RESEARCH ARTICLE

Favorable Outcome in Elderly Asian Patients with Metastatic Renal Cell Carcinoma Treated with Everolimus: The Osaka Urologic Oncology Group

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Abstract

Background: In clinical trials with no upper age limit, the proportion of older patients is usually small, probably reflecting the more conservative approach adopted by clinicians when treating the elderly. An exploratory analysis of elderly patients in the RECORD-1 Trial showed that patients ≥ 65 y.o. had superior median PFS than overall RECORD-1 population (5.4 months and 4.9 months, respectively). We investigated the efficacy, relative benefit and safety of Everolimus (EVE) as sequential therapy after failure of VEGFr-TKI therapy for older patients with metastatic renal cell cancer (mRCC), in daily practice. Materials and Methods: 172 consecutive IRB approved patients with mRCC (median age 65, M:F 135/37, 78% clear cell) who received salvage EVE at 39 tertiary institutions between October 2009 and August 2011 were included in this analysis. Some 31% had progressed on sunitinib, 22% on sorafenib, 1% on axitinib, 41% on sequential therapy, and 5% had received other therapy. Patients with brain metastases were not included and 95% of the patients had a ECOG (Eastern Cooperative Oncology Group) performance status (PS) of 0 or 1. Previous radiotherapy was an exclusion criterion, but prior chemotherapy was permitted. Adequate organ function and hematologic parameters were mandatory. EVE administration was approved by the institutional review board at each participating institution and signed informed consent was obtained from all patients. Results: Median time of the whole cohort to last follow-up was 3.5 months (range 0.4-15.2 months). Forty four percent were continuing to take EVE at last follow-up. There were 86 (50%) patients ≥ 65 y.o. and 86 (50%) <65 y.o. The percentage of patients who showed PR/SD was higher in the older group than in the younger one (5.9%/61.2% *vs* 1.2%/46.5%, respectively). Median survival of older patients was also significantly longer (3.5 +/- 0.31 *vs* 3.1 +/- 0.34, hazard ratio=0.45, CI; 0.255-0.802). Analysis using Cox regression model adjusted for gender, PS, number of metastases, site of metastases, histology, smoking history and age detected an association between age and PFS (p=0.011). The frequency of adverse events in elderly patients treated with EVE was no greater than that in younger patients, although such toxicity may have had a greater impact on their quality of life. Conclusions: Older patients should not generally be excluded from accepted therapies (mTOR inhibitors after failure of VEGFr-TKI therapy) for mRCC.

Keywords: Elderly - mRCC - prognosis - therapy - toxicity

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Introduction

Metastatic renal cell carcinoma (mRCC) remains a challenging disease. Several potential therapeutic targets have been identified based on the molecular biology of renal cell carcinoma; among them vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR) pathways are known to be of clinical importance. According to a recently published population-based analysis using Surveillance, Epidemiology, and End Results (SEER), the incidence of renal cancer more than doubled from 1976-2006 (Siegel et al., 2012) (Reeve

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et al., 2009) (Brenner et al., 2004). The proportion of patients being diagnosed at 65 years of age or younger decreased by roughly 10% from 1991-2006, and the peak incidence still occurs in individuals who are 65 and older. However, treatments currently recommended for mRCC have not been vigorously evaluated specifically in elderly patients. Even in clinical trials with no upper age limit, the proportion of older patients is usually small, probably reflecting the more conservative approach adopted by clinicians when treating elderly patients. As a result, these patients are often under-represented in clinical trials; besides, studies devoted to elderly patients with mRCC are few and present several limitations (Escudier, 2010a; Escudier et al., 2010b). Approximately one-third of patients with mRCC enrolled in recent phase III trials that set the bases for treatment with sunitinib, sorafenib, temsirolimus and bevacizumab+IFN-α, were >65 years of age clearly showing an under-representation of elderly patients with mRCC (Bellmunt et al., 2009a). Inhibition of the mTOR pathway has emerged as one of the main approaches for the development of new targeted agents in mRCC. Everolimus (EVE) has already been shown to improve survival of mRCC patients in whom tyrosine kinase inhibitor (TKI) therapy (Calvo et al., 2012) (Atkins et al., 2009) (Busch et al., 2011) has not proved effective. The ability to identify those mRCC patients ≥65 years of age who will benefit from EVE may contribute to the design of treatment strategies aimed at prolonging their survival while minimizing EVE related morbidity.

The present retrospective analysis was therefore undertaken to assess the efficacy and safety of EVE in older patients with mRCC, where the balance between efficacy and toxicity is often more delicate, by comparison with younger mRCC patients.

Materials and Methods

Patient selection

We retrospectively reviewed the records of 172 consecutive patients with mRCC (median age 65, M:F 135/37, 78% clear cell) who received salvage EVE at 39 tertiary institutions members of the Osaka Urologic Oncology Group (OUOG) between October 2009 and August 2011. Thirty one percent of the patients had progressed on sunitinib, 22% on sorafenib, 1% on axitinib, 41% on sequential therapy (sunitinib:sorafenib), and 5% had received other therapy. This study was approved by the institutional review board at each site. Fifty percent had received cytokines prior to targeted therapies. All patients had histologically confirmed RCC with measurable or assessable unresectable disease. Patients with brain metastases were not included. 95% of the patients had a ECOG (Eastern Cooperative Oncology Group) performance status (PS) of 0 or 1. Previous radiotherapy was an exclusion criterion, but prior chemotherapy was permitted. Adequate organ function and hematologic parameters were mandatory. EVE administration was approved by the institutional review board at each participating institution and signed informed consent was obtained from all patients.

Study design

Overall survival (OS) and progression-free survival (PFS) were evaluated in patients <65 years old and in those 65 years old as a pooled analysis. PFS was defined as the time from on-treatment with EVE to disease progression or death from any cause during therapy. Deaths >30 days after the last drug administration during treatment were considered as events. Data for patients without disease progression or death at the time of analysis were censored at the last tumor assessment. Data for patients who discontinued any treatment component or received non-protocol-specified therapy before disease progression were censored at the time of the last tumor assessment during treatment.

Adverse events (AEs) of interest for EVE were assessed by age group. NCI-CTC grade 1-5 data were collected consistently and were pooled for the current analysis.

Statistical analysis

F-test was used to see if the standard deviations of the two groups were equal. Chi-square test was conducted to assess differences in covariate distributions between the two groups. Survival curves were estimated using the Kaplan-Meier method. Log-rank test was used to compare the survival curves. Cox proportional hazards regression model was used to verify the relevant variables that independently predicted PFS. In all statistical analyses, a two-sided p value <0.05 was considered significant. All data were analyzed using the PASW statistics version 17 statistical program (SPSS Japan Inc. Tokyo, Japan).

Results

Median time of the whole cohort to last follow-up was 3.5 months (range 0.4-15.2 months). Forty four percent had continued taking EVE at last follow-up. Table 1 shows the patient characteristics distributed by age (<65; ≥65). Of the 172 patients, 86 (50%) were ≥65 years old, including 10 patients ≥80 years old. The majority of patients (78.5%) were men and the percentage in both groups was similar. The median age was 64.5 y.o. (23-93). Most patients had a favorable PS with a smaller proportion of patients having a PS 3, or 4. There was a slightly higher number of patients with multiple metastatases in the younger age group, but the difference was not statistically significant (p=0.717). The proportion of patients with a PS of 0 or 1 was similar in the two groups, as was smoking history and site of metastasis (lung or other sites). There were fewer patients with clear cell histology in the younger age group.

Four point seven percent of the whole cohort showed a partial response (PR) and 51.7% had a stable disease (SD) as assessed by the treating physician. Response rates were better in the older age group (52 cases of SD and 5 cases of PR) than in the younger age group (40 cases of SD and 1 case of PR), (p=0.031). Nearly half of the responses were SD. The median PFS (Figure 1A) and OS (Figure 1B) in the whole cohort were 2.8 months and 3.2 months, respectively. The PFS and OS in each age group is illustrated in Figure 2. Median PFS were 2.6 months and 2.9 months in the <65 and ≥65 age groups respectively

(p=0.020, Figure 2A); and median OS were 3.1 months and 3.5 months, respectively (hazard ratio=0.452, CI; 0.255-0.802, p=0.0066, Figure 2B). Analysis using Cox regression model adjusted for gender, PS, number of metastases, site of metastases, histology, smoking history and age detected an association between gender and PFS (p=0.015) plus age and PFS (p=0.011) (Table 2).

All patients included in the efficacy analysis were fully analyzed for toxicity (Table 3). Infection represented the largest percentage (4.7%) of grade 3-5 toxicity in the whole cohort though grade 3-5 neutropenia was not observed (0%). Stomatitis was common (93.4%), although for the majority of patients in both groups it was grade 1-2. Hematologic toxicity was similar in both groups, except for thrombocytopenia (p=0.046), increased creatinin (p= 0.035) and increased CRP value (p=0.041) in response to

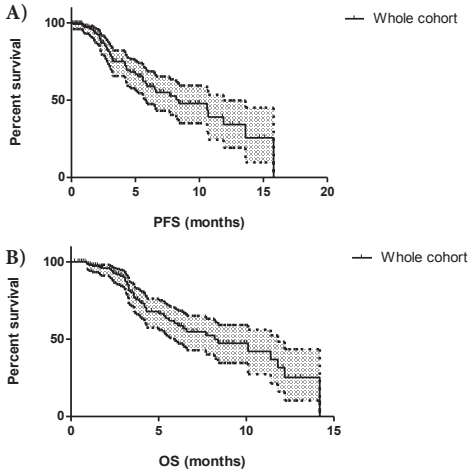

Figure 1. A) Kaplan-Meier Curves of PFS and B) OS, in the Whole Cohort. The study included all patients with mRCC. The solid lines represent survival curves and broken lines represent the 95% confidential interval (CI). Data plotted on the X-axis represent time (months) and those on the Y-axis the survival rate

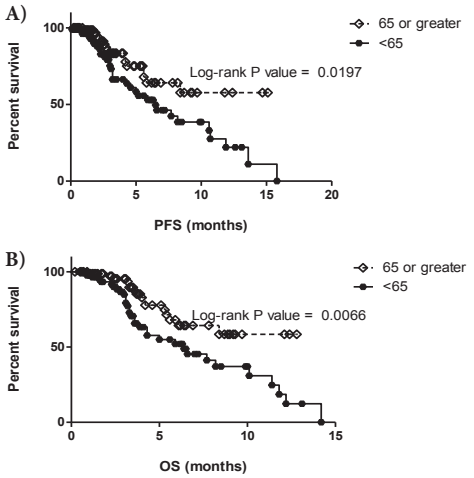

Figure 2. A) Kaplan-Meier Curves of PFS and B) OS, in Patients Distributed by Age. Survival curves for high (broken line) and low (solid line) age groups are plotted. Data plotted on the X-axis represent time (months) and those on the Y-axis represent survival rate. Results of the log-rank test indicated that PFS (p=0.0197) and OS (p=0.0066) were significantly higher in the older group

Table 1. Patients' Background Characteristics

		<65		≥65		p value
		No.	(%)	No.	(%)	
Gender	Male	65	37.8	70	40.7	0.458
	Female	21	12.2	16	9.3	
PS	0	54	34	55	34.6	0.931
	1	15	9.4	15	9.4	
	2	5	3.1	7	4.4	
	3	2	1.3	4	2.5	
	4	1	0.6	1	0.6	
No of mets	1	32	18.6	37	21.5	0.717
	2	29	16.9	27	15.7	
	3	16	9.3	16	9.3	
	4	8	4.7	4	2.3	
	5	1	0.6	2	1.2	
Site of mets	Others	66	38.4	59	34.3	0.305
	Lung	20	11.6	27	15.7	
Histology	Others	17	9.9	6	3.5	0.043
	Clear cell	59	34.5	73	42.7	
	Papillary	6	3.5	5	2.9	
	Spindle cell	1	0.6	1	0.6	
	Granular cell	3	1.8	0	0	
Smoking history	No	65	38	68	39.8	0.487
	Yes	21	12.3	17	9.9	

Table 2. Cox Multivariate Analysis of Variables Affecting Progression-free Survival

Variables	Hazard ratio	95%CI	p value
Gender	2.193	1.163-4.135	0.015
PS	0.623	0.358-1.084	0.094
Number of mets	1.315	0.884-1.958	0.177
Site of mets	2.298	0.872-6.058	0.092
Histology	0.992	0.667-1.476	0.969
Smoking history	0.789	0.320-1.944	0.606
Age2.402	1.227-4.703	0.011	

*CI, confidence interval; PS, performance status; mets, metastases

Table 3. Adverse Events of All Grade Grouped by Age

	Number of patients					
	<65	(%)	≥65	(%)	All	(%)	p value
Stomatitis	62	(40)	52	(36)	114	(76)	0.445
Cough	2	(2)	1	(1)	3	(3)	-
Infection	13	(7)	25	(11)	38	(18)	0.105
Asthenia	5	(3)	15	(7)	20	(10)	0.453
Rash	20	(14)	19	(13)	39	(27)	0.505
Ascites	8	(2)	6	(4)	14	(6)	0.112
Diarrhea	0	(0)	1	(1)	1	(1)	-
Anorexia	3	(1)	8	(6)	11	(7)	0.088
Nausea	1	(1)	2	(2)	3	(3)	-
Dyspnea	7	(3)	.	(0)	7	(3)	-
Pyrexia	8	(6)	7	(5)	15	(11)	0.231
Edema	9	(7)	13	(8)	22	(15)	0.186
Vomiting	0	(0)	2	(2)	2	(2)	-
Mucosal inflammation	1	(1)	4	(2)	5	(3)	0.081
Headache	0	(0)	5	(1)	5	(1)	-
Epistaxis	3	(3)	3	(3)	6	(6)	-
Dysgeusia	0	(0)	1	(1)	1	(1)	-
Pneumonitis	26	(15)	34	(15)	60	(30)	0.269
Pain in extremity	4	(3)	4	(2)	8	(5)	0.329
Dryskin	5	(2)	.	(0)	5	(2)	-
Pruritus	7	(6)	6	(4)	13	(10)	0.26
Abdominal pain	1	(1)	.	(0)	1	(1)	-
Thrombocytopenia	30	(24)	52	(29)	82	(53)	0.046
Neutropenia	20	(13)	35	(17)	55	(30)	0.057
Anemia	35	(17)	41	(20)	76	(37)	0.112
Hypertriglyceridemia	18	(12)	13	(10)	31	(22)	0.829
Hypercholesterolemia	14	(10)	14	(9)	28	(19)	0.786
Lymphopenia	11	(5)	25	(12)	36	(17)	0.969
Hyperglicemia	26	(13)	26	(15)	52	(28)	0.663
Hypophosphatemia	0	(0)	6	(3)	6	(3)	-
Hepatic dysfunction	26	(18)	10	(9)	36	(27)	0.317
Creatinin increased	24	(8)	12	(10)	36	(18)	0.035
CRP increased	26	(10)	9	(9)	35	(19)	0.041

EVE. The groups did not differ significantly in terms of nonhematologic toxicity.

Discussion

Elderly patients represent a heterogeneous population, and molecular targeted therapy in these patients should be evaluated alongside declining end organ function that can compromise the efficacy of molecular targeted therapy.

Recommendations for management of mRCC in the elderly are limited by a lack of evidence. Treatment using VEGFs-TKI and/or mTOR inhibitors is somewhat based on extrapolation of study results from younger patients. Tolerance may vary, and there are competing risks of mRCC-unrelated mortality. Many clinical trials therefore exclude older patients, particularly those with poor performance status, and few age-specific studies have been published, although evidence shows that targeted agents for mRCC are as effective and well tolerated in elderly patients as in younger patients (Porta et al., 2012). Data from clinical trials show that sorafenib reduces the risk of disease progression, compared with placebo, to the same extent in elderly patients and younger patients (Eisen et al., 2008). Median progression-free survival was similar in sorafenib-treated younger patients (23.9 weeks) and older patients (26.3 weeks) (Eisen et al., 2008). It is now believed that cancer control with sorafenib is independent of age. Also, the occurrence rate of sorafenib-related toxicities in older patients is similar to that in younger patients. In the TARGET study, except for fatigue, the incidence of treatment-related toxicities in elderly patients was similar to that in younger patients (Eisen et al., 2012). Porta et al. evaluated the efficacy of EVE in elderly patients enrolled in the RECORD-1 trial (Porta et al., 2012). They showed that PFS, OS, reduction in tumor burden, and overall response rate were all similar in the elderly patients with mRCC and the whole RECORD-1 population, concluding that EVE was effective in elderly patients with mRCC (Porta et al., 2012). The International Society of Geriatric Oncology (SIOG) recommends that patients should be managed based on biological rather than chronological age (Bellmunt et al., 2009a; Bellmunt et al., 2009b; Bellmunt et al., 2011). Because half of patients presenting with RCC are ≥65 (Bellmunt et al., 2009a), older patients should not be precluded access to effective molecular targeted therapy.

In this retrospective analysis, patients ≥65 with mRCC treated with mTOR inhibitor therapy achieved short term benefit comparable to that obtained in younger patients. It is reported that there is a tendency toward increased comorbidities in elderly patients with mRCC, which may result in an inherently different survival unrelated to the underlying malignancy in older patients compared to younger ones. This concept cannot be analyzed in our study as no baseline comorbidity data was recorded. Several reasons are possible for observed favorable results in older patients: older patients were more likely to be better fit, with 34.5% of patients aged <65 years and 42.7% aged ≥65 years having clear cell histology. Also, older patients had more comorbidities, as indicated especially by hematologic toxicities.

According to the phase III study of EVE, stomatitis, pneumonitis, fatigue and infections were the most commonly reported side effects, as previously described (Anandappa et al., 2010). In the RECORD-1 trial (Porta et al., 2012) toxicity rates were generally similar in older and younger patients, although peripheral edema, cough, rash, and diarrhea, increased in frequency with advancing age (Porta et al., 2012). The present study corroborates these reports in that the risk of EVE-related AEs does not increase with age, except for thrombocytopenia, increased creatinin and increased CRP value. The REACT (RAD001 Expanded Access Clinical Trial in RCC) study was initiated to address an unmet medical need by providing EVE prior to commercial availability, and also to further assess the safety and efficacy of EVE in patients with VEGFr-TKI-refractory mRCC (Reeve et al., 2009a). There was no apparent increase in toxicity rates with advancing age, consistent with the results of the RECORD-1 trial.

The present analysis is limited by its retrospective nature, although an advantage to this type of analysis is the ability to gather data on a larger group of elderly patients with mRCC by pooling data. In addition, mTOR inhibitor remains a standard therapy for mRCC making this analysis relevant to current patient care.

In conclusion, although treatment for patients with mRCC continues to evolve, TKI and mTOR inhibitor-based therapy remains the standard-of-care for patients with a favorable performance status in this molecular targeted therapy era. Our analysis suggests that while patients older than 65 may derive comparable initial benefit from mTOR inhibitor-based therapy compared to younger patients, long-term outcomes may not be as favorable.

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