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Sorafenib for the Treatment of Hepatocellular Carcinoma: A Systematic Review

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Abstract

Background—Sorafenib, a drug that inhibits Raf serine/threonine kinases mediating cell proliferation and receptor tyrosine kinases involved in angiogenesis, is approved for the treatment of advanced hepatocellular carcinoma (HCC).

Aims—To explore the efficacy and safety of sorafenib for treating advanced HCC, and to identify clinical factors that might influence that efficacy and safety.

Methods—We conducted a systematic review using PRISMA guidelines to identify prospective studies on sorafenib used alone or in combination with systemic and/or locoregional anti-tumor therapies for treating advanced HCC.

Results—We identified 21 prospective trials of sorafenib treatment alone (7) or combined with other treatments (14). In randomized, placebo-controlled trials, sorafenib prolonged overall survival (OS) by 2.3 to 2.8 months, extended the time to tumor progression (TTP) by 1.4 to 2.7 months, and increased the disease control rate (DCR) by 11% to 19%. Studies with the highest percentage of hepatitis B patients showed the lowest OS and DCRs. Most studies described major side effects (diarrhea, fatigue and hand-foot syndrome) in <15% of patients, with higher rates in patients with advanced cirrhosis and those treated in combination with 5-FU drugs.

Conclusions—Sorafenib provides statistically significant, but clinically modest, improvements in OS, TTP and DCR. Patients with hepatitis B appear to have a poorer response than those with hepatitis C. The frequency of hand-foot syndrome appears to be higher when sorafenib is used in advanced cirrhosis and combined with 5-FU drugs. It is not clear that sorafenib combined with other treatments is more effective than sorafenib alone.

Keywords

sorafenib; hepatocellular carcinoma; cirrhosis; transarterial chemoembolization; systematic review

Background

Worldwide, liver cancer is the sixth most common malignancy and the third most common cause of cancer-related deaths.¹ Hepatocellular carcinoma (HCC) accounts for 85% to 90% of all primary hepatic malignancies.^{2, 3} Cirrhosis is the major risk factor for HCC, and 60% to 80% of these tumors arise in the setting of cirrhosis. The major chronic liver diseases underlying the development of cirrhosis and HCC include chronic viral hepatitis (B and C), non-alcoholic steatohepatitis, and alcoholic liver disease. In the United States, the incidence

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of HCC has increased from 1.4 cases per 100,000 in 1976–1980 to approximately 5 cases per 100,000 in 2003–2006.^{4–6} A major factor underlying this rising incidence of HCC in Americans is the increased frequency of hepatitis C infection acquired in the 1960s and 1970s due to intravenous drug use, sexual contacts, and blood transfusion in the era prior to the availability of serologic tests for the hepatitis C.⁷

HCC develops in a stepwise process that involves activation of oncogenes and inactivation of tumor suppressor genes through genetic and epigenetic alterations that develop in the setting of chronic hepatitis and cirrhosis. Alterations that cause over-activation of the Raf/MEK/ERK mitogen-activated protein (MAP) kinase signaling pathway appear to be particularly important in the development of HCC.^{8–10} The MAP kinases are serine/threonine protein kinases that normally regulate a number of important cellular activities, such as proliferation and apoptosis. Abnormalities in cellular proliferation and apoptosis are key physiologic hallmarks of malignancy.

The Raf/MEK/ERK pathway can be over-activated through a variety of mechanisms including oncogenic mutations in the upstream Ras gene¹¹; over-expression of growth factors [e.g. platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF)] and their receptor tyrosine kinases that induce Raf activation; stimulation by the hepatitis B virus protein X (HBx) and PreS2-activator large surface protein; and stimulation by hepatitis C virus core proteins via signaling intermediates.^{12–14} Once the Raf/MEK/ERK pathway is activated, it can increase cell proliferation and survival directly, and can indirectly stimulate angiogenesis by increasing the production of VEGF and PDGF.¹⁵ (Figure 1) These processes are required for tumor growth and, thus, the molecular components of the Raf/MEK/ERK signaling pathway are potential therapeutic targets for HCC.¹⁶

Sorafenib is a biaryl urea that blocks the Raf/MEK/ERK pathway by inhibiting Raf serine/threonine kinase isoforms (e.g. Raf-1, B-Raf). In addition, sorafenib also inhibits the upstream receptor tyrosine kinases that play important roles in angiogenesis including VEGFR-2, VEGFR-3, PDGFR-beta and Kit. Thus, sorafenib can induce tumor cell death and inhibit angiogenesis. Sorafenib also has been shown to induce apoptosis in several tumor cell lines through mechanisms that are not well established.^{16, 17} Proposed mechanisms include inhibition of phosphorylation of eukaryotic translation initiation factor 4E (eIF4E), which (when phosphorylated) mediates the up-regulation of a number of oncogenic proteins, and the downregulation of myeloid cell leukemia-1 (Mcl-1), an anti-apoptotic protein. Both inhibition of eIF4E phosphorylation and loss of Mcl-1 have been documented in association with sorafenib-induced apoptosis, independent of the drug's effects on the MEK/ERK pathway.¹⁸ The pro-apoptotic activity of sorafenib can be enhanced significantly by the addition of certain chemotherapeutic agents (e.g. gemcitabine) and by agents that inhibit signal transduction pathways (e.g. sirolimus, an inhibitor of the mammalian target of rapamycin (mTOR) pathway).^{19, 20} These observations suggest that the combination of sorafenib with chemotherapeutic agents or signal transduction inhibitors might have better anti-tumor activity than any of these agents given alone.²¹

Sorafenib is the first FDA-approved systemic therapy for patients with advanced HCC not amenable to treatment by surgical resection or liver transplantation. In clinical practice, sorafenib generally is not given until such patients have failed to respond to locoregional therapies such as transcatheter arterial chemoembolization (TACE). A number of prospective clinical trials have assessed the anti-HCC effects of sorafenib alone, sorafenib with systemic chemotherapy, and sorafenib with locoregional therapy. We have conducted a systematic review of these studies to answer the following questions: (1) what is the efficacy of sorafenib in treating advanced HCC using overall survival, time to tumor progression and

disease control rate as evaluating parameters? (2) What is the safety of sorafenib treatment using the rate of major (Grade 3 or 4) side effects as the evaluation parameter? (3) Does the efficacy of sorafenib treatment vary depending on gender, age, stage of cirrhosis, and etiology of the underlying liver disease (especially hepatitis B and hepatitis C)? (4) What sorafenib combined therapies have been assessed in prospective clinical trials? (5) Are there advantages of sorafenib combined treatment over sorafenib alone?

Material and Methods

Search Strategy

We followed the PRISMA recommendations for systematic literature analysis.²² We performed computer-based searches of the PubMed database²³ and the ISI Web of Science database²⁴ for clinical trials in original articles or conference abstracts between January 2000 and November 2011. We searched using combinations of the following terms: “sorafenib” or “nexavor” and “hepatocellular carcinoma” or “HCC” in the title or abstract fields. Clinical trials published in English were identified. We screened each abstract resulting from these searches for eligibility. We also examined reference lists of each selected original article or conference abstract and protocol registration system of clinical trials²⁵ to identify additional articles that might meet our eligibility requirements. Any discrepancies among reviewers were resolved by consensus discussion.

Selection of clinical trials

Article selection was determined *a priori* using the following inclusion criteria: (i) only adults were included in the clinical trial; (ii) only patients with advanced HCC were included; (iii) the study used sorafenib alone or sorafenib-based therapy combined with one or more other treatments (systemic or locoregional therapy). We excluded: (i) review articles, (ii) editorials; (iii) letters to the editor (iv) retrospective studies; (v) research protocols; (vi) duplicated records; (vii) sub-analyses of the same clinical trial; (viii) preliminary results if the final study results had been published; (ix) interim reports if the final results had been published; (x) studies including patients with other malignancies besides HCC.

Data abstraction

For the sorafenib treatment alone clinical trials, the following data were extracted from each report: publication type (original article or conference abstract) ; phase of the clinical trial; number of patients; percentage of men; median age of study participants; percentage of patients with Child Pugh score A, B or C; percentage of patients with hepatitis B or hepatitis C; overall survival (OS); time to tumor progression (TTP); disease control rate (DCR); and frequency of the three major adverse effects of sorafenib (hand-foot syndrome, diarrhea and fatigue). Extracted information for the sorafenib combined with other treatment clinical trials included all of the information extracted for the sorafenib alone trials plus information on the combined treatment regimen.

Results

Systematic Review Flow

The flow chart of the systematic review is shown in Figure 2. Our initial search yielded 133 articles including 14 from PUBMED and 119 from ISI Web of Science, clinical trial registry and relevant references. Ultimately, 21 prospective clinical trials were chosen for review including 7 of sorafenib treatment alone and 14 of sorafenib plus other treatments; sorafenib was combined with systemic chemotherapy in 9 trials and with locoregional therapy in the other 5 trials.

Studies on Sorafenib-Alone Treatment

The 7 sorafenib-alone trials, which included a total of 1,072 patients, are summarized in Table 1. Two reports described phase 3 randomized, placebo-controlled clinical trials,^{26, 27} three described phase 2 trials^{28–30} and two described phase 1 trials^{31, 32}. The percentage of male patients ranged from 71%²⁸ to 100%³². Median age ranged from 51²⁷ to 72 years²⁹. Among the five trials providing precise OS and TTP data^{26–28, 30, 31}, OS ranged from 5³⁰ to 15.6 months³¹ and TTP ranged from 3³⁰ to 5.5 months²⁶ in the patients who received sorafenib. All seven reports described DCRs, which ranged from 26 %³⁰ to 82%³¹. All seven reports described major (grade 3 or 4) adverse events [hand-foot-syndrome (HFS), diarrhea and fatigue], with wide variations in frequency among reports. In patients who received sorafenib, the frequency of HFS ranged from 3%²⁶ to 27%³¹, diarrhea ranged from 0%³¹ to 82%³², and fatigue ranged from 0%³¹ to 91%³¹.

The SHARP and Asian-Pacific^{26, 27} studies were the two highest quality reports (phase 3 randomized, placebo-controlled trials). The large majority of patients in both studies had Child A cirrhosis (95% and 97%), but the frequency of hepatitis B infection was considerably higher in the Asian-Pacific trial (71% vs. 19%). For the sorafenib and placebo groups in the SHARP trial, the OS was 10.7 vs. 7.9 months ($P<0.05$) and the TTP was 5.5 vs. 2.8 months ($P<0.05$), respectively²⁶. For the sorafenib and placebo groups in the Asian-Pacific trial, the OS was 6.5 vs. 4.2 months and the TTP was 2.8 months vs. 1.4 months, respectively²⁷.

Among the six studies that provided data on Child-Pugh scores^{26–28, 30–32}, most patients had Child A cirrhosis. The frequency of Child B patients ranged from 3%²⁷ to 52%³¹, and only one study included any patients (two) with Child C cirrhosis³⁰. It appears that the development of HFS may be more frequent in patients with Child B cirrhosis. For example, the study with highest percentage of Child B patients (52%) also had the highest rate of HFS (27%)³¹ among these seven trials. However, the large, phase II trial by Abou-Alfa *et al.*, in which 28% of the total study population of 137 patients had Child B cirrhosis, had a relatively low frequency of HFS (5%).²⁸

It appears that hepatitis B infection might adversely influence the response to sorafenib. The studies with the highest percentages of patients with hepatitis B also showed the lowest OS and DCRs. For example, the Honkong trial³⁰, which had the highest percentage of hepatitis B patients (90%), described the lowest OS (5 months) and DCR (26%). In contrast, the Japanese trial, in which 74% of patients had hepatitis C, had the longest OS (15.6 months) and the highest DCR (82%)³¹.

Among 7 studies on sorafenib-alone that provided data on OS, 3 (43%) described an OS that clearly was >10 months. Among 6 studies on sorafenib-alone that provided data on TTP, none described a TTP >6 months. Among 7 studies on sorafenib-alone that provided data on DCR, 3 (43%) described a DCR >60%.

In summary, the seven studies summarized in Table 1 show that sorafenib-alone treatment results in statistically significant, but clinically modest, improvements in OS, TTP and DCR in patient populations comprised primarily of men under age 70 who have advanced HCC with Child A cirrhosis. Very few data are available on the effects of sorafenib in women, in patients older than age 70 years and in patients with advanced cirrhosis. Patients with hepatitis B appear to have a poorer response to sorafenib-alone treatment than patients with hepatitis C, and side effects of sorafenib are frequent, especially in patients with advanced cirrhosis.

Studies on Sorafenib Combined with Other Treatments

The 14 studies on sorafenib combined with other treatments, which included a total of 470 patients, are summarized in Table 2. Ten studies were Phase 2 trials^{33–41, Pawlik}, 3 were phase 1 trials^{42–44} and one was a phase 1/2 trial⁴⁵. Nine studies used sorafenib combined with other systemic therapies^{33–39, 42, 43}, and 5 used sorafenib combined with locoregional therapies.^{40, 41, 44, 45 Pawlik} Most of the reports are relatively small case series describing preliminary results, and complete data on patient populations and outcomes often are not provided. Nevertheless, the patient populations appear similar to those of the sorafenib-alone trials, comprising predominantly men under age 70 who have advanced HCC with Child A cirrhosis. OS ranged from 7.4 months³⁸ to 13.7 months³⁷, TTP ranged from 3.7 months³⁸ to 7.6 months³⁴, and DCRs ranged from 48%³⁴ to 100 %⁴¹. There was only one randomized, controlled trial³⁷ in which patients received doxorubicin plus sorafenib or doxorubicin plus placebo. Compared to the 49 patients who received doxorubicin plus placebo, the 47 patients treated with doxorubicin and sorafenib had significantly better OS (13.7 vs. 6.5 months), TTP (6.4 vs. 2.8 months) and DCR (62% vs. 29%). Generally, the frequency of side effects described in these studies is similar to that for patients treated with sorafenib alone. However, the frequency of hand-foot syndrome was especially high in a study in which sorafenib was combined with 5-FU (55%)³⁴, and another in which sorafenib was combined with oxaliplatin and the 5-FU pro-drug capecitabine (73%)³⁶. In one study in which sorafenib was combined with tegafur (another 5-FU pro-drug), however, the frequency of hand-foot syndrome was only 9%³⁸.

Among 5 studies on sorafenib combined with other treatments that provided data on OS, 4 (80%) described an OS that was >10 months. Among 5 studies on sorafenib combined with other treatments that provided data on TTP, 4 (80%) described a TTP >6 months. Among 11 studies on sorafenib combined with other treatments that provided data on DCR, 8 (73%) described a DCR >60%.

In summary, studies of sorafenib combined with other treatments have patient populations similar to those of sorafenib-alone studies (i.e. they are comprised primarily of men under age 70 who have advanced HCC with Child A cirrhosis). The number of patients included in each study generally is considerably smaller than that of the sorafenib-alone studies. Overall, reports on sorafenib combined with other treatments describe better OS, TTP and DCR than those described in reports on sorafenib alone, but the studies are not directly comparable. The combination of sorafenib with other agents does not appear to result in inordinate toxicity, but hand-foot syndrome appears to be especially frequent when sorafenib is combined with 5-FU or some of its derivatives.

Discussion

This systematic review shows that sorafenib treatment results in statistically significant, but clinically modest, improvements in OS, TTP and DCR in patient populations comprised predominantly of men under age 70 with advanced HCC and Child A cirrhosis. In two randomized, placebo-controlled trials, sorafenib treatment prolonged OS by 2.3 to 2.8 months (from 4.2 to 6.5 months in one study²⁷, and from 7.9 to 10.7 months in the other²⁶), extended the TTP by 1.4 to 2.7 months (from 1.4 to 2.8 months in one study²⁷, and from 2.8 to 5.5 months in the other²⁶), and increased the DCR by 11% to 19% (from 16% to 35% in one study²⁷, and from 32% to 43% in the other²⁶). Uncontrolled studies of sorafenib alone have described an OS as long as 15.6 months and a DCR as high as 82% but, with no control group, the contribution of sorafenib to these outcomes is not clear.

The most frequently described side effects of sorafenib are diarrhea, fatigue and hand-foot syndrome (palmoplantar erythrodysesthesia), a troublesome condition characterized by

painful, erythematous, blistering patches and plaques that involve the palms and soles of the feet primarily. Hand-foot syndrome has been associated with a number of antineoplastic agents, especially 5-fluoruracil (5-FU) and its derivatives, and the pathogenesis is not understood⁴⁶. In most of the reports included in this systematic review, major side effects of sorafenib were described in fewer than 15% of patients. However, the frequency of adverse events varied widely among studies, with some reports describing major side effects in more than 90% of cases. Our review suggests that advanced cirrhosis might predispose to the development of hand-foot syndrome with sorafenib treatment. The study of sorafenib-alone treatment that had the highest percentage of patients with Child B cirrhosis (52%) also had the highest rate of hand-foot syndrome (27%)³¹. However, most studies included too few patients with advanced cirrhosis (i.e. Child B and C) to establish this association. Our review also suggests that hand-foot syndrome might be especially likely when sorafenib is combined with 5-FU or some of its derivatives. The frequency of hand-foot syndrome was 55% in a study in which sorafenib was combined with 5-FU³⁴, and 73% in a study in which sorafenib was combined with oxaliplatin and capecitabine, a pro-drug that is enzymatically converted to 5-FU³⁶. However, the frequency of hand-foot syndrome was not inordinately high (9%) in one study in which sorafenib was combined with tegafur, another 5-FU pro-drug³⁸.

It is not possible to establish meaningful conclusions on the safety and efficacy of sorafenib for the treatment of HCC in women, the elderly, and patients with advanced cirrhosis (Child B and C). The large majority of patients included in the reports identified by our systematic review were men under the age of 70 who had HCC associated with Child A cirrhosis. Our systematic review does suggest that patients with hepatitis B infection might have a poorer response to sorafenib treatment than patients with hepatitis C. The trial with the highest percentage of hepatitis B patients (90%) described the lowest OS (5 months) and DCR (26%)³⁰, whereas the trial with the highest percentage of hepatitis C patients (74%) had the longest OS (15.6 months) and the highest DCR (82%)³¹. Further studies that directly compare the response to sorafenib in patients who have HCC associated with hepatitis B and C are needed to establish this relationship.

Prospective studies on the treatment of HCC have evaluated the safety and efficacy of sorafenib combined with a number of systemic chemotherapeutic agents including the anthracycline antibiotic doxorubicin, pyrimidine analogues (5-FU, capecitabine, tegafur/uracil, gemcitabine), DNA crosslinking agents (mitomycin c, cisplatin, oxaliplatin), octreotide, and AVE1642 (a humanized monoclonal antibody that binds the insulin-like growth factor 1 receptor). In addition, prospective studies have evaluated sorafenib combined with TACE, in which a chemotherapeutic agent mixed with embolic material is administered through a catheter positioned in branches of the hepatic artery that supply the HCC. TACE creates a hypoxic environment for the residual tumor cells (Chan, 2002). This hypoxia stimulates those surviving cells to express VEGF, which can lead to neovascularization and reestablishment of the tumor's blood supply (Shweiki, 1992) (Li, 2003) (Lee, 2002). Thus, an anti-angiogenesis agent like sorafenib, which can inhibit VEGF receptors, seems like a good choice for combination with TACE.

In general, the reports on sorafenib combined with other treatments summarized in Table 3 describe better OS, TTP and DCR than those described in reports on sorafenib alone. However, all but one of the studies on sorafenib combined with other treatments are relatively small and uncontrolled case series, and it is not appropriate to compare the results of these studies directly with those of the sorafenib-alone studies. The only published randomized, controlled trial of combined treatment found that patients who received doxorubicin and sorafenib had significantly better OS (13.7 vs. 6.5 months), TTP (6.4 vs. 2.8 months) and DCR (62% vs. 29%) than those treated with doxorubicin and placebo. This

shows that sorafenib plus doxorubicin is better than doxorubicin alone, but does not establish that combination therapy is better than sorafenib alone. Well designed, placebo controlled studies in this area are sorely needed.

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References

1. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005; 55:74–108. [PubMed: 15761078]
2. Pons-Renedo F, Llovet JM. Hepatocellular carcinoma: a clinical update. *MedGenMed.* 2003; 5:11. [PubMed: 14600648]
3. Cancer Facts & Figures 2010. American Cancer Society; Atlanta, Georgia: 2010.
4. El-Serag HB. Epidemiology of hepatocellular carcinoma in USA. *Hepatology Res.* 2007; 37 (Suppl 2):S88–94. [PubMed: 17877502]
5. El-Serag HB, Davila JA, Petersen NJ, et al. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med.* 2003; 139:817–23. [PubMed: 14623619]
6. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med.* 1999; 340:745–50. [PubMed: 10072408]
7. NHANES III data. 2008. http://www.cdc.gov/NCIDOD/Diseases/hepatitis/c/plan/HCV_infection.htm
8. Calvisi DF, Ladu S, Gorden A, et al. Ubiquitous activation of Ras and Jak/Stat pathways in human HCC. *Gastroenterology.* 2006; 130:1117–28. [PubMed: 16618406]
9. Marotta F, Vangieri B, Cecere A, et al. The pathogenesis of hepatocellular carcinoma is multifactorial event. Novel immunological treatment in prospect. *Clin Ter.* 2004; 155:187–99. [PubMed: 15344567]
10. Avila MA, Berasain C, Sangro B, et al. New therapies for hepatocellular carcinoma. *Oncogene.* 2006; 25:3866–84. [PubMed: 16799628]
11. Goodsell DS. The molecular perspective: the ras oncogene. *Oncologist.* 1999; 4:263–4. [PubMed: 10394594]
12. Stockl L, Berting A, Malkowski B, et al. Integrity of c-Raf-1/MEK signal transduction cascade is essential for hepatitis B virus gene expression. *Oncogene.* 2003; 22:2604–10. [PubMed: 12730674]
13. Giambartolomei S, Covone F, Levrero M, et al. Sustained activation of the Raf/MEK/Erk pathway in response to EGF in stable cell lines expressing the Hepatitis C Virus (HCV) core protein. *Oncogene.* 2001; 20:2606–10. [PubMed: 11420671]
14. Shimotohno K, Watashi K, Tsuchihara K, et al. Hepatitis C virus and its roles in cell proliferation. *J Gastroenterol.* 2002; 37 (Suppl 13):50–4. [PubMed: 12109666]
15. Gollob JA, Wilhelm S, Carter C, et al. Role of Raf kinase in cancer: therapeutic potential of targeting the Raf/MEK/ERK signal transduction pathway. *Semin Oncol.* 2006; 33:392–406. [PubMed: 16890795]
16. Wilhelm SM, Carter C, Tang L, et al. BAY 43–9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res.* 2004; 64:7099–109. [PubMed: 15466206]
17. Wilhelm SM, Adnane L, Newell P, et al. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. *Mol Cancer Ther.* 2008; 7:3129–40. [PubMed: 18852116]
18. Rahmani M, Davis EM, Bauer C, et al. Apoptosis induced by the kinase inhibitor BAY 43–9006 in human leukemia cells involves down-regulation of Mcl-1 through inhibition of translation. *J Biol Chem.* 2005; 280:35217–27. [PubMed: 16109713]

19. Yu C, Bruzek LM, Meng XW, et al. The role of Mcl-1 downregulation in the proapoptotic activity of the multikinase inhibitor BAY 43–9006. *Oncogene*. 2005; 24:6861–9. [PubMed: 16007148]
20. Molhoek KR, Griesemann H, Shu J, et al. Human melanoma cytolysis by combined inhibition of mammalian target of rapamycin and vascular endothelial growth factor/vascular endothelial growth factor receptor-2. *Cancer Res*. 2008; 68:4392–7. [PubMed: 18519701]
21. Takimoto CH, Awada A. Safety and anti-tumor activity of sorafenib (Nexavar) in combination with other anti-cancer agents: a review of clinical trials. *Cancer Chemother Pharmacol*. 2008; 61:535–48. [PubMed: 18026728]
22. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009; 6:e1000097. [PubMed: 19621072]
23. <http://www.ncbi.nlm.nih.gov/pubmed>.
24. <http://www.isiknowledge.com>.
25. <https://register.clinicaltrials.gov/>.
26. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008; 359:378–90. [PubMed: 18650514]
27. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009; 10:25–34. [PubMed: 19095497]
28. Abou-Alfa GK, Schwartz L, Ricci S, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol*. 2006; 24:4293–300. [PubMed: 16908937]
29. Massa ESC, et al. Efficacy, safety and impact on quality of life of a treatment with sorafenib in elderly cancer patients with advanced hepatocellular carcinoma. Result of a phase II study. *Annals of Oncology*. 2009; 20 (Suppl 8):s65.
30. Yau T, Chan P, Ng KK, et al. Phase 2 open-label study of single-agent sorafenib in treating advanced hepatocellular carcinoma in a hepatitis B-endemic Asian population: presence of lung metastasis predicts poor response. *Cancer*. 2009; 115:428–36. [PubMed: 19107763]
31. Furuse J, Ishii H, Nakachi K, et al. Phase I study of sorafenib in Japanese patients with hepatocellular carcinoma. *Cancer Sci*. 2008; 99:159–65. [PubMed: 17953709]
32. Castroagudin JFME, et al. Short-term efficacy and safety of treatment of advanced hepatocellular carcinoma with sorafenib. *Journal of Hepatology*. 2008; 48(362 Suppl 2):s141–s142.
33. Prete SD, Montella L, Caraglia M, et al. Sorafenib plus octreotide is an effective and safe treatment in advanced hepatocellular carcinoma: multicenter phase II So.LAR study. *Cancer Chemother Pharmacol*. 2010; 66:837–44. [PubMed: 20041325]
34. Petrini ILM, et al. A phase II trial of sorafenib in combination with 5-fluorouracil continuous infusion in patients with advanced hepatocellular carcinoma: preliminary data. *Journal of clinical oncology*. 2009; 27(15 Suppl):4592.
35. Gianluca DML, et al. Prospective phase II study of combination sorafenib plus mitomycin-c in the treatment of advanced hepatocellular carcinoma. *Annals of Oncology*. 2009; 63(Suppl 8):20.
36. Yau TCP, et al. Phase II trial of sorafenib with capecitabine and oxaliplatin (SECOX) in patients with locally advanced or metastatic hepatocellular carcinoma. *EJC supplements*. 2009; 7(3):20–21.
37. Abou-Alfa GK, Johnson P, Knox JJ, et al. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. *JAMA*. 2010; 304:2154–60. [PubMed: 21081728]
38. Hsu CH, Shen YC, Lin ZZ, et al. Phase II study of combining sorafenib with metronomic tegafur/uracil for advanced hepatocellular carcinoma. *J Hepatol*. 2010; 53:126–31. [PubMed: 20416968]
39. Giuliana FAR, et al. Sorafenib plus cisplatin and gemcitabine in the treatment of advanced hepatocellular carcinoma: a phase II study by the Gruppo Oncologico Dell'Italia Meridionale. (PROT. GOIM 2705). *Cancer treatment reviews*. 2010; 36(4 Suppl):S96.
40. Erhardt AKF, et al. First-in-men demonstration of sorafenib plus TACE for the treatment of advanced hepatocellular carcinoma (SOCRATES trial). *Hepatology*. 2009; 50(4 Suppl):1080A.
41. Reyes DKAN, et al. Phase II trial of sorafenib with doxorubicin eluting bead-transarterial chemoembolization (DEB-TACE) for patients with hepatocellular carcinoma: interim safety and efficacy analysis. *Hepatology*. 2009; 50(6):6A–7A. LB9. [PubMed: 19437494]

42. Richly H, Schultheis B, Adamietz IA, et al. Combination of sorafenib and doxorubicin in patients with advanced hepatocellular carcinoma: results from a phase I extension trial. *Eur J Cancer*. 2009; 45:579–87. [PubMed: 19101137]
43. Faivre SFL, et al. Phase I safety, pharmacokinetic, and pharmacodynamic study of AVE 1642, a human monoclonal antibody inhibiting the insulin-like growth factor-1 receptor (IGF-1R/CD221), administered as single agent and in combination with sorafenib as first line therapy in patients with advanced hepatocellular carcinoma. *Hepatology*. 2010; 52(4 Suppl S):466A, 288.
44. Dufour JF, Hoppe H, Heim MH, et al. Continuous administration of sorafenib in combination with transarterial chemoembolization in patients with hepatocellular carcinoma: results of a phase I study. *Oncologist*. 2010; 15:1198–204. [PubMed: 21036880]
45. Pinter MSW, et al. An interim safety analysis of sorafenib plus transarterial chemoembolization in hepatocellular carcinoma- A phase I/II pilot study (SORATACE-1 trial). *Hepatology*. 2010; 52(4 Suppl):1157A, 1759.
46. Yang CH, Lin WC, Chuang CK, et al. Hand-foot skin reaction in patients treated with sorafenib: a clinicopathological study of cutaneous manifestations due to multitargeted kinase inhibitor therapy. *Br J Dermatol*. 2008; 158:592–6. [PubMed: 18070211]

Figure 1.

Sorafenib targets cell proliferation, apoptosis and angiogenesis. Red Xs indicate inhibition by sorafenib. Black arrows/lines indicate established pathways. Pink arrows/lines indicate proposed pathways affected by sorafenib. In tumor cells, sorafenib blocks the Raf/MEK/ERK pathway and induces apoptosis by inhibiting Raf isoforms. Sorafenib also appears to induce apoptosis through mechanisms independent of the Raf/MEK/ERK pathway including inhibition of eIF4E phosphorylation, and downregulation of Mcl-1. In vascular endothelial cells, sorafenib inhibits receptor tyrosine kinases involved in angiogenesis including VEGFR and PDGFR.

Figure 2.
Trial selection flow

Table 1

Trials of treatment with sorafenib alone

Ref.	Phase of trial	No. of patients	Male (%)	Median age (years)	CPS (A/B/C %)	Etiology (HBV/HCV %)	OS (months)	TTP (months)	DCR (%)	AE (HFS/diarrhea/fatigue %)
[26]	3 (RPC)	Sor 299 PI 303	87	65	95/5/0	19/29	10.7	5.5	43	3/1/3
[27]	3 (RPC)	Sor 150 PI 76	87	66	98/2/0	18/27	7.9	2.8	32	0.3/1/0.6
			85	51	97/3/0	71/11	6.5	2.8	35	11/6/3
			87	52	97/3/0	78/4	4.2	1.4	16	0/1/0
[28]	2	137	71	69	72/28/0	17/48	9.2	4.2	36	5/8/10
[29]	2	16	88	72	NR	NR	>15	>3	64	6/6/6
[30]	2	51	88	56	71/26/3	90/6	5.0	3.0	26	16/20/8 ^a
[31]	1	27	93	70	48/52/0	15/74	15.6	4.9	82	27/0/0
[32]	1	13	100	64	92/NR/NR	0/23	>2	NR	62	18/82/91 ^a

AE, adverse effects grade 3/4; CPS, Child–Pugh score; DCR, disease control rate; HFS, hand–foot syndrome; OS, overall survival; PI, placebo; RPC, randomized placebo-controlled; Sor, sorafenib; TTP, time to tumor progression; NR, not reported

^a Adverse effects of all grades

Table 2

Trials of sorafenib combined with other treatment

Ref.	Phase of trial	Regimen	No. of patients	Male (%)	Median age (years)	CPS (A/B/C %)	Etiology (HBV/HCV %)	OS (months)	TTP (months)	DCR (%)	AE (HFS/diarrhea/fatigue %)
[36]	2 (RPC)	Dox ? Sor	47	66	66	100/0/0	NR	13.7	6.4	62	6/11/6
		Dox ? PI	49	86	65	96/4/0	NR	6.5	2.8	29	0/8/6
[33]	2	Oct ? Sor	50	86	NR	78/22/0	68/22	11.0	7.0	78	2/5/2
[34]	2	5FU ? Sor	38	84	68	92/8/0	NR	12.2	7.6	48	55/13/NR
[35]	2	Mit-c ? Sor	22	NR	NR	NR	NR	NR	NR	77	NR
[35]	2	Cap ? Oxa ? Sor	51	NR	58	98/NR/NR	84/NR	10.2	7.1	75	73/69/NR
[37]	2	TU ? Sor	53	89	57	100/0/0	72/25	7.4	3.7	57	9/2/15
[38]	2	Cis ? Gem ? Sor	11	77	67	NR	NR	NR	NR	63	13/13/NR
[39]	2	TACE ? Sor	38	NR	NR	NR	NR	NR	NR	NR	20 Overall
[40]	2	TACE ? Dox ? Sor	19	NR	65	95/NR/NR	NR	NR	NR	100	NR
[45]	2	TACE ? DEB ? Sor	35	74	63	89/11/0	6/37	NR	NR	95	21/0/36
[44]	1 and 2	TACE ? Sor	12	83	71	92/8/0	NR	NR	NR	58	58 Overall
[42]	1	AVE1642 ? Sor	13	77	70	100/0/0	NR	NR	NR	77	NR
[41]	1	Dox ? Sor	18	94	56	NR	NR	NR	NR	69	11/17/22
[43]	1	TACE ? Sor	14	78	64	93/7/0	0/29	NR	NR	NR	21/7/NR

AE, adverse effects; Cap, capecitabine; Cis, cisplatin; CPS, Child–Pugh score; DCR, disease control rate; DEB, doxorubicin-elutingbeads; Dox, doxorubicin; Gem, gemcitabine; HFS, hand–foot syndrome; Mit–c, mitomycin–c; Oct, octreotide; OS, overall survival; Oxa, oxaliplatin; PI, placebo; RPC, randomized placebo-controlled; Sor, sorafenib; TTP, time to tumor progress; TU, tegafur/uracil; NR not reported