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Efficacy and safety of sequential use of everolimus in Japanese patients with advanced renal cell carcinoma after failure of first-line treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitor: a multicenter phase II clinical trial

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Abstract

Objective: Many studies have shown the efficacy of everolimus after pretreatment with vascular endothelial growth factor receptor-tyrosine kinase inhibitors. We investigated the efficacy and safety of everolimus as a second-line treatment after the failure of vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy in Japanese patients with advanced renal cell carcinoma.

Methods: This was an open-label, multicenter, phase II trial conducted in Japan through the central registration system. A total of 57 patients were enrolled. Patients were administered 10 mg of everolimus q.d. orally. The primary efficacy endpoint was progression-free survival achieved by administration of everolimus.

Results: The median progression-free survival of patients administered everolimus was 5.03 months (95% confidence interval: 3.70–6.20). The median overall survival was not reached. The objective response rate was 9.4% (95% confidence interval: 3.1–20.7). The progression-free survival in the group of <100% relative dose intensity was 6.70 months (95% confidence interval: 4.13–11.60), and that in the group of 100% relative dose intensity was 3.77 months (hazard ratio: 2.79, 95% confidence interval: 2.77–5.63). The commonly observed adverse events and laboratory abnormalities were stomatitis (49.1%), hypertriglyceridemia (26.4%), interstitial lung disease (26.4%), anemia (22.6%) and hypercholesterolemia (22.6%).

Conclusion: The median progression-free survival was almost similar to that recorded in the RECORD-1 study, whereas prolongation of overall survival was observed in the present study compared with the RECORD-1 study. The treatment outcomes of first-line vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy and second-line everolimus treatment in Japanese patients were successfully established in the present study.

Key words: everolimus, renal cell carcinoma, mTOR, Japan

Introduction

Everolimus is a novel derivative of sirolimus and selectively targets mammalian target of rapamycin (mTOR), a serine-threonine kinase. mTOR is activated mainly by the PI3-kinase pathway and constitutes the PI3/AKT/mTOR signaling pathway. It is thought that everolimus forms a complex with FK506 binding protein 12 (FKBP12) in cells and that this complex then exerts an antitumor action by binding to mTOR and selectively inhibiting its function (1). While sorafenib and sunitinib mainly inhibit vascular endothelial growth factor receptors (VEGFRs), everolimus is considered to have a different action compared with other VEGFR-targeting agents in that it can inhibit the production of all the molecules associated with HIF-1α. In a joint international phase III controlled trial (renal cell cancer treatment with oral RAD001 administered daily, RECORD-1; conducted in 10 countries including Japan), everolimus was found to have an excellent clinical effect and a safety profile that allows for continual administration in patients with metastatic renal cell carcinoma (mRCC) that progressed even after pretreatment with VEGFR-tyrosine kinase inhibitors (VEGFR-TKIs) (2,3). One of the primary endpoints was progression-free survival (PFS), which was 4.90 months in the everolimus group and 1.87 months in the placebo group, indicating that everolimus treatment resulted in significant prolongation of PFS compared with the placebo group (hazard ratio [HR] = 0.33; 95% confidence interval [CI]: 0.25–0.43; log-rank test: $P < 0.001$). A phase II study was conducted to prospectively investigate a sequential therapy using VEGFR-TKIs, in which sorafenib was administered first and then followed by sunitinib, and the efficacy of sunitinib was reported as follows: the median PFS was 21.5 weeks, the PFS during the first year was 31%, and the overall survival (OS) during the first year was 60% (4). In this study, however, patients who received cytokine therapy as pretreatment using VEGFR-TKIs accounted for 54.5% of the total number of patients, suggesting that this study does not necessarily demonstrate the real efficacy of the first- and the second-line treatments with VEGFR-TKIs. Another phase II study was designed to prospectively investigate a sequential therapy with VEGFR-TKIs without performing pretreatment with cytokine therapy. In this study, sunitinib was administered as the first-line treatment and sorafenib was administered as the second-line treatment. The efficacy of sorafenib was reported as follows: the median time to progression (TTP) was 16 weeks and the median OS was 32 weeks (5). Owing to the fact that the efficacy of sequential therapy using VEGFR-TKIs (sorafenib and sunitinib) was not established and invalid/intolerable cases were included in these studies, it is expected that prolongation of PFS and OS in the second-line treatment after the treatment with VEGFR-TKIs can be achieved by administering mTOR inhibitors that have different mechanisms of action. In the RECORD-1 study, the mTOR inhibitor (i.e. everolimus) was shown to have excellent clinical efficacy in patients with mRCC that progressed after pretreatment with VEGFR-TKIs (sorafenib or sunitinib). However, this study included many patients who were pretreated with two VEGFR-TKIs (i.e. those who had a treatment history of using sorafenib and sunitinib (26%)), those who were treated with cytokine therapy as pretreatment (65%), and those who underwent chemotherapy (13%). Thus, the evidence as the real second-line treatment after VEGFR-TKI therapy remains unclear. The RECORD-4 study was an open-label, multicenter, international phase II study of patients with mRCC that assessed everolimus in a second-line setting (6). In first-line therapy, the median PFS and OS obtained after previous treatment with sunitinib were 5.7 months and 23.8 months, respectively. However, the patients in the RECORD-4 study were limited to those who had previously undergone a partial or total nephrectomy. Moreover, there were no Japanese data included in the RECORD-4 study.

Thus, in this study, because everolimus has a different mechanism of action from VEGFR-targeted TKIs, we planned a clinical trial expecting that PFS and OS of patients with curatively unresectable cancer or patients with mRCC may increase with the administration of everolimus as a second-line treatment after using only one VEGFR-TKI as the first-line treatment.

Patients and methods

Patients

Inclusion criteria of the study population were defined as follows: (i) age ≥ 18; (ii) confirmed diagnosis of clear cell renal cell carcinoma; (iii) treated with only one VEGFR-TKI as the first-line treatment; (iv) confirmed as having more than one measurable lesion using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0; (v) had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 or 0; (vi) no interstitial shadow was confirmed by chest CT scan in the lung; (vii) had normal bone marrow function, liver function, renal function, fasting blood sugar levels, total cholesterol levels and triglyceride levels; (viii) had no previous cytokine therapy or chemotherapy during the last year until the start of VEGFR-TKI therapy; and (ix) had no previous cytokine therapy or chemotherapy concomitantly as first-line treatment. Exclusion criteria were defined as follows: (i) had a history of hypersensitivity for a sirolimus derivative; (ii) pregnant or suspected of being pregnant, breast-feeding woman, patients planning to have a baby (including men); (iii) patients receiving chronic administration of corticosteroids or immunosuppressive drugs; and (iv) had a history of other primary malignant neoplasms within 3 years after the completion of treatment. Written informed consent was obtained from all the patients. This study protocol was approved by the institutional review board of each institute and was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines. The study was registered with the UMIN Clinical Trials Registry (UMIN 000004742).

Study design

This clinical trial was an open-label, multicenter, phase II trial conducted in Japan through the central registration system. Subjects were administered 10 mg of everolimus q.d. orally during a fasting state. Doses were delayed or reduced to 5 mg once daily if patients had significant laboratory abnormalities or clinically adverse events, as described previously (3).

In case of any adverse event, the dosage of everolimus was adjusted according to the guidelines for dose discontinuation/reduction/withdrawal due to adverse events of this clinical trial. The administration of everolimus was continued until any one of the following criteria was met: (i) judged as progressive disease (PD) by RECIST version 1.0; (ii) death of a participant; or (iii) occurrence of a severe adverse event that meets the withdrawal criteria. Concomitant use of any other anticancer drug, including cytokine agents, was prohibited during the course of the clinical trial.

Study assessments

The baseline evaluation included the following measurements: ECOG PS, height, weight, blood pressure, biochemical examination of blood, urinary test, chest/abdominal/pelvic CT or MRI, chest X-ray, brain CT or MRI, bone scan, electrocardiogram and lung function. Examinations and measurements such as ECOG PS, height, weight and chest/abdominal/pelvic CT or MRI were done every 2 months in the first year and every 3 months in the second year after the start of everolimus administration.

Health-related quality of life (HRQOL) survey was conducted before, 2 months after, and 4 months after the start of everolimus administration. The following instruments were used for assessing HRQOL: (i) EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core questionnaire 30) (version 3.0), (ii) FKSI-DRS (Functional assessment of cancer therapy Kidney Symptom Index-Disease Related Symptoms) and (iii) EQ-5D (EuroQol-5 Dimension).

The primary efficacy endpoint was PFS achieved by administration of everolimus. The secondary efficacy endpoints included the following measures: OS from the start of VEGFR-TKI therapy as the first-line treatment, OS from the start of the administration of everolimus, objective response rate (ORR; complete response, CR; partial response, PR) achieved by the administration of everolimus, time-to-treatment-failure (TTF) with the administration of everolimus, safety achieved by the administration of everolimus (the type, grade and occurrence rate of adverse events), and HRQOL.

Safety analyses

All the unfavorable clinical conditions and clinical test values found during the period of the clinical trial were defined as adverse events and laboratory abnormalities irrespective of the cause-and-effect relationship. Regarding new events that occurred after the completion or discontinuation of the administration of everolimus, those that occurred within one month after the completion or discontinuation of the administration of everolimus were defined as adverse events and laboratory abnormalities. When adverse events and/or laboratory abnormalities were observed, the type, date, grade, severity and outcome were recorded. The grades of adverse events and laboratory abnormalities were evaluated in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Statistical analyses

The target number of cases of this clinical trial was determined as 50. The rationales are as follows. From the results of a phase II trial in which sorafenib was administered to patients with sunitinib-refractory mRCC, the median TTP was reported as 16 weeks (5). In this clinical trial, we expected that we could obtain better results than this, and we assumed the PFS threshold to be 4.1 months and the PFS expectation to be 5.9 months. The sample size was calculated as 46 cases, assuming that we would perform a two-sided test with the following variables: the registration period (24 months), the follow-up period (24 months), the significance level ($\alpha = 0.05$) and the power (0.8). Taking into consideration four potentially unmeasurable cases, it was calculated that 50 cases would be necessary. The registration period was from April 2011 to March 2013, and the trial period was from April 2011 to March 2015. Among the registered patients, the group of patients excluding duplicated or incorrectly registered patients was defined as the 'all registered group'. Of the 'all registered group', the group of patients excluding ineligible patients was defined as the 'all eligible group'. Of the 'all eligible group', the group of all the patients who underwent a part of or the whole protocol treatment was defined as the 'all treated group'. In principle, we performed the following analyses for the 'all treated group'. Of the 'all registered group', patients who were actually administered everolimus were analyzed for safety.

PFS achieved by everolimus administration

The Kaplan–Meier method was used to estimate the PFS curve for the analysis of PFS achieved by everolimus administration, as well as to estimate the median value and the 95% CI of the PFS. In a post-hoc analysis, a potential association between PFS and changes in plasma levels of cholesterol was investigated using the log-rank test.

OS from the start of VEGFR-TKI therapy as the first-line treatment

The Kaplan–Meier method was used to estimate the survival curve for the analysis of OS from the start of VEGFR-TKI therapy as the first-line treatment, as well as to estimate the median value and the 95% CI of the OS. The log-rank test was used to compare OS from the start of VEGFR-TKI therapy in subpopulations based on baseline characteristics, including the length of the disease-free interval and nephrectomy as prior therapy.

OS from the start of everolimus administration

The Kaplan–Meier method was used to estimate the survival curve for the analysis of the OS from the start of everolimus administration, as well as to estimate the median value and the 95% CI of the OS. In a post-hoc analysis, a potential association between OS from the start of everolimus administration and changes in plasma levels of cholesterol was investigated using the log-rank test.

ORR achieved by everolimus administration

For the analysis of ORR achieved by everolimus administration, the ratio of patients with a response (CR or PR) in the group 'all treated patients' was estimated. The 95% CI was calculated using the exact method, also known as the Clopper–Pearson method.

TTF achieved by everolimus administration

The Kaplan–Meier method was used to estimate the TTF curve for the analysis of TTF achieved by everolimus administration, as well as to estimate the median value and the 95% CI of the TTF.

Safety achieved by everolimus administration

Safety was evaluated mainly by the frequency of occurrence of adverse events and laboratory abnormalities. The number and occurrence of adverse events and laboratory abnormalities were summarized by Medical Dictionary for Regulatory Activities terminology (MedDra). Information such as grade and severity was also summarized in a chart.

HRQOL

HR scores were assessed between at baseline and 2 or 4 months after the start of everolims administration.

Results

Patient demographics

A total of 57 patients were enrolled, three of whom were disqualified as ineligible because they did not meet the inclusion criteria, and 54 of whom were included in the all eligible group. Subsequently, one was disqualified because of the inability of data acquisition, resulting in 53 all treated patients. Table 1 shows the patient backgrounds; 34 male patients were included (64.2%), the median age was 64 (range: 40–86), and histopathological diagnosis revealed that all the cases were clear cell carcinomas (100%). The primary sites of distant metastasis were lung (37.7%) and bone (15.1%). Of the 53 patients, 42 patients (79.2%) had previously undergone nephrectomy. In the VEGFR-TKI as the first-line treatment group, 11 patients were administered sorafenib (20.8%), 38 patients with sunitinib (71.7%) and four patients with axitinib (7.5%).

Treatment administration

The median period of everolimus administration as the second-line treatment (the last date of administration minus the start date of administration plus 1) was 5.17 months (range: 0.47–29.67), and the median everolimus administration period (dosing days minus non-dosing days) was 4.97 months (range: 0.47–29.67). The median total dosage of everolimus was 1170 mg (range: 140–5130) and the mean dosage of everolimus (total dosage/treatment period) was 8.97 mg (range: 3.6–10). The median relative dose intensity (RDI) of everolimus was 100% (range 50–100). Of the 53 patients, 24 (45.3%) decreased the dosage of everolimus and 22 (41.5%) withdrew from everolimus during the period of everolimus administration. Of the 53 patients, 50 (94.3%) discontinued everolimus during this clinical trial, but three of them were still being administered everolimus at the end this clinical trial. The main reasons for discontinuation of everolimus were as follows: 14 cases of adverse events (26.4%), 33 cases (62.3%) of PD and two cases of loss to follow-up due to the patients' transfer to other hospitals (3.8%). The third-line treatment following everolimus administration was performed in 38 cases (71.7%). The following agents were used in third-line treatment: axitinib for 22 cases, sorafenib for five cases, sunitinib for four cases, investigational agent for three cases, temsirolimus for two cases, pazopanib for one case, and everolimus for one case.

Efficacy

Best overall response

The best overall responses achieved in 53 patients who were administered everolimus as the second-line treatment involved no cases of CR, five cases of PR (9.4%), 33 cases of stable disease (SD)

Table 1. Patient characteristics at baseline

Characteristics	Patients, *n*	RDI < 100%, *n*	RDI = 100%, *n*	*P* value
Overall population (%)	53 (100)	25	28	
Sex (%)				(Fisher's exact test)
Male	34 (64.2)	13 (52.0)	21 (75.0)	0.095
Female	19 (35.8)	12 (48.0)	7 (25.0)	
Age (years)				(Wilcoxon rank sum test)
Median (range)	64 (40–86)	69 (40–86)	62 (44–77)	0.007
Histologic subtype (%)				
Clear cell carcinoma	53 (100)	25 (100)	28 (100)	–
Sites of metastasis (%)				(Fisher's exact test)
Lung	20 (37.7)	8 (32.0)	12 (42.9)	0.571
Bone	8 (15.1)	3 (12.0)	5 (17.9)	0.708
Liver	2 (3.8)	0 (0.0)	2 (7.1)	0.492
Brain	2 (3.8)	0 (0.0)	2 (7.1)	0.492
Others	18 (34.0)	7 (28.0)	11 (39.3)	0.562
Prior therapies (%)				(Fisher's exact test)
Nephrectomy	42 (79.2)	23 (92.0)	19 (67.9)	0.043
Metastasectomy	21 (39.6)	8 (32.0)	13 (46.4)	0.4
Radiotherapy	12 (22.6)	6 (24.0)	6 (21.4)	1
Length of disease-free interval (%)				(Fisher's exact test)
<1 year between diagnosis and start of first VEGFR-TKI therapy	16 (30.2)	6 (24.0)	10 (35.7)	
≥1 year between diagnosis and start of first VEGFR-TKI therapy	30 (56.6)	16 (64.0)	14 (50.0)	0.364
Unknown	7 (13.2)	3 (12.0)	4 (14.3)	
Prior VEGFR-TKI therapy				(Fisher's exact test)
Sorafenib	11 (20.8)	4 (16.0)	7 (25.0)	
Sunitinib	38 (71.7)	18 (72.0)	20 (71.4)	0.532
Axitinib	4 (7.5)	3 (12.0)	1 (3.6)	

RDI, relative dose intensity; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

(62.3%), 14 cases of PD (26.4%) and one unevaluated case (1.9%), resulting in 9.4% of ORR (95% CI: 3.1–20.7).

In a post-hoc analysis, ORR achieved by sorafenib, sunitinib and axitinib in patients undergoing VEGFR-TKI therapy as the first-line treatment was 36.4% (4/11), 21.1% (8/38) and 50% (2/4), respectively. Among patients with the best overall response, PD was observed in three patients who were administered sorafenib (27.3%), 11 patients who were administered sunitinib (28.9%), and in none of the patients administered axitinib (0%). The administration of axitinib, sorafenib, sunitinib, investigational agents and temsirolimus as third-line treatment resulted in no cases of CR and PR, whereas everolimus that was administered as third-line treatment resulted in one case of PR. The best overall response of each agent that was administered as third-line treatment was as follows: SD (11/22), PD (3/22), unevaluated (8/22) among 22 cases of axitinib administration; SD (4/5), PD (0/5), unevaluated (1/5) among five cases of sorafenib administration; SD (2/4), PD (1/4), unevaluated (1/4) among four cases of sunitinib administration; SD (2/3), unevaluated (1/3) among three cases of investigational agents; PD (2/2) among two cases of temsirolimus administration; and PD (1/1) among one case of pazopanib administration.

TTF, PFS and OS

The median TTF of everolimus was 4.23 months (95% CI: 2.97–5.90). The median PFS of everolimus was 5.03 months (95% CI: 3.70–6.20) (Fig. 1A). The median OS from the start of VEGFR-TKI therapy as the first-line treatment was not reached by the end of the 36-month observation period (Fig. 1B). The 36-month OS rate from the start of VEGFR-TKI therapy as the first-line treatment was 56.1% (95% CI: 43.6–71.4). The median OS from the start of everolimus administration was also not reached by the end of the 24-month observation period (data not shown). The 24-month OS rate from the start of everolimus administration was 50.4% (95% CI: 34.9–64.0). In a post-hoc analysis of OS from the start of VEGFR-TKI therapy as the first-line treatment, the median OS of the group where less than one year passed from the date of diagnosis of renal cell carcinoma to the start of molecular target treatment was 19.47 months (95% CI: 13.27–27.93), which was significantly short compared to the OS (not reached) of the group with a treatment period of more than 1 year (HR, 0.11; $P < 0.001$). The 36-month OS rate of the group with a treatment period of more than 1 year was 73.4% (95% CI: 51.9–86.5). In a post-hoc analysis of OS from the start of VEGFR-TKI therapy as the first-line treatment, the median OS of the group with nephrectomy was not reached, which was significantly long compared to the OS of 14.37 months (95% CI: 9.53–19.80) of the group without nephrectomy (HR, 0.11; $P < 0.001$). The 36-month OS rate of the group with nephrectomy was 68.1% (95% CI: 50.4–80.7).

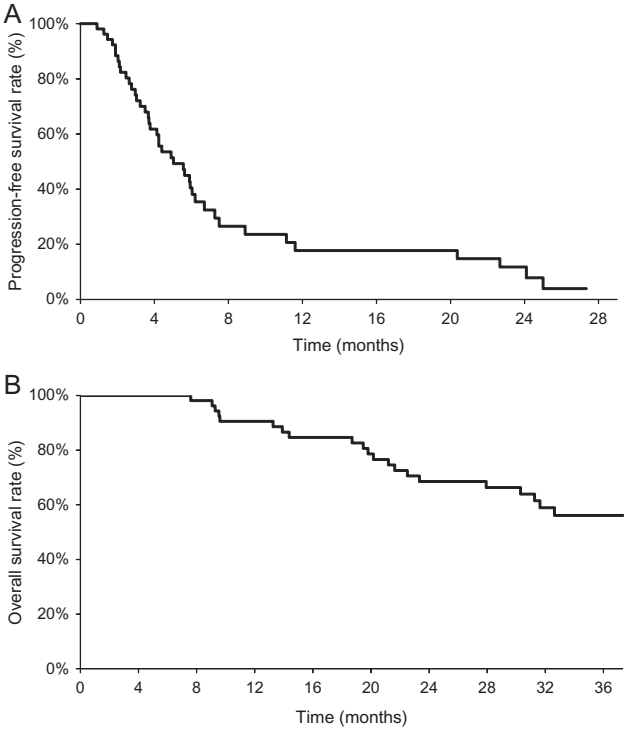

Figure 1. Kaplan–Meier estimates of progression-free survival (A) and overall survival (B).

Relative dose intensity

Basal characteristics of <100% RDI and 100% RDI groups were shown in table 1. The patients in the group with <100% RDI were significant older than those in the group with 100% RDI ($P < 0.01$). The patients in the group with <100% RDI had nephrectomy significantly more than those in the group with 100% RDI ($P < 0.05$). There was no significant difference in other basal characteristics of the two groups.

Wilcoxon's test was used to compare RDI of everolimus between the two groups. The median RDI of the group of patients aged less than 65 years (29 patients; 54.7%) was 100% (range: 51.1–100), whereas that of the group of patients aged 65 or older (24 patients; 45.3%) was 81.08% (range: 50.0–100). There was no significant difference in RDI between the two groups. In the analysis of the total dose of everolimus, the median total dose in the group of <100% RDI was 1863.9 ± 1445.3 mg, whereas that in the group of 100% RDI was 1127.1 ± 825.0 mg. There was no significant difference in the total dose of everolimus between the two groups. However, the total dose of everolimus in the group of <100% RDI tended to be larger than that in the group of 100% RDI ($P = 0.053$). In the analysis of the administration period of everolimus, the mean administration period in the group with <100% RDI was 9.25 + 7.73 months, whereas that in the group with 100% RDI was 3.76 + 2.75 months. The administration period in the group with <100% RDI was significantly longer than that in the group with 100% RDI ($P < 0.001$). In the analysis of the TTF with everolimus, the median TTF in the group with <100% RDI was 6.20 months (95% CI: 3.73–10.67), whereas that in the group with 100% RDI was 3.08 months (95% CI: 2.13–4.23). The TTF in the group with <100% RDI was significantly longer than that in the group with 100% RDI ($P < 0.001$) (Fig. 2). In the analysis of PFS of everolimus, the median PFS in the group with <100% RDI was 6.70 months (95% CI: 4.13–11.60), whereas that in the group with 100% RDI was 3.77 months (95% CI: 2.77–5.63). The PFS in the group with <100% RDI was significantly longer than that in the group with 100% RDI ($P = 0.004$) (Fig. 3).

There was no significant difference in OS from the start of everolimus administration between the two groups.

Patient-reported outcomes

HRQOL was assessed before, 2 and 4 months after the administration. In the analysis of EORTC QLQ-C30 scores, there was no significant difference of the scores in the 5 functional scales (physical

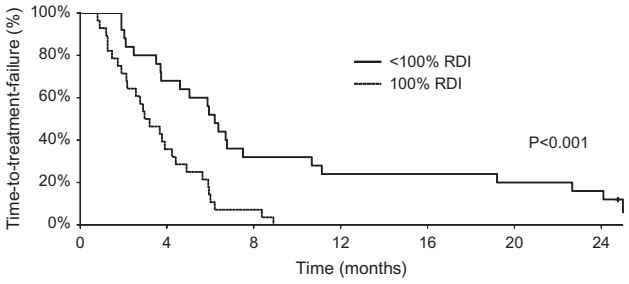

Figure 2. Kaplan–Meier estimates of time-to-treatment-failure by RDI. RDI, relative dose intensity.

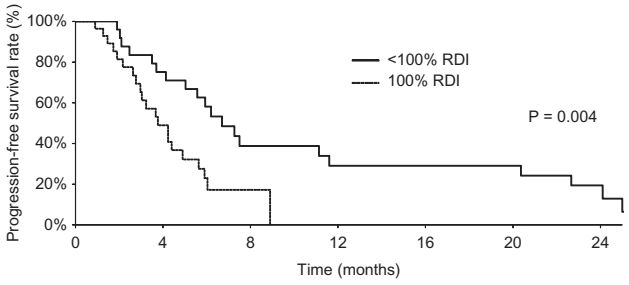

Figure 3. Kaplan–Meier estimates of progression-free survival by RDI.

functioning, role functioning, emotional functioning, cognitive functioning and social functioning) between at baseline and 2 or 4 months, whereas the global health status/quality of life score at 4 months was significantly lower than those at baseline ($P = 0.011$). In the EORTC QLQ-C30 symptom scales, there was no significant difference of the scores in fatigue, nausea/vomiting, pain, insomnia, appetite loss, constipation, diarrhea and financial difficulties between at baseline and 2 or 4 months after the administration, whereas the score of dyspnea at 4 months was significantly superior to those at baseline ($P = 0.030$). There was no significant difference in the FACIT FKSI-DRS scores between at baseline and 2 months, but the FACIT FKSI-DRS scores at 4 months were significantly lower than those at baseline ($P = 0.024$). As for EQ-5D scores, no significant difference was observed between at baseline and 2 months, but scores at 4 months were significantly lower than those at baseline ($P = 0.038$).

Safety

Adverse events and laboratory abnormalities were observed in 51 out of 53 patients (96.2%) (Table 2). The following are some of the commonly observed adverse events and laboratory abnormalities: stomatitis (26 cases; 49.1%), hypertriglyceridemia (14 cases; 26.4%), interstitial lung disease (14 cases; 26.4%), anemia (12 cases; 22.6%), hypercholesterolemia (12 cases; 22.6%), thrombocytopenia (10 cases; 18.9%) and high LDH levels (10 cases; 18.9%). Some of the main grade 3 adverse events were interstitial lung disease (five cases; 9.4%), stomatitis (four cases; 7.5%), and rash (three cases; 5.7%). Severe adverse events were observed in 10 out of 53 cases (18.9%). Commonly observed severe adverse events were rash (three cases; 5.7%), stomatitis (two cases; 3.8%) and interstitial lung disease (two cases; 3.8%). On the analysis of occurrence rate of adverse events and laboratory abnormalities by age, there was no significant difference between the group of patients aged less than 65 years and those aged 65 years or older (Table 3).

Table 2. Commonly observed adverse events and laboratory abnormalities

Adverse event	All grades		Grade 3>	
	n	%	*n*	%
Adverse event				
None	2	3.8	31	58.5
Any	51	96.2	22	41.5
Stomatitis	26	49.1	4	7.5
Interstitial lung disease	14	26.4	5	9.4
Anemia	12	22.6	2	3.8
Anorexia	9	17.0	3	5.7
Fatigue	7	13.2	1	1.9
Anorexia	5	9.4	0	0.0
Cough	4	7.5	0	0.0
Weight loss	4	7.5	0	0.0
nosebleed	3	5.7	0	0.0
Laboratory abnormality				
Triglycerides increased	14	26.4	1	1.9
Cholesterol increased	12	22.6	0	0.0
Platelets decreased	10	18.9	2	3.8
Lactate dehydrogenase increased	10	18.9	0	0.0
Glucose increased	8	15.1	2	3.8
Platelets decreased	7	13.2	1	1.9
Albumin decreased	6	11.3	0	0.0
C-reactive protein increased	6	11.3	0	0.0
Alkaline phosphatase increased	5	9.4	0	0.0
Phosphate decreased	4	7.5	1	1.9
Creatinine increased	3	5.7	0	0.0
Uric acid increased	3	5.7	0	0.0
Hemoglobin A1c increased	3	5.7	0	0.0
KL-6 increased	3	5.7	0	0.0
Alanine transaminase increased	2	3.8	0	0.0
Aspartate transaminase increased	2	3.8	0	0.0

Table 3. Number and incidence of common adverse events and laboratory abnormalities by type of event and age group

Adverse event type	Patients aged <65 years		Patients aged ≥65 years		Fisher's exact test
	n	(%)	*n*	(%)	
Total	29	100	24	100	–
Stomatitis	14	48.3	12	50	$P = 1.000$
Triglycerides increased	7	24.1	7	29.2	$P = 0.760$
Interstitial lung disease	5	17.2	9	37.5	$P = 0.124$
Anemia	7	24.1	5	20.8	$P = 1.000$
Cholesterol increased	7	24.1	5	20.8	$P = 1.000$
Platelets decreased	5	17.2	5	20.8	$P = 1.000$
Lactate dehydrogenase increased	7	24.1	3	12.5	$P = 0.318$

On the analysis of the occurrence rate of adverse events and laboratory abnormalities by RDI, the levels of cholesterol in the group with <100% RDI were significantly increased compared with those in the group with 100% RDI ($P = 0.047$). In terms of other adverse events and laboratory abnormalities, there were no significant differences between the group with <100% RDI and the group with 100% RDI (Table 4). There was no significant difference in the severity of adverse events and laboratory abnormalities between the group with <100% RDI and the group with 100% RDI.

Table 4. Number and incidence of commonly adverse events and laboratory abnormalities by the type of event and RDI

Adverse event type	RDI < 100%		RDI 100%		Fisher's exact test
	n	(%)	*n*	(%)	
Total	25	100.0	28	100.0	–
Stomatitis	16	64.0	10	35.7	$P = 0.056$
Triglycerides increased	8	32.0	6	21.4	$P = 0.534$
Interstitial lung disease	8	32.0	6	21.4	$P = 0.534$
Anemia	8	32.0	4	14.3	$P = 0.190$
Cholesterol increased	9	36.0	3	10.7	$P = 0.047$
Platelets decreased	6	24.0	4	14.3	$P = 0.488$
Lactate dehydrogenase increased	5	20.0	5	17.9	$P = 1.000$

In a post-hoc analysis of PFS by adverse events and laboratory abnormalities, the median PFS of 11.13 months (95% CI: 3.50–25.00) in the hypercholesterolemic group was significantly long compared to the median PFS of 4.23 months (95% CI: 3.03–5.90) in the non-hypercholesterolemic group ($P = 0.008$) (Fig. 4 A). In addition, the median OS (not reached) from the start of everolimus administration in the hypercholesterolemic group was significantly long compared to that of 16.20 months from the start of everolimus administration (95% CI: 11.50–∞) in the non-hypercholesterolemic group ($P = 0.003$) (Fig. 4B). The 24-month OS rate from the start of everolimus administration in the hypercholesterolemic group was 91.7% (95% CI: 53.9–98.8).

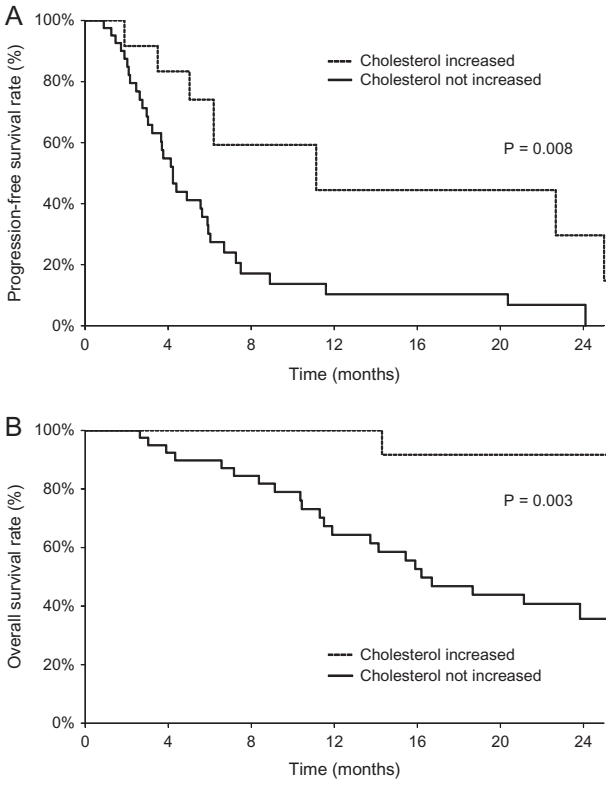

Figure 4. Kaplan–Meier estimates of progression-free survival (A) and overall survival according to cholesterol levels (B).

Discussion

In the RECORD-1 study, the mTOR inhibitor everolimus was shown to have excellent clinical efficacy in patients with mRCC that progressed after pretreatment with VEGFR-TKIs (2,3). However, this study included patients who were administered two VEGFR-TKIs (sorafenib and sunitinib) as pretreatment (26%), as well as those who were administered cytokine therapy as pretreatment (65%), and those who underwent chemotherapy (13%). Therefore, the evidence to support the use of everolimus as a second-line treatment after using VEGFR-TKI therapy as the first-line treatment without concomitant use of cytokine therapy is limited. Analysis of the RECORD-1 study in a Japanese subpopulation showed that one of the 15 Japanese patients who was administered everolimus was prescribed two agents (sorafenib and sunitinib), and that all the patients had a history of cytokine therapy (7). The RECORD-4 study was designed to assess everolimus in a second-line setting (6). In the RECORD-4 study, patients with mRCC had received various VEGFR-TKIs or cytokines as first-line treatment. However, the RECORD-4 study included only patients who had previously undergone a partial or total nephrectomy. A higher percentage of patients had favorable risk, according to the Memorial Sloan Kettering Cancer Center risk criteria, in the RECORD-4 study than in the RECORD-1 study (52 and 29%, respectively).

In this study, we are the first to report the efficacy of everolimus as the second-line treatment after failure of first-line treatment with VEGFR-TKIs in Japanese patients. This study included not only patients who underwent prior surgery (nephrectomy) but also patients with unresectable mRCC.

In the RECORD-1 study, the best overall responses of PR and SD were 1.8 and 66.8%, respectively, and no cases of CR were reported (2). In this clinical trial, among 53 cases of the best overall responses, there were no cases of CR (0%), five cases of PR (9.4%), and 33 cases of SD (62.3%), which showed high ORR compared with that reported in the RECORD-1 study.

In this clinical trial, the PFS achieved by everolimus was almost similar to that in the RECORD-1 study (5.03 vs. 4.90 months). The median OS from the start of everolimus administration in this study was shown to be longer than that in the RECORD-1 study (not reached vs. 14.78 months) (2). In this clinical trial, the 24-month OS rate from the start of everolimus administration was 50.4% (95% CI: 34.9–64.0). The median OS of the group of patients who started first-line VEGFR-TKI therapy more than one year after their diagnosis of renal cell carcinoma was prolonged compared to that observed for the group of patients who started first-line VEGFR-TKI therapy within one year after their diagnosis of renal cell carcinoma (not reached vs. 19.47 months). Moreover, the median OS of the group of patients who underwent nephrectomy prior to molecular target treatment was prolonged compared to that recorded for those who

did not undergo nephrectomy prior to molecular target treatment (not reached vs. 14.37 months). These results may suggest that a poor prognosis can be expected for cases in which nephrectomy was not indicated for renal cell carcinoma and for cases that resulted in metastatic relapse at an early stage after nephrectomy.

In the analysis of RDI of everolimus between the age brackets, there was no significant difference between RDIs in the group of patients aged less than 65 years and those aged 65 or above. There was also no significant difference between RDIs in the group of patients aged less than 70 years and those aged 70 or above (data not shown). Everolimus would be used for the treatment of elderly patients as well, without decreasing the RDI.

The analysis of the administration period of everolimus showed that the administration period in the group with <100% RDI was significantly longer than that in the group with 100% RDI (9.25 vs. 3.76 months; $P < 0.001$). The total dose of everolimus in the group of <100% RDI tended to be larger than that in the group of 100% RDI (1863.9 vs. 825.0 mg; $P = 0.053$). Eight out of 25 patients (32.0%) in the group with <100% RDI discontinued treatment with everolimus, as opposed to 12 out of 28 patients (42.9%) in the group with 100% RDI, indicating that the number of patients who discontinued treatment was larger in the group with 100% RDI than in the group with < 100% RDI. The TTF in the group with < 100% RDI was significantly longer than that in the group with 100% RDI (6.20 vs. 3.08 months; $P < 0.001$). Furthermore, the PFS in the group with <100% RDI was significantly longer than that in the group with 100% RDI (6.70 vs. 3.77 months; $P = 0.004$), suggesting that 10 mg/d everolimus may be an overdose for the Japanese patients and may deteriorate their medication adherence.

In this clinical trial, we performed HRQOL analysis before and after the administration of everolimus. All the scores of EORTC QLQ-C30 global health status/quality of life, FACIT FKSI-DRS and EQ-5D decreased 4 months after the administration of everolimus compared with the baseline, suggesting that the decrease in QOL was caused by everolimus. Other than everolimus, however, exacerbation of overall status because of the progression of cancer is also responsible for the decrease in QOL. This clinical trial is a single arm study, which does not allow a comparison with a placebo group. Therefore, it is impossible to judge whether everolimus decreased QOL significantly or not. In the analysis of EORTC QLQ-C30 symptom scales, only dyspnea was significantly high 4 months after administration of everolimus compared with the baseline ($P = 0.030$). Among the adverse events caused by everolimus, interstitial lung disease was observed in 14 out of 53 cases (26.4%), and grade 3 interstitial lung disease was observed in five cases (9.4%), leading us to the assumption that interstitial lung disease caused by everolimus is associated with the aggravation of dyspnea, although progression of cancer also causes dyspnea.

In the subgroup analysis of the Japanese patients in the RECORD-1 study, the adverse events that occurred in the study were similar to those in the overall population. The following are some of the commonly observed adverse events in the Japanese patients of the RECORD-1 study: stomatitis (73%), infections (67%), rash (67%), dysgeusia (47%), epistaxis (40%) and diarrhea (40%). Laboratory abnormalities such as a reduction in hemoglobin (93%), an increase in cholesterol (87%), an increase in triglycerides (60%) and an increase in glucose (53%) were mainly included (7). In this clinical trial, commonly observed adverse events were stomatitis (49.1%) and interstitial lung disease (26.4%), and laboratory abnormalities such as an increase in triglycerides (26.4%), a reduction in hemoglobin (22.6%), and an increase in cholesterol (22.6%) were mainly included. In addition, the rate of occurrence of grade 3 adverse events in the RECORD-1 study was similar to that in the overall population. We observed similar rates of grade 3 or 4 adverse events in this clinical trial compared with those in the RECORD-4 study. Based on the results that hypercholesterolemia significantly prolonged PFS and OS from the start of the administration of everolimus, it was suggested that hypercholesterolemia could be the predictor of PFS and OS from the start of the administration of everolimus.

In conclusion, the following inclusion criteria were used in this clinical trial: (i) subjects were not treated with cytokine therapy for a year before the first-line treatment; (ii) subjects were not treated with cytokine therapy in combination with the first-line treatment; and (iii) subjects were treated with only one VEGFR-TKI as the first-line treatment. This clinical trial is the first to evaluate everolimus as the second-line treatment after failure of the first-line VEGFR-TKI therapy in mRCC Japanese patients who had no history of cytokine pretreatment. Both patients who underwent prior surgery (nephrectomy) and who had unresectable mRCC were included. PFS achieved by everolimus was almost the same as PFS in the RECORD-1 study, whereas prolongation of OS was observed compared with the RECORD-1 study. Although many clinical trials for molecular target therapy for mRCC patients are being conducted worldwide, few Japanese cases are registered, and therefore, there are limitations for the subgroup analysis of the Japanese patients. This clinical trial successfully demonstrated the treatment outcomes of the first-line VEGFR-TKI therapy and the second-line treatment using everolimus in Japanese patients. Prolongation of OS can be expected by using everolimus as the second-line treatment after the failure of the first-line VEGFR-TKI therapy. However, a clinical trial including more cases is required to strengthen the evidence for the efficacy of everolimus.

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Conflict of interest statement

None declared.

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