angiogenesis drug, which can block the tumor blood flow through inhibiting VEGF, hence inhibiting the tumor spread *in vivo* and further enhancing the clinical therapeutic effect [18]. In our study, the expression level of VEGF in the OG at 2 months after treatment declined more significantly than that in the CG, indicating that sorafenib combined with avastin was significantly better in improving the VEGF levels in RCC patients.

Studies have demonstrated that the serious inhibition on immune function is one of the important factors leading to RCC, and peripheral T lymphocyte subsets are classic cellular immune indexes. The expressions of peripheral T lymphocyte subsets (CD3+, CD4+, CD4+/CD8+, and NK) in RCC patients are significantly lower than those in normal people [19]. The results of our study revealed that sorafenib combined with avastin could remarkably increase the expression levels of CD3+, CD4+, CD4+/CD8+, and NK in the peripheral blood of RCC patients and improve the immune function of patients, thereby controlling the metastasis and spread of lesions and prolonging survival.

Adverse reactions are inevitable clinical phenomena in the process of radiotherapy and chemotherapy. According to relevant survey data regarding sorafenib, fever, nausea, vomiting, diarrhea, hand-foot syndrome and fatigue are common clinical adverse reactions. Avastin may increase the risks of hemorrhage, hypertension and congestive heart failure [20]. In this study, adverse reactions occurred in different degrees in both groups, with no statistically significant differences. In addition, the disease control rate and the improvement in QoL in the OG were significantly superior to those in the CG, suggesting that sorafenib combined with avastin had significant effects in improving the QoL and controlling the disease in RCC patients.

In conclusion, sorafenib combined with avastin can significantly improve the immune function, reduce the expression level of VEGF, improve the QoL, prolong the survival, and obtain satisfactory short-term efficacy in RCC patients, thus having an important application value in the treatment of RCC.

Conflict of interests

The authors declare no conflict of interests.

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