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REVIEW

Everolimus: Emerging Evidence of its Therapeutic Impact in Patients with Advanced Renal Cell Carcinoma

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Abstract: The treatment of patients with advanced renal cell carcinoma (RCC) has been revolutionized by the development of agents directed against vascular endothelial growth factor (VEGF) signaling. These agents, such as sorafenib and sunitinib, have been advocated as first-line treatments for RCC. However, responses to these agents are neither complete nor durable and nearly all patients will require second-line therapy. Everolimus (RAD001) is an oral inhibitor of mammalian target of rapamycin (mTOR) which has recently been shown to significantly prolong the progression free survival of patients with RCC who have failed either sorafenib or sunitinib (or both) as compared to placebo. Based on these results, everolimus was approved by the Food and Drug Administration (FDA) on March 30, 2009 and is now considered a standard therapeutic option for patients who have failed front-line VEGF-targeted therapy. Everolimus is now actively undergoing further evaluation in multiple clinical scenarios including sequential, combinational, and adjuvant therapy as well as in non-clear cell RCC.

Keywords: everolimus, renal cell carcinoma, RCC, VEGF-targeted therapy

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Introduction

Recently, agents targeting mammalian Target of Rapamycin (mTOR) have been shown to have significant clinical activity in patients with advanced renal cell carcinoma (RCC). Everolimus (Affinitor®, RAD001), an allosteric inhibitor of mTOR, was approved by the Food and Drug Administration (FDA) on March 30, 2009 for the treatment of patients with advanced RCC following the failure of treatment with sorafenib and/or sunitinib. Everolimus now joins five other FDA approved molecularly targeted and/or antiangiogenic agents (sorafenib, sunitinib, pazopanib, bevacizumab, temsirolimus) and prior immunotherapies (interferon and interleukin-2) in a crowded therapeutic field in RCC. In this article, we will review the mechanism of action and pharmacologic properties of everolimus, examine completed clinical trials involving everolimus, review its current place in the treatment of patients with RCC and finally discuss opportunities for future investigation with everolimus including sequential and combination treatment approaches, adjuvant clinical trials and potential patient selection strategies.

Mechanism of Action, Metabolism, and Pharmacokinetic Profile

Mechanism of action: molecular basis

Everolimus is a synthetic ester of the natural product rapamycin. Similar to rapamycin, everolimus binds with high affinity to the cytoplasmic protein FK506 binding protein-12. This resulting complex interacts with and inhibits the kinase activity of mTOR.[1] Activated downstream of the phosphatidylinositol 3-kinase (PI3-K)/Akt pathway, mTOR executes its biologic functions as a critical component of two distinct complexes, TORC1 and TORC2, which have differential sensitivities to rapamycin (Fig. 1). TORC1, which includes mTOR, LST8 (GβL), and raptor (regulatory protein associated with TOR), is inhibited by rapamycin whereas TORC2, which includes mTOR, LST8, and rictor (rapamycin insensitive companion

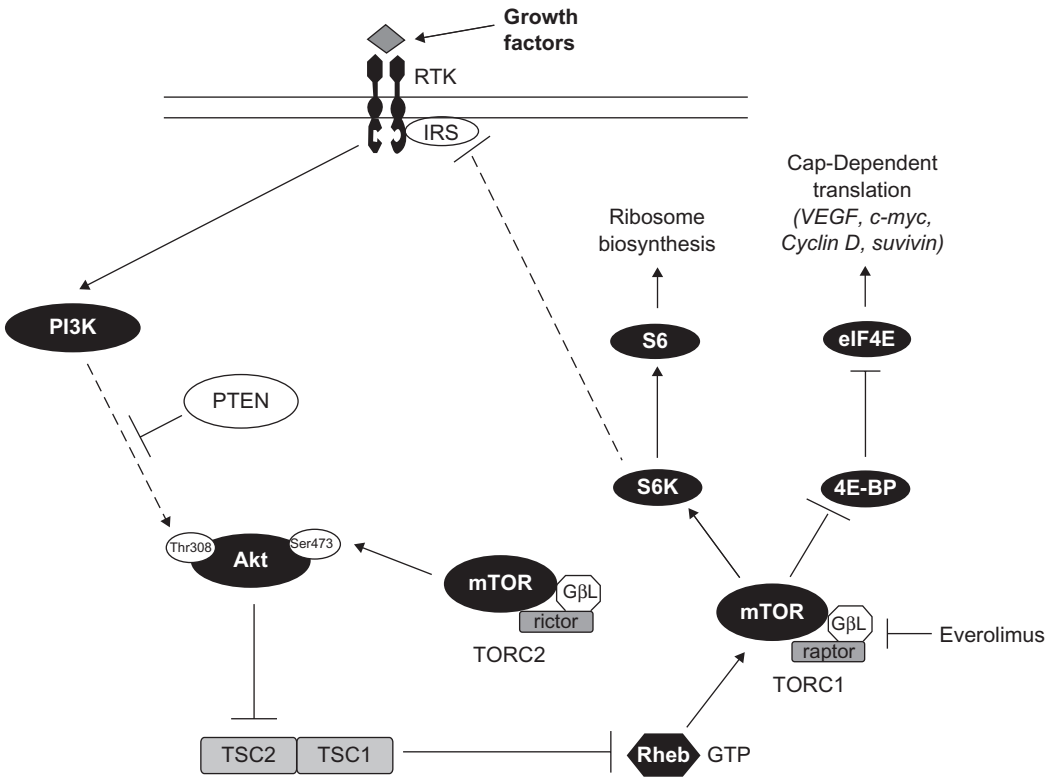

Figure 1. Activation of the mTOR signaling pathway by growth receptor signaling through receptor tyrosine kinases.
Abbreviations: RTK, receptor tyrosine kinase; IRS, insulin receptor substrate; PI3-K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homologue; Akt, protein kinase B; TSC, tuberous sclerosis complex; Rheb, ras homologue enriched in brain; mTOR, mammalian target of rapamycin; Rictor, rapamycin insensitive companion of TOR; Raptor, regulatory associated protein of TOR; S6K, P70 S6 kinase; 4E-BP, 4E-binding protein; eIF4E, elongation initiation factor 4E.

of TOR), is largely believed to be insensitive to rapamycin. Therefore, the clinical efficacy of everolimus and other rapalogues, such as temsirolimus, is believed to be primarily mediated through inhibition of TORC1 activity.

TORC1 serves to integrate growth factor signaling and nutrient availability with growth and cell cycle progression. This complex acts through its downstream effectors, namely the S6 ribosomal protein kinase (S6K) and the eukaryotic elongation factor 4E-binding protein (4E-BP), to control such cellular functions as the shuttling of glucose and amino acid transporters between cytoplasmic vesicles and the plasma membrane, the biogenesis of ribosomes, and cap-dependent translation of cellular messenger RNAs (mRNA). The S6K is known to regulate the function of TORC1 primarily responsible for ribosomal biogenesis.[2] The regulation of cap-dependent translation by TORC1 is mediated through its effects on the activity of eIF4E, a protein that binds the 5' m^7G cap structure of cellular mRNAs and facilitates translation by enhancing the association of the mRNA with the RNA helicase eIF4A and the ribosome-interacting scaffolding protein eIF4G.[3] The control of eIF4E by TORC1 is mediated by the mTOR-dependent phosphorylation (and inactivation) of 4E-BP1, an inhibitory eIF4E binding protein.

The extent to which the translation of a particular transcript depends on TORC1 (and eIF4E) activity is determined by the length and complexity of the mRNA 5' untranslated region (UTR). Approximately 3 percent of cellular mRNAs have 5'UTRs that extend to greater than one-third of the transcript length.[4] The 5'UTRs of these mRNAs often have high GC content and stem loop structures that preclude translation except when TORC1 is activated. Many of these "weak", otherwise untranslated mRNAs encode proteins essential for cell cycle progression (e.g. cyclins, c-Myc, ornithine decarboxylase), survival (e.g. the IAPs XIAP and survivin), and angiogenesis (e.g. VEGF).[4] Although the exact molecular basis for the clinical benefit observed with mTOR inhibitors remains unclear, it is possible the translation of these "weak" mRNAs is important to the maintenance of the malignant phenotype in RCC.

Attenuation of the mTOR activity may also be particularly beneficial in RCC because activation of this pathway has been shown to increase hypoxia inducible factor (HIF) 1α gene expression, both at the levels of messenger RNA (mRNA) translation and protein stabilization.[5,6] Inappropriate accumulation of HIF-1α and HIF-2α as a result of biallelic alterations in the von Hippel-Lindau (VHL) gene observed in the majority of clear cell RCC is believed to be a critical step in RCC tumorigenesis.[7,8] Inhibition of TORC1 by temsirolimus has been shown to reduce expression of HIF-1α under both normoxic and hypoxic conditions in mouse xenograft models and remains a possible mediator of the clinical response observed in RCC.[9]

Inhibition of TORC1, however, can also be associated with compensatory activation of the PI3-K/Akt pathway, possibly driving a resistance mechanism to TORC1 inhibitors. Treatment of some cells with rapamycin has been shown to result in activation of PI3-K due to attenuation of a feedback loop driven by S6K through insulin response substrate 1 (IRS-1).[10,11] Although pharmacologic inhibition of TORC1 has been shown in some cases to drive TORC2 activation, it has also been suggested that prolonged inhibition of TORC1 can lead to suppression of TORC2 formation.[12] The activity of the rapalogues against TORC2 is of particular relevance to RCC given the recent assertion that the expression of HIF-2α, argued by many to be the more relevant HIF in RCC,[13] is dependent only on TORC2 activity.[14] Thus, both the compensatory activation of PI3-K/Akt and failure to inhibit TORC2 activity may be important mechanisms of resistance to the rapalogues.

Pharmacokinetics and metabolism

Everolimus is available as an oral dispersible tablet with an estimated bioavailability of 90%, approximately 74% of which will be plasma protein bound.[15,16] In studies of daily oral dosing in patients with advanced solids tumors, Tmax was approximately 1–2 hours following dosing with steady state achieved within 1–2 weeks. Everolimus is extensively metabolized in the liver and is a substrate of CYP3A4 and P-glycoprotein (PgP).[16] Therefore, enhanced area under the curve (AUC) and serum levels may be observed in patients with impaired hepatic function. Not surprisingly, common drug interactions are with agents that are known to be inducers or inhibitors of CYP3A4. Impaired creatinine clearance has not been observed to affect the clearance of everolimus. Unlike some rapalogues, everolimus is not a

pro-drug of rapamycin and is therefore not known to be metabolized into rapamycin.[17] Everolimus is primarily excreted through the bile and feces and has an elimination half-life of 18–35 hours.

Completed Clinical Studies

Everolimus first demonstrated promising single-agent efficacy in RCC in two separate phase 2 trials in patients who had largely received prior therapy. In the first trial, patients with metastatic RCC who had no more than one prior therapy were treated with everolimus at a daily dose of 10 mg.[18] Each treatment cycle was 28 days and patients were evaluated for response every 2 cycles using RECIST criteria. Forty-one patients with metastatic RCC were enrolled (31 of whom had prior therapy) and 37 were evaluable for both response and toxicity. Five (14%) patients showed partial response and stable disease lasting ≥6 months was observed in 21 (57%) patients. The median progression-free survival (PFS) was 11.2 months (95% CI 1.7–36.2) and the median overall survival was 22.1 months (95% CI 1.4–36.4). The most common Grade 1 or 2 adverse events included: anorexia (38%), nausea (38%), diarrhea (31%), stomatitis (31%), (pneumonitis (31%), and rash (26%). The most common Grade 3 of 4 adverse events included pneumonitis (18%); transaminase elevations (10%); thrombocytopenia (8%), hyperglycemia (8), alkaline phosphatase elevations (8%), and hyperlipidemia (5%).

In the second trial, patients who had failed either sorafenib or sunitinib and had no more than 2 prior therapies were again treated with a daily dose of everolimus at 10 mg.[19] As before, each treatment cycle was 28 days and patients were evaluated for response every 2 cycles using RECIST criteria. Twenty-two patients were enrolled and 19 were evaluable for response. Three (16%) patients showed partial response and 14 (74%) patients experienced stable disease for ≥3 months. Median PFS was 5.5 months (95% CI 1–12 months) and the median overall survival was 8 months (95% CI 1–14 months). The most common Grade 1 or 2 events included: hypertriglyceridemia (73%), hyperglycemia (59%). hypercholesterolemia (64%), stomatitis (45%), rash (32%), nausea (27%), and diarrhea (18%). The most common Grade 3 or 4 adverse events was pneumonitis (27%). Together, these two phase 2 trials suggested that everolimus may have single-agent activity in metastatic RCC, in particular following failure of VEGF-targeted therapy.

Based on these promising results, everolimus was assessed in a randomized, double-blind, placebo-controlled phase 3 in patients with advanced RCC who had failed prior treatment with either sorafenib or sunitinib, or both within the last 6 months (**RE**nal Cell cancer treatment with **O**ral **R**AD001 given **D**aily-1 [RECORD-1]).[20] Patients were additionally required to tumor showing at least a component of clear cell histology. Prior therapy with bevacizumab, interleukin-2, or interferon-α was also permitted. Overall, 416 patients from 86 centers in Australia, Canada, Europe, Japan, and the United States, were enrolled and randomized in a 2:1 fashion to receive either everolimus 10 mg PO once daily (n = 277) or placebo with best supportive care (n = 139) with a primary endpoint of PFS. Patients were stratified by MSKCC risk factors and prior therapy. As in the phase 2 trials, each treatment cycle was 28 days and patients were evaluated for response every 2 cycles using RECIST criteria. Randomization was unblinded at time of progression and patients on placebo were allowed to crossover to open-label everolimus. The trial was halted at the second interim analysis after 191 progression events had been observed. At the final central radiology assessment the median PFS for patients treated with everolimus was 4.88 months as compared with 1.87 months in the placebo group (hazard ratio 0.33, [95% CI 0.25–0.43] $p < 0.0001$).[21] For the 124 patients previously treated with only sorafenib the median PFS was 5.88 months for the everolimus treated patients vs. 2.83 months for the placebo group, while patients previously treated with sunitinib alone had a 3.88 months median PFS with everolimus vs. 1.84 months with placebo. Five patients (2%) in the everolimus group experienced partial responses vs. 0 in the placebo group. Median overall survival was not different between the two arms (14.78 months with everolimus vs. 14.39 months for placebo; $p = 0.177$), although this was felt likely to be due to the built in crossover to open label everolimus in patients exhibiting disease progression on placebo. As with the phase II trials, everolimus was felt to have a favorable side effect profile with most common adverse events seen with everolimus relative to placebo being stomatitis (40% vs. 8%), rash (25% vs. 4%), fatigue (20% vs. 16%). Pneumonitis was observed in 22 patients (8%)

compared with 0 in the placebo group. Based on these results, everolimus was approved the FDA in March, 2009 for the treatment of patients with advanced RCC who failed either sorafenib, sunitinib, or both.

Safety

Although in general well-tolerated, treatment with everolimus can be associated with many of the same side-effects observed with the VEGF-targeted TKIs, most commonly including rash, nausea, diarrhea, stomatitis/mucositis, cytopenias, and fever. However, everolimus, along with the other rapalogues, can also induce toxicities which are distinct from those seen with other molecularly targeted therapies in RCC and are worthy of specific discussion. These toxicities include pneumonitis, endocrine abnormalities, and the possibility of immunosuppression.

Pneumonitis

Pneumonitis has been observed with all the rapalogues and appears to be a class effect of the allosteric inhibitors of TORC1.[22,23] The exact incidence of this toxicity seems to vary widely from study to study. As noted above, in the phase III RECORD-1 trial, the incidence of pneumonitis was (8%) with 22 of the 269 patients treated with everolimus experiencing this side effect and only 8 (3%) graded as higher than grade 2. However, in a retrospective study in patients with non-small cell lung cancer, White et al reported that 16 (25%) of 64 patients examined showed radiographic evidence of pneumonitis which was felt attributable to everolimus.[24] Other studies have suggested that pneumonitis from TORC1 inhibitors may be more common in patients with pre-existing pulmonary conditions.[25] In patients treated with everolimus, pneumonitis may be more commonly appreciated radiographically, where it most frequently presents as ground glass-opacity and occasionally as parenchymal consolidations and pleural effusion, than clinically. When symptoms are present, most patients experience dypsnea on exertion and cough, occasionally accompanied by fever, malaise, and hypoxia. While many mechanisms have been proposed, including cell-mediated auto-immunity and T-cell-mediated delayed-type hypersensitivity,[22,26] the exact molecular basis for this toxicity remains unknown. Although there are currently no specific guidelines to the management of everolimus-associated pneumonitis, other etiologies, particularly infectious, should be first excluded. Most investigators appear to agree that treatment should be held in patients with overt symptoms attributable to pneumonitis and a brief course of steroids may be considered. Treatment resumption, usually at a lower dose, may be considered following resolution of symptoms. There does not appear to be consensus for patients with only radiographic findings of pneumonitis, but continuing therapy with careful observation or lowering the dose appear to be common interventions.

Endocrine side effects

Treatment with rapalogues has also been associated with several endocrine abnormalities, namely hyperlipidemia and hyperglycemia. These toxicities appear quite common in patients with RCC treated with everolimus. In the RECORD-1 study, the incidence of hypercholesterolemia, hypertriglyceridemia, and hyperglycemia in patients treated with everolimus was 76%, 71%, and 50%, respectively. Studies with rapamycin suggest that the hyperlipidemia (observed as elevations in HDL, LDL, cholesterol, and triglycerides) induced by rapalogues is due to reduced catabolism of lipoprotein particles.[27] While this toxicity is quite common and therefore requires continuous monitoring, everolimus-induced hyperlipidemia is usually manageable with statins or gemfibrozil (for hypertriglyceridemia) and typically does not require treatment cessation. Similarly, animal studies with rapamcyin have shown that hyperglycemia is a direct side effect of treatment with rapalogues due to enhancement of insulin resistance and reduction of β-islet cell mass and function.[28] Therefore, monitoring of fasting glucose levels is recommended for all patients treated with everolimus, particularly those with pre-existing diabetes, and initiation of oral antiglycemic agents or escalation of current diabetic regimen may be indicated.

Immunosuppression

As the rapalogues were developed first as immunosuppressive agents in the transplant setting, treatment with drugs such as everolimus has always raised concerns regarding the potential for immunosuppression in cancer patients. Recent studies have actually suggested that rapamycin may actually enhance the immune response to infections by both enhancing the

CD8+ T-cell response and by increasing the differentiation of effector cells into potent memory T-cells.[29,30] Nonetheless, in the RECORD-1 trial, the incidence of all infections was higher in patients treated with everolimus (27 patients [10%]) as compared with those treated with placebo (3 patients [2%]). Therefore, the issue of whether everolimus may be immunosuppressive cannot be considered completely resolved. Although current data does not support the use of antibiotic prophylaxis, clinical vigilance to the possibility of increased frequency of infections is recommended, particularly in those patients with pre-existing chronic viral infections or immunosuppressive conditions. In particular, recent reports filed through Medwatch, have indicated that treatment with everolimus may trigger the activatation of Hepatitis B in patients with history of resolved or inactive hepatitis B.[31] In these patients, initiation of anti-hepatitis medication such as lamuvidine is recommended prior to the initiation of everolimus.

Place in Therapy

Current approval

Everolimus is currently approved by the FDA for treatment of patients with advanced RCC following failure of treatment with either sorafenib or sunitinib. Although the FDA approval does not specifically limit everolimus to clear cell RCC, as patients enrolled in the phase 3 RECORD-1 trial were required to have RCC with a component of clear cell histology, currently available data primarily supports the use of everolimus in patients with clear cell RCC at this time. The treatment landscape for this patient population is even more complicated by the recent FDA approval of pazopanib and bevacizumab (plus interferon-α [IFN]) in the first-line setting as there is currently no data on the efficacy of everolimus specifically following failure of either of these two therapies. However, given the likely overlap in mechanism of action for these VEGF-targeted therapies, it may be reasonable to expect that everolimus may have efficacy following the failure of pazopanib or bevacizumab (plus IFN) similar to that seen following sunitinib or sorafenib. Much like many other novel therapies in RCC, it is likely that the role of everolimus in RCC therapy will continue to evolve as many questions regarding its efficacy in specific therapeutic situations are addressed. For example, although a subset of patients treated with everolimus in the original phase 2 trial had not had prior therapy,[18] there is currently little experience with everolimus given in the first-line setting in patients with RCC. Not surprisingly, everolimus is now being studied in multiple other clinical scenarios and therapeutic strategies including the first-line setting given in sequential fashion with other therapies, combinational regimens, the adjuvant setting, and in patients with non-clear cell histology.

Sequential therapy

In general, none of the currently available VEGF pathway or mTOR inhibitors, everolimus included, produce complete or durable remissions that can be maintained off therapy in patients with advanced RCC. Therefore, the primary benefit of these agents may be to delay tumor progression. Multiple retrospective analyses have suggested that there is no true cross-resistance for these agents given in sequence.[32,33] Many investigators have proposed to examine specific sequences of novel agents given as single-agents in an effort to identify a particular sequence of agents which may result in maximal disease control duration while perhaps also minimizing toxicity. With respect to everolimus, this is specifically being examined in the RECORD-3 trial, a large phase 2 trial in which previously untreated patients with metastatic clear cell RCC will be randomized to receive either first-line everolimus followed by second-line sunitinib or first-line sunitinib followed by second-line everolimus. Overall, 390 patients are expected to be enrolled with a primary endpoint of progression-free survival either a consequence of first-line or sequential first and second-line treatment. This trial should also provide some further information on the efficacy of everolimus in the first-line setting in patients with clear cell RCC.

Combinational therapy

Given the distinct targets of recently approved treatments for patients with RCC (i.e. inhibition of VEGF signaling vs. inhibition of mTOR), there has been considerable interest in whether combinations of these two classes of agents may lead to additional therapeutic efficacy. Given its oral availability and favorable toxicity profile, everolimus is an attractive agent to investigate in combinational regimens, particularly those targeting VEGF-signaling. Table 1 shows the some of the key on-going or planned combinational

Table 1. Combinational therapeutic trials containing everolimus.

Trial	Setting	Institution	Status
Phase II: Everolimus + Bevacizumab vs. Bevacizumab + IFN (RECORD-2)	1st-Line	Multi-center	Recruiting
Phase I/II: Everolimus plus Sorafenib	2nd-Line	Methodist hospital system	Completed
Phase I: Everolimus plus Sunitinib	Multiple Prior Rx	MSKCC	Completed accrual
Phase I: Everolimus plus Pazopanib	Multiple Prior Rx	DF/HCC	Not yet active
Phase I: Everolimus plus Pabinostat	Multiple Prior Rx	Roswell park	Not yet active
Phase II: Everolimus plus Imatinib	After 1st-Line	Oregon health and sci. univ.	Completed accrual

trials which include everolimus. Perhaps the most interesting combinatorial approach involves the combination of everolimus with bevacizumab. A phase 2 studies with this combination produced 5 partial responses (17%) and a median PFS of 11 months in 29 patients who had received prior VEGF receptor TKI therapy.[34] This data, plus the desire to examine the role of maintained VEGF pathway blockade following sunitinib or sorafenib resistance has led the CALGB to propose an intergroup phase 3 trial randomizing patients whose disease has progressed following sorafenib and/or sunitinib to either everolimus alone or the combination of everolimus and bevacizumab.

Adjuvant therapy

Although there are no therapies approved for the adjuvant treatment of patients with high-risk RCC, the recent approval of multiple therapies in the metastatic setting has prompted the assessment of many of agents in the adjuvant setting. Studies involving sorafenib and/or sunitinib are currently underway and anticipated to reach accrual goals within the near future, but mature results are not envisioned for several years. The efficacy of everolimus in patients with metastatic RCC, together with its novel mechanism of action, favorable toxicity profile and oral mode of administration make it an attractive agent to also test in the adjuvant setting. Accordingly, a large randomized placebo controlled phase 3 trial is being planned within the U.S. Intergroup mechanism to formally assess the role of adjuvant everolimus in patients with resected high-risk resected RCC.

Non-clear cell histology

As discussed earlier, the clinical data which is available thus far supports the use of everolimus in patients with clear cell RCC. There is currently no significant experience with respect to the efficacy of everolimus in patients with non-clear cell RCC. However, further analysis of the pivotal phase 3 trial leading to the FDA approval of temsirolimus suggested this TORC1 inhibitor may be even more effective compared with interferon in patients with non-clear cell RCC than clear cell RCC.[35,36] The median overall survival of temsirolimus versus interferon was 11.6 vs. 4.3 months in patients with non-clear cell histology (75% of which were of papillary sub-type) compared with 10.7 vs. 8.2 months in patients with clear cell RCC. It should be noted, however, that these results may be somewhat limited in that there was no central histology review as part of this study. Nonetheless, the possibility that TORC1 inhibitors in general may have unique efficacy in non-clear cell RCC has prompted the initiation of a phase 2 trial of everolimus in papillary RCC. The RAPTOR (RAD001 in Advanced Papillary Tumor Program in Europe) Clinical Trial will enroll 60 previously untreated patients with metastatic papillary RCC who will begin therapy with the standard 10 mg once daily dose of everolimus. Although the primary endpoint of this study will be median PFS, this trial should provide critical information regarding the efficacy on everolimus in patients with the largest subset of non-clear cell histology RCC.

Patient Selection Strategies

As with other targeted therapies, not all patients benefit from treatment with everolimus and at present, there are no clinically validated predictive clinicopathologic features or biomarkers of benefit from therapy. Although temsirolimus has demonstrated specific efficacy in patients with poor risk MSKCC features, the same finding has yet to be observed with everolimus. Several lines of evidence suggest, however, that treatment outcome is likely to be determined by the

particular genetic alterations and signaling pathways activated in individual tumors. Therefore, much effort has been directed towards identifying candidate predictive biomarkers of response to TORC1 inhibitors. We and others have suggested that the pre-treatment activation status of the PI3-K/Akt signaling pathway may be one such predictor. The loss of PTEN, for example, is associated with an enhanced antiproliferative response to rapamycin *in vitro*.[37] Moreover, in a study carried out in parallel with a recent Phase 2 trial of temsirolimus in patients with RCC,[38] we were able to demonstrate a correlation between tumor cell Akt and S6 phosphorylation as defined by immunohistochemistry and clinical response. The significance of this study was, however, limited because of its retrospective nature and the small number of tumors examined. Moreover, an analysis of archived tumor specimens from patients enrolled in the phase III trial of temsirolimus versus IFN[36] failed to show a correlation between PTEN expression and likelihood of clinical benefit from temsirolimus.[39] Thus the question of whether pre-treatment activation of the PI3-K/Akt/mTOR pathway can predict for response to TORC1 inhibitors must be considered far from answered. To potentially address this question for definitively, a phase 2 biomarker trial of everolimus in patients with advanced RCC is on-going. This study differs from most other biomarker trials in RCC in the use of biopsies of *metastases* rather than primary tumors (i.e. nephrectomy specimens) and in the strict control over the processing of the tissue to minimize epitope loss. Overall, 40 patients with biopsy-accessible metastatic RCC will be enrolled with the primary endpoint of validating the pre-treatment activation status of the PI3-K/Akt signaling pathway as predictive for clinical benefit to everolimus.

Several lines of evidence suggest that the antitumor effects of mTOR inhibitors are mediated in part through the downmodulation of glucose import and the resulting reduction in ATP generation.[40] In fact, changes in glucose uptake as measured by FDG PET imaging have been used to optimize everolimus dosing *in vivo*.[41] To address the possibility that changes in FDG-PET scanning may serve as an early predictor of response or resistance to everolimus treatment, a phase 2 trial is on-going in which 60 patients with metastatic RCC will undergo FDG-PET imaging before and after initiating therapy with everolimus. The primary objective of this study is to determine if high basal FDG-avidity is predictive of greater likelihood of response to everolimus as determined by changes in RECIST-based tumor measurements after 8 weeks of therapy. The study will also investigate whether changes in FDG-avidity as a result of therapy are associated with clinical responses. Hopefully, these two phase 2 biomarker-based studies will aid in the construction of a selection strategy to determine which patients would be most likely to benefit from therapy with everolimus.

Conclusions

With its recent approval by the FDA, everolimus is now considered a standard therapeutic option for patients with advanced RCC following failure with other FDA approved VEGF-targeted tyrosine kinase inhibitors. However, the role of everolimus in patients RCC therapy will almost certainly continue to evolve as it enters clinical assessment in a multitude of clinical settings including sequential, combinational, and adjuvant therapy as well as in patients with non-clear cell RCC. With the rapidly crowding therapeutic landscape of RCC, it will be critical to develop effective patient selection strategies to determine which patients should be treated with TORC1 inhibitors. Therefore, simultaneous with the assessment of everolimus in different clinical scenarios, effort must be focused on identifying predictive biomarkers of response to this class of agents.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

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