Temsirolimus in Metastatic Chromophobe Renal Cell Carcinoma after Interferon and Sorafenib Therapy

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Abstract. *Chromophobe renal cell carcinoma (chRCC) is a common subtype of renal cell carcinoma (RCC), occurring in 6-11% of renal carcinoma patients. Limited clinical trial data have shown minimal activity with cytokines and chemotherapy, although small-molecule inhibitors of the vascular endothelial growth factor and platelet-derived growth factor pathways such as sunitinib and sorafenib, which are associated with significant clinical activity in clear-cell RCC (ccRCC), have been associated with a 25% response rate in chRCC. The mammalian target of rapamycin kinase inhibitor temsirolimus demonstrates good clinical activity in ccRCC patients with poor prognosis, with further data suggesting it is an effective treatment for all RCC tumour histologies. This report describes the case of a patient with chRCC who experienced rapid improvement in his general condition and stable disease on treatment with temsirolimus, following disease progression on interferon alfa and sorafenib treatment. This case report suggests that temsirolimus is an effective and appropriate treatment for this RCC tumour subtype.*

Chromophobe renal cell carcinoma (chRCC) is a distinctive and common subtype of renal cell carcinoma (RCC), occurring with an incidence of 6-11% of renal neoplasms (1). This RCC subtype is characterized by a solid, 'pavement' or 'cobblestone' morphology and lacks the rich vascular network observed in clear-cell carcinomas (1). Although no first-line treatment options are available for chRCC, it is generally associated with a better prognosis than clear-cell RCC (ccRCC), with five-year survival reaching more than 90% (2).

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Earlier studies with cytokines (such as interferon) or chemotherapy, predominantly small series and case reports, as clinical trials have tended to include fewer than 10% of patients with non-clear cell histologies (3), have reported minimal activity in patients with chRCC (4). The small-molecule inhibitors of the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors sunitinib and sorafenib are associated with significant clinical activity in ccRCC (5, 6). In a retrospective multicentre study of 53 patients with chRCC (n=12) or papillary RCC (n=41), 25% of the chRCC patients (3/12) achieved a response, two with sorafenib and one with sunitinib, with a progression-free survival (PFS) of 10.6 months (4).

In subgroup analysis of patients enrolled in the sunitinib expanded-access programme for patients with mRCC (N=5,464), 11% of patients with non-ccRCC histology (48/437) achieved an objective response, while the respective figure for all evaluable patients was 17% (603/3,464). In addition, patients with non-ccRCC (n=588) demonstrated a PFS of 7.8 months (95% confidence interval [CI], 6.3-8.3 months) *versus* 10.9 months (95% CI, 10.3-11.2 months) in the total population (N=4,349 evaluable patients) and overall survival (OS) of 13.4 months (95% CI, 10.7-14.9 months) *versus* 18.4 months (95% CI, 17.4-19.2 months), respectively (7).

Temsirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) kinase, disruption of which suppresses the production of proteins involved in the regulation of the cell cycle and angiogenesis (8-10). In a phase III trial in patients with untreated, predominantly advanced metastatic ccRCC with poor prognostic features, temsirolimus was associated with prolonged OS (hazard ratio for death, 0.73; $p=0.008$) and PFS ($p<0.001$) compared with interferon alfa (IFN-α) (11). In this study, temsirolimus monotherapy demonstrated greater efficacy than IFN-α or temsirolimus in combination with IFN-α, in the treatment of patients with poor prognostic risk. Consequently, in treatment guidelines, temsirolimus monotherapy is recommended for the first-line treatment of these patients (12).

The mechanism of action of temsirolimus in metastatic chRCC is currently unclear, with some evidence suggesting that it involves the down-regulation of the hypoxia-inducible factor which is implicated in angiogenesis (13). Data from a recent subgroup analysis of a randomised, open-label, phase III data study comparing IFN-α alone, temsirolimus alone and temsirolimus in combination with IFN-α, in patients with previously untreated poor prognosis advanced RCC, suggested that temsirolimus may be equally effective against non-ccRCC as it is against clear-cell histology, with hazard ratios for death for treatment with temsirolimus *versus* IFN-α of 0.49 (95% CI, 0.29-0.85) and 0.82 (95% CI, 0.64-1.06), respectively (14).

This report describes the case of a patient with chRCC treated with temsirolimus following prior treatment with IFN-α and sorafenib.

Case Report

In December 2006, a 57-year-old man was referred to the Henri Mondor-Albert Chenevier hospital in Paris, France after a 6 cm mass in the left kidney was discovered during a computed tomography (CT) scan of the abdomen. The patient had presented with abdominal pain, had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 and had no relevant family history. A laparoscopic left nephrectomy was performed in January 2006 and histopathological analysis identified a pT2 chRCC of Fuhrman grade 2–3. Immunochemistry demonstrated tumoural cell positivity for keratin antibody KL1, epithelial membrane antigen (EMA) and negativity for vimentin.

In February 2007, a CT scan of the abdomen, performed as part of a routine three-monthly follow-up, revealed peritoneal and retroperitoneal nodules, despite the patient presenting with no symptoms. A biopsy confirmed the presence of a large cancerous mass corresponding to a recurrence of chRCC. In May 2007, the patient began treatment with subcutaneous IFN-α-2a (9 MIU three times weekly for three weeks). The best response achieved with IFN-α-2a was stable disease.

An abdominopelvic CT scan in September 2007 revealed tumour progression and treatment with sorafenib (800 mg/day) was initiated because this agent inhibits the enzymatic activity of the KIT receptor overexpressed in chRCC (4, 15). The patient was followed up systematically during sorafenib treatment with an abdominal CT scan performed every three months. Three months after the start of treatment, he developed hand–foot syndrome, fatigue and diarrhoea, all at grade 3. These adverse events were managed symptomatically and by reducing the dose of sorafenib to 400 mg/day.

In January 2008, an abdominal pelvic CT scan showed stability of both the peritoneal and retroperitoneal lesions and sorafenib was continued at a dose of 400 mg/day until July 2008, when treatment was halted due to tumour progression and grade 3 plantar cutaneous toxicity. In total, the patient received sorafenib for 10 months and his ECOG PS score improved to 1-2.

At this point, treatment with temsirolimus was started at a dose of 25 mg/week. Temsirolimus was continued until July 2009 and was well tolerated with no haematological toxicity and a rapid improvement in the patient's general condition (Karnofsky performance status >80). A magnetic resonance imaging scan of the abdomen and pelvis showed stability of the peritoneal lesion and surgical resection of residual nodular lesions was performed. However, surgery was not curative due to the presence of peritoneal carcinomatosis, which contraindicated further resection. One month after surgery, treatment with temsirolimus restarted at a dose of 25 mg/week.

In May 2010, after 26 months of temsirolimus therapy, the patient's general condition was good with an ECOG PS score of 0. A review was performed including a positron-emission tomography CT scan. The scan showed a persistence of tissue formation on the left iliac with a maximum standardised uptake value of 5.7, corresponding to peripheral calcification visible on scan. A 3 cm reduction in the size of the lesion was noted along the main axis. An additional lesion was noted on the left iliac fossa. This lesion also reduced in size without central fixation and was probably necrotic. The lesion was no longer visible by control scintigraphy. The distribution of fluorodeoxyglucose was normal, particularly at the nephrectomy site. Treatment with temsirolimus is still ongoing.

Discussion

The patient of this case report, who had chRCC, experienced tumour progression with both cytokine-based therapy and targeted therapy using sorafenib, in accordance with the known limited activity of these treatments in non-ccRCC (3, 4).

In studies where patients with mRCC (the majority with clear-cell histology) begin therapy with either sorafenib or sunitinib and are switched to the other drug at disease progression, the median OS is approximately 24 months in patients who had received sorafenib first (16, 17). This is similar to the OS (26 months) experienced by the patient in this report after he was switched from sorafenib to temsirolimus. This indicates that temsirolimus has clinical activity in a subset of RCC patients whose tumour growth is driven by mechanisms other than the von Hippel-Lindau mutation.

Despite a reduction in size, the presence of hypermetabolic areas in the iliac tumoural lesion may reflect the activation of other metabolic pathways in certain tumour cell populations. By inhibiting only mTOR C1, temsirolimus causes reactivation of phosphoinositide 3-kinase (PI3K) within the tumour cell populations. The PI3K/mTOR pathways contain negative feedback loops downstream of

mTOR; inhibition of mTOR C1 abolishes this negative feedback loop, which activates the kinase AKt through mTOR C2-mediated phosphorylation (18). Dual kinase inhibitors (*e.g.* NVP-BEZ235 and GDC-O941) that inhibit both PI3K and mTOR activity will be of great interest in chRCCs that develop resistance to temsirolimus treatment by binding to the ATP-binding site of these enzymes (19).

Although randomised, prospective trials are needed to further investigate the preliminary observations of this report, it would seem appropriate to offer temsirolimus as a treatment option for patients presenting with chRCC in the clinic. These observations concur with the conclusion of the phase III sub-analysis which stated that temsirolimus shows activity in both clear- and non clear-cell histologies and may, therefore, be used for the treatment of all types of RCC (14).

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