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Early primary renal tumor response predicts clinical outcome in patients with primary unresectable renal cell carcinoma with synchronous distant metastasis receiving molecularly targeted therapies

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Abstract. The aim of the present study was to investigate the prognostic factors for patients with primary unresectable renal cell carcinoma (RCC) with synchronous distant metastasis receiving molecularly targeted therapies. A total of 26 patients with primary unresectable RCC with synchronous distant metastasis underwent molecularly targeted therapies at the Kurume University Hospital (Kurume, Japan) between March 2008 and March 2016. Early primary renal tumor response was evaluated at 8-12 weeks after the introduction of molecularly targeted therapy and a 10% decrease in the diameter of primary renal tumor was used as the cut-off value. The median overall survival from the initiation of first-line molecularly targeted therapy was 18.3 months. Univariate analyses for various factors identified early primary renal tumor response (P=0.0004) and best response to first-line treatment (P=0.0002) as prognostic variables. Multivariate analyses also identified early primary renal tumor response (P=0.0099) and best response to first-line treatment (P=0.0054) as independent prognostic factors. A comparison of clinical characteristics between the group with ≥10% shrinkage and the group with disease progression or <10% shrinkage revealed that the number of metastatic sites and pretreatment monocyte-to-lymphocyte ratio tended to be predictive factors for primary renal tumor response. These results suggest that early primary renal tumor shrinkage is highly variable for patients with primary unresectable RCC with synchronous distant metastasis receiving molecularly targeted therapies.

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Key words: early tumor response, primary unresectable renal cell carcinoma, molecularly targeted therapy, prognosis, metastasis

Introduction

Over the last several years, the therapeutic strategy for metastatic renal cell carcinoma (mRCC) has included the administration of molecularly targeted agents, such as multitargeted tyrosine kinases inhibitors and mammalian target of rapamycin inhibitors, rather than immunotherapy as first-line therapy. In the targeted therapy era, several studies have reported an overall survival (OS) benefit in mRCC patients receiving cytoreductive nephrectomy (CN) (1,2). However, certain patients may be unable to receive CN due to locally advanced disease, multiple metastases or poor performance status (PS) at initial diagnosis. These patients occasionally receive molecularly targeted therapies as initial treatment. Several studies have demonstrated that early primary tumor shrinkage predicted a better overall primary tumor response (3,4). These studies validated 10% primary tumor shrinkage as a reliable early predictor of outcome in mRCC patients receiving vascular endothelial growth factor (VEGF)-targeted therapies, and this may provide a practical measure to guide therapeutic decisions (4). However, there is no consensus on the optimal treatment of mRCC patients with synchronous distant metastasis.

The aim of the present study was to investigate the prognostic factors for patients with primary unresectable RCC with synchronous distant metastasis receiving molecularly targeted therapies.

Patients and methods

Patient evaluation. A total of 26 patients with primary unresectable RCC with synchronous distant metastasis underwent molecularly targeted therapies at the Kurume University Hospital (Kurume, Japan) between March 2008 and March 2016. These patients were considered unable to receive CN due to locally advanced disease, multiple metastases and/or poor PS at initial diagnosis. Clinical data, including age, gender, Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification, CN status, tumor stage, lymph node stage, number

of metastatic sites, site of metastasis, anemia, pretreatment C-reactive protein level, pretreatment neutrophil-to-lymphocyte ratio, pretreatment monocyte-to-lymphocyte ratio (MLR) and pretreatment platelet-to-lymphocyte ratio were retrieved from medical records and retrospectively analyzed.

Prior to the initiation of molecularly targeted therapy, radiological evaluations were performed for all patients by computed tomography (CT). Tumor measurements were conducted by CT prior to the initiation of treatment. Early primary renal tumor response was evaluated at 8-12 weeks after the introduction of molecularly targeted therapy and a 10% decrease in the diameter of the primary renal tumor was used as the cut-off value based on previous reports (3,4). Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1 (https://ctep.cancer.gov/protocoldevelopment/docs/recist_guideline.pdf).

Statistical analysis. The OS from the initiation of molecularly targeted therapy to the date of death was determined using the Kaplan-Meier method and analyzed using the log-rank test. To identify the prognostic factors associated with OS, Cox proportional hazards regression was used. Univariate and multivariate analyses were performed for independent prognostic factors for OS. The associations between groups were compared using the Chi-squared test, Fisher's exact test or Student's t-test. All the statistical analyses were performed using JMP software, version 11 (SAS Institute, Inc., Cary, NC, USA) and a value of $P<0.05$ was considered to indicate a statistically significant difference. This study was approved by the Ethics Review Committee of the Kurume University School of Medicine.

Results

Patient characteristics. The patient characteristics are summarized in Table I. All the patients had metastatic disease at diagnosis. The median patient age was 69 years (range, 47-81 years) and the majority of the patients were male (73.1%). All the MSKCC risk groups were represented among the patients, with 57.7% of the patients being classed as intermediate- and 42.3% as poor-risk. The majority of the patients had lung metastases, and half of all patients had lymph node metastases. A total of 17 (65.4%) patients had ≥2 metastatic sites at diagnosis; 5 (19.2%) patients underwent CN during the course of treatment.

Treatment. The profile of first-line molecularly targeted therapy and pretreatment laboratory data are shown in Table II. The majority of the patients received sunitinib (69.2%) as the first-line molecularly targeted agent.

Survival analysis. The OS curve for all patients is shown in Fig. 1. The median OS from the start of first-line molecularly targeted therapy was 18.3 months [95% confidence interval (CI): 4.0-32.2 months]. Cox proportional hazards regression was used to identify the associations with OS among known prognostic factors (Table III). Univariate analyses for various factors revealed early primary renal tumor response [hazard ratio (HR)=10.956, 95% CI: 2.691-74.262, P=0.0004) and best response to first-line treatment (HR=26.067, 95% CI: 4.111-510.816, P=0.0002) as prognostic variables. Multivariate analyses also identified early primary renal tumor response (HR=8.060, 95% CI: 1.644-58.233, P=0.0099) and best response to first-line treatment (HR=12.580,

Table I. Characteristics of 26 patients with primary unresectable renal cell carcinoma with synchronous distant metastasis receiving molecularly targeted therapies.

Patient and tumor characteristics	No. (n=26)
Age, years (range)	69 (47-81)
Gender	
Male	19
Female	7
ECOG PS	
0,1	17
≥2	9
MSKCC risk classification	
Favorable	0
Intermediate	15
Poor	11
Cytoreductive nephrectomy	5
Clinical T stage	
T1	3
T2	4
T3	7
T4	12
N stage	
N0	12
N1	4
N2	10
Number of metastatic sites	
1	9
≥2	17
Site of metastasis	
Lung	21
Bone	8
Liver	5
Brain	3
Others	4
Anemia	
No	11
Yes	15
NLR, median (range)	3.65 (1.7-22.6)
MLR, median (range)	0.32 (0.16-1.07)
PLR, median (range)	217.4 (107.7-494.4)
CRP, mg/dl, median (range)	1.56 (0.13-15.66)

ECOG PS, Eastern Cooperative Oncology Group performance status; MSKCC, Memorial SloanKettering Cancer Center; NLR, neutrophil-to-lymphocyte ratio; MLR, monocytetolymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein.

Table II. Profile of molecularly targeted therapy.

Patient and tumor characteristics	No. (n=26)
First-line treatment	
Sunitinib	18
Pazopanib	3
Sorafenib	2
Temsirolimus	2
Axitinib	1
Best response to first-line treatment	
PR	3
SD	15
PD	8

PR, partial response; SD, stable disease; PD, progressive disease.

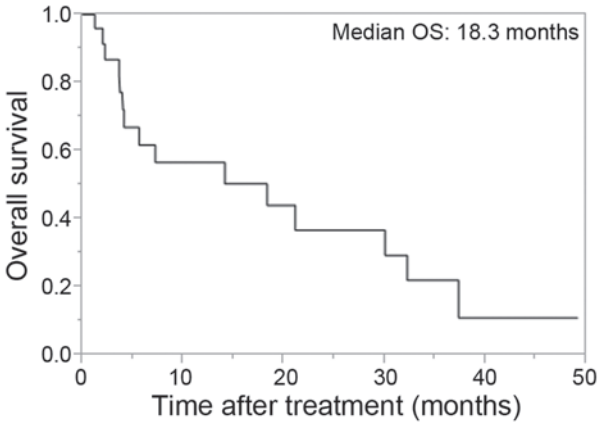

Figure 1. Overall survival (OS) in patients with primary unresectable renal cell carcinoma with distant metastasis receiving molecularly targeted therapies.

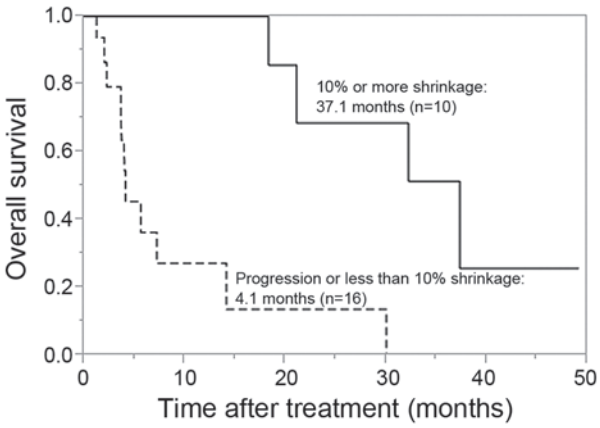

Figure 2. Overall survival in patients with primary unresectable renal cell carcinoma with distant metastasis receiving molecularly targeted therapies stratified according to early primary tumor response. Patients with ≥10% shrinkage on the first follow-up computed tomography had a significantly longer overall survival compared with patients exhibiting disease progression or <10% shrinkage (P=0.0005).

95% CI: 1.971-247.566, P=0.0054) as independent prognostic factors.

Patients in the CN group tended to have a longer OS compared with patients in the non-CN group. However, there was no significant difference between the CN and the non-CN groups (P=0.079).

Early primary renal tumor response was analyzed for its association with OS (Fig. 2). The median OS was 37.1 months in the group with ≥10% shrinkage on the first follow-up CT and 4.1 months in the group with progression or <10% shrinkage. There was a significant difference in the OS rates between the two groups (P=0.0005).

Table IV shows a comparison of baseline characteristics between the group with ≥10% shrinkage and the group with progression or <10% shrinkage on the first-follow up CT. Metastasis to ≥2 organs (P=0.0313) and pretreatment MLR (P=0.0459) were higher in the group with progression or <10% shrinkage compared with in the group with ≥10% shrinkage. The patients with progression or <10% shrinkage on the first follow-up CT tended to have lymph node metastasis (P=0.0513) and bone metastasis (P=0.0556), but there was no significant difference between the two groups.

Discussion

Recent reports have suggested that up to 17% of patients with RCC have metastatic disease at diagnosis (5). CN is often indicated as part of an integrated management strategy for mRCC. However, certain patients cannot receive CN due to locally advanced tumor, multiple metastatic disease or poor PS at initial diagnosis. For patients with primary unresectable RCC with synchronous distant metastasis, molecularly targeted therapies are introduced as initial treatment. However, there have been few reports of prognostic factors for unresectable RCC with synchronous distant metastasis.

In the present study, early primary renal tumor response and best response to first-line treatment were reliable predictors of clinical outcome. Seidel *et al* (6) and Miyake *et al* (7) suggested that early tumor shrinkage is a prognostic tool, and more extensive tumor shrinkage is associated with a favorable prognosis. Furthermore, Krajewski *et al* (8) demonstrated that a 10% tumor shrinkage is validated as a reliable early predictor of outcome in mRCC patients receiving VEGF-targeted therapies. Although these studies support the present findings, patients receiving CN were included in the majority of these studies.

RECIST is the most widely accepted method for objectively assessing the response to therapy in RCCs treated with molecularly targeted therapies (9). However, the proportion of patients not receiving CN who exhibited tumor shrinkage of >30% following molecularly targeted therapies [partial response (PR)] is low, suggesting the limited utility of best response according to RECIST. Previous studies on primary renal tumors treated with molecularly targeted therapies have reported a PR rate of 6% (3). Several studies have demonstrated that molecularly targeted agents frequently produce attenuation, which is not evaluated using RECIST, and has led several authors to recommend alternative systems (10,11).

In our analysis, early primary renal tumor response and best response to first-line treatment were independent

Table III. Univariate and multivariate analyses of overall survival in patients with primary unresectable renal cell carcinoma with distant metastasis receiving molecularly targeted therapies.

	Univariate analysis		Multivariate analysis	
Parameters	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Age, years				
<69	1			
≥69	2.638 (0.920-8.129)	0.0711		
Gender				
Male	1			
Female	0.393 (0.061-1.452)	0.1769		
ECOG PS				
0,1	1			
≥2	2.068 (0.717-5.826)	0.1730		
Clinical T stage				
T1/2	1			
T3/4	0.428 (0.113-1.734)	0.2203		
N stage				
N0	1			
N1/2	1.227 (0.440-3.676)	0.6975		
Number of metastatic sites				
1	1			
≥2	1.608 (0.497-7.147)	0.4499		
Bone metastasis				
Absent	1			
Present	2.118 (0.694-6.017)	0.1784		
MSKCC risk classification				
Intermediate	1			
Poor	1.244 (0.415-3.474)	0.6828		
Cytoreductive nephrectomy				
Yes	1			
No	2.952 (0.890-13.454)	0.079		
Early primary renal tumor response				
≥10% shrinkage	1		1	
Progression or <10% shrinkage	10.956 (2.691-74.262)	0.0004	8.060 (1.644-58.233)	0.0099
Best response to first-line treatment				
Partial response or stable disease	1		1	
Progressive disease	26.067 (4.111-510.816)	0.0002	12.580 (1.971-247.566)	0.0054
Anemia				
No	1			
Yes	1.395 (0.494-4.241)	0.5313		
Neutrophil-to-lymphocyte ratio				
<3.7	1			
≥3.7	2.318 (0.755-7.844)	0.1418		
Monocyte-to-lymphocyte ratio				
<0.32	1			
≥0.32	2.745 (0.921-9.159)	0.0699		
Platelet-to-lymphocyte ratio				
<217.4	1			
≥217.4	1.186 (0.426-3.551)	0.7457		
C-reactive protein				
<1.56	1			
≥1.56	2.098 (0.678-6.711)	0.1954		

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

Table IV. Correlation between early primary renal tumor response and clinical factors.

Clinical factors	Early primary renal tumor response		P-value
	≥10% shrinkage (n=10)	Progression or <10% shrinkage (n=16)	
Age, years (range)	62.5 (47-81)	70.5 (49-78)	0.084
Gender			
Male	7	12	0.7806
Female	3	4	
ECOG PS			
0,1	8	9	0.2054
≥2	2	7	
Clinical T stage			
T1/2	1	6	0.1904
T3/4	9	10	
N stage			
N0	7	5	0.1054
N1/2	3	11	
Number of metastatic sites			
1	6	3	0.0461
≥2	4	13	
Bone metastasis			
Absent	9	9	0.0989
Present	1	7	
MSKCC risk classification			
Intermediate	6	9	0.8505
Poor	4	7	
Anemia			
No	4	7	0.8505
Yes	6	9	
NLR (range)	3.15 (1.7-5.6)	5.25 (1.8-13.9)	0.0777
MLR (range)	0.24 (0.16-0.54)	0.37 (0.17-1.07)	0.0459
PLR (range)	180.5 (112.9-494.4)	240.6 (107.7-425.8)	0.6231
CRP (range)	0.77 (0.19-4.03)	2.52 (0.13-15.66)	0.0598

ECOG PS, Eastern cooperative oncology group performance status; MSKCC, Memorial Sloan-Kettering Cancer Center; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein.

prognostic factors in Japanese mRCC patients. Previously, Abel *et al* reported that 10% primary tumor shrinkage within the first 60 days of treatment predicted a better overall primary tumor response (3). Furthermore, it was demonstrated that an early 10% decrease in the diameter of the primary renal tumor was predictive of longer OS (4). These findings are consistent with our results. In addition, our results suggest that an early primary tumor response predicts the therapeutic effectiveness of molecularly targeted agents for patients with primary unresectable RCC with synchronous distant metastasis.

The number of metastatic sites was reported to be an important prognostic factor for mRCC (12-14). Yildiz *et al* reported that the number of sites was a significant prognostic factor for patients receiving sunitinib (15). MLR was previously described as an independent prognostic factor in RCC patients (16). Hutterer *et al* demonstrated that a high MLR was associated with a 2.3-fold increased mortality risk (17). Our clinical characteristics comparison between the group with ≥10% shrinkage and the group with progression or <10% shrinkage shows that the number of metastatic sites and pretreatment MLR tend to be predictive factors for primary renal tumor response.

There were several limitations to our study, including its retrospective design and the limited number of patients from a single institution. A prospective investigation of clinical and molecular characteristics in a large number of patients with primary unresectable RCC with synchronous distant metastasis receiving molecularly targeted therapies is required.

In conclusion, early primary renal tumor shrinkage varies widely among patients with primary unresectable RCC with

synchronous distant metastasis receiving molecularly targeted therapies. Further research is required for continued progress in the identification of prognostic factors for mRCC.

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