Everolimus in metastatic renal cell carcinoma patients intolerant to previous VEGFr-TKI therapy: a RECORD-1 subgroup analysis

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BACKGROUND: A relevant percentage of patients with metastatic renal cell carcinoma develop intolerance to vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFr-TKIs) and require careful selection of subsequent treatment. This retrospective analysis evaluated the safety and efficacy of everolimus in patients enrolled in the phase-III RECORD-1 trial who discontinued previous VEGFr-TKI therapy because of toxicity.

METHODS: Patients with an adverse event (AE) as their primary reason for discontinuation of previous VEGFr-TKI therapy were included. Median progression-free survival (PFS) for VEGFr-TKI-intolerant patients in each arm was estimated using the Kaplan–Meier method, and effect on PFS (hazard ratio (HR)) was calculated using the Cox proportional hazard model.

RESULTS: In VEGFr-TKI-intolerant patients (n = 58, 14%), median PFS was 5.4 months with everolimus and 1.9 months with placebo (HR: 0.32; P = 0.004). In sunitinib-intolerant patients (n = 26), median PFS was 5.1 months with everolimus and 2.8 months with placebo (HR: 0.28; P = 0.033). Grade 3/4 AEs reported with everolimus in VEGFr-TKI-intolerant patients included infections (16%), fatigue (7%) and stomatitis (4%). The toxicity profile of everolimus was similar in the VEGFr-TKI-intolerant and overall study populations.

CONCLUSION: Everolimus is well tolerated and efficacious with no increased toxicity in patients intolerant to VEGFr-TKI therapy.

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Sequential treatment with targeted therapies is the current standard of care for patients with metastatic renal cell carcinoma (mRCC) (de Reijke et al, 2009; Escudier and Kataja, 2010; Ljungberg et al, 2010; National Comprehensive Cancer Network, 2012). Targeted therapies approved for use in patients with mRCC include the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab, the VEGF receptor-tyrosine kinase inhibitors (VEGFr-TKIs) sorafenib, sunitinib and pazopanib, and the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus.

First-line systemic treatment options supported by the highest level of clinical evidence for patients with mRCC are the VEGFr-TKI-targeted agents sunitinib, pazopanib and bevacizumab (plus interferon-α) for patients of good or intermediate Memorial Sloan–Kettering Cancer Center (MSKCC) risk and the mTOR inhibitor temsirolimus for patients of poor MSKCC risk (de Reijke et al, 2009; Escudier and Kataja, 2010; Ljungberg et al, 2010; National Comprehensive Cancer Network, 2012). Although many patients obtain significant clinical benefit in terms of progression-free survival (PFS) from treatment with VEGF-targeted therapies, these agents are not well tolerated by all patients, leading to treatment discontinuation in a relevant percentage of cases.

Adverse events (AEs) commonly observed in patients treated with VEGFr-TKIs include hypertension, hand-foot skin reaction (palmoplantar erythrodysesthesia), rash/desquamation, alopecia, diarrhea, fatigue, hyponatremia, neutropenia and thrombocytopenia (Ravaud, 2011). The onset of treatment-related AEs may necessitate dose interruptions, dose adjustments and/or treatment discontinuation in some patients. In a phase-III trial of patients with mRCC treated with sunitinib (n = 375) or interferon-α (n = 375), 8% and 13% of patients, respectively, discontinued treatment because of AEs (Motzer et al, 2007). In the phase-III TARGET trial of patients with mRCC receiving sorafenib (n = 451) or placebo (n = 452), 21% of sorafenib-treated patients required dose interruptions primarily because of the occurrence of hand-foot skin reaction, whereas 6% of patients in the placebo group...
required dose interruptions (Escudier et al, 2007). In a phase-III study of patients with mRCC who received pazopanib (n = 290) or placebo (n = 145), 14% and 3% of patients, respectively, discontinued treatment because of AEs (Sternberg et al, 2010). Tolerability of first-line VEGFr-TKIs may be an even more relevant issue in clinical practice compared with clinical trials (Choueiri et al, 2010; Porta et al, 2011b). Results of two retrospective chart reviews from tertiary oncology centres in the United States (Choueiri et al, 2010) and Italy (Porta et al, 2011b) found that 26–37% of patients treated with first-line sunitinib or sorafenib required dose reductions because of AEs, 19–32% of patients required dose interruptions because of AEs and 5–18% discontinued treatment because of AEs.

For patients who are intolerant to first-line VEGF-targeted therapy (i.e., discontinue therapy because of unacceptable toxicity), careful selection of second-line treatment is particularly critical in order to achieve maximum clinical benefit while minimising the occurrence of further treatment-related AEs. VEGF-targeted agents and mTOR inhibitors have distinct class effect toxicities (Ravaud, 2011); thus, patients who are intolerant to first-line VEGF-targeted therapy may be less likely to experience significant toxicity with a second-line mTOR inhibitor than a second-line VEGF-targeted agent. The phase-III RECORD-1 study evaluated the efficacy of the oral mTOR inhibitor everolimus in patients with mRCC whose disease had progressed on, or who were intolerant to, previous VEGFr-TKI therapy (sunitinib and/or sorafenib) (Motzer et al, 2008, 2010). Median PFS was prolonged from 1.9 months (95% CI: 1.8–1.9) to 4.9 months (95% CI: 4.0–5.5) for patients who received placebo or everolimus, respectively (Motzer et al, 2010). Risk of disease progression was reduced by 67% for patients in the everolimus group, compared with patients in the placebo group (hazard ratio (HR): 0.33; P < 0.001). Based on these results, current clinical practice guidelines recommend everolimus as the standard of care for patients with mRCC who have failed initial VEGFr-TKI therapy (de Reijke et al, 2009; Escudier and Kataja, 2010; Ljungberg et al, 2010; National Comprehensive Cancer Network, 2012).

Herein we present the results of a retrospective analysis of RECORD-1 that evaluated the efficacy and safety of everolimus in the subgroup of patients who discontinued previous VEGFr-TKI therapy because of toxicity.

MATERIALS AND METHODS

Patient population

The study design of RECORD-1, an international, multicentre, double-blind, randomised phase-III trial, has been previously reported (Motzer et al, 2008). Adult patients (aged ≥ 18 years) with measurable clear cell mRCC (according to RECIST 1.0 (Therasse et al, 2000)), which had progressed within 6 months of stopping treatment with sunitinib, sorafenib or both were included in the study. Previous treatment with bevacizumab, interleukin 2 or interferon-α also was permitted. Other key inclusion criteria were a Karnofsky performance status of at least 70% (scale 0–100, higher scores indicated better performance) and adequate bone marrow, hepatic and renal function. Patients in all MSKCC-risk categories (favourable, intermediate and poor) were included. Key exclusion criteria were previous treatment with temsirolimus, untreated central nervous system metastases and uncontrolled medical conditions (e.g., unstable angina pectoris, symptomatic congestive heart failure, recent myocardial infarction or diabetes).

Study treatments

Patients were stratified according to whether they received one or two previous VEGFr-TKIs and by MSKCC-risk group. Patients were then randomly assigned 2:1 to receive either continuous treatment with oral everolimus 10 mg once daily (n = 277) or placebo (n = 139), both in conjunction with best supportive care (Motzer et al, 2010). A cycle was 28 days of treatment. Doses were delayed or reduced (to 5 mg once daily) if patients had clinically significant haematological or other AEs that were considered by the investigator to be related to everolimus. Treatment continued until disease progression, unacceptable toxicity, death or discontinuation for any other reason. Patients randomly assigned to placebo who experienced disease progression were permitted to cross over to open-label everolimus.

Assessments

The primary reason for discontinuation of each previous anti-neoplastic therapy (AE, disease progression or other) was collected for all patients. Patients for whom an AE was the primary reason for discontinuation of previous sunitinib therapy, sorafenib therapy or both (i.e., discontinuation of previous VEGFr-TKI therapy because of unacceptable toxicity) were included in this subgroup analysis and assessed for PFS and safety. PFS was defined as the time from randomisation to the first documentation of disease progression or death from any cause and was documented according to RECIST 1.0 and assessed via blinded, independent central review (Motzer et al, 2008). Tumour measurements were assessed by CT or MRI scans and were performed at screening and every 8 weeks thereafter. Safety was assessed in all patients who received at least one dose of study drug. AEs and laboratory evaluations were monitored and graded according to the National Cancer Institute's Common Terminology Criteria for AEs, version 3.0 (National Cancer Institute, 2006). Vital signs were measured, physical examinations were performed and all concomitant medications and therapies were recorded.

Analysis

The Kaplan–Meier method was used to estimate median PFS for patients intolerant to previous VEGFr-TKI therapy in each treatment arm and the Cox proportional hazard model was used to calculate the HR of treatment effect on PFS.

Ethical conduct

RECORD-1 was conducted according to the ethical principles of the Declaration of Helsinki. The study protocol was reviewed by the independent ethics committee or institutional review board for each centre. Each patient provided written informed consent before screening procedures were initiated.

RESULTS

In the overall RECORD-1 population, 14% of patients (n = 58) discontinued previous VEGFr-TKI therapy because of unacceptable toxicity. Among the subgroup of 58 patients who were intolerant to previous VEGFr-TKI therapy, 45 patients and 13 patients were randomly assigned to everolimus and placebo, respectively. Baseline characteristics in this subgroup of patients were generally similar to those of the overall study population; however, some differences between placebo-treated patients who were VEGFr-TKI-intolerant and all placebo-treated patients were noted (e.g., younger median age and higher percentage of women) (Table 1). When stratified by previous VEGFr-TKI therapy, of the 45 patients who received everolimus, 21 were intolerant to previous sunitinib, 19 were intolerant to previous sorafenib and 5 were intolerant to previous sunitinib and sorafenib. Of the
13 patients who received placebo, 5 were intolerant to previous sunitinib and 8 were intolerant to previous sorafenib.

Among patients who were intolerant to previous VEGFr-TKI therapy and subsequently received everolimus or placebo, 42.2% and 84.6%, respectively, discontinued treatment because of disease progression, whereas 13% and 0%, respectively, discontinued treatment because of AEs (Table 2). AEs that led to discontinuation of everolimus treatment were asthenia, increased blood creatinine, dehydration, dyspnoea, increased gamma-glutamyltransferase, general physical health deterioration, pathological fracture, pleural effusion and pneumonitis.

As was observed in the overall RECORD-1 population, everolimus significantly prolonged PFS compared with placebo in patients who were intolerant to previous VEGFr-TKI therapy (Figure 1). Median PFS was 5.4 months (95% CI: 3.8–5.9) with everolimus and 1.9 months (95% CI: 1.8–3.7) with placebo. Risk of disease progression was decreased by 68% with everolimus compared with placebo (HR: 0.32; 95% CI: 0.13–0.77; \( P = 0.004 \)).

PFS benefit of everolimus compared with placebo was similar for patients who were intolerant to previous sunitinib or sorafenib therapy (Table 3). Among patients who were intolerant to previous sunitinib therapy, median PFS was 5.1 months (95% CI: 3.7–not available) with everolimus and 2.8 months (95% CI: 1.9–3.7) with placebo (HR: 0.28; 95% CI: 0.07–1.18; \( P = 0.033 \)). Among patients who were intolerant to previous sorafenib therapy, median PFS was 5.6 months

### Table 1
Patient demographics in the subgroup of patients who were intolerant of previous VEGFr-TKI therapy and all patients in the RECORD-1 trial

| VEGFr-TKI-intolerant patients | All patients (Motzer et al, 2010) |
|-------------------------------|----------------------------------|
| **Everolimus+BSC** | **Placebo+BSC** | **Everolimus+BSC** | **Placebo+BSC** |
| \( n = 45 \) | \( n = 13 \) | \( n = 277 \) | \( n = 139 \) |
| **Age in years, median (range)** | 66 (44–81) | 41 (29–74) | 61 (27–85) | 60 (29–79) |
| **Sex, n (%)** | | | | |
| **Men** | 28 (62) | 5 (39) | 216 (78) | 106 (76) |
| **Women** | 17 (38) | 8 (62) | 61 (22) | 33 (24) |
| **KPS score, n (%)** | | | | |
| **100** | 10 (22) | 1 (8) | 79 (28) | 41 (30) |
| **90** | 16 (36) | 6 (27) | 98 (35) | 53 (38) |
| **80** | 18 (40) | 5 (22) | 72 (26) | 30 (22) |
| **70** | 1 (2) | 1 (8) | 28 (10) | 15 (11) |
| **Missing** | 0 | 0 | 1 (<1) | 0 |
| **MSKCC-risk group, n (%)** | | | | |
| **Favourable** | 13 (29) | 3 (23) | 81 (29) | 39 (28) |
| **Intermediate** | 30 (67) | 8 (62) | 156 (56) | 79 (57) |
| **Poor** | 2 (4) | 2 (15) | 40 (14) | 21 (15) |

**Abbreviations:** BSC = best supportive care; KPS = Karnofsky performance status; MSKCC = Memorial Sloan–Kettering Cancer Center; VEGFr-TKI = vascular endothelial growth factor receptor-tyrosine kinase inhibitor.
Table 3  PFS in patients intolerant to previous sunitinib and/or sorafenib therapy

|               | Intolerant to previous sunitinib | Intolerant to previous sorafenib |
|---------------|----------------------------------|----------------------------------|
|               | Everolimus+BSC                    | Placebo+BSC                      | Everolimus+BSC                    | Placebo+BSC                      |
| Patients, n   | 26c                              | 5                                | 24c                              | 8                                |
| PFS in months, median (95% CI) | 5.1 (3.7–NA)                     | 2.8 (1.9–3.7)                    | 5.6 (3.8–NA)                     | 1.9 (1.7–3.5)                    |
| Hazard ratio (95% CI) | 0.28 (0.07–1.18), P = 0.33        |                                  | 0.29 (0.09–0.91), P = 0.012      |

Abbreviations: BSC = best supportive care; CI = confidence interval; NA = not available; PFS = progression-free survival. *Patients who had an adverse event (AE) as the primary reason for discontinuation of previous sunitinib. Patients may have also received previous sorafenib. **Patients who had an AE as the primary reason for discontinuation of previous sorafenib. Patients may have also received previous sunitinib. Of the 45 VEGF-TKI-intolerant patients randomly assigned to everolimus, 5 patients were intolerant to both previous sunitinib and sorafenib and were included in both previous treatment groups.

Table 4  Commonly reported adverse events and laboratory abnormalities, irrespective of relation to treatment, in patients intolerant to previous VEGF-TKI therapy and the overall RECORD-1 population

| Adverse event | All grade | Grade 3 | Grade 4 | All grade | Grade 3 | Grade 4 | All grade | Grade 3 | Grade 4 | All grade | Grade 3 | Grade 4 | All grade | Grade 3 | Grade 4 |
|---------------|-----------|---------|---------|-----------|---------|---------|-----------|---------|---------|-----------|---------|---------|-----------|---------|---------|
|               | Everolimus+BSC, n = 45 | Placebo+BSC, n = 13 | Everolimus+BSC, n = 274 | Placebo+BSC, n = 137 |
|               |           |         |         |           |         |         |           |         |         |           |         |         |           |         |         |
| Stomatitisa | 49        | 13      | 2       | 92        | 8       | 0                   | 92        | 12      | 1       | 79        | 5       | <1       | 137       | 14      | 16      |
| Fatigue       | 38        | 7       | 7       | 33        | 0       | 0                   | 31        | 2       | 0       | 37        | 7       | 3        | 274       | 27      | 3       |
| Infectionsb   | 33        | 9       | 7       | 31        | 0       | 0                   | 30        | 1       | 0       | 29        | 1       | 0        | 137       | 10      | 0       |
| Diarrhoea     | 31        | 2       | 0       | 0         | 0       | 0                   | 29        | 1       | 0       | 26        | 1       | 0        | 274       | 15      | 0       |
| Rash          | 31        | 0       | 0       | 32        | 0       | 0                   | 30        | 0       | 0       | 28        | 0       | 0        | 137       | 0       | 0       |
| Nausea        | 27        | 0       | 0       | 23        | 0       | 0                   | 26        | 0       | 0       | 21        | 0       | 0        | 137       | 0       | 0       |
| Asthenia      | 24        | 2       | 0       | 23        | 0       | 0                   | 23        | 1       | 0       | 22        | 1       | 0        | 137       | 16      | 0       |
| Peripheral oedema | 24    | 0       | 0       | 15        | 0       | 0                   | 25        | <1      | 0       | 25        | <1      | 0        | 137       | 19      | 1       |
| Mucosal inflammation | 16  | 2       | 0       | 0         | 0       | 0                   | 19        | 1       | 0       | 19        | 0       | 0        | 137       | 19      | 0       |

Laboratory abnormality, %

|                      | All grade | Grade 3 | Grade 4 | All grade | Grade 3 | Grade 4 | All grade | Grade 3 | Grade 4 | All grade | Grade 3 | Grade 4 | All grade | Grade 3 | Grade 4 |
|----------------------|-----------|---------|---------|-----------|---------|---------|-----------|---------|---------|-----------|---------|---------|-----------|---------|---------|
| Haemoglobin decreased | 96        | 13      | 2       | 92        | 8       | 0                   | 92        | 12      | 1       | 79        | 5       | <1       | 137       | 14      | 16      |
| Cholesterol increased | 78        | 4       | 0       | 38        | 0       | 0                   | 77        | 4       | 0       | 35        | 0       | 0        | 274       | 27      | 3       |
| Triglycerides increased | 76       | 0       | 0       | 0         | 0       | 0                   | 73        | <1      | 0       | 34        | 0       | 0        | 137       | 10      | 0       |
| Glucose increased    | 64        | 20      | 0       | 23        | 0       | 0                   | 57        | 16      | 2       | 28        | 0       | 0        | 137       | 23      | 5       |
| Platelets decreased  | 60        | 0       | 0       | 31        | 0       | 0                   | 50        | 1       | 0       | 34        | 0       | 0        | 137       | 26      | 0       |

Abbreviations: BSC = best supportive care; VEGF-TKI = vascular endothelial growth factor receptor-tyrosine kinase inhibitor. *Stomatitisa (including aphthous stomatitis), mouth ulceration and tongue ulceration. **All infections reported, including pneumonia, aspergillosis, candidiasis and sepsis. (95% CI: 3.8–not available) with everolimus and 1.9 months (95% CI: 1.7–3.5) with placebo (HR: 0.29; 95% CI: 0.09–0.91; P = 0.012).

Everolimus was generally well tolerated in patients who were intolerant to previous VEGF-TKI therapy, with low rates of grade 3 and grade 4 AEs, and the safety profile was similar to that observed in the overall RECORD-1 population (Table 4). In the everolimus cohort of patients intolerant to previous VEGF-TKI therapy, the most common AEs (all grade and grade ≥3 incidence, respectively) were stomatitis (49% and 4%), fatigue (38% and 7%) and infections (33% and 16%), and the most commonly reported grade ≥3 laboratory abnormalities were hyperglycaemia (20%), lymphopenia (20%) and anaemia (15%).

DISCUSSION

Targeted therapies in mRCC are rarely curative, and patients often rely on multiple lines of therapy to derive sustained clinical benefit (Oudard and Elaïdi, 2012). In patients with mRCC who are intolerant to first-line VEGF-targeted therapy and must discontinue treatment before disease progression, tolerability of subsequent therapy is of particular importance. Patients who require dose reductions/interruptions or cessation of treatment to manage toxicity associated with VEGF-targeted therapy may experience reduced efficacy of that agent. A recent pharmacokinetic/pharmacodynamic meta-analysis of sunitinib-treated patients with various types of cancer, including mRCC, demonstrated a positive relationship between drug exposure and time to progression or overall survival (Houk et al, 2010). However, increased sunitinib exposure was also associated with increased incidence of class-effect toxicities such as hypertension, neutropenia and fatigue.

In previous studies of sequential administration of VEGF-targeted agents, overlapping toxicity profiles of these agents have resulted in high incidences of certain treatment-related AEs, such as hypertension, skin toxicities, fatigue and gastrointestinal toxicities, some of which have required dose modifications (Rini et al, 2008, 2011; Di Lorenzo et al, 2009; Garcia et al, 2010). The AXIS phase-III trial evaluated the safety and efficacy of axitinib vs sorafenib in patients with mRCC who had failed first-line treatment with a sunitinib-, bevacizumab-, temsirolimus- or cytokine-based regimen; 62% of patients received first-line VEGF-targeted therapy (sunitinib or bevacizumab) (Rini et al, 2011). In the overall AXIS population, class-effect AEs reported in the axitinib and sorafenib arms included diarrhoea (55% and 53%, respectively), hypertension (40% and 29%, respectively), fatigue (39% and 32%, respectively), palmar-plantar erythrodysesthesia...
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The retrospective nature of this analysis, small sample size, and lack of patient stratification within the subgroup suggest use of caution when interpreting these results. Furthermore, this analysis was not powered or designed to enable statistical comparison of efficacy or safety profiles between patients intolerant to VEGFr-TKI therapy and the overall RECORD-1 population. Further studies of everolimus in patients intolerant to VEGF-targeted therapy are warranted to confirm our observations.

Recent evidence has indicated that sequential treatment with a VEGFr-TKI and an mTOR inhibitor may permit eventual rechallenge with a third-line VEGFr-TKI. A subset of RECORD-1 patients from French sites (n = 36) demonstrated a median PFS of 5.3 months for sorafenib, 8 months for sunitinib and 12 months for dovitinib (TKI258) after disease progression on at least one VEGFr-TKI and everolimus (Blesius et al, 2010). Another subset of RECORD-1 patients from a German institution (n = 39) achieved a median PFS of 5.1 months after receiving sorafenib, sunitinib or dovitinib follow/ing previous treatment with at least one VEGFr-TKI and everolimus (Gruenwald et al, 2010). In a retrospective Italian study (n = 34), third-line sorafenib following sequential therapy with sunitinib followed by everolimus or temsirolimus was associated with a median PFS of 4 months and a median overall survival of 7 months from initiation of sorafenib treatment (Di Lorenzo et al, 2010). A phase-III study designed to compare the safety and efficacy of dovitinib and sorafenib in patients with mRCC whose disease has progressed on one previous VEGFr-TKI and one previous mTOR inhibitor is currently ongoing (ClinicalTrials.gov identifier: NCT01223027).

In conclusion, appropriate selection of second-line therapy to maximise clinical benefit and minimise the occurrence of treatment-related AEs for patients who are intolerant of initial VEGF-targeted therapy is a key clinical issue. Results of this subgroup analysis of the phase-III RECORD-1 study demonstrate that everolimus can be safely given to patients with a previous intolerance to VEGFr-TKI therapy. These results further support everolimus as the treatment of choice in patients who have failed initial VEGFr-TKI therapy.

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