SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 7: 454-460, 2017

Progression-free survival of first-line treatment with molecular-targeted therapy may be a meaningful intermediate endpoint for overall survival in patients with metastatic renal cell carcinoma

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Received December 7, 2016; Accepted May 22, 2017

DOI: 10.3892/mco.2017.1320

Abstract. The aim of the present study was to investigate the association between clinical parameters and the overall survival (OS) of Japanese patients with metastatic renal cell carcinoma (mRCC). The medical records of 59 consecutive mRCC patients receiving molecular-targeted therapy were retrospectively assessed. Kaplan-Meier and log-rank analyses were used to evaluate the progression-free survival (PFS) and OS, and a multivariate Cox proportional hazard model was used to analyze the clinical parameters for their prognostic relevance. The median OS for all patients was 23.7 months [95% confidence interval (CI): 17.9-30 months], and the median OS stratified by the Memorial Sloan Kettering Cancer Center risk classification was 28.5, 20.9 and 8.1 months for the favorable-, intermediate- and poor-risk groups, respectively (P=0.137; degree of freedom: 2). Univariate analyses identified prior nephrectomy, number of metastatic sites, anemia, best response to first-line treatment and PFS with first-line treatment as prognostic variables. Multivariate analyses identified number of metastatic sites [2: hazard ratio (HR)=3.351, 95% CI: 1.460-8.201, P=0.004; ≥3: HR=6.397, 95% CI: 1.939-20.209, P=0.003], time from diagnosis to therapy (≥1 year: HR=0.334, 95% CI: 0.137-0.755, P=0.008), PFS with first-line treatment (≥5.1 months: HR=0.353, 95% CI: 0.156-0.766, P=0.008) and number of lines of molecular-targeted agents (≥3: HR=0.248, 95% CI: 0.091-0.664, P=0.006) as independent prognostic factors. The results indicated that the PFS of first-line treatment may be a meaningful intermediate endpoint for OS in patients with mRCC who received treatment with molecular-targeted therapy.

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Key words: metastatic renal cell carcinoma, molecular-targeted therapy, progression-free survival, overall survival, Memorial Sloan Kettering Cancer Center risk classification

Introduction

Renal cell carcinoma (RCC) accounts for 2-3% of all adult cancers and represents the third most common urological malignancy in Europe (1). At diagnosis, one-third of patients present with locally advanced or metastatic disease, and one-third of patients undergoing nephrectomy will eventually develop metastasis (2,3). Previously, immunotherapy agents, such as interleukin-2 and interferon (IFN)-α, were the only treatments available and achieved response rates of ~10-22% (4-9). In recent years, however, the strategy for treating metastatic RCC (mRCC) has changed from immunotherapy to the administration of molecular-targeted therapies, such as multitargeted inhibitors of tyrosine kinases, and mammalian target of rapamycin. Therefore, the establishment of a tool for predicting the effect of targeted agents for mRCC is of critical importance.

One of the most well-established classification systems for patients with mRCC is the Memorial Sloan Kettering Cancer Center (MSKCC) system reported by Motzer *et al* in 1999 (10) and modified in 2002 (11). This model was independently validated by investigators at the Cleveland Clinic and has been used for the study and interpretation of cytokine and targeted drug therapies (12). In this era of molecular-targeted therapy, prognostic factors for mRCC other than the MSKCC risk classification system have been identified, such as the serum C-reactive protein (CRP) level (13,14), metastatic status (15,16) and tumor shrinkage (17). However, there have been few reports on independent prognostic factors.

To further investigate the association between clinical parameters and overall survival (OS) in mRCC, a retrospective analysis of consecutive patients treated with molecular-targeted therapy at the Kyushu Cancer Center (Fukuoka, Japan) was performed.

Patients and methods

Patients and survival. A total of 59 patients undergoing molecular-targeted therapy for mRCC at the Kyushu Cancer Center (Fukuoka, Japan) between May 2008 and September 2015 were retrospectively investigated.

Progression-free survival (PFS) was assessed and defined as the time from the initiation of first-line molecular-targeted therapy to the day tumor progression was proven or death occurred. The patients were censored at the date of the last follow-up. The OS was investigated from the initiation of first-line molecular-targeted therapy to the time of death as a result of any cause or censored at the date of the last follow-up.

Pre- and post-treatment factors. The evaluated pretreatment factors included age, gender, pre-treatment therapy, histological type, number of metastatic sites, low Eastern Cooperative Oncology Group performance status, low hemoglobin levels (men <13.5 g/dl and women <11.5 g/dl), high serum lactate dehydrogenase levels (LDH; >1.5-fold the upper limit of normal), high corrected serum calcium levels (>10 mg/dl), short time from diagnosis to therapy (<1 year), MSKCC risk classification, and pre-treatment serum CRP level (normal, <0.3 mg/dl). The post-treatment factors included best response to first-line treatment, worst adverse event with first-line treatment, PFS of first-line molecular-targeted agents and the number of lines of molecular-targeted agents.

Toxicity and response to treatment. Decisions regarding adverse events were made based on the Common Terminology Criteria for Adverse Events, version 4.0 (18). Tumor response was evaluated as the best response according to the Response Evaluation Criteria In Solid Tumors, version 1.1 (19).

Ethical considerations. All the patients provided their written informed consent to participate in this study, and the study protocol was approved by the Ethics Committee of the Kyushu Cancer Center (Fukuoka, Japan).

Statistical analysis. The statistical analyses were performed using the JMP Pro software package, version 11.0.0 (SAS Institute, Inc., Cary, NC, USA). PFS and OS were determined using the Kaplan-Meier method, and the log-rank test was used to determine the differences between the MSKCC risk groups and the PFS of first-line treatment groups. The significance of the clinicopathological parameters associated with OS was assessed using the Cox proportional hazards regression model. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. The study cohort comprised 59 patients who underwent molecular-targeted therapy for mRCC, the characteristics of whom are listed in Table I. Of these 59 patients, 10 were not treated by nephrectomy, but instead underwent needle biopsies of either the primary or metastatic tumor to determine the histological subtype. Therefore, all the included patients were pathologically diagnosed with primary RCC. The majority of the patients were diagnosed with mRCC of clear cell histology. According to the MSKCC criteria, the favorable-, intermediate- and high-risk groups comprised 17 (28.8%), 34 (57.6%) and 8 (13.6%) patients, respectively.

OS and profile of molecular-targeted therapy for mRCC. The median OS for all the patients was 23.7 months [95% confidence interval (CI): 17.9-30 months; Fig. 1 and Table II], and the median duration of first-line treatment was 5.1 months (95% CI: 2.1-8.1 months). A total of 44 patients (74.6%) were treated with sunitinib as first-line treatment. Regarding the response to first-line treatment, 13 patients (22.1%) achieved objective tumor remission (complete or partial response), 32 patients (54.2%) had stable disease, and 14 patients (23.7%) had progressive disease. Regarding the number of lines of molecular-targeted agents, 22 patients (37.3%) received 1, 15 (25.4%) received 2, and 22 (37.3%) received ≥3 lines of treatment.

OS for all patients with mRCC stratified using the MSKCC risk classification. The median OS stratified by MSKCC risk classification was 28.5, 20.9 and 8.1 months for the favorable-, intermediate- and poor-risk groups, respectively (Fig. 2, P=0.137; degree of freedom: 2). No significant difference in the OS was observed between the favorable- and intermediate-risk (P=0.271), the favorable- and poor-risk (P=0.066), or the intermediate- and poor-risk groups (P=0.143).

Univariate and multivariate analyses of the association between various factors and OS. To identify the prognostic factors associated with OS, univariate and multivariate analyses were performed using the Cox proportional hazards model (Table III). Univariate analyses for various factors identified prior nephrectomy, number of metastatic sites, anemia, best response to first-line treatment and PFS with first-line treatment as prognostic variables. Multivariate analyses identified the number of metastatic sites (2: HR=3.351, 95% CI: 1.460-8.201, P=0.004; ≥3: HR=6.397, 95% CI: 1.939-20.209, P=0.003), time from diagnosis to therapy (≥1 year: HR=0.334, 95% CI: 0.137-0.755, P=0.008), PFS with first-line treatment (≥5.1 months: HR=0.353, 95% CI: 0.156-0.766, P=0.008) and number of lines of molecular-targeted agents (≥3: HR=0.248, 95% CI: 0.091-0.664, P=0.006) as independent prognostic factors.

OS for all patients with mRCC according to PFS with first-line treatment. First-line PFS was analyzed to determine its association with OS (Fig. 3). Patients with PFS ≥5.1 months had a significantly longer OS (26.3 months) compared with those with PFS <5.1 months (OS: 15.1 months) (P=0.032; degree of freedom: 1).

Discussion

Molecular-targeted therapy has markedly changed the treatment strategy for mRCC, and several recent studies have investigated the clinical prognostic factors. At present, the most widely used system is the MSKCC classification, which may facilitate prognostic individualization in mRCC patients who received systemic therapy (11). However, despite being validated in the era of molecular-targeted therapy (20), this model was developed based on data from patients treated with

Table I. Patient characteristics (n=59).

Characteristics	No.
Age, years	
Median (range)	67 (38-82)
Gender	
Male	42
Female	17
Histological type	
Clear cell renal cell carcinoma	49
Papillary renal cell carcinoma	4
Carcinoma of the collecting ducts of Bellini	3
Renal cell carcinoma, unclassified	3
Pre-treatment	
Nephrectomy	49
Interferon-α	9
Interleukin-2	2
Metastatic sites	
Lung	40
Lymph node	20
Bone	16
Pancreas	5
Liver	5
Brain	4
Adrenal glands	4
Others	9
No. of metastatic sites	
1	26
2	25
3	5
≥4	3
ECOG PS	
0	44
1	13
2	1
3	0
4	1
High lactate dehydrogenase	
Yes	5
No	54
Low serum hemoglobin	
Yes	26
No	33
High corrected serum calcium	
Yes	6
No	53
Time from diagnosis to therapy <1 year	
Yes	38
No	21
MSKCC risk classification	
Favorable	17
Intermediate	34
Poor	8
High C-reactive protein	
Yes	28
No	31

MSKCC, Memorial Sloan Kettering Cancer Center; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table II. Overall survival and profile of molecular-targeted therapy for mRCC (n=59).

Variables	No.
Overall survival, months	
Median (range)	23.7 (1.2-70.1)
Duration of first-line treatment, months	
Median (range)	5.1 (0.2-55.2)
First-line treatment	
Sunitinib	44
Sorafenib	10
Axitinib	2
Temsirolimus	2
Pazopanib	1
Everolimus	0
Best response to first-line treatment	
CR or PR	13
SD	32
PD	14
Adverse event to first-line treatment	
Grade <3	21
Grade ≥3	28
No. of lines of molecular-targeted agents	
1	22
2	15
3	11
4	8
5	1
6	2

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; mRCC, metastatic renal cell carcinoma.

IFN-α in a clinical trial. Therefore, there is a need for a system that allows for a more precise assessment of the prognostic risk in patients with mRCC receiving molecular-targeted therapy, since such a tool would be useful for counseling patients, evaluating therapeutic options and planning treatment. However, only few reports have identified any independent prognostic factors. Therefore, the aim of the present study was to retrospectively investigate the prognostic factors for patients with mRCC treated with molecular-targeted agents.

The current estimates for the median OS in patients with mRCC range from 22.9 to 26.4 months (21,22). The OS of 23.7 months in the present study falls within this range (Fig. 1), indicating that molecular-targeted agents have been administered appropriately at our institution. The median OS stratified by the MSKCC risk classification was 28.5, 20.9 and 8.1 months for the favorable-, intermediate- and poor-risk groups, respectively (P=0.137; degree of freedom: 2). While the OS of the favorable-risk group was longer compared with that of the intermediate- and poor-risk groups, no significant difference in the OS was found between the favorable- and intermediate-risk (P=0.2713), the favorable- and poor-risk (P=0.0664), or the intermediate- and poor-risk groups (P=0.1426). Therefore, univariate and multivariate analyses were retrospectively performed using the Cox proportional hazards model in consecutive patients treated with molecular-targeted therapy, to determine the association between the OS and clinical parameters, including five risk factors of the MSKCC risk classification (Table III). Univariate analyses for various factors identified prior nephrectomy, number of metastatic sites, anemia, best response to first-line treatment and PFS with first-line treatment as prognostic variables. Furthermore, multivariate analyses identified the following as independent prognostic factors: Number of metastatic sites (2: HR=3.351, 95% CI: 1.460-8.201, P=0.004; ≥3: HR=6.397, 95% CI: 1.939-20.209, P=0.003) and time from diagnosis to therapy (≥1 year: HR=0.334, 95% CI: 0.137-0.755, P=0.008) as pre-treatment factors, and PFS with first-line treatment (≥5.1 months: HR=0.353, 95% CI: 0.156-0.766, P=0.008) and number of lines of molecular-targeted agents (≥3: HR=0.248, 95% CI: 0.091-0.664, P=0.006) as post-treatment factors.

The pre-treatment factor 'time from diagnosis to therapy' is included in the MSKCC system, and subsequent studies conducted to validate the prognostic factors for RCC have evaluated the time from diagnosis to the initiation of systemic therapy (23-25). However, a survival analysis stratified by the number of disease sites is not often performed in clinical trials, although it may represent an additional prognostic factor of outcome. Grassi *et al* reported that the presence of >2 disease sites was associated with a statistically significantly shortened PFS and OS (26). The number of metastatic sites may thus be a surrogate for the tumor burden, which may be easily evaluated, although it does not include the spread of metastases.

Currently, the most widely used prognostic factor model is based on the MSKCC (11). Adverse prognostic factors in a multivariable analysis included a low Karnofsky performance status (<80%), high LDH (>1.5 times the upper limit of normal), low serum hemoglobin levels, high corrected serum calcium levels (>10 mg/dl), and a time from initial diagnosis to treatment of <1 year. Based on these five risk factors, each patient was assigned to one of three risk groups: Favorable risk (0 risk factors), intermediate risk (1-2 risk factors) and poor risk (≥3 risk factors). This means that the MSKCC risk is classified based only on the number of factors present, not each risk factor or any combination. Therefore, the breadth of cases included, particularly in the intermediate- and poor-risk groups, is wide, and variations naturally exist among patients, even within each risk group. As such, urological oncologists recognize that even patients in the same risk group may not achieve the same results. From this standpoint, it may be

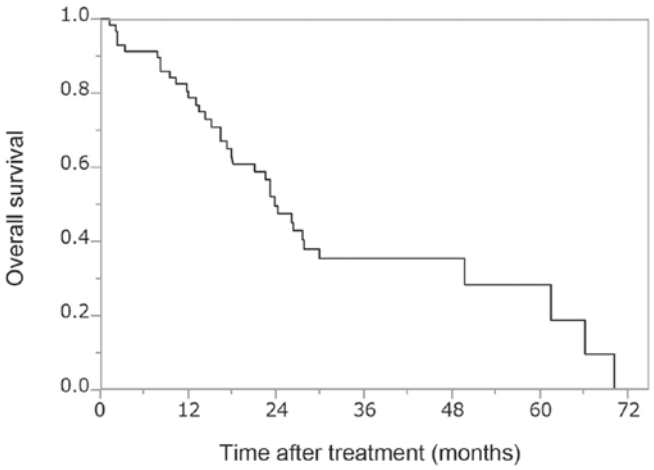

Figure 1. Kaplan-Meier estimates of OS for all patients with mRCC. The median OS was 23.7 months (95% CI: 17.9-30 months). OS, overall survival; CI, confidence interval; mRCC, metastatic renal cell carcinoma.

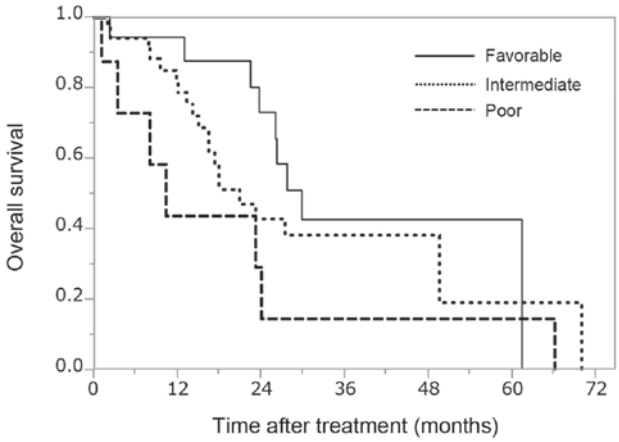

Figure 2. Kaplan-Meier estimates of OS for all patients with mRCC stratified using the MSKCC risk classification. The median OS stratified by the MSKCC risk classification was 28.5, 20.9 and 8.1 months for the favorable-, intermediate- and poor-risk groups, respectively (P=0.137; degree of freedom: 2). OS, overall survival; mRCC, metastatic renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center.

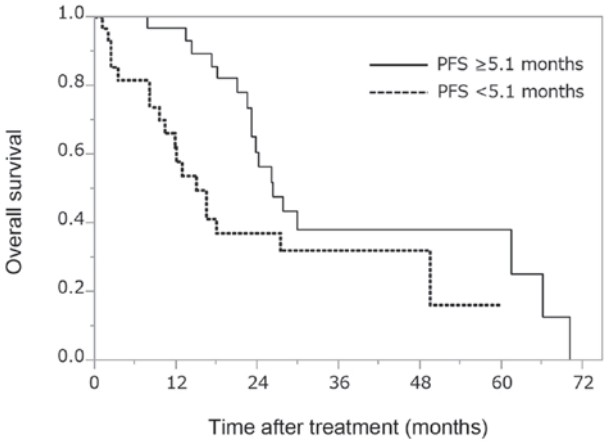

Figure 3. Kaplan-Meier estimates of OS for all patients with mRCC according to the PFS with first-line therapy. Patients with a PFS of ≥5.1 months had a significantly better OS (26.3 months) compared with those with a PFS of <5.1 months (15.1 months) (P=0.032; degree of freedom: 1). OS, overall survival; PFS, progression-free survival; mRCC, metastatic renal cell carcinoma.

Table III. Univariate and multivariate analyses of the association between various factors and overall survival.

	Univariate		Multivariate	
Factors	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age, years				
<67	1			
≥67	0.726 (0.365-1.432)	0.354		
Sex				
Men	1			
Women	0.610 (0.257-1.300)	0.208		
Prior nephrectomy				
Yes	1		1	
No	2.951 (1.160-6.611)	0.025	1.671 (0.573-4.569)	0.335
Histological type				
Clear cell	1			
Non-clear cell	1.354 (0.566-2.894)	0.472		
No. of metastatic sites				
1	1		1	
2	2.752 (1.256-6.475)	0.011	3.351 (1.460-8.201)	0.004
≥3	4.603 (1.526-12.966)	0.008	6.397 (1.939-20.209)	0.003
ECOG performance status				
0	1			
≥1	1.795 (0.815-3.674)	0.139		
Anemia				
No	1		1	
Yes	2.066 (1.043-4.160)	0.037	1.152 (0.479-2.963)	0.761
Elevated serum lactate dehydrogenase				
No	1			
Yes	1.321 (0.293-4.072)	0.679		
High corrected serum calcium				
No	1			
Yes	1.563 (0.462-3.997)	0.431		
Time from diagnosis to therapy, years				
<1	1		1	
≥1	0.545 (0.248-1.113)	0.097	0.334 (0.137-0.755)	0.008
Pre-treatment C-reactive protein level, mg/dl				
<0.3	1			
≥0.3	1.631 (0.838-3.217)	0.149		
Best response to first-line treatment				
Progressive disease	1		1	
Stable disease	0.391 (0.179-0.867)	0.022	0.589 (0.249-1.396)	0.226
Complete or partial response	0.211 (0.074-0.553)	0.002	0.536 (0.162-1.666)	0.285
Worst adverse event to first-line treatment				
Grade <3	1			
Grade ≥3	0.792 (0.401-1.626)	0.514		
PFS with first-line treatment, months				
<5.1	1		1	
≥5.1	0.479 (0.237-0.954)	0.036	0.353 (0.156-0.766)	0.008
No. of lines of molecular-targeted agents				
1	1		1	
2	1.066 (0.453-2.511)	0.882	0.977 (0.397-2.398)	0.959
≥3	0.437 (0.186-1.031)	0.059	0.248 (0.091-0.664)	0.006

PFS, progression-free survival; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

argued that post-treatment as well as pre-treatment variables are important as prognostic factors.

In the present study, a significant difference was observed, not in the best response to first-line treatment, but in PFS with first-line treatment (≥5.1 months: HR=0.353, 95% CI: 0.156-0.766, P=0.008) in the multivariate analysis, and these results were naturally obtained after molecular-targeted agent administration. Recent analyses have demonstrated that patients with insufficient response to first-line treatment have a dismal prognosis (27,28). Siedal *et al* suggested that early tumor shrinkage is a prognostic tool, and superior tumor shrinkage is associated with a favorable prognosis (17). The patients in that analysis were stratified into five groups according to the change in the tumor size at the first-treatment evaluation, whereas the present study stratified patients into three groups according to the best response to first-line treatment. However, the best response to first-line treatment was not found to be an independent prognostic factor in the present study. This result suggested that the clinical response rate may not reflect the survival time. In another study, Seidal *et al* suggested that a PFS with first-line treatment of >6 months was an independent prognostic marker (29). Heng *et al* also mentioned that a PFS of 6 months under first-line vascular endothelial growth factor-targeted treatment was applied as a cut-off marker and proved capable of significantly differentiating patients with favorable and poor prognosis (30). These descriptions are consistent with our observations in the present study, although the duration of PFS with the first-line treatment was slightly different in the previous study. The longer PFS with first-line treatment may thus be associated with the better prognosis observed in patients with mRCC. These results appear to be important, not only for urological oncologists, but also for patients in clinical practice; thus, even patients in the same risk group may achieve a different OS compared with what was expected prior to treatment administration. Given that urological oncologists naturally interact with patients from pre-treatment to post-treatment, they have several opportunities to explain to their patients their condition and prognosis. Urological oncologists may therefore be able to discuss a patient's prognosis with greater specificity after treatment administration. This information may greatly help patients make important decisions.

In addition, multivariate analyses also identified the number of lines of molecular-targeted agents (≥3: HR=0.243, 95% CI: 0.089-0.654, P=0.005) to be an independent prognostic factor. Ko *et al* demonstrated that patients with mRCC who were able to receive more lines of molecular-targeted therapy lived longer, with longer PFS (31). These results suggest that sequential therapy with molecular-targeted agents may prolong the survival of patients with mRCC.

Multiple candidate predictive and prognostic biomarkers have been evaluated (32-38). However, the association between the OS and these biomarkers was not examined in these previous studies. At present, no available biomarkers are superior to clinical parameters, such as those used for the MSKCC score.

The limitations of such an analysis are its retrospective nature and the small number of patients enrolled. However, our experience from everyday clinical practice has highlighted the potential use of such information on the prognostic role of PFS with first-line treatment with molecular-targeted therapy for mRCC. The results of the present study indicate that the PFS of first-line treatment may be a meaningful intermediate endpoint for OS in mRCC patients treated with molecular-targeted therapy.

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