First-line Treatment Result Influence Second-line Regimen Selection in Targeted Therapy for Metastatic Renal Cell Carcinoma

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Abstract. *Background: Sequential treatments using various targeted-therapies have been recommended for metastatic renal cell carcinoma. However, regimen selection remains difficult when adapting to various clinical situations. Patients and Methods: From 2006 to 2012, 29 patients who received sequential targeted-therapy at our hospital were included for analysis of the treatment regimens and outcome. Results: Patients who used sunitinib as first-line and axitinib as second-line treatment experienced a similar second-line treatment duration, as those used the same first-line and everolimus as the second-line regimen. The first-line sunitinib treatment duration was longer in the axitinib group. Conclusion: Our data showed a promising sequential treatment result using sunitinib-axitinib and sunitinib-everolimus. In patients whose first-line sunitinib treatment resulted in primary resistance, second-line everolimus was found to still contribute a fair degree of disease control. Patients who responded to first-line sunitinib could also achieved fair disease control using second-line axitinib.*

Targeted-therapy has become the most common treatment for metastatic renal cell carcinoma (MRCC). Thus far, seven regimens have been approved by the US Food and Drug Administration and have been used clinically (1-7). Sequential strategies with a one by one regimen have been proven to improve progression survival in several clinical trials (8-11). In real-world practice, regimen selection is still a challenging issue for physicians. Currently, based on clinical trial designs, patients are divided into outcome risk groups before treatment according to various scoring systems. The Memorial Sloan-Keterring Caner Center (MSKCC) risk score and Heng's score are the mostly widely used (12, 13). In first line regimens, tyrosin kinase inhibitors (TKI), including sunitinib, bevacizumab plus interferon and pazopanib have been recommended in treatment naive, good and intermediate risk groups with clear cell MRCC. Temsirolimus is recommended in the poor risk group or non-clear cell MRCC. In the second line setting, everolimus and axitinib are considered treatment options after first line TKI failure (14). In order to understand more about composition efficacy, we retrospectively collected out data and focused on sequences after first line sunitinib treatment failure.

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Patients and Methods

From December 2006 to June 2013, 66 patients who received at least 2 lines of targeted therapeutic agents for MRCC were included. Patients who had interruption of treatment for more than one month during each therapy were excluded. The one month design was based on clinical trial regulation. Patients who received cytokine therapy as the first line setting were also included. Finally, there were 29 patients that matched our inclusion criteria. Data collection was based on a retrospective chart review in a medical center in Taiwan. The patients' characteristics include initial pathologic cell type, MSKCC factors, first line, second line or third line therapy medication and treatment duration, as well as patient overall survival. The treatment duration was defined as continuous medication within the period without interruption for one month. The endpoint was recorded on each patient's chart or considered to be the time of the last drug prescription being issued. The decision to interrupt treatment was based on disease progression, severe adverse events, patient tolerability and other considerations of the physician. We selected our patients who received sunitinib as the

first line regimen into analysis and sub-grouped them into two major groups which were sunitinib-axitinib and sunitinib-everolimus. Statistical analysis could not be performed due to the small patient population. However, overall survival analysis between sunitinib-axitinib and sunitinib-everolimus groups was still performed with patients censored at the date of their death or at last follow-up.

Results

Seventy-two patients received targeted-therapy for treatment of metastatic renal cell carcinoma at our institute since 2006. Nineteen male patients and ten female patients with a mean age of 39.3 years (range 10 to 63 years) receiving at least two consequent targeted regiments were included. Among them, 11 patients also received third line targeted therapies. The majority of patients had clear cell features (83%) and, among them, 3 patients had also mixed sarcomatoid features. Papillary features account for 10% of all patients and there was only one patient with unclassified histology. Almost 90% of the patients had favorable or intermediate risk at the beginning of their MRCC treatment. There were 4 patients that had received previous cytokine therapy (Table I). The majority of patients received sunitinib as first-line targeted-therapy (22 in 29). There were also 5 patients who received sorafenib, 1 everolimus and 1 bevacizumab-plus-interferon as their first- line regimens. The first-line median treatment duration was 11.5 months using sunitinib, 5.1 months using sorafenib, 3.7 months using bevacizumab and 8.6 months using everolimus. In the second-line therapy, 8 patients received axitinib treatment, 10 received everolimus, 7 received sorafenib and 4 received temsirolimus. The second-line median treatment duration was 10.6 months in the axitinib group, 9.2 months in the everolimus group, 3.4 months in the sorafenib group and 3.0 months in temsirolimus group (Table II).

We sub-grouped patients who received sunitinib-everolimus and sunitinib-axitinib as a sequential treatment for comparison. There were 6 patients divided into the sunitinib-everolimus group and 8 patients into the sunitinib-axitinib group. The first-line sunitinib treatment duration was 8.8 months in the everolimus group and 14.7 months in the axitinib group. The second-line treatment duration was 9.2 months in the everolimus group and 10.6 months in the axitinib group (Figure 1). There were 3 patients who were in the sunitinib-axitinib group who received third-line everolimus treatment having 21.8, 24.0 and 27.6 months of third-line treatment duration, respectively. The survival analysis using log-rank test showed no statistical significance between the two groups with a median overall survival of 36 months in the sunitinib-everolimus group and 48 months in the sunitinib-axitinib group (Figure 2).

Table I. *Patient characteristics who received at least two lines of targeted therapy.*

	Patient number	%
Age (years)	52.8 (26-76)	
Gender		
Male	19	65.5
Female	10	34.5
Cell type		
Clear	25	86.2
Papillary	3	10.3
Unclassified	1	3.5
Sarcomatoid feature	3	10.3
MSKCC score		
0	12	41.4
1-2	14	48.3
≥3	3	10.3
Prior cytokine	4	13.8

MSKCC: Memorial Sloan-Keterring Caner Center risk score.

Table II. *Overall regimen selection and treatment duration.*

	Patient number	%
1st line regimen		
Sunitinib	22	75.9
Sorafenib	5	17.3
Everolimus	1	3.4
Bevacizumab	1	3.4
1st line duration	Median months (range)	
Sunitinib	11.5 (1.2-20.4)	
Sorafenib	5.1 (2.7-17.2)	
Everolimus	8.6	
Bevacizumab	3.7	
2nd line regimen		
Axitinib	8	27.6
Everolimus	10	34.5
Sorafenib	7	24.1
Temsirolimus	4	13.8
2nd line duration	Median months (range)	
Axitinib	10.6 (4.3-41.6)	
Everolimus	9.2 (0.7-18.7)	
Sorafenib	3.4 (3.1-23.4)	
Temsirolimus	3.0 (2.1-4.9)	

Discussion

The treatment of MRCC has tremendous progress shifting from cytokine therapy to targeted-therapy in the 21st century. Currently sunitinib, bevacizumab plus interferon and pazopanib are the most commonly recommended TKI in the first line setting in favorable and intermediate risk clear cell MRCC. Although these agents were supported by solid clinical evidence, the high expense of treatment still

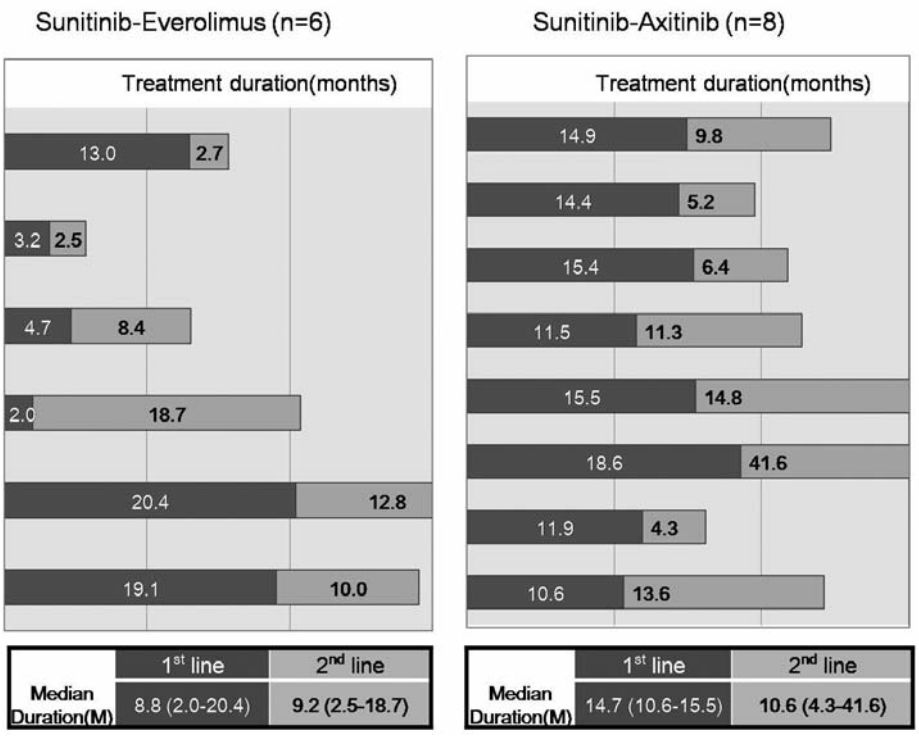

Figure 1. *Comparison of two groups in the treatment duration. Each bar represent the treatment duration of one patient. The second line treatment durations were similar in both groups. The first line treatment duration was longer in the sunitinib-axitinib group than in the sunitinib-everolimus group.*

influences regimen selections. Similar situations have also developed in the second-line targeted-therapy prescription. The RECORD-1 study showed a benefit in progression-free survival using the mammalian target of rapamycin inhibitor (mTORi) after first line TKIs failure (15). This scenario led to a possible anti-resistance treatment philosophy in the subsequent regimen selections. However, the AXIS trial revealed that newly-developed TKIs may still work after prior TKI treatment failed (7). This new evidence has made the concept of anti-resistance somewhat confusing and has influenced second-line regimen selection in clinical practice.

Some retrospective studies reported their experience in sequential treatments of MRCC. Busch *et al*. revealed a better overall survival using the TKI-mTORi-TKI sequence. In their treated patients, the majority of second-line TKI used was sorafenib. Axitinib accounted for only 1 percent of the total second-line TKI. Furthermore, the percentage of poor risk group patients was much more in the TKI-TKI-mTORi sequencing than in the TKI-mTORi-TKI. The selection bias may influence the treatment comparison and result in some misinterpretation (16). Vicker *et al*. reported a similar overall survival using second line TKI or mTORi. In their patients' groups, the first line TKI included sunitinib and sorafenib. The second line TKI included sunitinib, sorafenib, bevacizumab with interferon and axitinib. It is worth noting that the mTORi patients accounted for only 11% of the total number of patients (17). Clearly, combination comparison selection bias existed and we still could not definitively establish the ideal selection with regard to second-line regimen. An indirect comparison of axitinib and everolimus was reported by Sherman *et al*. They used a matching-adjusted comparison of patients who experienced sunitinib resistance during their first-line treatment. There were 43 patients collected in the everolimus group and 194 patients in the axitinib group. They found that median progression survival was similar in both groups with 4.8 months in the axitinib group and 5.1 months in the everolimus group. This result showed a similar potency of everolimus and axitinib in the second-line, sunitinib-refractory setting (18). Our data corresponded to this result which showed a similar second line treatment duration using everolimus (9.2 months) and axitinib (10.6 months) after first-line sunitinib failure. However, if we looked back to first line sunitinib treatment duration between both groups, the axitinib group revealed a longer treatment duration (14.7 months) than that of the everolimus group (8.8 months). This finding indicated a possible targeted sequencing after first line sunitinib failure. That is, if first-line treatment duration could reach a fair standard, such as 11 months in the sunitinib trial, then the second line treatment option would favor axitinib. If the first line treatment duration could not reach this standard,

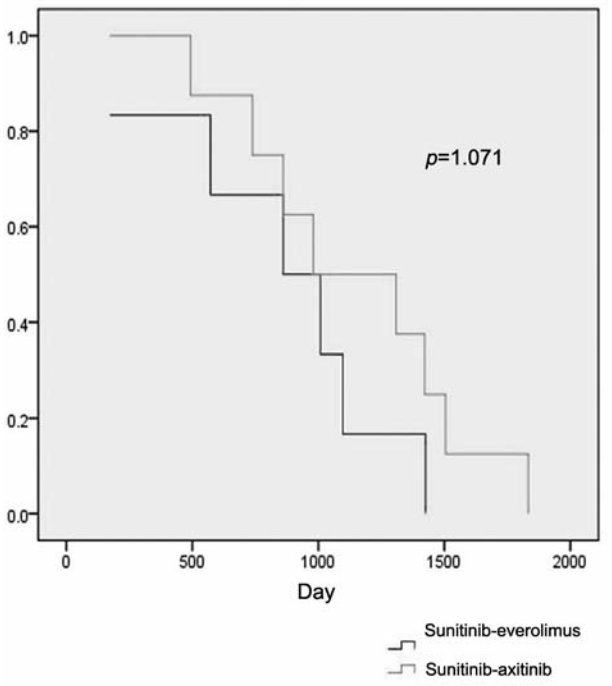

Figure 2. *Survival comparison in sunitinib-everolimus and sunitinib-axitinib groups. Log-rank survival analysis showed no difference in overall survival between two groups.*

then everolimus used in the second line setting could still maintain the disease control status. With this concept in mind, this study also indicated possible solutions in terms of management of primary resistance in some patients who encountered rapid progression during their initial TKI treatment. Besides, our individual patient treatment outcome seemed to correspond to this hypothesis. There were 3 patients who had third-line treatment and had a treatment duration of more than 20 months. Among them, the second-line regimens were all axitinib and the third-line regimens were everolimus. This reminded us that everolimus could still have a role to play after two lines of TKI therapy. Although our study showed only case experiences in the sequential treatment of MRCC and the existence of an obvious selection bias, these limited data do provide us with an indication of a suitable regimen selection after first-line sunitinib failure.

Conflicts of Interest

All Authors declares no conflict of interest

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