Annals of Oncology

Annals of Oncology 24: 1026–1031, 2013
doi:10.1093/annonc/mds582
Published online 23 November 2012

Phase II trial of everolimus for the treatment of nonclear-cell renal cell carcinoma

Y. Koh[1], H. Y. Lim[2], J. H. Ahn[3], J.-L. Lee[3], S. Y. Rha[4], Y. J. Kim[5], T. M. Kim[1] & S.-H. Lee[1]*

[1]*Department of Internal Medicine, Seoul National University Hospital, Seoul;* [2]*Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkunkwan University School of Medicine, Seoul;* [3]*Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul;* [4]*Department of Internal Medicine, Yonsei University College of Medicine, Seoul;* [5]*Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea*

Received 10 July 2012; revised 25 September 2012; accepted 26 September 2012

Background: We investigated the efficacy of everolimus against nonclear-cell renal cell carcinoma (nccRCC).
Patients and methods: Patients with nccRCC received 10-mg everolimus once daily until disease progression or unacceptable toxicity. Patients who had received a VEGF- tyrosine kinase inhibitor (TKI) previously were included.
Results: A total of 49 patients were enrolled. Twenty-three patients (46.9%) received prior anti-VEGF agents. A partial response was observed in five patients (10.2%) and stable disease in 25 patients (51.0%). The disease progressed in 16 patients (32.7%) despite the administration of everolimus. Two of the five patients who showed an objective response to everolimus had chromophobe carcinoma, whereas two had papillary carcinoma and one had unclassifiable carcinoma. Thirty-six patients experienced disease progression during follow-up, and the median progression-free survival (PFS) was 5.2 months. Chromophobe RCC patients seemed to have longer PFS than nccRCC patients with the other histological subtypes ($P = 0.084$). Previous VEGF-TKI treatment did not influence the efficacy of everolimus, and the toxicity profiles were in line with previous reports.
Conclusion: Everolimus shows certain efficacy against nccRCC, particularly in patients with chromophobe RCC, and prior treatment with a VEGF-TKI appears not influencing the outcome of everolimus therapy in nccRCC patients.
ClinicalTrials.gov number: NCT00830895.
Key words: everolimus, nonclear cell, RAD001, renal cell carcinoma

introduction

More than 10 000 patients died of renal cell carcinoma (RCC) in the United States in 2011 [1]. In Korea, more than 2500 patients develop RCC annually, and more than 1000 patients died of RCC in 2010 (http://www.cancer.go.kr/ncic/cics_f/02/022/index.html). RCC is the most common primary renal neoplasm, accounting for 80%–85% of primary renal neoplasm. RCC is composed of distinct subtypes designated clear cell (70%–80%), papillary (10%–20%), chromophobe (5%), collecting duct (<5%), medullary (<5%), and unclassifiable (~5%) [2, 3]. Clear-cell RCC (ccRCC) has provided the paradigm for translational research [4]. RCC is characterized by inactivation of the von Hippel–Lindau gene, which causes activation of the downstream effectors mammalian target of rapamycin (mTOR) and vascular endothelial growth factor (VEGF). Targeting the downstream effectors VEGF and mTOR with sunitinib (VEGF) [5], sorafenib (VEGF) [6], temsirolimus (mTOR), and everolimus (mTOR) [7] may provide effective treatment. Since the approval of these targeted agents, systemic management of advanced and metastatic RCC has improved over the past 5 years [4, 8].

Most trials testing these drugs excluded or under-represented nonclear-cell histology [5, 6, 9]. Hence, most data regarding the efficacy of sunitinib and sorafenib in nonclear-cell RCC (nccRCC) have come from the expanded access program of sorafenib and sunitinib. However, the Global Advanced Renal Cell Carcinoma (ARCC) trial that tested the efficacy of temsirolimus against RCC included a substantial number of patients with nccRCC (~20%) and showed considerable efficacy of temsirolimus in nccRCC patients (median progression-free survival [PFS], 7.0 months) [7]. However, the ARCC study did not include a central pathology review, and subclassification of nccRCC was not provided [4]. Hence, the appropriate treatment of metastatic nccRCC remains unclear.

A phase III trial (RECORD-1) of everolimus showed promising efficacy in ccRCC patients whose disease progressed while on sorafenib or sunitinib [10]. And RAD001 Expanded Access Clinical Trial in RCC (REACT) demonstrated an objective response rate (ORR) of 1.3% and a median PFS of 12.14 weeks in nccRCC patients [11]. However, there was not a single trial evaluating the efficacy of everolimus mainly in

*Correspondence to: Dr S.-H. Lee, Department of Internal Medicine, Seoul National University Hospital, 101 Daehagro, Jongno-Ku 110-744, Korea. Tel: +82-2-2072-0832; Fax: +82-2-764-2199; E-mail: shlee119@snu.ac.kr

nccRCC patients. Considering the similar mechanisms of action of temsirolimus and everolimus, we hypothesized that everolimus would show a clinical benefit in nccRCC patients.

Here, we examined the clinical efficacy of everolimus in nccRCC patients. First, we evaluated the exact ORR to everolimus and the PFS after everolimus administration in nccRCC patients. To analyze the clinical benefit of everolimus according to nccRCC subtype, we enrolled patients with all subtypes of nccRCC. Furthermore, we investigated the impact of previous anti-VEGF treatment on the clinical efficacy of subsequent mTOR inhibitor treatment.

materials and methods

study design and patient eligibility

We conducted the study at five centers in Korea. This open-label, single-arm, multicenter phase II study was conducted in accordance with the Declaration of Helsinki and was consistent with both the International Conference on Harmonization Good Clinical Practice and the applicable regulatory requirements. Written informed consent was obtained from all patients. The study protocol was reviewed and approved by the institutional review board of each participating hospital.

The entry criteria included pathologically proven nccRCC with a metastatic lesion, age >18 years, Eastern Cooperative Oncology Group (ECOG) performance scale (PS) 0–2, adequate renal (creatinine clearance ≥30 ml/min), cardiac, and hepatic [total bilirubin ≤1.5× upper limit normal (ULN)], AST, ALT ≤2.5× ULN, and alkaline phosphatase ≤2.5× ULN) function. Patients with the following RCC subtypes were eligible: papillary, chromophobe, collecting duct, sarcomatoid, oncocytic, and unclassifiable. Furthermore, patients who received previous anti-VEGF therapy were eligible.

Patients were deemed ineligible if they had previous treatment with an mTOR inhibitor, clinically uncontrolled central nervous system metastasis, interstitial pulmonary disease, QTc interval prolongation (QTc >450 ms for males and >470 ms for females), or other serious diseases or medical conditions (e.g. unstable heart disease despite treatment or a history of myocardial infarction within 6 months before the study).

treatment plan

After providing informed consent, patients received everolimus 10 mg/day orally. Four weeks was designated as one cycle. Doses were delayed or reduced to 5 mg/day based on the relevant hematological and nonhematological toxic effects according to National Cancer Institute-Common Terminology Criteria of Adverse Events (version 3.0) criteria. Treatment was continued until disease progression, death, unacceptable toxicity, or the withdrawal of consent.

study end points

The primary end point was PFS. Secondary end points included ORR, toxic effects, and overall survival (OS). Responses were classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the RECIST version 1.0 [12]. PFS was calculated as the time from study enrollment to documentation of disease progression or death from any cause, and OS was calculated as the time from study enrollment to death from any cause.

evaluation

Baseline patient evaluation included medical history, physical examination, PS, and laboratory measurements including a complete blood count, renal function tests, and hepatic function tests. Tumor measurements (assessed by computed tomography) were carried out at screening and repeated every 8 weeks throughout the study. Tumor measurements were carried out upon discontinuation of the study drug. During the study, we monitored adverse events, PS, and blood chemistry tests.

statistical analysis

This study was designed to achieve a PFS ≥6 months with an α-error of 10% and a β-error of 10%. Assuming 18 months of accrual and 6 months of follow-up with an α-error of 10% and a β-error of 10%, 48 patients were required.

As there were limited source data on nccRCC to determine the PFS in the null hypothesis, the following method was used. Because Patard et al. suggested OS does not differ between ccRCC and nccRCC [13], we used ccRCC data to assume a PFS of 4 months. As our inclusion and exclusion criteria did not set limitations regarding previous treatment, we assumed a ratio of previously treated to treatment-naïve patients of 1 : 1. Based on the results of the phase III trial of everolimus, we assumed PFS of 3.0 months for previously treated patients [10]. Alternatively, based on the phase III trials of sunitinib [5] and bevacizumab [14], we assumed PFS of 5.0 months for treatment-naïve patients. Therefore, based on a 1 : 1 ratio of previously treated to treatment-naïve patients, we assumed PFS of 4 months in our null hypothesis.

Statistical analyses of 2 × 2 contingency tables were carried out using Pearson's χ^2 test or Fisher's exact test, as appropriate. The Kaplan–Meier method was used to calculate PFS and OS. Comparisons between groups were made by log-rank tests. The impact of continuous variables on clinical outcomes was calculated with logistic regression and a Cox regression model. A multivariate analysis was carried out with a logistic regression model for response and Cox regression models for PFS and OS. All statistical tests were two sided with significance defined as $P < 0.05$. All analyses were carried out with SPSS for Windows Version 12.0 (IBM, Chicago, IL).

results

patient characteristics

Forty-nine Korean patients from five centers were enrolled from January 2009–July 2011. Median patient age was 57.0 years (range: 23.8–75.5 years), and the male : female ratio was 37 : 12. Based on histology, 29 patients had papillary RCC, 8 had chromophobe RCC, 6 had unclassifiable RCC, 4 had sarcomatoid RCC, and 2 had collecting duct RCC. Twenty-three patients (46.9%) received prior anti-VEGF agents (sunitinib or sorafenib). When patients were categorized by International mRCC DB Consortium risk groups [15], 3 patients (6.1%) were found to have favorable risk disease, 34 (69.4%) had intermediate risk disease, and 10 (20.4%) had poor risk disease (Table 1).

efficacy

Of the 49 patients, five achieved confirmed PR (10.2%), whereas 25 patients had SD (25%). Disease progression occurred regardless of everolimus administration in 16 patients (32.7%). Three patients were unable to undergo tumor assessment: one due to toxicity and two due to the withdrawal of consent before completion of the first cycle of everolimus treatment. Of the five patients who achieved PR, two had papillary RCC, two had chromophobe RCC, and one had

unclassifiable RCC (Table 2). Figure 1 shows the maximum reduction in tumor size for the 30 patients who achieved at least SD.

The ORR did not differ according to tumor histology ($P = 0.670$), previous immunotherapy ($P = 0.730$), previous anti-VEGF treatment ($P = 0.293$), or previous nephrectomy ($P = 0.602$) (Table 3).

During a median follow-up of 19.1 months (range: 1.4–36.1 months), 36 patients experienced disease progression, and 30 patients died. Median PFS of the study patients was 5.2 months (Figure 2A). Patients with chromophobe RCC tended to have longer PFS than those with the other RCC subtypes ($P = 0.084$, 13.1 versus 3.4 months) (Figure 2B). Previous anti-VEGF treatment did not significantly influence PFS (5.3 months in patients with previous anti-VEGF treatment versus 3.7 months in those without, $P = 0.110$, Figure 2C). Further, previous immunotherapy ($P = 0.804$) and previous nephrectomy ($P = 0.773$) also were not correlated with PFS. PS ($P = 0.275$), gender ($P = 0.909$), and age ($P = 0.054$) were not related to PFS. Risk stratification did not have predictive value in terms of PFS in these patients ($P = 0.902$) (Figure 2D). Interestingly, the duration from initial diagnosis to everolimus administration was predictive of PFS (i.e. patients who did not receive everolimus until 1 year after diagnosis had longer PFS than patients who received everolimus within the first year after diagnosis [7.1 versus 2.8 months $P = 0.005$]) (supplementary file 1A, available at *Annals of Oncology* online). Upon disease progression while receiving everolimus, 10 patients received anti-VEGF treatment, 4 received temsirolimus, and 8 received immunotherapy.

The median OS of the study patients was 14.0 months (Figure 2E), and OS did not differ according to tumor histology ($P = 0.393$) (Figure 2F). Prior treatment with an anti-VEGF agent ($P = 0.740$) (Figure 2G), immunotherapy ($P = 0.586$), or nephrectomy ($P = 0.727$) did not influence OS. Age ($P = 0.665$), gender ($P = 0.476$), and PS ($P = 0.311$) were not correlated with OS, and risk stratification did not have prognostic value for OS ($P = 0.828$) (Figure 2H). In contrast to its prognostic relationship with PFS, the duration from initial diagnosis to everolimus treatment was not predictive of OS ($P = 0.212$) (supplementary file 1B, available at *Annals of Oncology* online).

When patients with collecting duct carcinoma and sarcomatoid carcinoma were excluded and efficacy analysis was carried out on the remaining 43 patients, ORR was 11.6% and PFS was 5.3 months. Median OS for these 43 patients was 12.7 months, and ORR, PFS, and OS are summarized according to tumor histology in Table 4.

Table 1. Baseline characteristics of the 49 patients in the study

Characteristics	Number (%)	Median (Range)
Sex (M/F)	37/12	
Age, years (median)		57.0 (23.7–75.5)
ECOG performance scale		
0	8 (16.3)	
1	37 (75.5)	
2	4 (8.2)	
Histology		
Papillary	29 (59.2)	
Chromophobe	8 (16.3)	
Collecting duct	2 (4.1)	
Sarcomatoid	4 (8.2)	
Unclassifiable	6 (12.2)	
Nephrectomy		
Yes	35 (71.4)	
No	14 (28.6)	
Prior treatment		
Immunotherapy	5 (10.2)	
Sunitinib	21 (42.9)	
Sorafenib	6 (12.2)	
Anti-VEGF (either sunitinib or sorafenib)	23 (46.9)	
Time from diagnosis to everolimus		
<1 year	28 (57.1)	
≥1 year	21 (42.9)	
International mRCC DB Consortium risk group		
Favorable	3 (6.1)	
Intermediate	34 (69.4)	
Poor	10 (20.4)	
Unknown	2 (4.1)	

ECOG, Eastern Cooperative Oncology Group; VEGF, vascular endothelial growth factor; mRCC DB, Metastatic Renal Cell Carcinoma Database.

drug exposure and safety

During the study period, 288 cycles (range: 1–22 cycles) were given to the study patients. Dose reduction was carried out in 8 patients (16.3%), and dose delay in 10 patients (20.4%). Overall, 33 patients (67.3%) received full-dose intensity

Table 2. Characteristics of the five patients who achieved an objective tumor response to everolimus

ID	Sex	Age at diagnosis (years)	Age at Study (years)	Pathology	ImmunoTx	Anti-VEGF	Nephrectomy	Risk group*	PFS (months)	PD
1	Female	55.9	56.1	Chromophobe	0	0	1	Intermediate	3.8	No
2	Male	63.7	65.2	Papillary	0	0	1	Intermediate	5.2	Yes
3	Male	69.7	70.2	Unclassifiable#	0	0	1	Intermediate	10.6	No
4	Male	50.1	51.9	Papillary	1	0	1	Poor	5.3	Yes
5	Male	38.6	40.4	Chromophobe	0	1	0	Intermediate	9.1	No

*Risk group based on the International Metastatic Renal Cell Carcinoma Database Consortium risk groups.

#The patient (ID 3) with unclassifiable RCC had an Xp11.2 translocation.

ImmunoTx, immunotherapy; VEGF, vascular endothelial growth factor; PFS, progression-free survival; PD, progressive disease.

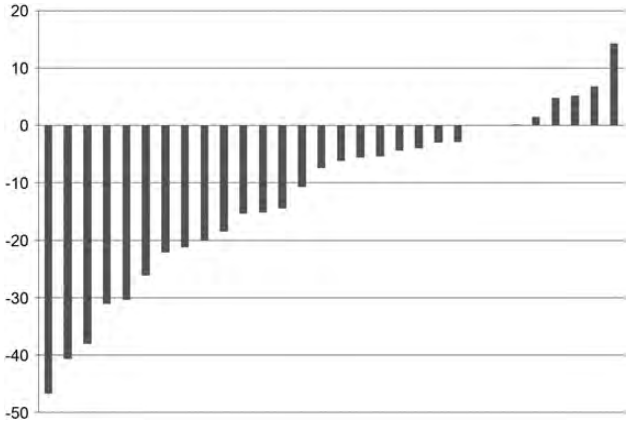

Figure 1. Waterfall plot showing the maximal tumor shrinkage of target lesions after everolimus administration in 49 patients.

Table 3. Correlation between clinicopathological factors and best response to everolimus

Characteristics	Partial response	Stable disease	Progressive disease	*P*
Histology				0.670
Papillary	2	14	12	
Chromophobe	2	4	1	
Collecting duct	0	1	1	
Sarcomatoid	0	2	1	
Unclassifiable	1	4	1	
Previous immunotherapy				0.730
Yes	1	2	2	
No	4	23	14	
Previous anti-VEGF*				0.293
Yes	1	14	7	
No	4	11	9	
Nephrectomy				0.602
Yes	4	17	13	
No	1	8	3	
Risk group				0.281
Favorable	0	3	0	
Intermediate	4	15	13	
Poor	1	6	2	

*Either sorafenib or sunitinib. VEGF, vascular endothelial growth factor.

treatment. The causes for dose delay or dose reduction included hematologic adverse events ($N = 4$), pneumonitis ($N = 2$), stomatitis ($N = 2$), hyperglycemia ($N = 1$), hypophosphatemia ($N = 1$), anorexia ($N = 1$), asthenia ($N = 1$), diarrhea ($N = 1$), abdominal pain ($N = 1$), dyspnea ($N = 1$), and intolerance ($N = 1$). At the time of analysis, six patients were still receiving treatment. Seven patients discontinued everolimus for reasons other than disease progression (infection [$N = 2$], patient refusal [$N = 2$], itching [$N = 1$], poor PS [$N = 1$], and dyspnea [$N = 1$]).

Adverse events exceeding grade 3 were observed in 23 patients (46.9%). Anemia (10.2%), hyperglycemia (8.2%), and infection (6.1%) were frequent complications experienced during everolimus administration. Pneumonitis was observed in three patients (6.1%) (grade 3 in two patients, grade 1 in one patient).

discussion

Patients with nccRCC treated with everolimus showed an ORR of 10.2% and a median PFS of 5.2 months. This seems somewhat less efficacious than the results of the ARCC trial, as temsirolimus treatment led to a median PFS of 7.0 months in nccRCC patients [16]. This discrepancy likely originates from the difference in patient composition. In the ARCC trial, 75% of nccRCC patients had papillary RCC, whereas in our trial, <60% of patients had papillary RCC. Also, we did not exclude sarcomatoid carcinoma and collecting duct carcinoma patients, as we intended to determine the efficacy of everolimus against the different tumor histology subtypes. This is in contrast to previous trials of targeted agents against nccRCC that usually excluded collecting duct carcinoma and sarcomatoid carcinoma in part due to the grave prognosis of these tumors [17].

Patients with chromophobe RCC seemed to have longer PFS than those with the other histological RCC subtypes examined in this study. Additionally, 25% (2/8) of the chromophobe RCC patients showed an objective tumor response to everolimus. This is interesting because RCC patients do not frequently show an objective tumor response to temsirolimus and everolimus despite the considerably long PFS that both drugs provide. In fact, the ORR after temsirolimus treatment was 8.6% in the ARCC trial [7], and the ORR after everolimus was 1% in the RECORD-1 trial [10]. Currently, little is known about the tumor characteristics predictive of objective tumor shrinkage after mTOR inhibitor treatment [18]. Notably, research focused on Birt–Hogg–Dube syndrome revealed that chromophobe RCC cells might have a genetic aberration in the *FLCN* gene located on the short arm of chromosome 17 [19], and FLCN−/− tumors have mTOR upregulation [20]. Hence, chromophobe RCC may be a 'real' target of mTOR inhibitors. More data from chromophobe RCC patients treated with an mTOR inhibitor are needed to confirm this assertion.

In this study, previous anti-VEGF treatment did not influence the efficacy of everolimus. However, prior treatment with an anti-VEGF agent did seem to prolong the PFS of nccRCC patients treated with everolimus (5.3 versus 3.7 months, Figure 2C). This finding is contrary to common conjecture because it was previously found that antiangiogenic therapy elicits the malignant progression of tumors [21]. To explain this somewhat seemingly contradictory result, another factor must be considered, the time from diagnosis to everolimus administration. The time from diagnosis to targeted therapy is a well-known prognostic factor, with longer time from diagnosis to targeted therapy leading to a better prognosis [22]. In our study, a long duration between diagnosis and everolimus administration was a good prognostic factor with strong statistical power. Interestingly, this time was significantly longer in patients with previous anti-VEGF treatment than in patients without (3.1 versus 2.0 months, $P < 0.001$). Also, in multivariate analysis of PFS considering these two variables (anti-VEGF treatment and time from

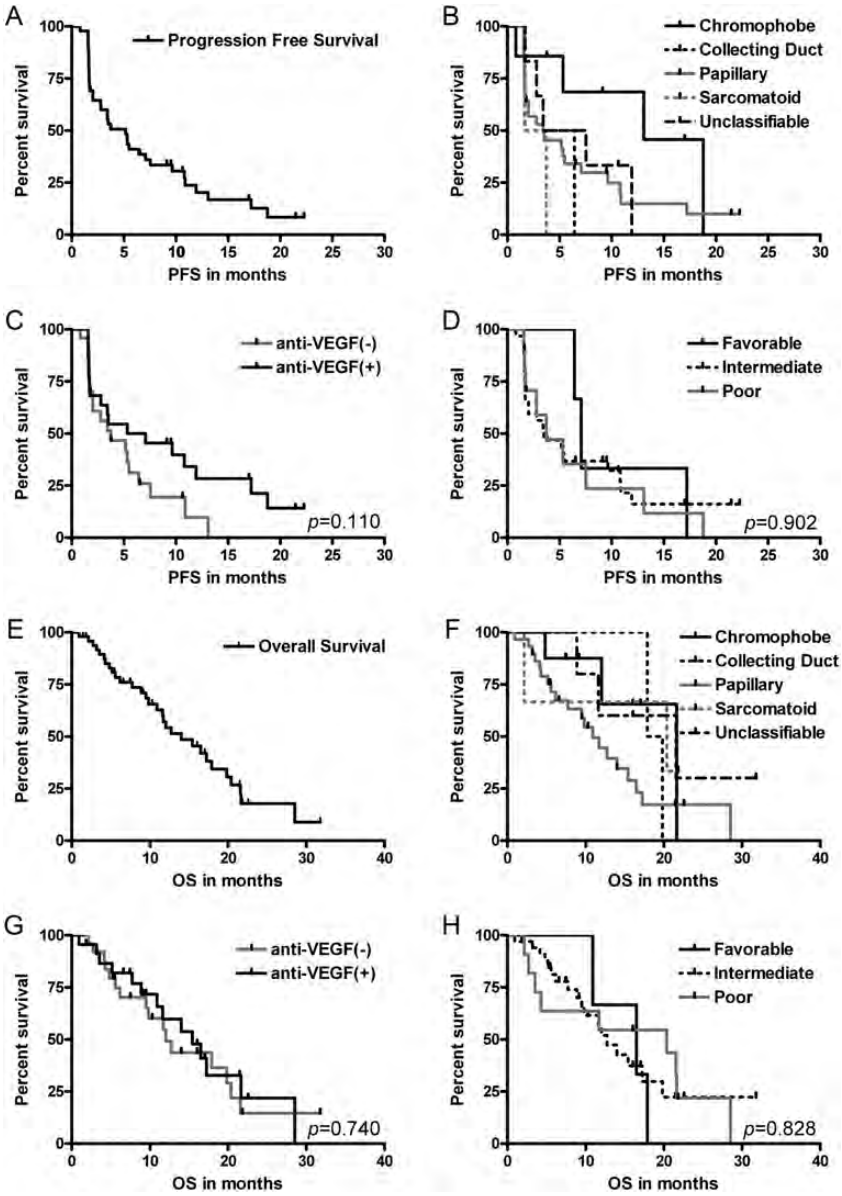

Figure 2. Progression-free survival (PFS) and overall survival (OS) of 49 patients (A, E), PFS according to tumor histology (B, F), PFS according to prior anti-VEGF treatment (C, G), and PFS according to risk grouping (D, H).

Table 4. Efficacy of everolimus according to tumor histology

	Papillary	Chromophobe	Others*
ORR (%)	6.9	25	8.3
Median PFS (months)	3.4	13.1	3.4
Median OS (months)	10.9	21.6	19.8

*includes collecting duct, sarcomatoid, and unclassifiable RCC.

diagnosis to everolimus administration), only time from diagnosis to everolimus administration was a significant independent factor for long PFS ($P = 0.049$, hazard ratio 0.692). Hence, the tendency for patients previously treated with anti-VEGF to have a long PFS after everolimus treatment in our study is due to a confounding effect. Accordingly, in nccRCC patients whose disease progressed while on anti-VEGF treatment, subsequent treatment with mTOR inhibitors should not be excluded.

Risk stratification by the International mRCC DB Consortium risk groups failed to show prognostic value in our study. The original patient cohort from which the International mRCC DB Consortium Risk Groups arose included only 35 nccRCC patients [15]. Hence, it is not surprising that this risk stratification system did not show a prognostic impact in our study. We believe that verification of the International mRCC DB Consortium stratification system in a greater number of nccRCC patients is necessary to identify the clinical value of this risk stratification system. Because this risk stratification system showed prognostic value in a recent phase II trial of sunitinib in 29 nccRCC patients [23], it might be influenced by the type of targeted agent administered. Unfortunately, we could not show any prognostic impact of the Memorial Sloan-

Kettering prognostic factors model [24] due to a lack of information regarding lactate dehydrogenase in our study population. In addition, it should be noticed that the aforementioned subgroup analysis needs validation in a large-scale prospective trial, because the number of patients in each subgroup was not large enough to derive confident conclusion.

After comparing our results with those of the RECORD-1 study, we concluded that nccRCC patients might earn a clinical benefit similar to that experienced by ccRCC patients from everolimus treatment. In the RECORD-1 study, median PFS was 4.9 months, which is comparable to that of our patients (5.2 months, or 5.3 months excluding collecting duct and sarcomatoid RCC). Conversely, the ORR was higher (10.2% overall or 11.6% excluding collecting duct and sarcomatoid RCC) in our study than in the RECORD-1 study (1%). This is in agreement with the result of a subsequent analysis of the ARCC trial by Dutcher et al. [25], and we believe these findings will be helpful for the future design of clinical trials concerning nccRCC and the clinical treatment of nccRCC patients.

Recently, Christian et al. presented data regarding the efficacy of everolimus in nccRCC patients at the ASCO-GU 2012 annual meeting [11]. Although these are not clinical trial results, but instead those of an expanded access program, they analyzed 75 nccRCC patients, a considerably large number. Therefore, based on our findings, we believe a full analysis of the REACT study with the patients grouped by tumor histology will provide valuable information regarding the treatment of nccRCC with everolimus. Also, a clinical trial evaluating the efficacy of everolimus (RAPTOR, http://clinicaltrials.gov/ct2/show/NCT00688753), and sunitinib (SUPAP, http://clinicaltrials.gov/ct2/show/NCT00541008) in papillary RCC would provide an important information in the treatment of papillary RCC.

In conclusion, everolimus shows considerable efficacy against nccRCC, and chromophobe RCC patients in particular may benefit from everolimus treatment. Also, previous treatment with a VEGF-TKI appears to not influence the outcome of everolimus therapy in nccRCC patients.

acknowledgements

We especially thank Ms. Hee-Kyung Koo.

disclosure

The authors have declared no conflicts of interest.

references

1. Siegel R, Ward E, Brawley O et al.. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011; 61: 212–236.
2. Lopez-Beltran A, Scarpelli M, Montironi R et al.. 2004 WHO classification of the renal tumors of the adults. Eur Urol 2006; 49: 798–805.
3. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med 2005; 353: 2477–2490.
4. Tazi el M, Essadi I, Tazi MF et al.. Advanced treatments in non-clear renal cell carcinoma. Urol J 2011; 8: 1–11.
5. Motzer RJ, Hutson TE, Tomczak P et al.. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007; 356: 115–124.
6. Escudier B, Eisen T, Stadler WM et al.. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007; 356: 125–134.
7. Hudes G, Carducci M, Tomczak P et al.. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007; 356: 2271–2281.
8. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. Lancet 2009; 373: 1119–1132.
9. Sternberg CN, Davis ID, Mardiak J et al.. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010; 28: 1061–1068.
10. Motzer RJ, Escudier B, Oudard S et al.. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008; 372: 449–456.
11. Christian UB, Petri B, James MGL et al.. Safety and efficacy of everolimus in patients with non-clear cell renal cell carcinoma refractory to VEGF-targeted therapy: Subgroup analysis of REACT. J Clin Oncol 2012; 30: abstr 402.
12. Therasse P, Arbuck SG, Eisenhauer EA et al.. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205–216.
13. Patard JJ, Leray E, Rioux-Leclercq N et al.. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. J Clin Oncol 2005; 23: 2763–2771.
14. Escudier B, Pluzanska A, Koralewski P et al.. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007; 370: 2103–2111.
15. Heng DY, Xie W, Regan MM et al.. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009; 27: 5794–5799.
16. Chowdhury S, Matrana MR, Tsang C et al.. Systemic therapy for metastatic non-clear-cell renal cell carcinoma: recent progress and future directions. Hematol Oncol Clin North Am 2011; 25: 853–869.
17. Motzer RJ, Bacik J, Mariani T et al.. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. J Clin Oncol 2002; 20: 2376–2381.
18. Albiges L, Molinie V, Escudier B. Non-clear cell renal cell carcinoma: does the Mammalian target of rapamycin represent a rational therapeutic target. Oncologist 2012; 17: 1051–1062.
19. Nickerson ML, Warren MB, Toro JR et al.. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dube syndrome. Cancer Cell 2002; 2: 157–164.
20. Hasumi Y, Baba M, Ajima R et al.. Homozygous loss of BHD causes early embryonic lethality and kidney tumor development with activation of mTORC1 and mTORC2. Proc Natl Acad Sci USA 2009; 106: 18722–18727.
21. Paez-Ribes M, Allen E, Hudock J et al.. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. Cancer Cell 2009; 15: 220–231.
22. Mekhail TM, Abou-Jawde RM, Boumerhi G et al.. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. J Clin Oncol 2005; 23: 832–841.
23. Lee JL, Ahn JH, Lim HY et al.. Multicenter phase II study of sunitinib in patients with non-clear cell renal cell carcinoma. Ann Oncol 2012; 23: 2108–2114.
24. Motzer RJ, Mazumdar M, Bacik J et al.. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999; 17: 2530–2540.
25. Dutcher JP, de Souza P, McDermott D et al.. Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. Med Oncol 2009; 26: 202–209.