Renal cell carcinoma and the use of sorafenib

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Abstract: Immunotherapy results in a small overall survival advantage in metastatic renal cell carcinoma (RCC), but there is a need to develop more effective systemic therapies. Angiogenesis has an important role in the pathophysiology of RCC and vascular endothelial growth factor (VEGF) is a key mediator of this process. Sorafenib (BAY 43-9006) is a new agent belonging to a class of drugs called kinase inhibitors and inhibits the VEGF, platelet-derived growth factor (PDGF), and c-KIT receptor tyrosine kinases, amongst others. Sorafenib has shown significant activity with manageable toxicity in metastatic RCC in phase 2 studies in patients pretreated with immunotherapy, whilst prolonged progression-free survival in comparison with placebo in a phase 3 study has been reported. Further phase 3 trials in advanced disease are ongoing and a trial of adjuvant sorafenib therapy in RCC is planned.
Keywords: Renal cell carcinoma; metastatic; systemic therapy; sorafenib

Introduction

Epidemiology and pathology of renal cell carcinoma

Carcinoma of the kidney accounts for 2%–3% of cancers (Landis et al 1999; Parkin et al 1999) and increased in incidence in the UK between 1991 and 2000 by almost 20% (Toms 2004). The reason for this increase in incidence is unknown. Approximately 70% of patients with renal cell carcinoma (RCC) present with localized disease that is potentially curable with nephrectomy.

Renal cell carcinomas have been classified histologically as clear cell (~60%–80%), papillary (~10%–15%), chromophobe (~5%–10%), medullary and collecting duct (< 1% each) (Cheville et al 2003; Beck et al 2004; Ficarra et al 2005). Clear cell histology is associated with a poorer outcome than either chromophobe or papillary histology (Cheville et al 2003; Beck et al 2004) for resectable disease although the reverse is true for metastatic disease (Motzer et al 2002).

Von Hippel-Lindau (VHL) disease is inherited in an autosomal dominant manner (Latif et al 1993) and is characterized by an increased incidence of hemangioblastomas of the retina and central nervous system (CNS) and clear cell carcinoma of the kidney (Kim and Kaelin 2004). Individuals with this disease are born with a mutated version of the VHL gene; tumor development is associated with subsequent somatic mutation of the remaining allele. Von Hippel-Lindau disease is the commonest basis for inherited RCC and is directly relevant to sporadic clear cell renal carcinoma as inactivation of both VHL genes occurs via mutation in approximately 40%–50% of cases (Brauch et al 2000; Kondo et al 2002; Yao et al 2002) and via promoter hypermethylation in 5%–20% of cases (Herman et al 1994; Clifford et al 1998; Brauch et al 2000; Kondo et al 2002; Yao et al 2002; Dulaimi et al 2004).

The VHL protein is involved in the cellular response to hypoxia (Figure 1). Under normoxic conditions, the VHL protein is bound to hypoxia inducible factor-1α (HIF-1α) and HIF-2α, which as a result become ubiquitinated and tagged for degradation in the proteasome (Ohh et al 2000). In hypoxic conditions or in the

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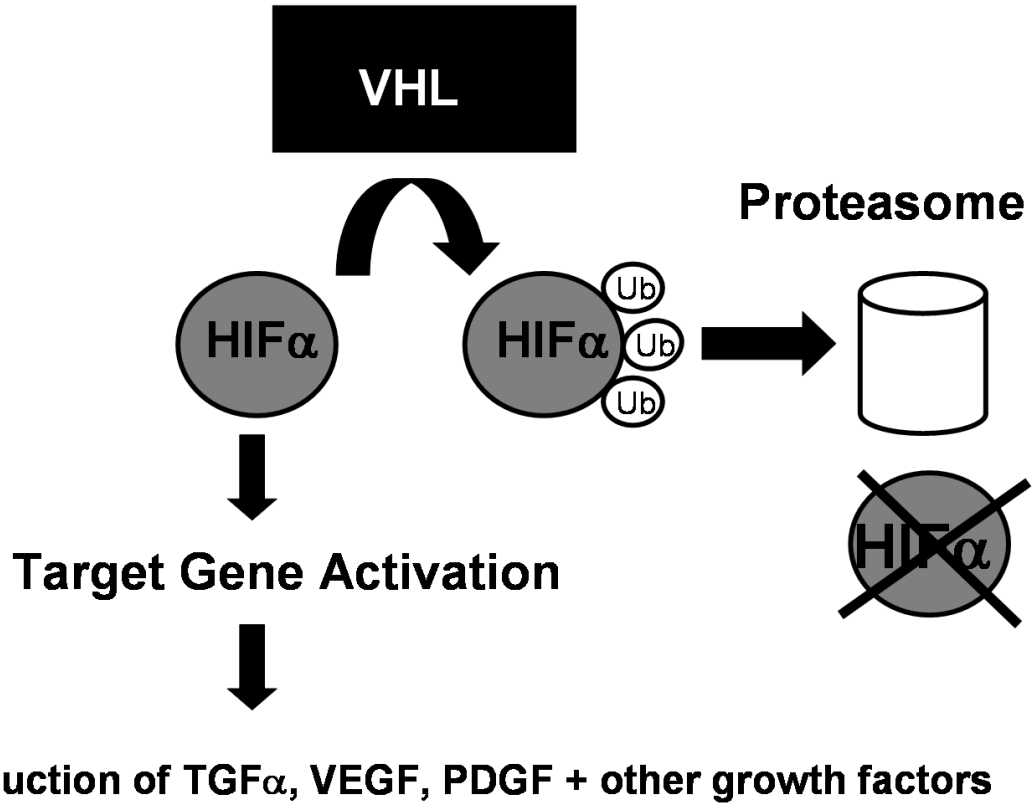

Figure 1 Under normoxic conditions the VHL protein binds to HIF-α which is ubiquitinated and tagged for degradation in the proteasome. In hypoxic conditions or in the absence of VHL, HIF-α accumulates, and stimulates the production of growth factors such as VEGF, TGFα, and PDGF. These factors act on receptor TKs, stimulating cell proliferation and angiogenesis.
Abbreviations: HIF-α, hypoxia inducible factor-α; PDGF, platelet-derived growth factor; TGFα, transforming growth factor α; TK, tyrosine kinase; VEGF, vascular endothelial growth factor; VHL, Von Hippel-Lindau.

absence of VHL, HIF-1a accumulates, stimulating the production of growth factors such as vascular endothelial growth factor (VEGF), transforming growth factor a (TGFα) and platelet-derived growth factor (PDGF), which in turn stimulate cellular proliferation and angiogenesis.

Treatment of metastatic RCC

The management of metastatic RCC is an important problem given that approximately 30% of patients initially present with disseminated disease. Furthermore, approximately 30% of patients treated with curative intent for localized disease subsequently relapse. Metastatic RCC is incurable and treatment intent is palliative. The prognosis for metastatic RCC is poor: median survival is 10–12 months (Selli et al 1983; MRC 1999; Motzer et al 2004a, 2004b).

Response rates to hormonal agents (Harris 1983) and to combination chemotherapy (Yagoda and Bander 1989) in metastatic RCC are 5%–10%, which may reflect the natural history of the disease rather than the effect of treatment (Oliver et al 1989; Gleave et al 1998). Subcutaneous interferon (IFN) therapy produces response rates of 10%–20% with median response durations of 3 to 16 months (Horoszewicz and Murphy 1989). Randomized controlled trials have reported a survival advantage with IFN therapy compared with non-immunotherapy (MRC 1999; Pyrhonen et al 1999) and a Cochrane review and meta-analysis has confirmed the value of IFN-α in metastatic RCC (Coppin et al 2005). In nonrandomized trials in metastatic RCC, approximately 10% of patients have a complete response to treatment with high dose intravenous interleukin-2 (HDIV IL-2) and in 70%–80% of these patients, disease control is prolonged (Rosenberg et al 1998) but this therapy causes substantial toxicity.

Surgery to remove the primary lesion in metastatic RCC results in a survival benefit when immunotherapy is given post-operatively. This has been reported in two randomized trials, Southwest Oncology Group (SWOG) 8949 (Flanigan et al 2001) and European Organization Research and Treatment of Cancer (EORTC) 30947 (Mickisch et al 2001; Flanigan et al 2004). Both trials randomized patients with good performance status to nephrectomy followed by treatment with IFN-α versus treatment with IFN-α alone. Median survival increased from 8 to 11 months and from 7 to 17 months respectively in the nephrectomy groups.

In summary, immunotherapy for metastatic RCC has significant toxicity and modest efficacy, but offers the possibility of prolonged disease control or cure. Careful patient selection for such therapy is vital: recent data suggest that high tumor carbonic anhydrase IX (Atkins et al 2005) expression is predictive of prolonged median survival after IL-2-based therapy; this antigen therefore may be a useful marker in selecting patients for therapy, but there is a clear need for effective treatment options in the majority of patients who do not benefit from immunotherapy.

Kinase inhibitors

Introduction

Sorafenib (Nexavar, BAY 43-9006) is a small molecule drug that, among other targets, inhibits tyrosine kinases (TKs), enzymes that catalyze the transfer of γ-phosphate groups from adenosine triphosphate (ATP) to the hydroxyl groups of tyrosine residues on target polypeptides or proteins. The phosphorylation of proteins such as signaling molecules is often an activating event that in tumors can cause increased cellular proliferation and promote angiogenesis and metastasis.

Tyrosine kinases can be categorized as receptor- and non-receptor kinases. Receptor TKs, eg, the epidermal growth factor receptor (EGFR/ERBB1), span the cell membrane and transduce extracellular signals to the cell interior. Ligand-binding induces autophosphorylation of the cytoplasmic domain, conformational changes, and increased TK activity. Multiple downstream intracellular signaling pathways (Schlessinger 2000) such as phosphoinositol 3′-kinase, Ras/Raf/mitogen-activated protein kinase kinase(MEK)/extracellular signal-regulated kinase (ERK) and protein kinase C may as a result be activated. Non-receptor TKs, eg, c-ABL(Abelson), relay intracellular signals and can be activated in various ways such as by phosphorylation by other kinases.

Tyrosine kinases may be dysregulated in cancer cells in a number of ways. An example is B cell receptor (BCR)–ABL in chronic myelogenous leukemia (CML) which results from the balanced (9;22) chromosomal translocation. This causes the production of the nonreceptor TK BCR–ABL fusion protein. A domain in BCR overcomes the auto-inhibition of ABL, resulting in constitutive TK activation. A second mechanism of TK dysfunction in malignant cells is via the overexpression of a TK or its ligand; eg, the overexpression of VEGFR, PDGFR, or EGFR or their ligands in RCC (Gomella et al 1989; Mydlo et al 1989; Atlas et al 1992; Uhlman et al 1995; Iliopoulos et al 1996; Ramp et al 2000; Gunningham et al 2001; Na et al 2003; Sulzbacher et al 2003, Yildiz et al 2004; Minardi et al 2005; Xu et al 2005). A third mechanism is via increased sensitivity of a receptor to its ligand, eg, mutations in EGFR in some non-small cell lung cancers (NSCLCs) resulting in altered receptor signaling (Pao et al 2004; Sordella et al 2004). It is unknown whether or not RCC is dependent on, or driven by, changes in receptor sensitivity to ligands.

Drugs that disrupt TK signaling are used increasingly in the treatment of cancer. There are 2 classes of such drugs: monoclonal antibodies, eg, trastuzumab, cetuximab, and bevacizumab and small molecules ('kinase inhibitors'), eg, imatinib, erlotinib, gefitinib, sorafenib, (BAY 43-9006) and sunitinib (SU011248).

Kinase inhibition by monoclonal antibodies

Monoclonal antibodies directed against receptor TKs or their ligands preventing ligand binding and receptor internalization. For example, cetuximab and trastuzumab bind to the EGFR and HER-2/neu receptor TKs respectively; these molecules are often overexpressed in colorectal (EGFR) and breast (HER-2/neu) cancers and the efficacy of cetuximab in the treatment of metastatic colorectal cancer (Cunningham et al 2004) and trastuzumab in the treatment of breast cancer (Slamon et al 2001; Piccart-Gebhart et al 2005; Romond et al 2005) has been demonstrated clearly. Bevacizumab is directed against VEGF, a key regulator of angiogenesis (Ferrara et al 2003, 2004), a process vital for tumor growth (Folkman 1972). In metastatic RCC, when bevacizumab is used as monotherapy, an increase in time to disease progression has been reported (Yang et al 2003).

Kinase inhibition by small molecules

Small molecule drugs disrupt TK signaling by preventing the binding of either protein substrates or ATP. For example, imatinib is a 2-phenylaminopyrimidine that inhibits the BCR-ABL fusion protein in CML (Druker et al 2001) and c-KIT (CD 117) in gastrointestinal stromal tumors (GISTs) (van Oosterom et al 2001) and has made a dramatic impact on the management of these diseases. The impact of small molecule kinase inhibitors has however been more modest in other settings. For example, neither gefitinib nor erlotinib, when used in combination with standard chemotherapy in the first-line treatment of NSCLC, show a benefit over chemotherapy alone (Giaccone et al 2004; Herbst et al 2004). Interestingly, both drugs have shown limited efficacy as single agents in NSCLC (Kris et al 2003; Shepherd et al

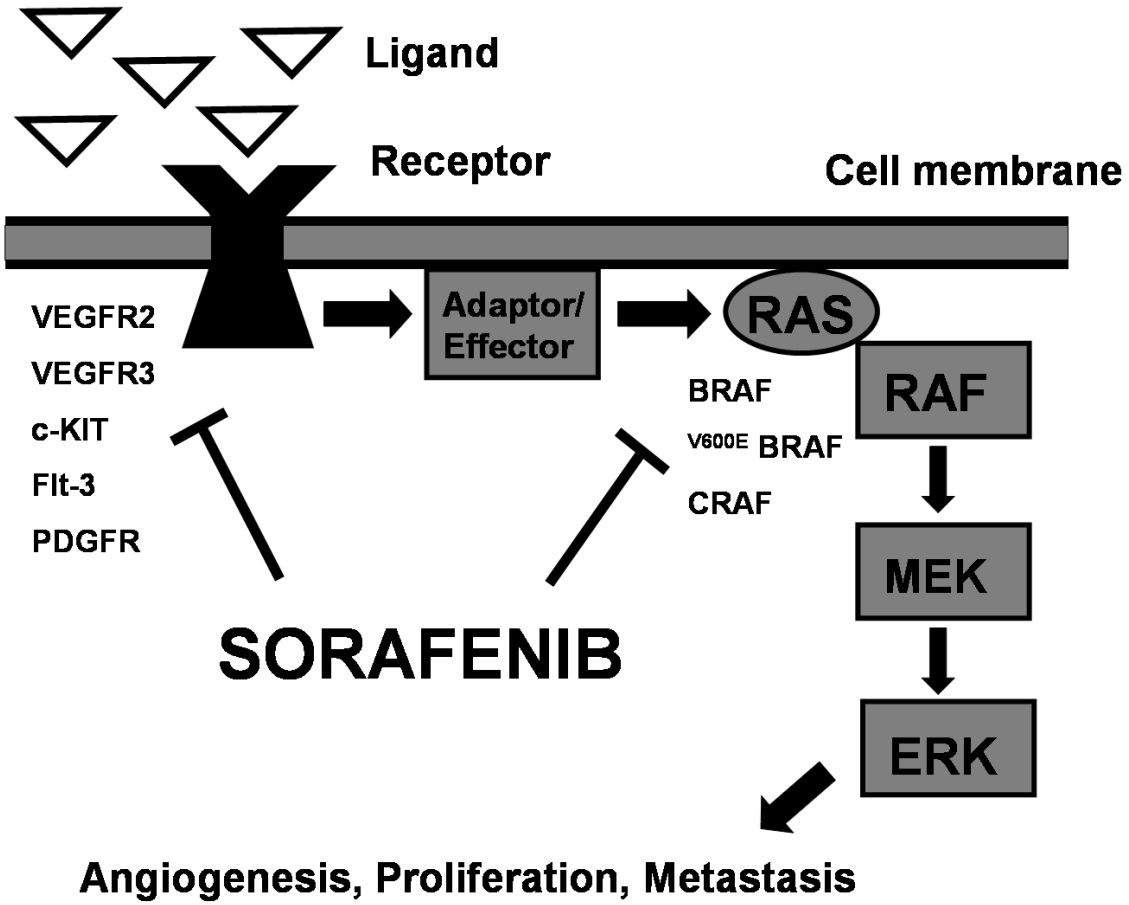

Figure 2 Ligand binding to a receptor TK induces oligomerization and autophosphorylation of the cytoplasmic domain and contingent increased TK activity. Multiple downstream intracellular signaling pathways such as Ras/Raf/MEK/ERK may as a result be activated, resulting in proliferation, angiogenesis and metastasis. Sorafenib is a dual action kinase inhibitor, targeting receptor TKs and BRAF.
Abbreviations: ERK, extracellular signal-mediated kinase; MEK, mitogen-activated protein kinase kinase; TK, tyrosine kinase.

2005), but the clinical benefit is mainly in specific subgroups of patients (Lynch et al 2004; Paez et al 2004; Pao et al 2004) such as female nonsmokers with adenocarcinomas. These findings highlight the potential need for careful patient selection for kinase inhibitor treatment.

This review will focus on the small molecule kinase inhibitor sorafenib in the treatment of RCC.

Sorafenib (Nexavar, BAY 43-9006) in RCC

Introduction

Sorafenib is an orally administered bi-aryl urea that was designed originally as an inhibitor of BRAF and CRAF, non-receptor serine threonine kinases. These kinases are members of the Raf/MEK/ERK intracellular signaling cascade, a downstream effector of Ras, which in turn can be activated by upstream receptor TK stimulation (Figure 2). Activation of the Raf/MEK/ERK cascade leads to changes in metabolism, transcription, and intracellular cytoskeletal arrangements (Marais et al 1997). This pathway is known to be involved in tumor cell survival and proliferation and is a therapeutic target in cancer (Sridhar et al 2005). It is unclear, however, whether dysfunction of this signaling cascade is important in RCC, although some data suggest that it may be relevant (Fujita et al 1988; Oka et al 1995). In addition to inhibition of Raf family non-receptor kinases, sorafenib also inhibits a number of receptor TKs in cell-free assays known to be involved in angiogenesis and tumorigenesis such as VEGFR2, VEGFR3, fetal liver tyrosine kinase 3 (Flt-3), c-KIT, and PDGFR. Sorafenib is also known to inhibit the BRAF mutant V600E which is present in over half of malignant melanomas (Davies et al 2002). This mutation is not reported in RCCs (Nagy et al 2003).

Preclinical data

In cell-free biochemical assays, varying concentrations of sorafenib were assayed for their capacity to inhibit phosphorylation of the non-receptor TK mitogen-activated protein kinase kinase (MEK) by the catalytic domains of

BRAF and V600E BRAF (Wilhelm et al 2004). Potent inhibition of both BRAF and V600E BRAF was noted with IC_{50} values between 20–40 nmol/L. The related CRAF (Raf-1) kinase was inhibited with an IC_{50} of less than 10 nmol/L (Table 1). The IC_{50} values for MEK and ERK were greater than 10 000 nmol/L. The receptor TKs c-KIT, murine PDGFR-β, and Flt-3 were inhibited with IC_{50} values in the range 40–80 nmol/L whilst VEGFR2 was inhibited with an IC_{50} of approximately 90 nmol/L. The IC_{50} values for the receptor TKs EGFR and HER-2 were greater than 10 000 nmol/L. Sorafenib has been co-crystallized in complex with BRAF and V600E BRAF (Wan et al 2004). The distal pyridyl ring of sorafenib was shown to interact with 3 amino acids in the ATP adenine-binding pocket and in addition, the urea moiety formed hydrogen bonds within the enzyme. As a result, sorafenib is thought to promote the formation of the inactive form of BRAF.

Sorafenib inhibited activation of the Raf/MEK/ERK pathway in a number of cell lines in Western blot assays and pERK immunoassays (Wilhelm et al 2004). In MDA-MB-231 breast cancer cell lines, sorafenib completely blocked activation of the Raf/MEK/ERK pathway. Dose-dependent inhibition of both MEK and ERK basal phosphorylation was noted (IC_{50} 40 nmol/L and 100 nmol/L, respectively). Inhibition of ERK phosphorylation by sorafenib was also observed in the pancreatic tumor cell line Mia PaCa 2 and the colon tumor cell lines HCT116 and HT-29 by Western blot analysis. Similar results were reported in the LOX melanoma and pancreatic BxPC-3 cell lines using the Bio-Plex pERK immunoassay, but no inhibition of ERK phosphorylation was noted in the non-small cell lung cancer cell lines A549 and NCI-H460 at sorafenib concentrations up to 10 000 nmol/L.

Inhibition of VEGFR2 autophosphorylation by sorafenib has been investigated in the HUVEC (human umbilical vein endothelial cell) and NIH 3T3 VEGFR2 (murine embryonic fibroblast) cell lines. At a sorafenib concentration of 100 nmol/L, over 50% inhibition of VEGFR2 phosphorylation was noted in HUVEC cell lysates. Sorafenib also inhibited PDGFR autophosphorylation in primary human aortic smooth muscle cells (HAoSMCs); Flt-3 was also sensitive to inhibition of receptor phosphorylation by sorafenib in cell-based assays.

Table 1 Targets of sorafenib in cell-free assays

Kinase	IC_{50}
CRAF	< 10nM
mVEGFR3	10–20 nM
mPDGFR, BRAF, BRAF V600E	20–40 nM
Flt-3, c-KIT	40–80 nM
VEGFR2	80–160 nM
MEK, ERK, EGFR, HER-2	Inactive at 10 000 nM

Abbreviations: EGFR, epidermal growth factor receptor; ERK, extracellular signal-mediated kinase; Flt-3, fetal liver tyrosine kinase 3; HER-2, human epidermal growth factor receptor 2; IC_{50}, concentration of drug required to cause 50% inhibition of an enzyme; m, murine; MEK, mitogen-activated protein kinase kinase; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

Sorafenib has also demonstrated activity in xenograft mouse models of human colon, lung, breast, pancreatic, and melanoma neoplasms (Wilhelm et al 2004). Mice were treated with sorafenib at doses from 7.5 mg/kg to 60 mg/kg orally for 9 days. Tumor growth inhibition was dose-dependent and mice treated with sorafenib maintained body mass in comparison with untreated controls, ie, drug toxicity was not excessive. Complete inhibition of tumor growth was noted during sorafenib administration at 30 mg/kg to 60 mg/kg in the HT-29, Colo-205, and DLD-1 colorectal models, the MDA-MB-231 breast model, and in the A549 NSCLC model. All these cell lines express a kRas and/or a BRAF mutation that constitutively activates signaling through the Raf/MEK/ERK pathway. Interestingly, complete inhibition of tumor growth was not seen in the NCI-H460 NSCLC model at a dose of 60 mg/kg despite the presence of a kRas mutation, suggesting that a mutation in the Raf/MEK/ERK pathway is not in itself predictive of sorafenib sensitivity. The fact that A549 and NCI-H460 growth was inhibited in vivo is of interest given that sorafenib did not reduce ERK phosphorylation in these cell lines in vitro (see above) and suggests that another mechanism, eg, inhibition of other TKs such as c-KIT, Flt-3, and VEGFR2 may be responsible. In parallel experiments, mice similarly treated with sorafenib were culled and Western blotting to investigate MEK and ERK activation was performed. In the HT-29 and MDA-MB-231 models, levels of phosphorylated MEK and ERK were reduced in treated animals in comparison with untreated controls, thus tumor growth retardation was correlated with inactivation of the Ras/Raf/MEK/ERK pathway. In Colo-205 xenografted tumors, ERK phosphorylation was not inhibited by sorafenib as assayed by Western blotting and immunohistochemistry, although it was blocked in cell culture, suggesting that ERK may be activated by a mechanism independent from the Ras/Raf/MEK pathway in these tumors. Given that sorafenib inhibits receptor TKs known to be involved in angiogenesis, microvessel area (MVA) and density (MVD) were assessed in the xenograft tumor models. Sorafenib treatment resulted in a reduction in both parameters in HT-29, Colo-205, and MDA-MB-231 tumors.

In summary, the preclinical data demonstrate that sorafenib inhibits multiple receptor TKs involved with tumor angiogenesis and non-receptor TKs of the Raf family involved with tumor cell proliferation, and that both mechanisms may account in part for the activity of the drug.

Phase 1 data

Four phase 1 studies in 163 patients identified 400 mg twice daily continuous dosing as the recommended phase 2 dose of sorafenib (Strumberg et al 2002, 2005; Awada et al 2005; Clark et al 2005; Moore et al 2005). Drug-related toxicities were reported in approximately three quarters of subjects and were generally mild to moderate. The most frequent toxicities were diarrhea (~50% of patients), skin toxicity (~50%), fatigue (~40%), anorexia (~40%), alopecia (~25%), and nausea (~20%). Stomatitis, pancreatitis, and elevation of serum bilirubin were reported in less than 5% of patients. The commonest dose-limiting toxicities were grade 3 diarrhea, fatigue, and skin toxicity whilst grade 3 pancreatitis, anorexia, nausea, stomatitis, alopecia, and elevation of bilirubin were rarely reported. All toxicities were reversible on cessation of sorafenib.

Sorafenib was absorbed at a moderate rate after the first dose and C_{max} occurred between 2.5 and 12.5 hours after administration. Plasma concentrations of sorafenib subsequently decreased slowly and there was no dose-dependency in plasma concentration-time profiles after the first dose of 100 mg to 800 mg twice daily. Significant accumulation in plasma was noted after multiple twice daily administration of sorafenib. Food intake prior to dosing had no relevant impact on sorafenib pharmacokinetics apart from a mild prolongation of t_{max}. Area under the curve (AUC) and C_{max} values were variable following multiple twice daily doses of sorafenib and maximum mean AUC_{0-12} values were noted at 600 mg twice daily although there was little difference between 400 mg and 600 mg twice daily.

The effect of sorafenib on phorbol myristate acetate (PMA)-stimulated ERK phosphorylation in peripheral blood lymphocytes (PBLs) was studied using flow cytometry (Strumberg et al 2005). Almost complete inhibition of PMA-stimulated ERK phosphorylation was reported at doses of 400 mg twice daily continuous dosing and above on day 21, confirming biological activity at these doses.

Seven patients with RCC were treated in the phase 1 studies; there was 1 partial response of 104 days duration (Awada et al 2005) and 5 patients had stable disease: 1 of the 5 patients, who had previously received 3 prior lines of treatment, experienced disease stabilisation for almost 2 years (Strumberg et al 2005). These findings provided the basis for phase 2 studies of sorafenib in RCC.

Phase 2 data

The results of a phase 2 multicenter randomized discontinuation trial (RDT) of sorafenib in RCC were updated recently in abstract form (Ratain et al 2005). The RDT design allows the disease stabilizing effect of a study agent to be distinguished from slowly-growing disease (Rosner et al 2002; Stadler et al 2005). All patients are treated initially with the study agent (stage 1) and those with stable disease undergo double-blinded randomization between continued therapy and placebo (stage 2). Patients with responses at the end of stage 1 continue the study agent until disease progression whilst therapy is stopped in patients with progressive disease at the end of stage 1.

The phase 2 RDT of sorafenib in metastatic RCC investigated the effect of the drug on tumor growth in patients with stable disease after 12 weeks of treatment in stage 1. Two hundred and two patients with advanced RCC were treated at a dose of 400 mg orally twice daily in stage 1. All histological subtypes were eligible and the study population was heterogeneous with regard to prior therapy; most patients received sorafenib as second-line (56%) or third-line (34%) therapy. All patients were of PS < 1 and 56% had undergone nephrectomy. Sixty five patients with stable disease (response between 25% tumor reduction and 25% tumor growth) at 12 weeks were randomized to sorafenib (n = 32) or placebo (n = 33); patient characteristics were matched between the groups. After 24 weeks, 6 patients (18%) on placebo were progression-free compared with 16 patients (50%) on sorafenib ($p = 0.0077$). Median progression-free survival (PFS) after randomization was greater with sorafenib than placebo (23 versus 6 weeks, $p = 0.0001$, hazard ratio [HR] 0.29). Sorafenib was restarted in the 25 patients who progressed on placebo after a median time from randomization of 7 weeks. Median PFS after restarting sorafenib in these patients was 24 weeks and 13 patients remained on therapy at the time of reporting. The most common drug-related toxicities were rash (62%), hand-foot skin reaction (61%) and fatigue (56%). The authors conclude that sorafenib has a marked effect on PFS in metastatic RCC and an acceptable toxicity profile and that the trial demonstrates the utility of the RDT design. A randomized phase 2 trial comparing sorafenib with IFN as first-line therapy for metastatic RCC recently completed accrual.

Phase 3 data

The results of a phase 3 multicentre randomized placebo-controlled double-blind trial of sorafenib in advanced RCC in patients who had progressed after 1 prior systemic therapy have also been updated in abstract form (Escudier et al 2005a). The primary endpoint of the trial was overall survival (OS) in patients with advanced clear cell renal carcinoma randomized to sorafenib versus placebo and best supportive care. The results of a planned analysis on the secondary endpoint, progression-free survival (PFS) were reported. Subjects had PS 0 or 1, had received one prior systemic therapy for advanced RCC and were randomized to receive continuous oral sorafenib 400 mg twice daily or placebo and best supportive care. At the time of the PFS analysis, 769 of the planned 884 patients had been randomized and 342 PFS events had been reported. Baseline prognostic characteristics were similar between both groups; 93% had undergone nephrectomy and 82% of patients had received prior cytokine therapy.

Median PFS was 24 weeks for sorafenib versus 12 weeks for placebo (HR 0.44; $p < 0.00001$) and the 12 week progression-free rate was 79% for sorafenib versus 50% for placebo (Figure 3). Reported toxicities for sorafenib versus placebo were diarrhea (33% versus 10%), hand-foot skin reaction (27% versus 5%), rash (34% versus 13%), fatigue (26% versus 23%) and hypertension (11% versus 1%). Grade 3 or 4 adverse events were reported in 30% of patients on sorafenib versus 22% of patients on placebo.

Response data were updated recently in an oral presentation (Escudier et al 2005b). 903 patients had been enrolled by the data cut off on May 31st 2005. At this time, there had been 1 complete response to treatment (in the sorafenib arm) and 51 partial responses (43 in the sorafenib arm versus 8 in the placebo arm, 10% versus 2%). Stable disease was reported in 333 patients in the sorafenib arm versus 239 patients in the placebo arm (74% versus 53%) and progressive disease in 56 patients in the sorafenib versus 167 in the placebo group (12% versus 37%). Many of the patients with stable disease in the sorafenib group had tumor regression insufficient to meet the Response Evaluation Criteria in Solid Tumors (RECIST) criteria for a partial response; further follow-up is needed to ascertain the clinical significance of this observation. Preliminary overall survival data from a planned interim analysis after 220 events were also presented. Median overall survival in the placebo group was 14.7 months and had not been reached in the sorafenib group (HR 0.72; $p = 0.018$). The threshold for statistical significance for this interim analysis was $p < 0.0005$ and so the results, whilst encouraging, should be interpreted with caution.

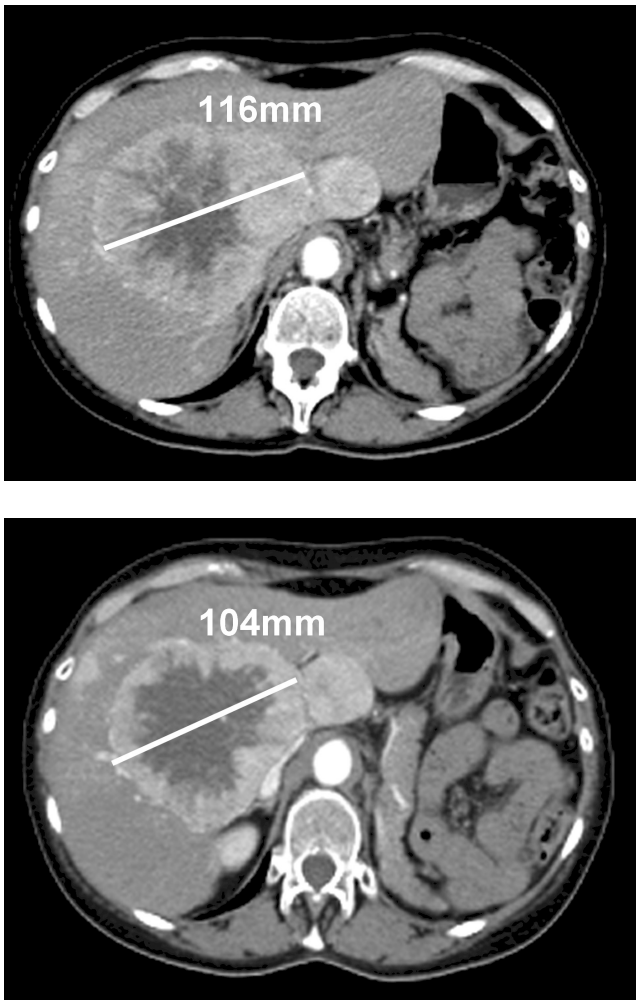

Figure 3 Tumor shrinkage after 6 weeks of therapy with sorafenib (reproduced with permission from Bernard Escudier).

Key outstanding issues

Several questions concerning the use of sorafenib in RCC are unresolved.

First, the mechanism of action of sorafenib in vivo has not been established. The administration of neoadjuvant sorafenib with biopsies both before and on treatment may allow this issue to be addressed (Potti and George 2004). Neoadjuvant therapy may also allow the identification of biomarkers of response prediction and radiological changes can be correlated with pathological and molecular changes as a result of therapy (Chang et al 1999).

Second, there are no data on the treatment of non-clear cell renal carcinoma with sorafenib; VHL dysfunction is

less common in non-clear cell than clear cell carcinoma and it may that antiangiogenic therapies have less efficacy in this setting but this premise has not been tested experimentally.

Third, there are few data on the efficacy of sorafenib by site of metastatic disease. Data from the phase 3 trial of sorafenib versus placebo (Escudier et al 2005c) indicate that PFS is superior in the sorafenib group irrespective of the presence or absence of lung or liver metastases. It is unclear whether or not sorafenib or any small molecule kinase inhibitor crosses the blood brain barrier and would therefore be active in the setting of brain metastases. Conflicting data have been reported from the treatment of NSCLC with the EGFR inhibitors gefitinib and erlotinib. The CNS was the first site of relapse in 7/21 patients with adenocarcinoma of the lung relapsing after responding to erlotinib therapy in a recent case series. Four of the patients with disease recurrence in the CNS had stable disease in the lung (Omuro et al 2005), suggesting that erlotinib may not penetrate the blood brain barrier. In contrast, in a further case series (Namba et al 2004), 15 patients with recurrent NSCLC with brain metastases were treated with gefitinib and a response rate of 60% was reported for both brain metastases and primary lesions.

Fourth, an intriguing aspect of the use of kinase inhibitors for the treatment of cancer has been reported in the treatment of gastrointestinal stromal tumors (GISTs) with imatinib. In this disease, imatinib dose can be increased safely on disease progression and approximately a quarter of patients will experience renewed disease stabilisation as a result (Zalcberg et al 2005). This begs the question as to whether this observation is specific to either kinase inhibitors or to GISTs. Although no trial data have been reported, anecdotally, sorafenib toxicity often attenuates with prolonged therapy, which allows dose escalation. The reason for this reduction in toxicity over time is unknown.

Fifth, there are interesting comparisons between sorafenib and other kinase inhibitors active in RCC such as sunitinib (SU011248). Sunitinib and sorafenib inhibit a similar spectrum of TKs (with the exception that Raf kinases are not inhibited by sunitinib), but it is clear that the toxicity profile differs between the drugs: skin toxicity is probably the most problematic side effect of sorafenib (Robert et al 2005), whilst sunitinib can cause significant myelosuppression (Faivre et al 2006; Motzer et al 2006). Given that kinase inhibitors are often cytostatic, long term therapy is likely in many cases and toxicity is likely to be a key issue in selection of therapy. The efficacy of sorafenib and sunitinib may also differ. Partial or complete responses to treatment are relatively rare with sorafenib, but disease stabilization is often seen. In contrast, responses to treatment appear more common with sunitinib in advanced RCC (Motzer et al 2006). It is tempting to speculate that the toxicity and efficacy profiles of sunitinib and sorafenib in advanced RCC reflect differences in the spectrum of kinases inhibited, but there are no data to support such a contention.

Sixth, data on the combination of sorafenib with other other active therapies in the treatment of RCC are limited. However, in an interim analysis of a phase II trial, sorafenib (400 mg twice daily) in combination with IFN-α 2b (10 MIU three times weekly) showed 5% had a RECIST-defined complete response and 32% had a partial response, which generally occurred within the first 2 cycles. A further 47% of patients had stable disease, including two patients (11%) who experienced 20% tumor regression. This combination was well tolerated with a two week treatment break between every 8-week cycle. Clearly these are early results but must at least be considered promising. Semaxinib (SU5416), an inhibitor of the VEGFR1 and VEGFR2 TKs, has also been studied in combination with INF-α therapy in a phase 2 trial (Lara et al 2003). However, in this study there were no responses to therapy in 23 patients and significant toxicity was reported including 3 on-study deaths. Semaxinib was given intravenously twice weekly with pulsed steroids, the latter to prevent allergic reactions as it is soluble only in Cremophor. The authors of the study speculate that pulsed steroids may have contributed to the regimen's toxicity and could have attenuated the antiangiogenic and immunomodulatory effects of IFN. The EGFR receptor TK inhibitor erlotinib has been administered with bevacizumab in a phase 2 trial in metastatic RCC recently reported in abstract form (Spigel et al 2005). Toxicity was generally manageable although 1 episode of grade 4 toxicity was reported (a gastrointestinal bleed). In summary, the safety of combining a kinase inhibitor with a monoclonal antibody but not with IFN has been established in small studies. Trials investigating the combination of sorafenib with bevacizumab, IFN, and erlotinib, are ongoing.

Seventh, the questions of how systemic treatment might be sequenced and to what extent there is cross-resistance between different kinase inhibitors and other systemic therapies in RCC are important. Controversy still surrounds the optimum immunotherapy of metastatic RCC (Larkin and Gore 2005) and biomarkers are needed to select patients for different therapies. For example, carbonic anhydrase IX expression has been reported as a predictor of outcome

in patients with RCC receiving IL-2-based therapy (Atkins et al 2005) and microarray technology has been used to classify RCCs (Kosari et al 2005; Yang et al 2005). The use of such techniques in other tumor types has generated interest (Bhattacharjee et al 2001; Beer et al 2002; Pomeroy et al 2002; Rosenwald et al 2002; van de Vijver et al 2002; Yeoh et al 2002; Iizuka et al 2003; Ramaswamy et al 2003), but presents considerable challenges (Michiels et al 2005).

Finally, a further area for the investigation of sorafenib in RCC is as adjuvant therapy. Although immunotherapy has proven efficacy in metastatic disease, no benefit has been shown for adjuvant therapy (Pizzocaro et al 2001; Clark et al 2003; Messing et al 2003) and in fact a reduction in overall survival has been reported with immunotherapy in comparison with placebo (Atzpodien et al 2005). Given the activity of sorafenib and other kinase inhibitors in advanced disease, there is a logical interest in evaluating these drugs in early stage disease to minimize the likelihood of relapse after surgery and toxicity is again important as cytostatic adjuvant therapies may be administered for prolonged periods.

Conclusions

Sorafenib inhibits multiple targets including the BRAF, V600E BRAF, and CRAF non-receptor TKs and the VEGF, PDGF, and c-KIT receptor TKs. It is orally administered and has shown significant activity with manageable toxicity in a phase 3 trial in metastatic RCC in immunotherapy-refractory patients. Given the activity of sorafenib in advanced RCC, investigation in the adjuvant setting to attempt to minimize the risk of disease recurrence is planned. There is also interest in the use of kinase inhibitors in the neoadjuvant setting to investigate the mechanism of drug action in vivo and to identify biomarkers of response to therapy.

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