Temsiriolimus in the treatment of advanced renal cell carcinoma

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Introduction
The incidence of renal cell cancer (RCC) is increasing and surgery is the only curative treatment for patients presenting with localized disease at diagnosis. The treatment of metastatic RCC is palliative and, until recently, immunotherapy has been the standard treatment approach with response rates between 10 and 20%. However, only patients with good-risk prognostic features obtain any real benefit [1–3].

An increase in the appreciation of the biology of this disease has resulted in a number of novel ‘targeted’ therapies being developed. Most notable are the tyrosine kinase inhibitors, which have significant clinical activity in both treatment-naive and cytokine-refractory RCC. Tyrosine kinases are enzymes that catalyse the transfer of γ-phosphate groups from adenosine triphosphate (ATP) to the hydroxyl groups of tyrosine residues on the signal transduction molecules. Phosphorylation of signalling molecules activates multiple cellular pathways and in tumours can result in increased cellular proliferation, survival, motility and angiogenesis [4].

Tyrosine kinases can be divided into receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nonRTKs). nonRTKs are intracellular and involved in propagation of the RTK signal. Dysregulation of both types of tyrosine kinases is common in malignancy and provides the rationale for the development of agents that inhibit their function. Temsirolimus is an example of a nonRTK inhibitor.

The target
The mammalian target of rapamycin (mTOR) is a large polypeptide kinase which forms part of the PI3K/Akt pathway. This pathway has an important role in angiogenesis in that its integrity appears to be essential for vascular endothelial growth factor (VEGF)-mediated endothelial proliferation [5]. In addition, mTOR is an activator of hypoxia inducible factor 1α (HIF-1α), which in turn acts as a transcriptional cofactor activating a number of so-called hypoxia-inducible genes [6]: these include VEGF, epidermal growth factor receptor, platelet-derived growth factor, glucose transporters, transforming growth factor alpha and erythropoietin [7]. HIF activation also occurs as a result of von Hippel-Lindau (VHL) gene mutations and hypermethylation, abnormalities which are present in approximately 80% of sporadic cases of clear cell renal cell carcinomas [8, 9].

Temsiriolimus is an ester of rapamycin and forms a complex with FKBP-12, a member of the immunophilin family of FK506-binding proteins. It is this complex that inhibits mTOR [10].

The clinical data
A randomised phase II trial of 111 patients with metastatic RCC used weekly doses of 25, 75 or 250 mg intravenously. Fifty one percent of patients had previously received two or more therapies including immunotherapy and chemotherapy. Only 7% of patients had an objective response [including 1 complete response (CR)] and the main benefit was disease stabilization with 51% of patients achieving a response or stable disease for more than 24 weeks. Neither the efficacy nor the toxicity appeared to correlate significantly with dose. There was a suggestion of an improvement in survival for patients in the poor-risk category compared with historical data for patients receiving immunotherapy [11].

A phase III trial of 626 previously untreated patients with intermediate or poor-risk metastatic RCC has also been reported after the second planned interim analysis [12]. Enrolment was between July 2003 and April 2005: an accrual time of 20 months. The study was reported 13 months after the last patient was enrolled and 442 deaths had occurred. The primary endpoint of the study was a 40% improvement in median overall survival (OS) when single agent Temsirolimus was compared with single agent interferon alpha (IFN) and when Temsirolimus plus IFN was compared with single agent IFN. Secondary endpoints of the study were progression-free survival (PFS) (investigator and independent assessment), time to treatment failure, overall response [CR + partial response (PR)] and clinical benefit [CR + PR + stable disease (SD) ≥ 16 wks].

The assumption was that the median survival in the IFN alone arm would be approximately 4.9 and 6.9 months for Temsirolimus when given as a single agent. Other statistical considerations were: 80% power, a final analysis after 504 deaths, two-sided log-rank test at 2.5% significance and...
two planned interim analyses on after 164 deaths and the other after approximately 430 deaths.

The main inclusion criteria were histological confirmed advanced (stage IV or recurrent disease) RCC, no prior systemic therapy, Karnofsky performance status ≥ 60, measurable disease by response evaluation criteria in solid tumours (RECIST) criteria, adequate bone marrow, renal and hepatic function, fasting serum cholesterol ≤ 350 mg/dL, triglycerides ≤ 400 mg/dL and at least 3 of 6 poor-risk features. These features were:

- Lactate dehydrogenase (LDH) > 1.5x upper limit of normal,
- Haemoglobin < lower limit of normal
- Corrected calcium > 10 mg/dL
- Time from diagnosis to first treatment < 1 year
- Karnofsky Performance Status 60–70
- Multiple organ sites of metastasis

Patients were randomised to receive treatment with IFN up to 18 MU three times per week, Temsirolimus 25 mg weekly, or a combination of Temsirolimus (15 mg weekly) and IFN (6 MU three times per week).

Response rates and clinical benefit were 7 and 29% (IFN), 9 and 46% (Temsirolimus), 11 and 41% (IFN + Temsirolimus), respectively.

Patients receiving Temsirolimus had a significantly longer PFS (3.7 months) than patients receiving IFN (1.9 months, \( P < 0.0001 \)) as did those receiving the combination (3.7 months, \( P = 0.002 \)). Patients receiving Temsirolimus had a significantly longer OS (10.9 months) than patients receiving IFN (7.3 months, \( P < 0.007 \)), and OS was non-significantly longer than the combination arm (8.4 months, \( P = 0.69 \)).

The most common subjective drug-related toxicities in the Temsirolimus single agent arm were fatigue (54%, grade 3/4 12%), nausea (37%, grade 3/4 4%), rash (37%, grade 3/4 1%), dyspnoea (30%, grade 3/4 9%), diarrhoea (28%, grade 3/4 1%), oedema (27%, grade 3/4 0%), vomiting (21%, grade 3/4 1%) and stomatitis (20%, grade 3/4 1%). Objective toxicities in this arm of the trial were anaemia (50%, grade 3/4 21%), lipid disturbance (28%, grade 3/4 7%), hyperglycaemia (28%, grade 3/4 10%), hypercholesterolaemia (24%, grade 3/4 1%), raised creatinine (16%, grade 3/4 4%), thrombocytopenia (13%, grade 3/4 1%) and neutropaenia (7%, grade 3/4 3%) [12].

Dose reductions and delays (>2) occurred in 20–25% of patients treated with Temsirolimus alone.

**Conclusion**

The treatment options for patients with metastatic RCC are expanding and will now include approaches other than immunotherapy. Our growing understanding of the biology of RCC has contributed to the successful development of a number of new ‘targeted’ therapies.

Temsirolimus is a well-tolerated treatment that has produced a statistically significant survival benefit in patients with poor-risk metastatic RCC. There are very few studies that have produced a statistically significant survival benefit in this disease and Temsirolimus is the first to do so in a patient population entirely made up of patients with intermediate and poor-risk features. It remains to be seen whether this benefit can be translated into a good-risk population. Temsirolimus is clearly well tolerated and this means that it is a good candidate for combination with other agents.

**References**