

Sorafenib

In Hepatocellular Carcinoma

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Abstract

- ▲ Sorafenib is an orally active multikinase inhibitor with anti-tumour activity. It was recently approved in the US and the EU for the treatment of patients with hepatocellular carcinoma.
- ▲ Oral sorafenib 400 mg twice daily significantly improved survival in patients with advanced hepatocellular carcinoma in the randomized, double-blind, multicentre, phase III SHARP trial (n = 602); the median duration of survival was 10.7 months with sorafenib and 7.9 months with placebo. In addition, the median time to progression was significantly longer in patients receiving sorafenib than in those receiving placebo (5.5 vs 2.8 months).
- ▲ Combination therapy with oral sorafenib 400 mg twice daily and intravenous doxorubicin has potential in the treatment of patients with advanced hepatocellular carcinoma, according to the results of a randomized, double-blind, phase II study (n = 96). Although the addition of sorafenib to doxorubicin did not significantly delay the time to progression, the median durations of overall survival and progression-free survival were significantly longer with sorafenib plus doxorubicin than with doxorubicin alone.
- ▲ Monotherapy with oral sorafenib 400 mg twice daily was generally well tolerated in patients with advanced hepatocellular carcinoma, with a manageable adverse event profile.

Features and properties of sorafenib (Nexavar®)

Featured indication

Hepatocellular carcinoma

Mechanism of action

Multikinase inhibitor

Dosage and administration

Dose 400 mg

Route of administration Oral

Frequency of administration Twice daily

Pharmacokinetic profile of oral sorafenib 400 mg twice daily in patients with advanced hepatocellular carcinoma (according to Child-Pugh class)

Geometric mean maximum plasma concentration (C_{max}) 4.9 and 6.0 mg/L (Child-Pugh class A and B)

Median time to C_{max} 1 and 0.5 h (Child-Pugh class A and B)

Geometric mean area under the plasma concentration-time curve from 0 to 8 h 25.4 and 30.3 mg • h/L (Child-Pugh class A and B)

Drug-related adverse events

Most frequent (all grades) Diarrhoea, hand-foot skin reaction, anorexia, alopecia, nausea, weight loss, abdominal pain, bleeding and vomiting

The incidence of hepatocellular carcinoma in the US and Europe has been increasing in recent decades, mainly as a result of the increasing prevalence of chronic hepatitis C virus infection.^[1] Systemic treatment options for patients with hepatocellular carcinoma who are not eligible for, or decline, liver surgery have traditionally been limited and minimally effective.^[1]

Up-regulated signalling through the mitogen-activated protein kinase (MAPK) intracellular signal transduction pathway plays a crucial role in the development of hepatocellular carcinoma, as does tumour angiogenesis.^[2] The MAPK pathway comprises Raf, MAPK kinase (MEK) and extracellular signal-regulated kinase (ERK), and is a mediator of tumour cell proliferation, differentiation and survival.^[3,4] The identification of pivotal pathways, such as the MAPK cascade, led to the development of targeted treatments, such as sorafenib (Nexavar®).¹

Sorafenib is an orally active multikinase inhibitor that inhibits cell surface tyrosine kinases, as well as downstream intracellular Raf kinases in the MAPK cascade.^[3,4] Sorafenib is widely available for use in the treatment of advanced renal cell carcinoma and has been reviewed in this indication previously.^[5] Recently, sorafenib was also approved in the US and the EU for use in the treatment of hepatocellular carcinoma, the first systemic drug to be approved in this indication.^[6,7] Indeed, current US treatment guidelines recommend sorafenib as a first-line treatment option in patients with unresectable hepatocellular carcinoma who are Child-Pugh class A or B.^[8] This article reviews the pharmacological properties of sorafenib and its clinical efficacy and tolerability in patients with hepatocellular carcinoma.

1. Pharmacodynamic Profile

The pharmacodynamic properties of sorafenib have been reviewed previously.^[5] This section pro-

vides a brief overview, focusing on data most relevant to hepatocellular carcinoma.

- The bi-aryl urea sorafenib is an orally active multikinase inhibitor.^[3,9] Kinases inhibited by sorafenib include the receptor tyrosine kinases vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, FIP1 like 1-platelet-derived growth factor receptor (PDGFR)- α , PDGFR- β , c-KIT, FLT-3 and RET, and the intracellular Raf kinases Raf-1, wild-type B-Raf and mutant B-Raf.^[3,9,10] These kinases are implicated in tumour cell proliferation and tumour angiogenesis.^[3,9]

- *In vitro*, sorafenib inhibited proliferation and induced apoptosis in two human hepatocellular carcinoma cell lines (PLC/PRF/5 and HepG2).^[2] Sorafenib dose dependently inhibited cell proliferation (concentration inhibiting 50% of tumour cells was 6.3 $\mu\text{mol/L}$ in the PLC/PRF/5 cell line and 4.5 $\mu\text{mol/L}$ in the HepG2 cell line); after 24 hours of exposure to the drug, there was dose-dependent induction of apoptosis.^[2]

- Sorafenib inhibited the Raf/MEK/ERK signalling pathway in the PLC/PRF/5 and HepG2 cell lines, as shown by the inhibition of MEK and ERK phosphorylation, for example.^[2] In addition, some actions of sorafenib (e.g. downregulation of the anti-apoptotic protein myeloid cell leukaemia-1) appeared to be independent of its inhibitory effect on MEK/ERK signalling.^[2]

- Sorafenib also had antitumour activity in a PLC/PRF/5 human hepatocellular carcinoma tumour xenograft model in mice.^[2] Mice received oral sorafenib 10, 30 or 100 mg/kg/day for 16 or 21 days. Sorafenib 10 and 30 mg/kg/day resulted in significant ($p < 0.001$ vs vehicle) tumour growth inhibition of 49% and 78%. In addition, 50% of mice receiving sorafenib 100 mg/kg/day had durable partial tumour regression.^[2]

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

- Sorafenib also reduced tumour angiogenesis, reduced signalling through the MAPK cascade and induced apoptosis in the PLC/PRF/5 tumour xenograft model.^[2] Administration of oral sorafenib 30 and 100 mg/kg/day for 5 days significantly reduced tumour microvessel area (showing inhibition of tumour angiogenesis) [$p < 0.05$ vs vehicle], reduced ERK phosphorylation (indicating inhibition of Raf/MEK/ERK signalling) [p -value not reported], and significantly increased TUNEL (terminal deoxynucleotidyl transferase d-uridine triphosphate nick end labelling)-positive staining (showing induction of apoptosis) [$p < 0.05$ vs vehicle].^[2]

2. Pharmacokinetic Profile

Pharmacokinetic data in patients with hepatocellular carcinoma were obtained from a noncomparative, multicentre, phase II study ($n = 137$) in which sorafenib 400 mg twice daily was evaluated in 22 patients with advanced hepatocellular carcinoma (14 patients were Child-Pugh class A and 8 were Child-Pugh class B).^[11] Pharmacokinetics were assessed after at least 28 days of treatment had elapsed. Blood samples were collected for up to 8 hours post-dose in most patients and data are, therefore, limited.

Where relevant, pharmacokinetic data from healthy volunteers^[12] and patients with advanced, refractory solid tumours have been included,^[13,14] supplemented by data from the manufacturer's prescribing information.^[15]

- In patients with hepatocellular carcinoma who received oral sorafenib 400 mg twice daily, the geometric mean maximum plasma concentration (C_{max}) was 4.9 mg/L in Child-Pugh class A patients and 6.0 mg/L in Child-Pugh class B patients, the median time to C_{max} was 1 hour and 0.5 hours, and the geometric mean area under the plasma concentration-time curve (AUC) from 0 to 8 hours was 25.4 and 30.3 mg • h/L.^[11] Pharmacokinetic data are not

available in patients with severe hepatic impairment (Child-Pugh class C).^[15]

- Drug accumulation (2.5- to 7-fold) was observed with multiple doses of sorafenib compared with a single dose;^[15] steady state was achieved after 7 days' administration in patients with advanced, refractory solid tumours who received twice-daily oral sorafenib.^[13]

- Sorafenib tablets had a mean relative bioavailability of 38–49%, compared with oral solution.^[15] Sorafenib bioavailability was similar when the drug was taken with a moderate-fat meal or in the fasting state, but was reduced by 29% when taken with a high-fat meal. Thus, it is recommended that sorafenib be administered without food.^[15] *In vitro*, sorafenib was 99.5% bound to human plasma proteins.^[15]

- Sorafenib is mainly metabolized in the liver; oxidative metabolism is mediated via the cytochrome P450 (CYP) 3A4 isoenzyme and glucuronidation via uridine diphosphate glucuronosyltransferase 1A9.^[15] The pyridine *N*-oxide metabolite of sorafenib, which is the main circulating metabolite in plasma, had similar potency to the parent drug *in vitro*.^[15] At steady state, this metabolite accounted for about 9–16% of circulating analytes and the parent drug accounted for about 70–85%.^[15]

- Following oral administration of sorafenib 100 mg as a solution, 77% of the dose was excreted in the faeces and 19% was excreted in the urine as glucuronidated metabolites.^[15] Unchanged drug accounted for 51% of the dose and was found in the the faeces, but not in the urine.^[15] The terminal elimination half-life of sorafenib was ≈25–48 hours.^[15]

- The sorafenib dosage does not need to be adjusted on the basis of age, gender or renal impairment.^[15]

- Concomitant administration of the CYP3A inhibitor ketoconazole 400 mg/day did not alter the

pharmacokinetics of a single dose of sorafenib 50 mg to a clinically significant extent in healthy volunteers.^[12] It is thought that sorafenib exposure following the administration of 400 mg twice daily is unlikely to be increased by the concomitant administration of CYP3A inhibitors.^[12]

- In patients with advanced, refractory solid tumours, coadministration of oral sorafenib 400 mg twice daily (as 200 mg tablets) and intravenous doxorubicin 60 mg/m² every 3 weeks did not alter the C_{max} or AUC of either drug to a significant extent.^[14] However, the prescribing information notes that sorafenib can increase doxorubicin plasma concentrations and recommends caution when these drugs are coadministered.^[15]

3. Therapeutic Efficacy

Sorafenib Monotherapy

Phase II Trial

The results of a noncomparative, multicentre, phase II trial^[11] suggesting the potential of sorafenib in patients with advanced hepatocellular carcinoma will be discussed only briefly, given the availability of data from the well designed, phase III, SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trial.^[16] In the phase II trial, patients (n = 137) had histologically proven, measurable, unresectable hepatocellular carcinoma with no prior systemic therapy.^[11] Inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, Child-Pugh class A or B, and a life expectancy of ≥12 weeks. Patients received oral sorafenib 400 mg twice daily in 4-week cycles, with dose reductions permitted for adverse effects.^[11] The median study duration was 3.4 months and the median number of treatment cycles was four.

In terms of baseline characteristics, median patient age was 69 years, 71% of patients were male,

50% had an ECOG performance status of 0 and 72% were Child-Pugh class A.^[11]

- According to independent assessment, 3 of 137 (2.2%) sorafenib recipients had a partial response (response duration of 12.0–14.5 months), 8 (5.8%) had a minor response, 46 (33.6%) had stable disease for ≥16 weeks and 48 (35.0%) had progressive disease (the remaining 32 patients [23.4%] were not available for independent review).^[11]

- With sorafenib, the median time to progression was 4.2 months (investigator assessment) or 5.5 months (independent assessment), and the median overall survival duration was 9.2 months.^[11]

Phase III Trial

The clinical efficacy of oral sorafenib was examined in patients with advanced hepatocellular carcinoma in a randomized, double-blind, placebo-controlled, multicentre, phase III trial (the SHARP study).^[16] Inclusion criteria were histologically proven, advanced hepatocellular carcinoma, with at least one measurable untreated lesion, an ECOG performance status of 0–2, Child-Pugh class A and no prior systemic treatment. 902 patients were screened and 602 were randomized to receive oral sorafenib 400 mg twice daily (n = 299) or placebo (n = 303). The median duration of treatment was 23 weeks in sorafenib recipients and 19 weeks in placebo recipients. Prior to randomization, patients were stratified according to macroscopic vascular invasion and/or extrahepatic spread, ECOG performance status and geographical region.

In terms of baseline characteristics, mean patient age was 65.5 years; 87% of patients were male; 87.5% of patients were from Europe; 96.5% of patients were Child-Pugh class A; 54%, 38.5% and 7.5% of patients had an ECOG performance status of 0, 1 or 2 at baseline; 17.5% and 82.5% of patients had Barcelona Clinic Liver Cancer Group stage B and C cancer; and 70% of patients had vascular invasion and/or extrahepatic spread.^[16]

The primary endpoints were overall survival and time to symptomatic progression (defined as the time from randomization to a 4-point decline from baseline in patient responses to the Functional Assessment of Cancer Treatment Hepatobiliary Symptom Index [FHSI-8] confirmed at next visit, deterioration to ECOG performance status 4, or death).^[16] The time to progression (assessed by independent central review) was a prespecified secondary endpoint. Tumour response rates were assessed using Response Evaluation Criteria in Solid Tumours (RECIST).

Analyses were conducted in the intent-to-treat (ITT) population.^[16] The SHARP study is available as an abstract and slide presentation.^[16]

- Sorafenib significantly improved survival in patients with advanced hepatocellular carcinoma in the SHARP trial.^[16] The median duration of survival was 10.7 months with sorafenib and 7.9 months with placebo, yielding a hazard ratio (HR) of 0.69 (95% CI 0.55, 0.88; $p = 0.00058$). Following the second planned interim analysis, the SHARP study was terminated early on the basis of this survival result.

- At the time of study termination, there was no significant difference between sorafenib and placebo recipients in the time to symptomatic progression (assessed using FHSI-8 criteria).^[16] The median time to progression (assessed by independent central review) was significantly longer in patients receiving sorafenib than in those receiving placebo (5.5 vs 2.8 months), with an HR of 0.58 (95% CI 0.44, 0.74; $p < 0.0001$).

- No patient experienced a complete response, and a partial response was seen in 2.3% of patients receiving sorafenib and 0.7% of patients receiving placebo.^[16] Stable disease was seen in 71% of sorafenib recipients and 67% of placebo recipients, with 18% and 24% of patients in the corresponding treatment groups experiencing disease progression. The progression-free rate at 4 months was 62% in sorafenib recipients and 42% in placebo recipients.

In Combination with Doxorubicin

The clinical efficacy of combination therapy with sorafenib plus doxorubicin was examined in a randomized, double-blind, multicentre, phase II study in patients with advanced hepatocellular carcinoma ($n = 96$).^[17] Inclusion criteria were histologically proven, measurable disease, ECOG performance status of 0–2, Child-Pugh class A and no prior systemic therapy. Patients received six cycles of intravenous doxorubicin 60 mg/m² every 21 days plus either oral sorafenib 400 mg twice daily ($n = 47$) or placebo ($n = 49$). Beyond 18 weeks, patients continued with sorafenib monotherapy or placebo until withdrawal, disease progression or death.

In terms of baseline characteristics, mean patient age was 62.5 years, 76% of patients were male, 84.5% had an ECOG performance status of 0 or 1, 99% were Child-Pugh class A, 58% had extrahepatic spread and 67.5% had no macroscopic vascular invasion.^[17]

The primary endpoint was the time to progression (independently assessed) and secondary endpoints included overall survival, progression-free survival and response rates (assessed using RECIST).^[17] Analyses were conducted in the ITT population. An interim analysis was not planned for this study, but was conducted by an independent data monitoring committee on the basis of the favourable results seen with sorafenib in the SHARP trial.^[16] The phase II trial is available as an abstract and slide presentation.^[17]

- The addition of sorafenib to doxorubicin did not significantly delay the time to progression in patients with advanced hepatocellular carcinoma.^[17] The median time to progression was 8.6 months with sorafenib plus doxorubicin compared with 4.8 months with doxorubicin alone, yielding an HR of 0.60 (95% CI 0.3, 1.22).

- However, the median duration of overall survival was significantly longer with sorafenib plus doxorubicin than with doxorubicin alone (13.7 vs 6.5 months) [HR 0.45; 95% CI 0.24, 0.84; $p < 0.005$], as was the median duration of progression-free survival (6.9 vs 2.8 months) [HR 0.57; 95% CI 0.35, 0.93; $p = 0.01$].

- A complete or partial response was seen in 4% of patients receiving sorafenib plus doxorubicin and 2% of patients receiving doxorubicin alone; disease stabilization occurred in 77% and 55% of patients in the corresponding treatment groups.^[17]

4. Tolerability

The tolerability of monotherapy with oral sorafenib 400 mg twice daily was evaluated in patients with advanced hepatocellular carcinoma in the well designed, placebo-controlled, phase III SHARP study (assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 3.0)^[16] and in a smaller non-comparative phase II trial (assessed using NCI Common Toxicity Criteria, version 2.0)^[11] [see section 3 for study design details]. Tolerability data are also available from the phase II trial examining the use of combination therapy with oral sorafenib 400 mg twice daily and intravenous doxorubicin in patients with advanced hepatocellular carcinoma^[17] (assessed using NCI-CTCAE, version 3.0) [see section 3 for study design details]. Additional data were obtained from the manufacturer's prescribing information.^[15]

Sorafenib Monotherapy

- In the SHARP study, sorafenib 400 mg twice daily was generally well tolerated in patients with advanced hepatocellular carcinoma, with a manageable adverse event profile.^[16] The most commonly occurring drug-related adverse events (all grades) in sorafenib recipients were diarrhoea, hand-foot skin

reactions, anorexia, alopecia, nausea, weight loss, abdominal pain, bleeding and vomiting (figure 1).

- In terms of grade 3 drug-related adverse events, diarrhoea occurred in 8% of sorafenib recipients and 2% of placebo recipients, hand-foot skin reaction occurred in 8% and <1%, abdominal pain occurred in 2% and <1%, and weight loss occurred in 2% and 0%.^[16] Other grade 3 drug-related events, such as anorexia, nausea, vomiting, liver dysfunction or bleeding, occurred in $\leq 1\%$ of sorafenib or placebo recipients. No sorafenib recipients experienced grade 4 drug-related adverse events and <1% of placebo recipients experienced grade 4 bleeding.

- The incidence of serious drug-related adverse events in the SHARP study was 13% in sorafenib recipients and 9% in placebo recipients.^[16]

- Hypertension was reported in 9% of sorafenib recipients and 4% of placebo recipients; 4% of sorafenib recipients and 1% of placebo recipients had NCI-CTCAE grade 3 hypertension.^[15]

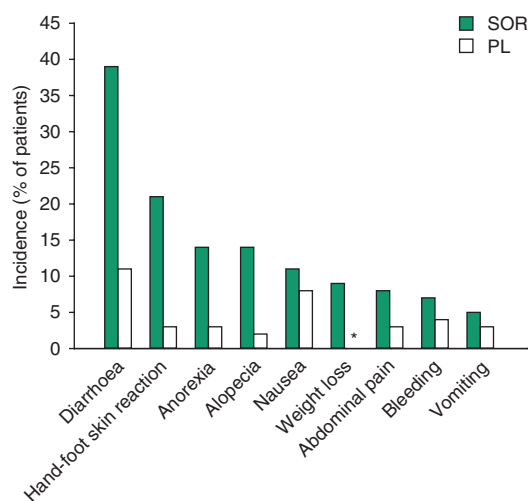


Fig. 1. Tolerability of oral sorafenib (SOR) in patients with advanced hepatocellular carcinoma. Incidence of drug-related adverse events in patients with advanced hepatocellular carcinoma included in the randomized, double-blind, multicentre, phase III, SHARP study.^[16] Patients received oral SOR 400 mg twice daily ($n = 297$) or placebo (PL; $n = 302$) [safety population]. Statistical analysis was not provided. * indicates an incidence of <1%.

- In the phase II study, the most frequently reported drug-related adverse events (any grade) in patients receiving oral sorafenib 400 mg twice daily included diarrhoea (43.1% of patients), hand-foot skin reaction (30.7%) and fatigue (29.9%). These events were also the grade 3 drug-related adverse events that were the most frequently reported (by 8.0%, 5.1% and 9.5% of patients, respectively); there were no grade 4 drug-related adverse events reported.^[11]

In Combination with Doxorubicin

- In the phase II combination therapy study, drug-related adverse events occurred in 92% of patients receiving sorafenib plus doxorubicin and in 88% of patients receiving doxorubicin alone, with serious drug-related adverse events occurring in 21% and 17% of patients in the corresponding treatment groups.^[17]

- The most commonly occurring adverse events (all cause and all grades) included fatigue (75% of sorafenib plus doxorubicin recipients vs 65% of doxorubicin alone recipients), neutropenia (66% vs 60%), diarrhoea (51% vs 25%), elevated bilirubin levels (34% vs 31%), abdominal pain (34% vs 29%), hand-foot skin reactions (30% vs 4%), left ventricular dysfunction (19% vs 2%), hypertension (17% vs 0%) and febrile neutropenia (4% vs 15%).^[17]

- The most commonly occurring grade 3 or 4 adverse events (all cause) included neutropenia (53% of sorafenib plus doxorubicin recipients vs 46% of doxorubicin alone recipients), fatigue (15% vs 15%), diarrhoea (11% vs 10%), elevated bilirubin levels (11% vs 6%), abdominal pain (10% vs 8%), hand-foot skin reactions (9% vs 0%), febrile neutropenia (4% vs 10%) and left ventricular dysfunction (2% vs 0%).^[17]

5. Dosage and Administration

In the US and the EU, the recommended dosage of oral sorafenib in patients with hepatocellular carcinoma is 400 mg twice daily.^[15,18] Temporary interruption or dose reduction of sorafenib therapy may be necessary to manage adverse events; discontinuation of treatment may be needed in some circumstances (e.g. US prescribing information recommends discontinuation on the fourth occurrence of grade 2 skin toxicity or the third occurrence of grade 3 skin toxicity).^[15]

Local prescribing information should be consulted for information regarding contraindications, warnings, precautions and dosage modifications.

6. Sorafenib: Current Status in Hepatocellular Carcinoma

Sorafenib is approved for the treatment of patients with unresectable hepatocellular carcinoma in the US^[7] and the treatment of patients with hepatocellular carcinoma in the EU.^[6]

Sorafenib significantly improves overall survival and time to progression in patients with advanced hepatocellular carcinoma, and is generally well tolerated. In addition, combination therapy with sorafenib plus doxorubicin appears to have potential in this indication.

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