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ORIGINAL PAPER

Efficacy and safety of axitinib in elderly patients with metastatic renal cell carcinoma

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Abstract The objective of this study was to analyze the impact of age on clinical outcomes of metastatic renal cell carcinoma (mRCC) patients receiving axitinib. This study included 144 consecutive mRCC patients who received axitinib for at least 12 weeks as second-line therapy in a routine clinical setting. The efficacy, safety and quality of life (QOL) were compared between patients aged <75 ($n = 116$) and ≥75 ($n = 28$) years. No significant differences in the clinicopathological characteristics were noted between younger and older patients. There was no significant difference in the response rate, clinical benefit rate or proportion of patients going on to receive third-line therapy between these two groups. In addition, the progression-free and overall survivals in older patients were similar to those in younger patients. There were no significant differences in the incidences of adverse events between these two groups, except for that of fatigue, which was significantly more frequent in older than younger patients. There was no significant difference in the incidence of the discontinuation of axitinib due to adverse events between the two groups. QOL assessment at 12 weeks after the introduction of axitinib using the Medical Outcomes Study 36-Item Short Form showed no significant differences in any of the eight scale scores between the two groups. Taken together, it might be possible to achieve clinical outcomes in older patients receiving axitinib comparable to those in younger patients, suggesting that advanced age should not be a contraindication to treatment with axitinib as a second-line setting in mRCC patients.

Keywords Axitinib · Metastatic renal cell carcinoma · Age · Efficacy · Safety

Introduction

Age is widely regarded as one of the main factors associated with the development of cancer [1]. For renal cell carcinoma (RCC) as well, its incidence peaks between the ages of 60 and 70 years, and >25 % of newly diagnosed patients are older than 75 years [2]. Despite the conflicting findings with respect to the impact of age on the prognosis of patients with RCC [3, 4], survival tends to be generally poorer in older cancer patients due to specific characteristics that can influence patient care. For example, elderly patients are usually more likely to have a poorer performance status (PS), lower tolerance to therapies and severer comorbidities compared with younger patients [5]. Therefore, for elderly patients with RCC, it is necessary to consider therapeutic options different from those for younger patients.

In recent years, various types of molecular targeted agent, developed based on intensive investigation of the molecular mechanisms underlying the progression of RCC, have been introduced into clinical practice, resulting in the marked improvement of the prognosis of patients with metastatic RCC (mRCC) compared with that in the era of cytokine therapy [6]. Of these, axitinib, a potent and selective tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor receptors 1, 2 and 3 [7], was shown to reduce vascular permeability, angiogenesis and

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tumor volume in several preclinical studies [8]. Furthermore, in the randomized phase 3 axitinib second-line (AXIS) trial including 723 patients with mRCC, who were randomized into either treatment with axitinib or sorafenib after failure of a single previous systemic treatment, the excellent antitumor activity of axitinib was observed, with significantly longer progression-free survival (PFS) in the axitinib group than in the sorafenib group [9]. Accordingly, axitinib is currently regarded as the standard second-line agent for the treatment of mRCC patients [10].

Since clinical trials for the evaluation of molecular targeted agents against mRCC have under-represented the actual proportion of elderly patients in the general population of mRCC patients, there have been several studies evaluating the outcomes of these agents, such as sunitinib and sorafenib, in elderly patients [11–15]. To date, however, very limited data have been available with respect to the efficacy as well as safety of axitinib for elderly mRCC patients. Considering these findings, this study included a total of 144 consecutive mRCC patients who were treated with axitinib as second-line systemic therapy, and the clinical outcomes in these patients were comprehensively compared between patients aged <75 and ≥75 years.

Patients and methods

This was conducted as a retrospective study reviewing clinicopathological data from a total of 144 consecutive Japanese patients with mRCC who were treated with axitinib for at least 12 weeks as second-line therapy after the failure of first-line systemic therapy between August 2012 and December 2015 in a routine clinical setting at our institution. Thirteen patients, who did not receive radical nephrectomy, underwent needle biopsies of the primary kidney tumor to determine the histopathological subtype; thus, all 144 were pathologically diagnosed with primary RCC. The Institutional Research Ethics Committee approved the design of this study, and informed consent for conducting this study was obtained from all of the included patients.

In this series, axitinib was initially administered to all patients based on the standard dosing schedule, as previously reported [9]; that is, they orally received 5 mg of axitinib twice daily with a continuous dosing schedule, and treatment with axitinib was continued until disease progression occurred or an intolerable adverse event (AE) developed. As a rule, when patients tolerated the standard dosing schedule for at least 2 weeks, they were allowed to receive an elevated dose of axitinib of 7 mg twice daily, unless the blood pressure was >150/90 mmHg or antihypertensive medication was being administered. However, the axitinib dose could be reduced to 3 mg twice daily and then further to 2 mg twice daily according to the severity of AE in each patient.

As baseline evaluations at the start of treatment with axitinib, the clinicopathological examinations and performance status (PS) were assessed according to the 7th edition of the UICC TNM classification system and Karnofsky PS scale, respectively, while risk classification was determined using the Memorial Sloan-Kettering Cancer Center (MSKCC) and International Renal Cell Carcinoma Database Consortium (IMDC) systems [16, 17]. Prior to the initial administration of axitinib, all patients received radiological examinations by computed tomography (CT) of the brain, chest and abdomen and/or radionuclide bone scintigraphy. In general, tumor measurements were taken by CT before and every 6–12 weeks after the introduction of axitinib. Responses and AEs were evaluated by each treating physician according to the Response Evaluation Criteria in Solid Tumors v.1.1 and National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, respectively.

The Medical Outcomes Study 36-Item Short Form (SF-36) Japanese version 2.0 was used to evaluate the HRQOL 3 months after the introduction of axitinib [18]. This questionnaire consists of 36 self-administered questions to quantitatively assess the health-related QOL with eight multi-item scales covering both mental and physical aspects, including the physical function (PF), role limitations because of physical health problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social function (SF), role limitations because of emotional problems (RE) and mental health (MH). Each domain is scored on a scale ranging from 0 to 100, with higher scores indicating a favorable health status. These scores were standardized by Japanese population norms to yield mean scores of 50 and standard deviations of 10 [18, 19].

All statistical analyses were performed using StatView 5.0 software (Abacus Concepts Inc., Berkeley, CA, USA), and a P value <0.05 was considered significant. Differences between the two groups according to the age were compared using the Chi-square test. The PFS and overall survival (OS) rates were calculated by the Kaplan–Meier method, and differences were analyzed by the log-rank test.

Results

Of the 144 included patients, 116 (80.6 %) and 28 (19.4 %) were <75 and ≥75 years old, respectively. Table 1 summarizes their major clinicopathological factors according to the age, and no significant differences in these factors were noted between younger and older patients.

Table 2 presents a comparison of the oncological outcomes between younger and older patients. There was no

Table 1 Patient characteristics

Variables (%)	Age (years)		*P* value
	<75 ($n = 116$)	≥75 ($n = 28$)	
Gender			0.85
Male	85 (73.3)	21 (75.0)	
Female	31 (26.7)	7 (25.0)	
Nephrectomy			0.96
Yes	108 (93.1)	26 (92.9)	
No	8 (6.9)	2 (7.1)	
MSKCC risk classification			0.79
Favorable	8 (6.9)	2 (7.1)	
Intermediate	78 (67.2)	21 (25.0)	
Poor	30 (25.9)	5 (17.9)	
IMDC risk classification			0.57
Favorable	7 (6.0)	2 (7.1)	
Intermediate	77 (66.4)	21 (25.0)	
Poor	32 (27.6)	5 (17.9)	
C-reactive protein			0.46
<0.8 mg/dL	70 (60.3)	19 (67.9)	
≥0.8 mg/dL	46 (39.7)	9 (32.1)	
Major metastatic organs			
Lung	80 (69.0)	21 (75.0)	0.53
Lymph node	33 (28.4)	8 (28.6)	0.99
Bone	33 (28.4)	6 (21.4)	0.45
Liver	15 (12.9)	2 (7.1)	0.39
Brain	9 (7.8)	1 (3.6)	0.43
Number of metastatic organs			0.97
1	52 (44.8)	12 (42.9)	
2	55 (47.4)	14 (50.0)	
≥3	9 (7.8)	2 (7.1)	
Histology of primary tumor			0.84
Clear cell cancer	105 (90.5)	25 (89.3)	
Non-clear cell cancer	11 (9.5)	3 (10.7)	
Sarcomatoid feature			0.46
Positive	14 (12.1)	2 (7.1)	
Negative	102 (87.9)	26 (92.9)	

MSKCC Memorial Sloan-Kettering Cancer Center, *IMDC* International Renal Cell Carcinoma Database Consortium

Table 2 Oncological outcomes following treatment with axitinib

	Age (years)		*P* value
	<75 ($n = 116$)	≥75 ($n = 28$)	
Response (%)	20 (17.2)	6 (21.4)	0.61
Clinical benefit (%)	106 (91.4)	25 (89.3)	0.73
Median progression-free survival (months)	9.3	12.7	0.87
Median overall survival (months)	27.2	25.9	0.66
No. of patients receiving third-line therapy (%)	60 (51.7)	16 (57.1)	0.61

significant difference in the response rate, clinical benefit rate or proportion of patients who went on to receive third-line therapy between these two groups. In this series, the median PFSs in younger and older groups were 9.3 and 12.7 months, respectively, while the median OSs in younger and older groups were 27.2 and 25.9 months,

respectively. As shown in Fig. 1, the PFS and OS in the older group were similar to those in the younger group.

Table 3 shows a comparison of the profiles of commonly observed AEs associated with axitinib between younger and older patients. Although the incidence of fatigue in older patients was significantly higher than that in younger patients, no significant differences in the incidences of the remaining AEs were observed between these groups. With respect to AEs ≥ grade 3, there were no significant differences in the incidences of any of the AEs examined between these two groups. Furthermore, there was no significant difference in the incidence of dose reduction, interruption or discontinuation of axitinib between these two groups.

The health-related QOL of the 144 patients included in this study was evaluated at 3 months after the introduction of axitinib using the SF-36 survey. As shown in Fig. 2, there were no significant differences in any of the eight scale scores for the SF-36 between younger and older patients.

Discussion

With the recent progress in the field of molecular targeted therapy for mRCC, the proportion of mRCC patients who receive sequential therapy with targeted agents has markedly increased [6, 10]. Of several targeted agents sequentially used following the failure of first-line therapy, axitinib is the most widely used drug as second-line therapy for patients with mRCC [9, 10]. In recent years, such a prevalence of sequential targeted therapy against mRCC and its subsequent improvement of the prognosis of mRCC patients have raised new questions concerning the usefulness of targeted agents in the elderly population. In fact, elderly cancer patients, including those with mRCC, are characterized by the frequent presence of other medical conditions, such as hypertension, diabetes, cardiovascular and cerebrovascular diseases, suggesting that anticancer therapy might not be well tolerated in these patients, and thus, its efficacy could be limited [5]. In this study, therefore, we comparatively analyzed the clinical outcomes of second-line therapy with axitinib between mRCC patients aged <75 and ≥75 years.

The definition of elderly can be arbitrary, and for some patients, their chronological age could be different from their physiological age; therefore, controversy regarding the age threshold differentiating elderly from non-elderly patients continues to provoke debate [20]. In this study, when the cutoff point was set at 75 years, 28 (19.4 %) of the 144 included patients were classified into elderly population. This proportion of patients ≥75 years seems to be clearly higher than in clinical trials [12], which underrepresent the actual proportion of elderly patients in a routine clinical setting. Furthermore, there have been several studies showing age-dependent differences in the biological features of RCCs [21, 22]. However, similar to the findings in previous studies [11, 12], no significant differences in major clinicopathological factors were noted between younger and older patients in this series.

We then compared the oncological outcomes, including response rate, clinical benefit rate, proportion of patients receiving third-line therapy, PFS and OS after the introduction of axitinib, between patients with mRCC aged <75 and ≥75 years, and found no significant differences in these parameters between the two groups. We also assessed these parameters according to two additional age thresholds (i.e., <65 vs ≥65 years and <70 vs ≥70 years), and no apparent differences in oncological outcomes with second-line treatment with axitinib were observed regardless of the age cutoff points (data not shown). To date, several studies have revealed a trend similar to that in this study for elderly

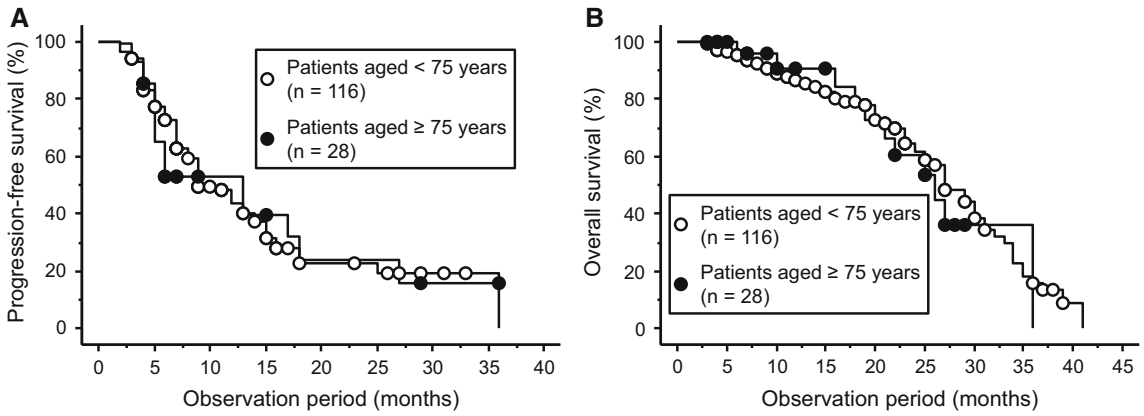

Fig. 1 **a** Progression-free survival (PFS) of the 144 patients with metastatic renal cell carcinoma (mRCC) after receiving second-line treatment with axitinib according to the age. **b** Overall survival (OS) of the 144 patients with mRCC after receiving second-line treatment with axitinib according to the age

Table 3 Adverse events associated with axitinib

Adverse events (%)	All grades		*P* value	≥Grade 3		*P* value
	Age (years)			Age (years)		
	<75 ($n = 116$)	≥75 ($n = 28$)		<75 ($n = 116$)	≥75 ($n = 28$)	
Hypertension	66 (56.9)	16 (57.1)	0.98	37 (33.3)	10 (35.7)	0.70
Dysphonia	60 (51.7)	14 (50.0)	0.87	0 (0)	0 (0)	–
Proteinuria	60 (51.7)	15 (53.6)	0.86	12 (10.3)	3 (10.7)	0.95
Diarrhea	59 (50.9)	13 (46.4)	0.67	0 (0)	0 (0)	–
Hand–foot syndrome	58 (50.0)	12 (42.9)	0.49	11 (9.5)	2 (7.1)	0.70
Hypothyroidism	46 (39.7)	13 (46.4)	0.51	10 (8.6)	3 (10.7)	0.73
Fatigue	37 (31.9)	15 (53.6)	0.032	10 (8.6)	4 (14.2)	0.36
Anemia	15 (12.9)	3 (10.7)	0.75	0 (0)	0 (0)	–
Leukopenia	14 (12.1)	3 (10.7)	0.84	0 (0)	0 (0)	–
Thrombocytopenia	9 (7.8)	3 (10.7)	0.61	0 (0)	0 (0)	–

Outcomes (%)	Age (years)		*P* value
	<75 ($n = 116$)	≥75 ($n = 28$)	
Dose reduction (%)	81 (69.8)	22 (78.6)	0.36
Dose interruption (%)	34 (29.3)	10 (35.7)	0.51
Discontinuation of treatment (%)	11 (9.5)	3 (10.7)	0.84

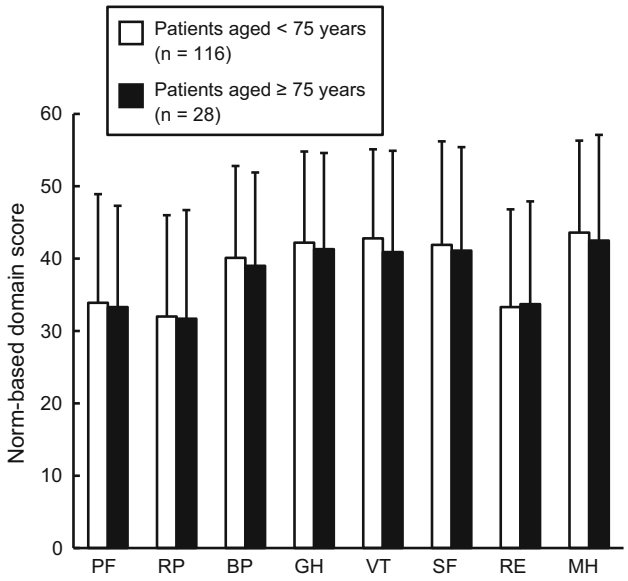

Fig. 2 Comparison of scale scores using the Medical Outcomes Study 36-Item Short Form survey between the 144 patients with metastatic renal cell carcinoma who received second-line treatment with axitinib 3 months after the initiation of axitinib treatment. *PF* physical function, *RP* role limitations because of physical health problems, *BP* bodily pain, *GH* general health perception, *VT* vitality, *SF* social function, *RE* role limitations because of emotional problems, *MH* mental health

patients receiving molecular targeted therapy [11, 12]. For example, Khambati et al. [12] reported that an age ≥75 years was not associated with a poorer OS or shorter treatment duration in mRCC patients treated with first-line antivascular endothelial growth factor therapy. A few studies, however, showed conflicting findings with respect to the impact of age on the prognosis of mRCC patients receiving targeted therapy [15, 23]. Collectively, these findings suggest the absence of a powerful prognostic significance of age in mRCC patients in the era of molecular targeted therapy, but an appropriately designed randomized study is necessary to draw a definitive conclusion on this point.

In a real-world setting, elderly cancer patients are likely to have several comorbidities, which warrant special consideration in association with the risk of AEs due to anticancer therapies, including molecular targeted therapy [5]. In this series, however, the AE profile also appeared to be broadly similar in younger and older patients, except for the incidence of fatigue, which was significantly more frequent in older patients compared with younger patients. In addition, there was no significant difference in the incidence of dose reduction, interruption or discontinuation of axitinib between younger and older patients. In previous studies as well, despite a higher incidence of some AEs in older patients, no apparent differences in the AE profile associated with the use of targeted agents against mRCC were reported [11, 12].

It is of interest to evaluate the QOL status in mRCC patients receiving second-line axitinib according to age, since limited data remain available with respect to the relation between age and QOL in mRCC patients treated with targeted agents. In this study, as expected based on the

findings showing the lack of major differences in the oncological outcomes as well as AE profiles between younger and older patients, there were no significant differences in any of the eight scale scores of SF-36 surveys performed at 3 months after the introduction of axitinib between these two groups. In elderly patients with advanced malignant diseases, the selection of therapeutic options is likely to be made considering the impact on the QOL in addition to that on the prognosis, since it is the major therapeutic objective for such patients to maintain their physical function by relieving symptoms caused by disease progression due to a limited life expectancy [24]. Accordingly, from the viewpoint of the QOL, axitinib could be an optimal second-line agent for both elderly and non-elderly patients.

Here, several limitations of this study should be described. Initially, this was a retrospective study including a comparatively small number of patients, particularly those $\geq$75 years. Secondly, elderly cancer patients with comorbidities are frequently treated with multiple drugs [25]; thus, the potential exists that drugs used to treat comorbidities may interact with axitinib, resulting in increased toxicity and/or reduced efficacy. Thirdly, there may be patients with too many comorbidities or a very poor PS that would preclude them from treatment with targeted agents. The proportion of such patients in the elderly cohort might be high compared with that in the non-elderly, which may impose a selection bias. Finally, this study included only Japanese patients with mRCC, who have been shown to exhibit profiles associated with the use of molecular targeted agents different from those of Western populations [26]; hence, it should be assessed whether the present findings could be applied to an overall cohort with mRCC receiving second-line axitinib.

In conclusion, this may be the first study conducting a comparison of clinical outcomes between younger and older patients with mRCC who received axitinib as a second-line therapy, and the findings presented in this study indicate that the oncological outcome, AE profile and QOL status appear almost comparable in mRCC patients aged $<$75 and $\geq$75 years. Although understanding an individual patient's level of tolerance and goals of targeted therapy can help tailor the appropriate treatment regimen for an elderly mRCC patient, these findings suggest that advanced age alone should not be a contraindication to the introduction of axitinib as a second-line agent into the elderly population with mRCC following the failure of first-line targeted therapy.

Compliance with ethical standards

Conflict of interest H. Miyake, KI. Harada, S. Ozono and M. Fujisawa have received lecture fees from Pfizer.

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