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Sorafenib
In Advanced Renal Cancer

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Contents

Abstract

▲ Sorafenib is an oral multikinase inhibitor that targets the mitogen-activated protein kinase signalling pathway and receptor tyrosine kinases involved in tumour proliferation and angiogenesis.

▲ In the large, phase III, randomised, double-blind, multicentre Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) of patients with advanced clear-cell renal cell cancer in whom previous systemic therapy had failed, median progression-free survival was doubled in patients receiving sorafenib compared with those receiving placebo (5.9 vs 2.8mo).

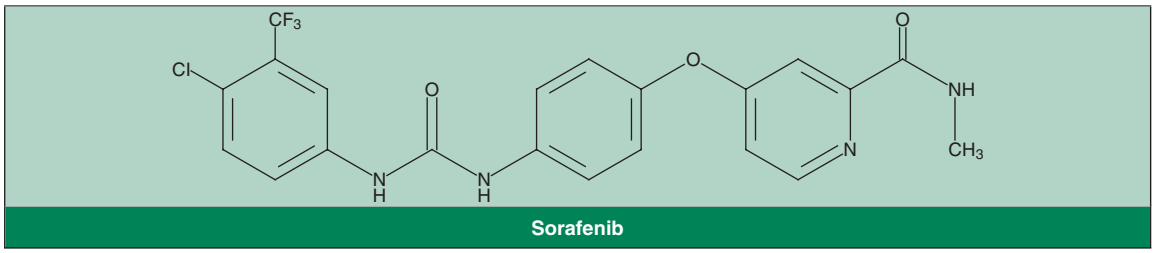
▲ Significantly more patients receiving sorafenib than those receiving placebo in the phase III trial experienced complete or partial responses or stable disease.

▲ Age, risk-assessment score, prior treatment, metastasis in lung or liver, or time from diagnosis did not affect the improved progression-free survival in sorafenib recipients.

▲ In a randomised, phase II discontinuation trial of patients with advanced renal cancer, in which only those showing stable disease with sorafenib were randomised to further sorafenib or placebo, more patients receiving sorafenib were free of progressive disease 12 weeks after randomisation than were those receiving placebo, and median progression-free survival was longer in sorafenib recipients.

▲ In clinical trials, most drug-related adverse events were mild to moderate in severity. Grade 3/4 hand-foot skin reaction and hypertension occurred more often with sorafenib than with placebo.

Features and properties of sorafenib (BAY 439006; Nexavar®)	
Indication	
Advanced renal cell carcinoma	
Mechanism of action	
Multikinase inhibitor	
Dosage and administration	
Dose	400mg
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile of oral sorafenib 400mg twice daily for 7 days (steady-state values) in patients with advanced, refractory solid tumours	
Peak plasma concentration (C_{max})	9.90 mg/L
Time to C_{max}	≈3h
Area under the plasma concentration-time curve from 0 to 12h	82.7 mg • h/L
Elimination half-life	25–48h
Adverse events	
Most frequent	Diarrhoea, rash, fatigue, hand-foot skin reaction, alopecia, nausea



Until recently, patients with advanced renal cancer had a median survival of about 6–12 months[1] and few treatment options.[2] At present, a nephrectomy is standard treatment in localised disease, and often in metastatic disease, but about half of the patients who have a nephrectomy for localised disease will develop metastases.[3] Pharmacological treatment is based on cytokine therapy, but response rates are low and treatment often causes marked toxicity.[4]

Recent progress in the understanding of certain pathways and processes involved in carcinogenesis has helped identify new targets for anticancer therapies.[5] Sorafenib (Nexavar®)[1] was developed as a small molecule inhibitor of the Raf kinase pathway, which is controlled by receptor tyrosine kinase activity and leads to cell proliferation.[5] The drug also appears to target other important receptor tyrosine kinases involved in tumour angiogenesis.[5] This article reviews the pharmacological properties of sorafenib monotherapy, and its clinical efficacy and tolerability in patients with advanced renal cancer.

1. Pharmacodynamic Profile

- Sorafenib is an orally active, potent bi-aryl urea that inhibits Raf-1, a member of the mitogen-activated protein kinase (MAPK) intracellular signal transduction pathway (which comprises Raf, MAPK kinase [MEK] and extracellular signal-regulated kinase [ERK], and regulates cellular proliferation and survival[6]), as well as suppressing the activity of several receptor tyrosine kinases.[7]
- In *in vitro* biochemical assays, sorafenib demonstrated potent inhibition of Raf-1, wild type B-Raf, and V599E mutant B-Raf.[7]
- Sorafenib also showed *in vitro* inhibition of the activity of several receptor tyrosine kinases including the proangiogenic vascular endothelial growth factor receptors (VEGFR)-1, 2 and 3, platelet-derived growth factor receptor (PDGFR)-β, fibroblast growth factor receptor (FGFR)-1, Flt-3, c-KIT and RET.[6,7]
- Sorafenib did not inhibit the activity of MEK-1, ERK-1, epidermal growth factor receptor, insulin-like growth factor receptor-1, c-met, or HER-2.[7]
- Sorafenib induced down-regulation of Mcl-1, a member of the antiapoptotic Bcl-2 family, in a range of human tumour cells including renal cancer cells (ACHN cell line).[8]
- Immunohistochemistry analysis of tumour xenograft models in mice receiving once-daily sorafenib 30–60 mg/kg demonstrated a close association between inhibition of tumour growth and inhibition of the extracellular signal-regulated kinases known to promote angiogenesis.[7] Furthermore, analyses of microvessel density and area in the same tumours demonstrated significant inhibition of neovascularisation, as determined using antimurine CD31 antibodies.[7]
- Oral sorafenib 7.5–60 mg/kg administered daily for 9 days dose-dependently inhibited tumour growth in a panel of human tumour xenograft models in mice.[7] Sorafenib inhibited the mitogen-activated protein kinase pathway in a range of human cancers that exhibit mutations in KRAS and B-Raf

1 The use of trade names is for product identification purposes only and does not imply endorsement.

genes, including colon, pancreas and breast tumour cell lines.[7]

- Biomarker soluble VEGFR-2 plasma levels decreased significantly (weakly correlated with target lesion reductions) in 838 patients with advanced renal cell carcinoma receiving oral sorafenib 400mg twice daily for 3 weeks in a randomised, double-blind study[9] (and remained low into week 8), versus no change in patients receiving placebo.[10] Median progression-free survival did not appear to be correlated with baseline soluble VEGFR-2 levels.
- In the same study, plasma VEGF levels increased significantly after 3 weeks of sorafenib but not after placebo; there was a trend towards a greater benefit in sorafenib recipients with high baseline VEGF levels versus placebo recipients.[10] While progression-free survival was shorter in placebo recipients with high baseline VEGF levels than in those with low baseline levels, this correlation was not seen in sorafenib recipients.
- The effect of sorafenib on tumour perfusion and vascular permeability in index lesions of patients (n = 12) with metastatic renal cell carcinoma was studied using dynamic contrast-enhanced magnetic resonance imaging.[11] Sorafenib 400mg twice daily for 28 days reduced the rate constant for gandolinium transfer from the vasculature to the interstitium by 61% (correlated with time to progression) and the volume fraction of the tissue extracellular and extravascular space by 23% (normalised for the arterial input function).[11]
- Using flow cytometry, the effect of sorafenib on phorbol myristate acetate-stimulated ERK phosphorylation in peripheral blood lymphocytes was measured in patients with advanced cancers.[12] Sorafenib accumulation and dose-limiting skin toxicity showed a significant correlation with the inhibition of ERK phosphorylation ($p < 0.01$), as well as with the dose level ($p < 0.05$).[12]
- Sorafenib has been associated with consistent increases in blood pressure (BP) [see also section 4]. Increases in systolic BP (SBP) of ≥10mm Hg were seen in 15 of 20 patients with metastatic solid tumours, while 12 patients had increases of ≥20mm Hg, after 3 weeks of sorafenib 400mg twice daily in a small open study.[13] The mean increase in SBP from baseline at 3 weeks was 20.6mm Hg ($p < 0.0001$). SBP remained ≥10mm Hg higher than baseline in 12 of 17 patients after 18 weeks of treatment. Serological investigations indicated no associated humoral mechanism for the induced hypertension.

2. Pharmacokinetic Profile

The pharmacokinetics of oral sorafenib were consistent in four phase I studies using different dose schedules in patients with advanced or refractory solid tumours.[14] Data from one of these studies,[15] as well as the manufacturer's prescribing information,[16] are summarised here.

- Sorafenib is rapidly absorbed after oral administration and maximum plasma concentrations (C_{max}) are reached within approximately 3 hours.[16] The bioavailability of sorafenib was reduced by 29% when it was given with a high fat meal compared with administration in the fasted state (see section 5).[16] *In vitro*, sorafenib was 99.5% bound to human plasma proteins.[16]
- Accumulation (2.5- to 7-fold) occurs after multiple sorafenib doses compared with single-dose administration.[16] Steady-state conditions are achieved after 7 days and no further accumulation was detected after a further 14 days of treatment.[15]
- The mean C_{max} values on days 1 and 7 in patients (n = 10) receiving sorafenib 400mg twice daily were 3.04 and 9.90 mg/L.[15] The mean areas under the plasma concentration-time curve from 0 to 12 hours (AUC_{12}) for the same dose level and time points were 24.0 and 82.7 mg • h/L, respectively. There was little change in the C_{max} and AUC_{12} values between days 7 and 21; day 21 values were 10.0 mg/L and 76.5 mg • h/L, respectively.[15]
- The elimination half-life ($t_{1/2}$) of sorafenib is about 25–48 hours.[16] The drug is metabolised mainly in the liver via the cytochrome P450 (CYP) isoenzyme CYP3A4 and via glucuronidation.[16] After administration of sorafenib 100mg in an oral solution, 96% of the drug was recovered within 14 days: 77% in faeces and 19% in urine.[16]

- Coadministration of sorafenib with CYP3A4 inhibitors does not appear to alter its metabolism.[16] Ketoconazole 400mg given once daily for 7 days did not alter the mean AUC, C_{max}, or $t_{1/2}$ values of a single oral dose of sorafenib 50mg in healthy volunteers (n = 16).[17]
- When sorafenib was co-administered with doxorubicin to patients (n = 24) with solid tumours, the C_{max} and AUC values for doxorubicin increased with escalating dosages of sorafenib.[18] Patients with liver metastases and elevated levels of aspartate amine transferase and conjugated bilirubin had higher AUC values for doxorubicin than patients with normal liver function.
- The combined administration of sorafenib and irinotecan resulted in a 67–120% increase in the AUC of SN-38, the active metabolite of irinotecan, and a 26–42% increase in the AUC of irinotecan, but had negligible effect on the pharmacokinetics of sorafenib in a study in patients with advanced refractory solid tumours.[16,19]
- No clinically relevant pharmacokinetic interactions were demonstrated when escalating dosages of sorafenib were co-administered with gemcitabine (n = 13),[20] capecitabine (n = 19),[21] oxaliplatin,[16] combined carboplatin and paclitaxel (n = 11),[22] or combined fluorouracil and leucovorin (n = 24)[23] in patients with solid tumours.

3. Therapeutic Efficacy

The efficacy of oral sorafenib in confirmed advanced renal cancer has been evaluated in two randomised, double-blind, multicentre trials. One was the large, placebo-controlled, phase III Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET) in patients with histologically confirmed, metastatic, low- or intermediate-risk, clear-cell renal cell carcinoma in whom a previous systemic therapy had failed.[9] The other was a phase II discontinuation trial in patients with histologically or cytologically confirmed metastatic renal cell carcinoma, with or without a history of prior therapy.[24] In the latter trial, the original protocol had also included patients with other solid tumours (n = 501), but was amended to refocus on renal cell carcinoma (n = 202) when sorafenib appeared to be associated with early antitumour activity in these patients.

Eligible patients in both trials had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.[9,24] The median age was approximately 58 years and about two-thirds of patients were male. Metastases were present at two or more sites in 57% and 38% of patients in the phase III and phase II trials, 82% and 84% had received prior systemic anticancer therapy, and 94% and 89% had undergone a nephrectomy.[9,24]

Phase III Trial (TARGET)

In the phase III trial, adult patients were randomised to receive either continuous oral sorafenib 400mg twice daily (n = 451) or placebo (n = 452).[9] The primary efficacy endpoint (intent-to-treat cohort) was duration of overall survival from randomisation to death, and secondary efficacy endpoints included progression-free survival and best response rate. Progression was established using magnetic resonance imaging, clinical progression, death or independently assessed computed tomography.

An independent, planned interim analysis of progression-free survival (during which the study investigators remained blind to the results), held when progression had occurred in about 360 patients, showed potentially favourable results for sorafenib and, after discussion with regulatory authorities, an ethical decision was made to unblind the study and allow patients receiving placebo to cross over to sorafenib therapy.[9] Results are available for overall survival immediately before and 6 months after crossover, and for progression-free survival at the time of the independent review and 4 months later, at the time of unblinded crossover.[9]

- Immediately before crossover, 97 sorafenib recipients (22%) and 123 placebo recipients (27%) had died.[9] This equated to a median actuarial overall survival of 14.7 months in the placebo group (median not yet reached in the sorafenib group) after a median follow-up of 6.6 months (hazard ratio

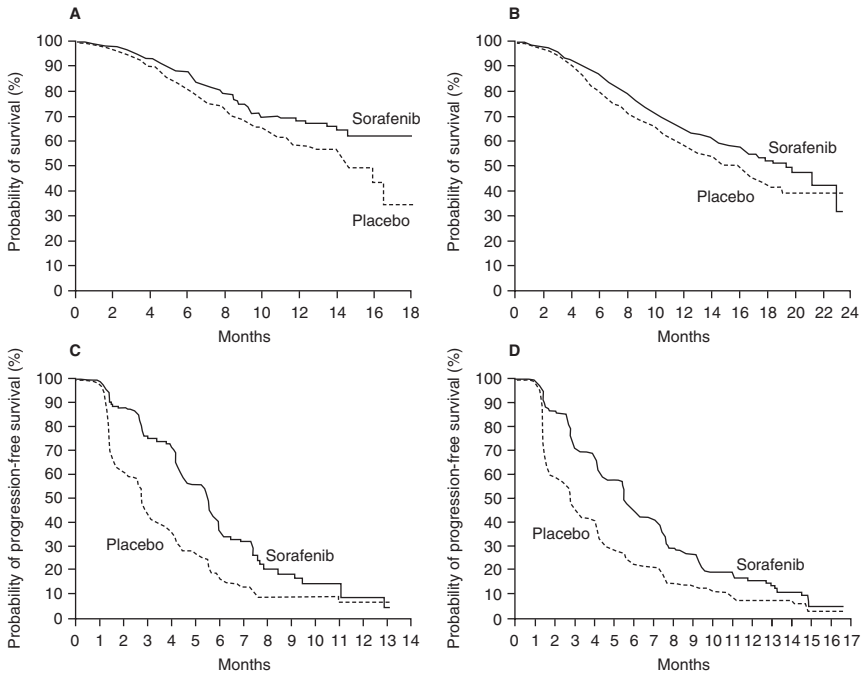


Fig. 1. Therapeutic efficacy of oral sorafenib in patients with advanced clear-cell renal cell carcinoma. Kaplan-Meier analysis of overall survival and progression-free survival.[9] Panel A shows the probability of overall survival among 903 patients — 451 receiving sorafenib and 452 receiving placebo — in May 2005, when patients receiving placebo were allowed to switch to sorafenib (p = 0.02 for the comparison between the two study groups; O'Brien-Fleming threshold for statistical significance, p = 0.0005). Panel B shows the probability of overall survival among the same patients in November 2005 (p = 0.02; O'Brien-Fleming threshold for statistical significance, p = 0.0094). Panel C shows the probability of progression-free survival among 769 patients — 384 patients receiving sorafenib and 385 patients receiving placebo — who were assessed in an independent review in January 2005 (p < 0.001). Panel D shows the probability of progression-free survival among all 903 patients, according to a review by investigators in May 2005 (p < 0.001).

[HR] 0.72; 95% CI 0.54, 0.94; p = 0.02; see figure 1A).

- Six months later, after 216 placebo recipients had transferred to sorafenib therapy, 171 (38%) of the original sorafenib cohort and 196 (43%) of the original placebo cohort had died. At this stage, median overall survival was 19.3 months with sorafenib and 15.9 months with placebo (HR 0.77; 95% CI 0.63, 0.95; p = 0.02; figure 1B). Prespecified O'Brien-Fleming statistical significance was not reached.

- Median progression-free survival at the time of the interim data review was twice as long in the sorafenib group (5.9mo; n = 384) as that in the placebo group (2.8mo; n = 385; p < 0.001).[9] The risk of progression was substantially reduced by sorafenib (HR 0.44; 95% CI 0.35, 0.55; figure 1C). Four months later, at the time of crossover, progression-free survival in all 903 patients was 5.5 months with sorafenib vs 2.8 months with placebo (p < 0.001) and the risk of progression had been approximately halved by sorafenib (HR 0.51; 95% CI 0.43, 0.60; figure 1D).

- This outcome remained robust on assessment of patient subgroups, including age less than or greater than 65 years, low or intermediate risk assessment score, prior treatment with interleukin-2 or interferon, metastasis in the lung or liver at baseline, and time from diagnosis less than or greater than 1.5 years.[9]

- The best responses (intent-to-treat) for sorafenib and placebo recipients just before crossover were as

follows: complete response 1 (<1%) and 0, partial response 43 (10%) and 8 (2%), and stable disease (i.e. unchanged for ≥28d) 333 (74%) and 239 (53%).[9]

- Partial responses or stable disease occurred more frequently in the sorafenib group than in the placebo group ($p < 0.001$). The disease control rate (sum of the percentages of those with complete or partial response or stable disease) was 62% for sorafenib recipients and 37% for placebo recipients.[9]
- Complete or partial responses were achieved by the relevant sorafenib recipients in a median of 80 (range 35–275) days and lasted for a median of 182 (range 36–378) days.[9]
- Independently assessed tumour measurement decreased in 74% of sorafenib recipients.[25]

Phase II Discontinuation Trial

In the phase II trial, all patients (n = 202) received sorafenib 400mg twice daily for 12 weeks followed by assessment of disease status using modified WHO criteria (bidimensional tumour measurement). Patients with <25% tumour shrinkage (stable disease) were randomised to double-blind treatment with sorafenib (n = 32 patients) or placebo (n = 33) for a further 12 weeks. Patients with ≥25% tumour shrinkage (n = 73; 36%) continued open-label sorafenib and those with ≥25% tumour growth (n = 51; 25%) discontinued treatment. Subsequently, six further patients were granted permission to continue open-label sorafenib. In the initial 12-week sorafenib run-in period, tumour shrinkage or disease stabilisation occurred in 68% of patients. The primary efficacy parameter was the percentage of randomised patients remaining progression-free at 24 weeks (12 weeks after randomisation). Secondary efficacy endpoints included progression-free survival.

- Twelve weeks after randomisation, 16 sorafenib recipients (50%) and six placebo recipients (18%) were free of progressive disease ($p < 0.01$).[24]
- Median progression-free survival from the time of randomisation was 24 weeks in sorafenib recipients and 6 weeks with placebo ($p < 0.01$).[24]
- In the placebo group, sorafenib was restarted in 28 patients who experienced disease progression after a median 7 weeks from randomisation.[24] The median time from restarting sorafenib to progression or toxicity in these patients was 24 weeks.
- Median progression-free survival from study entry was 29 weeks for all 202 patients and 40 weeks for the 79 patients who received open-label sorafenib.[24]

Pharmacoeconomic Considerations

- A Markov model of sorafenib plus best supportive care (BSC) versus BSC alone, developed from the perspective of the Spanish National Health Service and based on the phase III efficacy trial (see section 3 for trial details), demonstrated cost effectiveness for sorafenib in patients with advanced renal cell carcinoma.[26] Lifetime costs per patient (discounted annually at 3%, 2005 costs) were €44 904 and €10 502 for sorafenib plus BSC and BSC alone, respectively, representing an incremental cost-effectiveness ratio (ICER) of €37 667 per quality-adjusted life year gained.
- A similar study, from a US managed care payor perspective and also using a Markov model based on the phase III trial, showed lifetime costs per patient (discounted annually at 3%, 2004 costs) of $US85 571 and $US36 634 for sorafenib plus BSC and BSC, respectively, representing an ICER of $US75 354 per life year gained (i.e. within the $US50 000–$US100 000 that society is assumed to be willing to pay).[27]
- The Functional Assessment of Cancer Therapy-General test was used to assess health-related quality of life (HR-QOL) in patients in the phase III trial.[28] Sorafenib did not worsen overall HR-QOL versus placebo, and some individual HR-QOL symptoms were significantly improved (e.g. 'worry that condition will worsen', $p < 0.001$; 'ability to enjoy life', $p < 0.05$).

4. Tolerability

The tolerability of sorafenib 400mg twice daily has been evaluated in patients with advanced renal

cancer in two well designed trials[9,24] (see section 3 for study design details). Additional preliminary data on the comparative tolerability of sorafenib and interferon in treatment-naive patients with metastatic renal cancer are available (as an abstract).[29] Results from a pooled analysis of the association between rash and treatment outcome are also summarised.[30]

- In the phase III trial (TARGET), 10% and 8% of sorafenib and placebo recipients discontinued treatment because of adverse events, mainly constitutional, gastrointestinal, dermatological or pulmonary/upper respiratory tract symptoms.[9]

- After a median of 23 weeks' sorafenib and 12 weeks' placebo, the most common adverse events in the phase III trial were diarrhoea, rash, fatigue, hand-foot skin reaction, alopecia and nausea (figure 2).[9] The only significant difference pertaining to adverse events of all grades was for cardiac ischaemia or infarction, which occurred in 12 sorafenib recipients (3%) and 2 placebo recipients (<1%; p = 0.01). Most events were grade 1 or 2 in severity.

- Grade 3/4 adverse events occurring significantly more often in patients receiving sorafenib than in placebo recipients in the phase III trial included hand-foot skin reaction (6% vs 0%; p < 0.001) and hypertension (4% vs <1%; p = 0.001).[9]

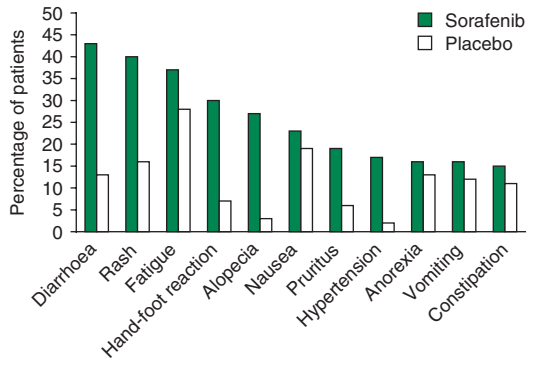


Fig. 2. Tolerability of sorafenib compared with placebo in patients with advanced clear-cell renal cell carcinoma. The graph shows the adverse events occurring at an incidence of ≥15% in patients randomised to sorafenib 400mg twice daily (n = 451) or placebo (n = 451) in the double-blind, multicentre, phase III TARGET study.[9]

- In the discontinuation trial (n = 202), the most common drug-related adverse events were fatigue (73%), rash/desquamation (66%), hand-foot skin reaction (62%), pain (other than abdominal, headache, joint or muscle pain: 58%; total pain: 78%) and diarrhoea (58%).[24] Grade 3/4 adverse events were reported in 65% of patients; the most common of these were hypertension (31%), hand-foot skin reaction (13%) and pain (12%). Discontinuation of sorafenib due to adverse events was required in 6% of patients. No deaths were associated with treatment.

- Pooled data from four dose-escalation trials of sorafenib 300–600mg twice daily in 81 patients with advanced and/or metastatic solid tumours refractory to standard therapies indicated that time to progression of disease was significantly increased in patients who experienced skin toxicity or diarrhoea at ≥grade II severity versus those without such adverse effects (approximately 5 months vs 1.6 months; p < 0.05; values estimated from a graph).[30]

- At dosages of 300–600mg twice daily, 44% of patients in the pooled data analysis experienced hand-foot skin reactions (16% at grade III severity, including 31% of 39 patients receiving 600mg twice daily and 3% of 37 receiving 400mg twice daily), 42% experienced diarrhoea (5% of 37 receiving 400mg twice daily at grade III severity), and 23% experienced rash (5% of 39 receiving 600mg twice daily at grade III severity). Mean time to progression was 2.4, 3.8, and 3.7 months in patients receiving sorafenib 300mg, 400mg and 600mg twice daily, respectively.[30]

- Drug-related adverse events of any severity occurred in similar overall proportions (51% vs 52%) of patients receiving sorafenib 400–600mg twice daily (n = 97) or interferon 9×10^6 units three times a week (n = 91) [duration not reported].[29] These included diarrhoea (25% vs 6%), fatigue (14% vs 21%), fever (2% vs 19%), hypertension (13% vs 0%), nausea (5% vs 13%). Events of severity grade 3 or higher occurred in 8% vs 11%. Hypophosphataemia occurred in 22% vs 0%, lipase elevation in 6% vs 11%, anaemia in 0% vs 5% and hypoalbuminaemia in 0% vs 4%.

5. Dosage and Administration

Sorafenib is available as a 200mg oral tablet.[16] The currently recommended sorafenib dosage regimen is 400mg twice daily.[14,16] The tablets should not be taken with food (i.e. should be taken at least one hour before or two hours after eating). Treatment with sorafenib should continue until the patient is no longer responding or until unacceptable toxicity occurs.[16] Local prescribing information should be consulted for more detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

6. Sorafenib: Current Status in Advanced Renal Cancer

Sorafenib has been approved in the US and Mexico for the treatment of advanced renal cell carcinoma and in Europe and Canada for the treatment of advanced renal cell carcinoma in patients unresponsive to prior cytokine-based therapy or who are unsuitable for such therapy; approval applications have also been filed in Australia, Brazil, Japan and Turkey. The drug has shown some clinical efficacy in extending progression-free survival in two well controlled trials in this indication.

Disclosure

During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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