Sorafenib in hepatocellular carcinoma

Sorafenib, a small molecule multikinase inhibitor, is the standard of care in the USA and Europe for the treatment of advanced hepatocellular carcinoma. This article reviews its development from the basis of molecular hepatocarcinogenesis to phase III trials and discusses the future for sorafenib in hepatocellular carcinoma.

Hepatocellular carcinoma is the fifth most common malignancy worldwide and the third leading cause of cancer-related death, exceeded only by lung and gastric cancers (Parkin et al, 2005). While it has a high incidence in parts of Africa and Asia, in Europe and North America its incidence is low although increasing. The estimated incidence in the UK almost tripled from 1.4/100 000 in 1975 to 3.9/100 000 in 2006 (Cancer Research UK, 2009). According to Cancer Research UK data for 2008, 2034 men and 1356 women died from hepatocellular carcinoma (Cancer Research UK, 2010). This has increased by 40% in the last decade.

Untreated advanced hepatocellular carcinoma has a median survival of 4–6 months from the time of diagnosis. The only potentially curative treatments are surgery, either hepatic resection or liver transplantation, or locoregional procedures such as radiofrequency ablation or percutaneous ethanol injection, but only a small proportion of patients will be eligible for such treatments. For most patients, clinical management may include transarterial chemoembolization, or systemic therapy with drugs such as doxorubicin, cisplatin and fluorouracil, tamoxifen, interferon or other biological agents. Until recently, however, no systemic therapy had shown a significant survival benefit in the treatment of patients with advanced hepatocellular carcinoma.

In 2007 sorafenib, an oral small molecule multikinase inhibitor, was approved for the treatment of unresectable hepatocellular carcinoma by the US Food and Drug Administration and for the treatment of hepatocellular carcinoma by the European Medicines Agency, and has now become the standard of care for the treatment of advanced hepatocellular carcinoma. This article reviews the development of sorafenib in this context, from the basis of molecular hepatocarcinogenesis to phase III trials, and discusses the future for sorafenib in hepatocellular carcinoma.

Aetiology

Liver cirrhosis is the strongest predisposing factor for the development of hepatocellular carcinoma. The cellular changes induced by chronic liver injury and the subsequent regeneration process provide a mitogenic and mutagenic environment that precipitates random genetic and epigenetic alterations, which result in the malignant transformation of hepatocytes and the subsequent development of hepatocellular carcinoma. Indeed 70–90% of hepatocellular carcinomas develop in a cirrhotic liver (Velazquez et al, 2003), and hepatocellular carcinoma is the leading cause of death among cirrhotic patients (D'Amico et al, 2006).

The aetiological factors of hepatocellular carcinoma vary by geographical region (Llovet et al, 2003). Hepatitis virus infection is a significant risk factor in the Asia-Pacific region, with about 70% of patients with hepatocellular carcinoma presenting with chronic hepatitis B virus (HBV) infection and 20% presenting with chronic hepatitis C virus (HCV) infection. These rates are roughly reversed for European and North American patients. Liver cirrhosis induced by causes other than HBV and HCV, such as alcoholic liver disease, non-alcoholic steatohepatitis, hereditary haemochromatosis, primary biliary cirrhosis and autoimmune hepatitis, is also a risk factor for hepatocarcinogenesis.

Staging

The specific treatment strategy for individual patients with hepatocellular carcinoma is chosen in a stage-dependent manner. Among the most commonly used staging systems for hepatocellular carcinoma are the Okuda (Okuda et al, 1985), Barcelona Clinic Liver Cancer (Llovet et al, 1999), Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire (GETCH) (Chevret et al, 1999), and Cancer of the Italian Liver Program (CLIP) classifications (Cancer of the Liver Italian Program Investigators, 1998). There have been different views to the validity of these staging systems and it remains unknown which one is most informative in patients with advanced hepatocellular carcinoma with regard to survival outcome and direction of care.

A recent study (Huitzil-Melendez et al, 2010) attempted to define which staging system should be used for the evaluation of patients with hepatocellular carcinoma. It found that, of the staging systems listed above, CLIP and GETCH were the most informative in predicting survival in patients with advanced hepatocellular carcinoma. Perhaps the most widely used staging system however is the Barcelona Clinic Liver Cancer classification (*Table 1*), which consists of 5 stages, 0 to D, and defines patients suitable for different types of treatments

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Table 1. Definition of the Barcelona Clinic Liver Cancer (BCLC) staging for hepatocellular carcinoma

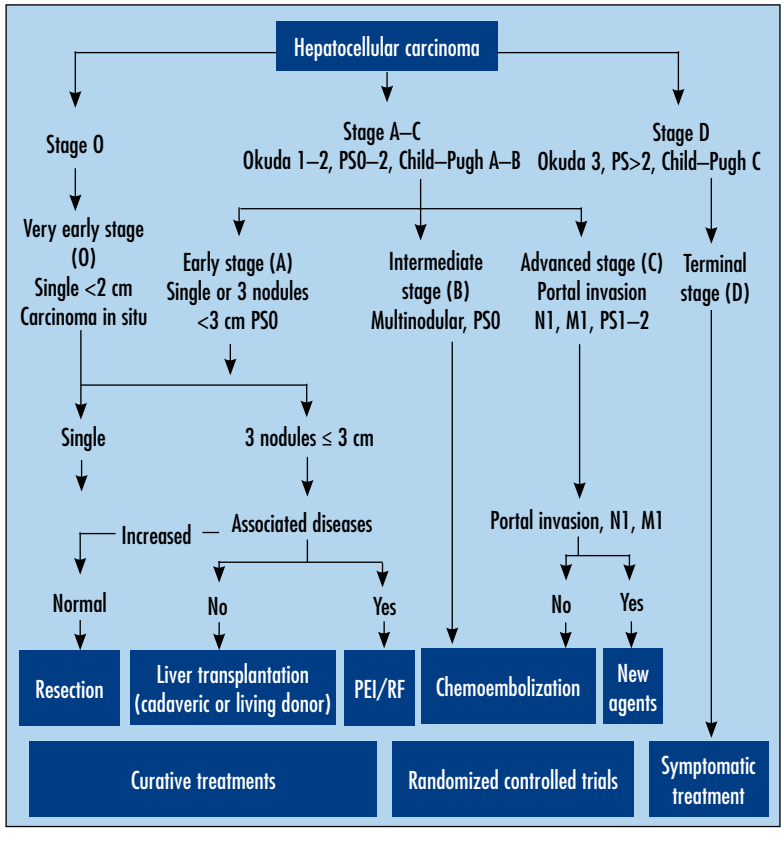
BCLC stage	Performance status	Tumour status	Liver function status
Stage A: early HCC	0		
A1	0	Single, <5 cm	No portal hypertension, normal bilirubin
A2	0	Single, <5 cm	Portal hypertension, normal bilirubin
A3	0	Single, <5 cm	Portal hypertension, abnormal bilirubin
A4	0	Three tumours <3 cm	Child–Pugh A–B
Stage B: intermediate hepatocellular carcinoma	0	Large multinodular	Child–Pugh A–B
Stage C: advanced hepatocellular carcinoma	1–2*	Vascular invasion or extrahepatic spread*	Child–Pugh A–B
Stage D: end stage hepatocellular carcinoma	3–4†	Any	Child–Pugh C†

Stages A and B: all criteria should be fulfilled; Stage C: at least one criterion; *performance status 1–2 or vascular invasion or extrahepatic spread; Stage D: at least one criterion; †performance status 3–4 or Child–Pugh C. Adapted from Kudo et al (2003)

(Llovet et al, 1999). As illustrated in *Figure 1*, only stages 0 and A are indications for radical treatments, principally tumour resection, when portal pressure and bilirubin levels are normal. When portal hypertension is present, other potentially curative treatments such as liver transplantation or local ablation are recommended. For stage B transarterial chemoembolization is the standard of care, achieving partial responses in 15–55% of patients and prolongation of median survival of up to 20 months (Llovet and Bruix, 2003). In selected cases, transarterial chemoembolization can also be used effectively and safely for patients with portal vein involvement (stage C), but until recently no effective cytotoxic systemic therapy for stage C has existed (Lopez et al, 2006).

In addition, a Child–Pugh score can also be assigned to hepatocellular carcinoma, which can be used to predict the prognosis and dose of required treatment. The score uses five clinical measures of liver disease, and classifies liver disease into Child–Pugh A, B or C class; patients with Child–Pugh class A liver function have the best prognosis.

Figure 1. Barcelona Clinic Liver Cancer classification treatment strategy according to staging. PEI = percutaneous ethanol injection; PS = ECOG performance status; RF = radiofrequency ablation. Adapted from Llovet et al (2003).



Treatment of hepatocellular carcinoma

Treatment strategies for hepatocellular carcinoma can be divided into four categories: surgical interventions including tumour resection and liver transplantation, locoregional procedures such as radiofrequency ablation or percutaneous ethanol injection, transarterial chemoembolization and systemic therapies. Surgical resection, liver transplantation and locoregional procedures are the only curative therapies, but only 25% of patients will present with localized disease and are therefore appropriate for such treatments (Llovet et al, 2003). Liver transplantation provides a 5-year survival rate of 60–70% in well-selected patients (Llovet et al, 2003), whereas local ablation or resection show lower rates of 50–60% owing to the high rate of tumour recurrence and metachronous primaries (Llovet and Bruix, 2003).

Most patients with newly diagnosed hepatocellular carcinoma present with invasive or metastatic disease and/or poor liver function, and have a median survival of only a few months because of the underlying liver disease and lack of effective treatment options (Bruix and Sherman, 2005). A small proportion of these patients (those with poor liver function) fulfil the hepato-oncological criteria for liver transplantation, but for the majority of these patients, palliative treatments include transarterial chemoembolization or systemic therapies. Systemic cytotoxic chemotherapy agents, however, are minimally effective in the treatment of advanced hepato-

cellular carcinoma and can have significant toxicity. Indeed, a meta-analysis conducted in 1997, which evaluated the results of 37 randomized clinical trials of systemic and regional chemotherapy in 2803 hepatocellular carcinoma patients, concluded that non-surgical therapies were ineffective or minimally effective at best (Simonetti et al, 1997).

The failure of conventional systemic cytotoxic therapies can be explained by the inherent chemotherapy resistance of hepatocellular carcinoma. This is mediated via enhanced cellular drug efflux of cytotoxic agents by hepatocellular carcinoma cells, in association with an increase in the adenosine triphosphate-binding cassette proteins, a drug transporter family containing multidrug resistance-1 (MDR1), p-glycoprotein (p-gp) and the multidrug resistance protein (MRP) (Ng et al, 2000). In addition, large hepatocellular carcinomas commonly develop areas of central necrosis, which may interfere with drug delivery to the growing tumour, and underlying cirrhosis and hepatic dysfunction complicate administration of systemic therapy as a result of pharmacokinetic properties (intrahepatic shunting, drug absorption, plasma protein binding, distribution and renal excretion).

Therefore in order to improve the outcome for patients with advanced hepatocellular carcinoma, alternatives to traditional cytotoxic chemotherapy agents are clearly needed.

Molecular hepatocarcinogenesis

The molecular pathogenesis of hepatocellular carcinoma is complex and involves genetic, epigenetic and environmental factors. As for the majority of cancers, hepatocellular carcinogenesis is a multistep process originating from cancer stem cells or from the genetic or epigenetic modification of mature hepatocytes, and ultimately leading to malignant transformation of the hepatocyte (Mishra et al, 2009). Hepatocellular carcinomas are phenotypically and genetically heterogeneous and this in turn translates to a heterogeneous disease in terms of its molecular carcinogenic mechanisms. Nearly every pathway involved in carcinogenesis is altered to some degree in hepatocellular carcinoma.

Intact signalling pathways are central to the maintenance and regulation of normal function of cells, tissue and organs, including regulation of cell apoptosis, invasion and angiogenesis. Many malignancies are caused by a disruption of such signalling pathways, which leads to overactivation of downstream regulatory genes. In hepatocellular carcinoma, the key signal transduction pathways that have been recognized as important for hepatocellular carcinogenesis include the Ras/Raf/Mek/Erk (MAPK) pathway (Huynh et al, 2003), the phosphoinositol 3-kinase (PI3k)/Akt/mammalian target of rapamycin (mTOR) pathway and the Wnt/β-catenin pathway. In addition, several growth and angiogenic factors and their receptors such as the epidermal growth factor, platelet-derived growth factor, fibroblast growth factor and vascular endothelial growth factor are known to play a crucial role in hepatocarcinogenesis and tumour cell proliferation, survival, migration and metastasis. Molecular therapeutic agents targeted at these pathways or receptors have generated significant interest over recent years, in an attempt to discover an efficacious systemic therapy for advanced hepatocellular carcinoma.

One of the most intensively studied signalling pathways in hepatocellular carcinoma, the MAPK pathway includes a cascade of phosphorylation of four major cellular kinases, Ras, Raf, mitogen-activated protein extracellular kinase (MEK) and extracellular signal-regulated kinase (ERK), and plays a key role in governing hepatocellular proliferation, differentiation and survival (Kolch, 2000). Calvisi et al (2006) showed the ubiquitous activation of the Ras/MAPK pathway in hepatocellular carcinoma, mainly as a result of loss of function of tumour suppressor genes, and of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. In addition, Raf-1 kinase is overexpressed in a high number of hepatocellular carcinoma tumours, and the Raf/MEK/ERK pathway can be activated by major aetiological factors such as HBV or HCV infection and mitogenic growth factors.

MAPK signalling is transmitted along the Ras/Raf/MEK/ERK pathway by initial recruitment of Raf-1 to the inner surface of the cell membrane by activated Ras (Beeram et al, 2005). Raf-1 then phosphorylates MEK, which subsequently phosphorylates and activates ERK downstream. Activated ERK then translocates to the cell nucleus and regulates gene expression by interacting with various transcription factors. The ligands epidermal growth factor, hepatocyte growth factor, vascular endothelial growth factor and platelet-derived growth factor, among others, activate the MAPK pathway and induce the transcription of genes involved in hepatocellular carcinoma proliferation and differentiation (Robinson et al, 2000). The most promising molecular targeted agent acting upon this pathway is sorafenib, an oral small molecule multikinase inhibitor with both antiproliferative and antiangiogenic effects.

Sorafenib

Sorafenib has multiple known protein kinase targets as identified in biochemical and cellular assays in vitro (Wan et al, 2004; Wilhelm et al, 2004). It inhibits the activity of the serine/threonine kinases c-Raf (Raf-1) and B-Raf (both wild-type and oncogenic B-Raf V600E); and the mitogen-activated protein kinases MEK and ERK. In addition it exhibits strong inhibitory activity for the receptor tyrosine kinases involved in angiogenesis and cell growth, such as vascular endothelial growth factor receptor-1, 2 and 3, platelet-derived growth factor receptor-α and β, the cytokine receptor c-KIT, the receptor tyrosine kinases Fms-related tyrosine kinase-3 (Flt-3) and RET (REarranged during Transfection), and the JAK/STAT pathway (Wilhelm et al, 2006).

In pre-clinical experiments, sorafenib had antiproliferative activity in liver cancer cell lines, and it reduced tumour angiogenesis and tumour cell signalling and increased tumour cell apoptosis in a mouse xenograft model of human hepatocellular carcinoma (Liu et al, 2006). Results of an uncontrolled phase II study involving 137 patients with advanced hepatocellular carcinoma and Child–Pugh class A or B liver function indicated that single-agent sorafenib might have a beneficial therapeutic effect. Sorafenib treatment resulted in a median overall survival of 9.2 months and a median time to progression of 4.2 months (Abou-Alfa et al, 2006). Interestingly, patients with higher phosphorylated ERK (pERK) staining in tumour biopsies had a significantly longer time to progression (178 *vs* 46 days), suggesting Raf inhibition as an important mechanism of action of sorafenib, and pERK as a potential predictive marker of response.

Based on this data, a large multicentre double-blind, randomized phase III Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol (SHARP) study was conducted (Llovet et al, 2008). In this pivotal study, sorafenib was the first agent to demonstrate a statistically significant improvement in overall survival in patients with advanced hepatocellular carcinoma. A total of 602 patients with advanced hepatocellular carcinoma, ECOG performance status 0–2 and Child–Pugh class A liver function, who had not received previous systemic therapy, were randomly assigned to placebo or sorafenib 400 mg twice a day. The primary end points of the study were overall survival and time to symptomatic progression, with secondary end points including time to radiological progression and safety.

On final analysis, the median overall survival was significantly longer in the sorafenib group (10.7 months) than in the placebo group (7.9 months) showing a 44% improvement (hazard ratio=0.69, P=0.0006), but median time to symptomatic progression did not differ significantly between the study groups (4.1 months *vs* 4.9 months, P=0.77). This may be attributed to the tool used to assess this novel outcome (Yount et al, 2002), which has been open to criticism because it was designed using outcomes from a selection of hepatobiliary and pancreatic cancer patients, the majority of whom had pancreatic cancer.

Median time to radiological progression was significantly longer in the sorafenib group (5.5 months) than in the placebo group (2.8 months), showing a 73% prolongation (hazard ratio=0.587, P=0.000007). The most common drug-related adverse events for all grades of severity in the sorafenib and placebo groups respectively included diarrhoea (39% *vs* 11%), fatigue (22% *vs* 16%), hand-foot skin reaction (21% *vs* 3%) and rash or desquamation (16% *vs* 11%).

The SHARP study was designed for regulatory approval of sorafenib in the USA, Europe and other geographical regions; subsequent to this study, in 2007 sorafenib was approved for the treatment of unresectable hepatocellular carcinoma by the US Food and Drug Administration and for the treatment of hepatocellular carcinoma by the European Medicines Agency, and became a standard of care treatment option for advanced hepatocellular carcinoma with or without vascular invasion or extrahepatic metastasis.

To achieve regulatory approval in China, a parallel study of sorafenib in patients from the Asia-Pacific region was undertaken (Cheng et al, 2009). A total of 226 patients who had not received prior systemic therapy and had Child–Pugh class A liver function were randomly assigned to receive placebo or sorafenib 400 mg twice a day. There was no predefined primary end point, but overall survival, time to progression, time to symptomatic progression, disease control rate and safety were assessed. In contrast to the SHARP trial in western countries where the main aetiologies of underlying cirrhosis were HCV and alcoholic liver disease, this trial was performed in HBV-endemic areas. Median overall survival was again significantly longer in the sorafenib group (6.5 months) than in the placebo group (4.2 months, P=0.014), but again there was no meaningful difference in time to symptomatic progression between the two groups (3.5 months *vs* 3.4 months, P=0.50). Median time to progression was significantly longer in the sorafenib group (2.8 months; range 2.63–3.58 months) than in the placebo group (1.4 months; range 1.35–1.55 months) (P=0.0005). In contrast to the SHARP trial, the most common toxicity was hand-foot skin reaction, followed by diarrhoea and fatigue.

Sorafenib has subsequently been tested in combination with conventional systemic chemotherapies or other targeted agents in order to improve outcome of unresectable hepatocellular carcinoma (Abou-Alfa et al, 2008; Del Prete et al, 2008; Shen et al, 2008). A randomized, controlled, phase II study which was presented at the American Society of Clinical Oncology (ASCO) annual conference in 2008 investigated the efficacy of doxorubicin and sorafenib in combination *vs* that of doxorubicin alone in 96 patients with advanced hepatocellular carcinoma (Abou-Alfa et al, 2008). Although the objective response rates were similar in both groups (<5%), the median overall survival for patients receiving combination therapy was 13.7 months compared with 6.5 months for those receiving doxorubicin only. Progression-free survival was 6.9 months and 2.8 months for the combination therapy and doxorubicin-only groups respectively. Further phase III studies should clarify whether this is the result of a true synergistic effect or if it represents a benefit of sorafenib in a selected subgroup of patients. In fact the median survival of 13.7 months is similar to that obtained in the subgroup of sorafenib-treated patients within the SHARP trial who were Barcelona Clinic Liver Cancer stage B (Llovet et al, 2008).

The positive results of sorafenib in advanced or metastatic hepatocellular carcinoma have opened new avenues for this agent in less advanced stages of hepatocellular carcinoma. Trials exploring the role of sorafenib as adju-

vant treatment following such curative treatment options as liver transplantation, resection and radiofrequency ablation are currently ongoing. Feun et al (2009) reported data on the use of sorafenib in hepatocellular carcinoma patients after liver transplantation at the 2009 ASCO annual conference. They concluded that the response rate and time to progression for patients treated with sorafenib for recurrent hepatocellular carcinoma after liver transplantation was similar to hepatocellular carcinoma patients without transplantation (Llovet et al, 2008). However, the majority of patients required either dose reduction or cessation as a result of toxicity and therefore a lower starting dose with dose escalation was suggested. Proposed contributing factors for toxicity included the anti-rejection drugs used for liver transplantation which might affect the pharmacokinetics of sorafenib. As the response rate of hepatocellular carcinoma to sorafenib is only very low (2–3%), it is very unlikely that sorafenib could turn out to be effective as an induction therapy to try and make an unresectable hepatocellular carcinoma resectable. However, there is a strong rationale for combining transarterial chemoembolization with sorafenib in order to enhance efficacy (Sergio et al, 2008; Strebel and Dufour, 2008), and several trials are currently underway to investigate this.

Several challenges remain despite the significant improvement that sorafenib has exerted on the treatment of patients with advanced hepatocellular carcinoma. In clinical practice the median survival of patients on sorafenib is often lower than that reported on the SHARP trial (Zhu and Clark, 2009). This may be a result of more advanced tumour stage or advanced cirrhosis. Both safety and efficacy of sorafenib in patients with more advanced cirrhosis (Child–Pugh class B/C liver function) are still unknown because 97% of the patients enrolled in the SHARP trial had underlying Child–Pugh class A liver function. However, patients with more advanced cirrhosis have only modest clinical benefit with respect to survival.

In the phase II study of sorafenib in hepatocellular carcinoma (Abou-Alfa et al, 2006), although there were no significant pharmacokinetic differences between patients with Child–Pugh class A and B liver function, the overall survival clearly differed between them (41 *vs* 14 weeks). In addition, more hyperbilirubinaemia, encephalopathy and ascites developed in patients with Child–Pugh class B liver function. The efficacy and safety of single agent sorafenib in 58 patients with either Child–Pugh A cirrhosis with poor risk factors or with Child–Pugh B or C cirrhosis was evaluated (Yau et al, 2008). Sorafenib demonstrated modest activity but with significant toxicities: 22% of patients discontinued treatment prematurely because of toxicity. In the remaining 45 patients, there were four (9%) partial responses and five (11%) with stable disease. The overall response rate was 20%. Therefore patients with advanced cirrhosis should be treated with caution until larger trials specifically looking at this population are conducted.

The Hepatobiliary UK Group, who specialize in treatment of hepatocellular carcinoma, launched national guidelines for the UK which state that sorafenib is the standard of care for patients with advanced hepatocellular carcinoma for whom no potential curative option is available (Ryder, 2009). However, sorafenib has not been approved by the National Institute for Health and Clinical Excellence for this indication. In October 2008 the National Institute for Health and Clinical Excellence began their appraisal of the clinical and cost effectiveness of sorafenib for the first-line systemic treatment of advanced hepatocellular carcinoma, and in September 2009 they issued a second appraisal consultation document, the preliminary outcome of which was that sorafenib was not recommended for this indication. The final appraisal, published in November 2009, has confirmed this position on the basis that sorafenib is not cost-effective from an NHS resource perspective, assessed in accordance with cost per quality-adjusted life year.

Conclusions

Increasing knowledge of molecular hepatocarcinogenesis has allowed the discovery of an effective systemic treatment for the management of patients with advanced hepatocellular carcinoma, after years of therapeutic nihilism because of the lack of efficacy of conventional cytotoxic chemotherapy. Sorafenib is the first agent to significantly improve overall survival for patients with advanced hepatocellular carcinoma and is now considered the standard of care in these patients. The value of sorafenib in the adjuvant setting after transplantation, resection or ablation is under investigation, with the hope of decreasing the rate of recurrence. In addition, there is a strong rationale for combining transarterial chemoembolization with sorafenib to enhance efficacy.

However, sorafenib therapy has limitations, particularly as a result of differences between patients in the SHARP trial and the majority of patients in clinical practice. There is only a preliminary picture of both safety and efficacy of sorafenib in patients with more advanced liver cirrhosis (Child–Pugh class B/C liver function). Moreover, median survival of patients with advanced hepatocellular carcinoma is often still less than 1 year, indicating the need for further research and the development of novel therapies. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Hepatocellular carcinoma is the fifth most common malignancy worldwide and the third leading cause of cancer-related death.
- The only potentially curative treatments for hepatocellular carcinoma are surgery or locoregional procedures such as radiofrequency ablation or percutaneous ethanol injection, but only a small proportion of patients are eligible for such treatments. For most patients, clinical management may include transarterial chemoembolization or systemic therapy.
- In hepatocellular carcinoma, the key signal-transduction pathways that have been recognized as important for hepatocellular carcinogenesis include the Ras/Raf/Mek/Erk pathway.
- Sorafenib, an oral small molecule multikinase inhibitor, has multiple known protein kinase targets. It inhibits the activity of the serine/threonine kinases c-Raf and B-Raf and the mitogen-activated protein kinases MEK and ERK among others.
- Sorafenib is the first agent to demonstrate a significant improvement in overall survival for patients with advanced hepatocellular carcinoma.
- In 2007 sorafenib was approved for the treatment of unresectable hepatocellular carcinoma by the US Food and Drug Administration and for the treatment of hepatocellular carcinoma by the European Medicines Agency. It is now considered the standard of care in these patients.