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Mammalian Target of Rapamycin Inhibitors in Clinical Practice: Case Reports of Everolimus in Renal Cell Carcinoma

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Abstract

Metastatic renal cell carcinoma (mRCC) is largely considered to be resistant to chemotherapy, and treatment with cytokines is associated with low response rates. Recently, therapies that target specific pathways involved in the pathogenesis of mRCC have been developed. These include vascular endothelial growth factor (VEGF)–targeted therapies (eg, sunitinib, sorafenib, bevacizumab) and mammalian target of rapamycin (mTOR) inhibitors (eg, everolimus, temsirolimus). Everolimus has been shown to have particular benefit in patients who are refractory to VEGF-targeted therapy. In this paper, the use of everolimus in two patients with mRCC is presented. Everolimus demonstrated clinical efficacy in these patients and was generally well tolerated. The case studies reported support the activity of everolimus in the treatment of mRCC in patients who had progressed on previous targeted therapy, showing the possibility of achieving extended periods of disease control.

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1. Case reports

1.1. Background

There were approximately 200 000 new kidney cancer cases worldwide in 2002, and renal cell carcinoma (RCC) accounts for approximately 90% of renal tumours [1,2]. Around 25–30% of patients with RCC present with metastatic RCC (mRCC) at time of diagnosis; 20–30% of patients with localised tumours relapse after nephrectomy and develop metastasis [3,4]. Because mRCC is largely considered to be resistant to chemotherapy and because treatment with cytokines is associated with a low response rate, patients with this disease usually have an extremely poor prognosis [5]. However, new targeted therapies are beginning to supersede cytokines as preferred treatments for mRCC. In particular, the vascular endothelial growth factor (VEGF) pathway has been targeted by a number of new agents, and this has led to improved outcomes for patients [6,7]. Sunitinib, an anti-VEGF receptor (VEGFR) agent that inhibits angiogenesis by blocking VEGFRs, and bevacizumab plus interferon alfa (IFN-α) are currently the recommended first-line therapies for patients with good- or intermediate-risk mRCC [8].

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The mammalian target of rapamycin (mTOR) plays a central role in regulating cellular pathways leading to growth, proliferation, and angiogenesis. Everolimus (RAD001) is an orally administered mTOR inhibitor. Everolimus and temsirolimus (an intravenous mTOR inhibitor) have the potential to be of clinical benefit in patients with cancers that have progressed on a VEGF-targeted therapy such as sunitinib or sorafenib. A recent phase 3 clinical trial evaluating the efficacy of everolimus in patients with mRCC who had progressed on sunitinib, sorafenib, or both demonstrated an improvement in progression-free survival for everolimus over placebo (second interim analysis: 4.0 mo vs 1.9 mo, $p < 0.0001$ [9]; end of double-blind analysis: 4.9 mo vs 1.9 mo, $p < 0.001$ [10]). Everolimus has been shown to have particular benefit in patients who are refractory to anti-VEGF targeted therapy [9,11]. Additionally, a recent phase 2 study demonstrated that everolimus also has encouraging antitumour activity in patients with mRCC who have received one or no prior therapy, including patients who are refractory to cytokines (14% had a partial response and 73% had stable disease $\geq$3 mo; $n = 37$) [12]. Everolimus has been approved in the United States by the US Food and Drug Administration (March 2009) for patients with advanced RCC after treatment failure with sunitinib or sorafenib. European Union approval for use of everolimus in patients with advanced RCC whose disease progressed on or after treatment with VEGF-targeted therapy was granted in August 2009.

In this paper, the use of everolimus in two patients with mRCC is presented. The first patient had tumour relapse and metastasis after nephrectomy. Subsequent treatment with sunitinib led to uncontrolled arterial hypertension, prompting dose reduction of sunitinib. The patient developed progressive disease, and dose escalation of sunitinib was not an option because of the risk of uncontrolled hypertension. The patient was treated with everolimus as part of the phase 3 Renal Cell Cancer Treatment with Oral RAD001 Given Daily (RECORD-1) trial [9], and tumour shrinkage representing a partial response was achieved and sustained for >16 mo.

The second patient with mRCC had progressed on cytokines. Subsequent treatment with sorafenib gave an initial partial response, but disease progression followed. The patient was then enrolled in the phase 3 RECORD-1 trial [9] and was randomised to placebo. After disease progression, the patient was offered open-label everolimus, which led to disease stabilisation and tumour shrinkage.

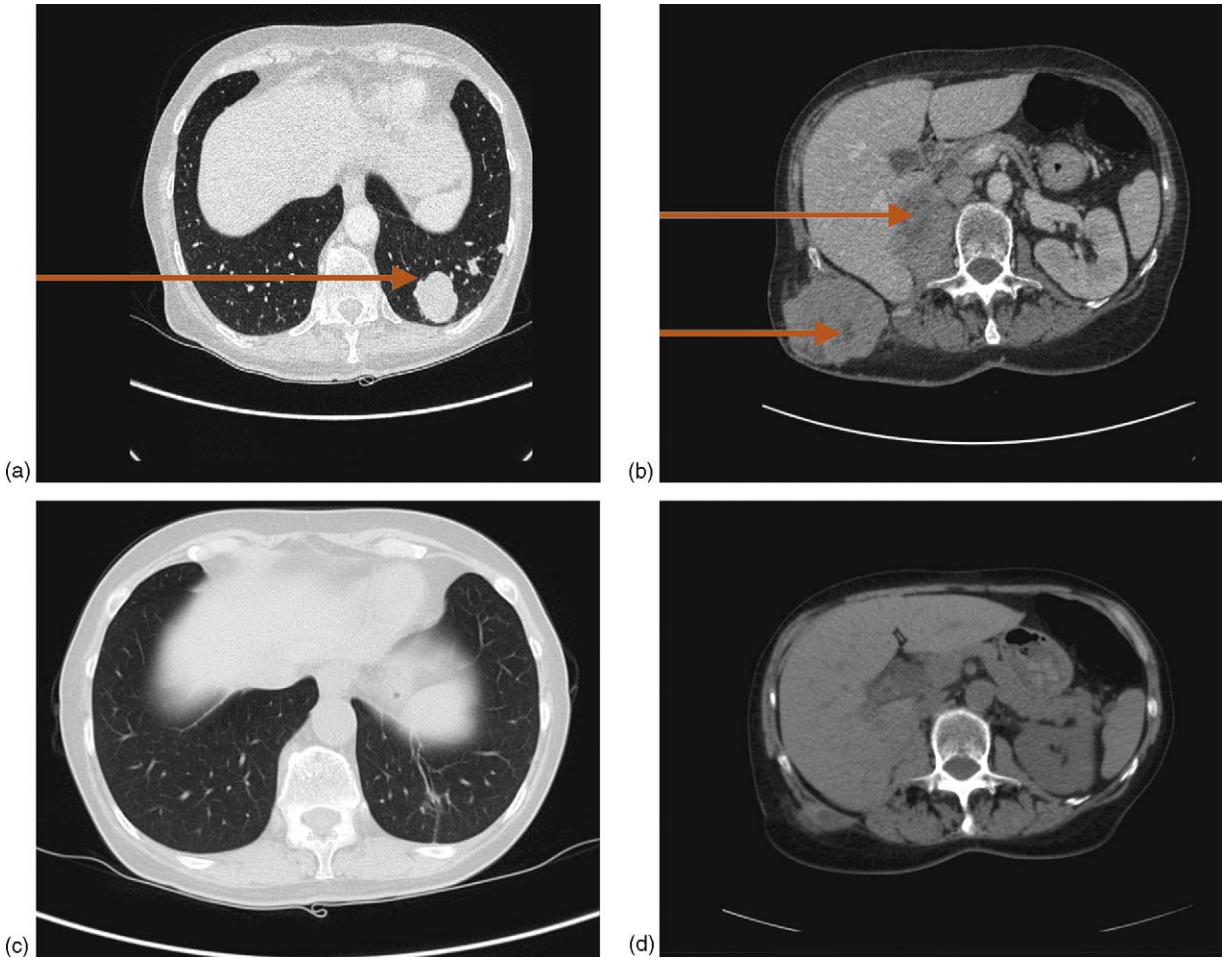

Fig. 1 – (a) Lung computed tomography (CT) scan and (b) abdominal CT scan of a patient with metastatic renal cell carcinoma prior to treatment with everolimus; (c) lung CT scan and (d) abdominal CT scan of patient 16 mo after initiation of everolimus treatment. Arrows indicate metastases.

1.2. Case report 1 supplied by Dr. Ravaud: Everolimus after progression on sunitinib

The patient was a 57-yr-old female with a previous history of tobacco smoking. In 2005, the patient underwent radical nephrectomy for a histologically confirmed clear cell RCC (stage pT3a N1; Fuhrman nuclear grade III).

In mid-2006, the patient had disease progression and began treatment with sunitinib (6-wk cycles: 50 mg given orally once daily for 4 wk, followed by 2 wk without treatment) in November 2006. The patient, however, required several dose reductions, from 50 mg to 25 mg, and then to 12.5 mg once daily, because of uncontrolled arterial hypertension. There was a decrease in general well-being to an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2.

In July 2007, sunitinib treatment was halted because of disease progression, inducing an improvement of the patient's general well-being to an ECOG PS of 1; therefore, the patient was referred to Bordeaux University Hospital. Dose escalation of sunitinib was not considered to be the optimal treatment approach at this point because of the risk of the patient developing subsequent uncontrolled arterial hypertension. Alternatively, the patient was enrolled in the phase 3 RECORD-1 trial, investigating everolimus versus placebo [9], and was subsequently randomised to what was revealed after unblinding to be the active treatment arm (everolimus, 10 mg once daily). At this time, the patient had a pretreatment ECOG PS of 1, a haemoglobin (Hb) level of 7 g/dl (that was corrected to 10.6 g/dl with a blood transfusion), and a normal corrected calcium level. Metastatic sites were identified at the site of nephrectomy, in the lungs and subcutaneously (Fig. 1a and b). Treatment with everolimus was initiated in August 2007. Side-effects were mainly limited to the first month of treatment, due, in part, to a decrease in general well-being, despite the patient still having an ECOG PS of 1. Over time, ECOG PS improved to 0. Because of an increase in creatininaemia and a lowering of the creatinine clearance, a computed tomography (CT) scan was performed (without vascular injection but still allowing interpretation of response). Tumour shrinkage was observed as early as 6 wk into treatment, which reached a partial response at the second evaluation at wk 12. The partial response was maintained at the last evaluation in December 2008, 16 mo after initiation of everolimus (Fig. 1c and d).

1.3. Case report 2 supplied by Professor Bracarda and Dr. Chiodi: Everolimus after progression on sorafenib

A 56-yr-old female was diagnosed with bone metastases in December 2005. A bone biopsy was positive for metastasis of clear-cell RCC and a subsequent CT evaluation confirmed bilateral renal tumours. In February 2006, the patient began treatment with capecitabine plus IFN-α2a, but a CT evaluation in April 2006 showed disease progression in the lungs, kidney, and bone sites. Treatment was changed to sorafenib (400 mg twice daily) at the beginning of May 2006. At this time, the patient had a baseline ECOG PS of 1, an Hb level of 10.7 g/dl (upper level of normal [ULN] 15 g/dl), a lactate dehydrogenase (LDH) level of 383 U/l (ULN 480 U/l), and a serum calcium level of 7.8 mg/dl. The patient showed a partial response that was confirmed by CT scans in July and October 2006 (tumour shrinkage of 43.2%). In October 2006, the sorafenib dose was reduced to 400 mg once daily because of treatment-related diarrhoea, and progressive disease was confirmed in February 2007.

In March 2007, the patient was enrolled in the phase 3 RECORD-1 trial [9] and was randomly assigned to treatment with either everolimus or placebo. At this time, the patient had multiple metastatic sites (lungs, mediastinal lymph nodes, renal bilateral masses, and bone lesions), a Karnofsky performance score of 70, a Hb level of 10.8 g/dl, an LDH level of 216 U/l (ULN 250 U/l), and a corrected calcium level of 8.6 mg/dl. This blinded treatment achieved stationary disease (+15.5%) at the first evaluation, but disease progression was observed in July 2007 (Fig. 2a). After unblinding, it was revealed that the patient was in the placebo group and therefore was offered open-label everolimus (10 mg once daily). After everolimus treatment was initiated, CT evaluation in September 2007 showed stable disease, with shrinkage of lung nodules. In October 2007, the dose of everolimus was reduced to 5 mg once daily because of treatment-related grade 3 stomatitis. CT evaluations in November 2007 and January 2008 showed

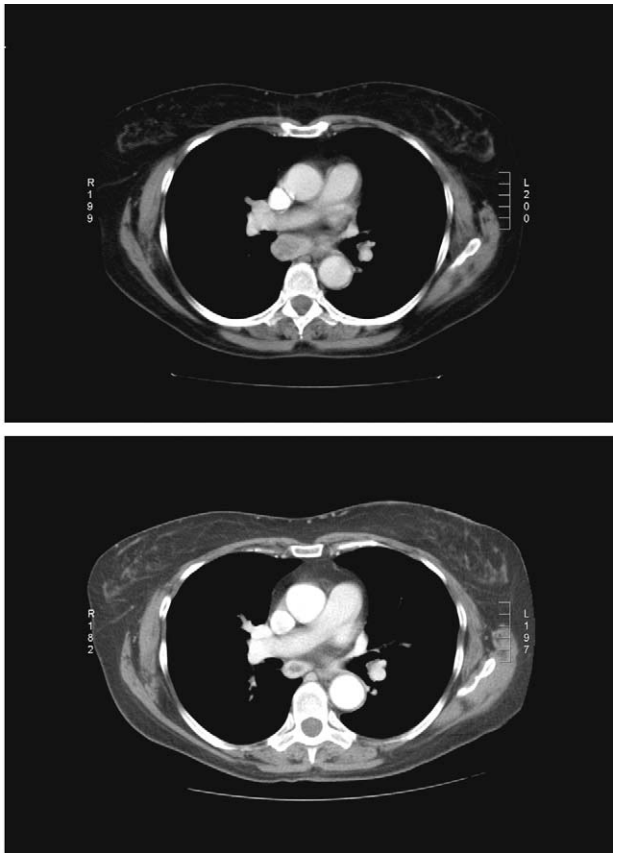

Fig. 2 – (a) Computed tomography scan showing mediastinal lymph node metastases; (b) evidence of significant reduction after 8 mo of treatment with open-label everolimus.

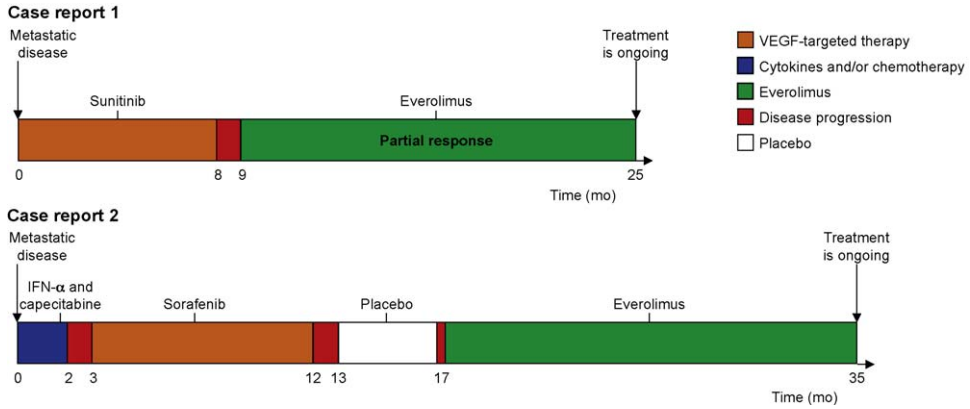

Fig. 3 – Summary of responses to treatment over time in two patients with metastatic renal cell carcinoma. Approximate timelines are given. IFN-α = interferon alfa; VEGF = vascular endothelial growth factor.

further shrinkage of lung nodules and initial shrinkage of mediastinal lymph nodes and renal tumours, classified as overall stable disease. Subsequent CT evaluations in March and October 2008 indicated slight increases in tumour size (+4.5% and +12.2%, respectively), with ongoing overall stable disease (Fig. 2b).

Control visits in November and December 2008 indicated that the patient's condition continued to be generally good; in December 2008, she had anaemia (grade 2; Hb level 8.6 g/dl), anorexia (grade 1), hypercholesterolaemia (grade 1), hypertriglyceridaemia (grade 1), and hyperuricaemia (grade 1). Similar adverse events were present at the most recent patient evaluation (January 2009), with anaemia progressing in severity to grade 3 and increased creatinine levels (grade 1). The CT scan did not show any evidence of progression; the patient was judged to have overall stable disease, and everolimus treatment was continued.

2. Discussion

Advanced RCC is associated with poor prognosis and has mainly been treated with cytokines for the past two decades. Therapies that target specific pathways involved in the pathogenesis of mRCC have emerged recently and are discussed in detail elsewhere in this supplement [13–15]. The first of these therapies to be approved were VEGF-targeted agents (bevacizumab, sunitinib, and sorafenib); however, current treatments are not curative, and many patients become refractory to these targeted therapies. More recently, the mTOR inhibitors temsirolimus and everolimus have been developed. Through inhibition of mTOR, these agents are able to inhibit pathways involved in growth, proliferation, and angiogenesis. Because their mechanism of action differs from that of VEGF-targeted agents, they have the potential to be effective in patients who are refractory to VEGF-targeted therapy. Phase 3 clinical trial data have demonstrated that everolimus is effective in patients with mRCC after failure of VEGF-targeted therapy. Furthermore, everolimus is generally well tolerated, and most adverse events are mild to moderate in severity and are manageable. The case studies reported in this paper support the activity of everolimus in the treatment of mRCC, especially in patients who have progressed on a previous targeted therapy, showing the possibility of achieving extended periods of disease control (Fig. 3). These clinical cases also confirm the favourable adverse event profile of everolimus, which is an issue of particular interest for second-line treatment settings, in which maintaining quality of life should remain a primary objective. Everolimus is currently in a number of clinical trials further evaluating its efficacy, including its effectiveness in the first-line treatment setting and also its activity in combination with other targeted therapies.

Conflicts of interest

Professor Bracarda has been an advisory board member for Bayer-Schering Pharma, GlaxoSmithKline, Novartis, Pfizer, Roche, and Wyeth and has received honoraria from Novartis. Dr. Ravaud is a member of the Global, European and/or French advisory boards for Bayer, GlaxoSmithKline, Novartis, Pfizer, Roche, and Wyeth for urological tumours; institutional funding support for research has been obtained from GlaxoSmithKline, Novartis and Roche. Dr. Marino Chiodi has nothing to disclose. The authors did not receive an honorarium or consultancy fee for writing this manuscript.

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