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Sorafenib in the Continuum of Care for Hepatocellular Carcinoma: Challenges in Defining Optimal Practice

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1. Introduction

Globally, liver cancer represents a major health care burden, accounting for almost 700,000 deaths annually. [1] Hepatocellular carcinoma (HCC) comprises 70% to 85% of primary liver cancers in most regions. [2] Although the incidence of HCC has historically been lower in the US than in many other countries, age-adjusted rates tripled between 1975 and 2005. [3] In fact, liver cancer is the fastest-growing cause of cancer-related death in American men. [4] Most patients with HCC are diagnosed at advanced stages and are ineligible for potentially curative treatments such as surgical resection and liver transplantation. [5] Prior to the introduction of sorafenib in 2007, systemic treatments were unavailable for patients with HCC.

In defining optimal treatment for patients with HCC, several questions remain unanswered. Clinical data are needed to evaluate sorafenib safety in patients with advanced liver disease (i.e., those with Child-Pugh [CP] B disease) and in those with HCC-associated portal hypertension. In addition, how best to utilize sorafenib in combination with sequential locoregional therapies (LRT) or post-surgery remains unclear. These challenges are further compounded by the ongoing uncertainties in determining the value of the modified Response Evaluation Criteria In Solid Tumors (mRECIST) and understanding the optimal timing for response assessment in patients treated with sorafenib and/or LRT. Proactive management of adverse events (AEs) associated with sorafenib also remains an area of active investigation. Finally, although sorafenib has demonstrated a clear benefit to patients with advanced HCC, the majority of patients will ultimately experience disease progression. Efforts are underway to evaluate the best approaches to treating these patients in a manner that minimizes the risk of mortality from deterioration of the underlying liver disease. In this review, we describe the current understanding of sorafenib’s efficacy and safety, and ongoing approaches to defining even better treatment options for patients with HCC.
2. Late-phase clinical development of sorafenib for unresectable, advanced HCC: Pivotal trials and subanalyses

Clinical trial design in HCC is challenging owing to the complex nature of the disease. The coexistence of cancer, liver disease, and other comorbidities, and the prior or concomitant use of locoregional therapies make selection and recruitment of an appropriately homogeneous patient cohort difficult. Geographical heterogeneities in disease etiology, patient characteristics, and practice patterns are significant and contribute to the need for, and confound, multi-institutional studies.

Both pivotal trials of sorafenib, the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) and Asia-Pacific (AP), were designed to elucidate the effect of the drug in a specific population of patients with preserved liver function (CP A). In these trials, sorafenib produced a significant survival advantage over placebo in patients with advanced HCC; these results led to regulatory approval of sorafenib [6,7] (Table 1).

In subanalyses of these pivotal trials, the safety profile of sorafenib was similar regardless of baseline liver function. In the SHARP trial, sorafenib treatment consistently improved overall survival (OS), time to progression (TTP), and disease control rate (DCR) irrespective of Eastern Cooperative Oncology Group performance status (ECOG PS); tumor burden, as evidenced by macroscopic vascular invasion or extrahepatic spread; tumor stage (Barcelona Clinic Liver Cancer [BCLC] stage B or C); prior curative treatments (including surgery, radiofrequency ablation, or percutaneous ethanol injection); or prior transarterial chemoembolization (TACE) [8] (Figure 1). However, patients with tumors confined to the liver, with no vascular invasion or metastases, had better outcomes. Substantially similar results were obtained in subanalyses of the AP trial, with the exception of patients with ECOG PS 0, who had a slightly reduced OS in the sorafenib treatment group [9] (Figure 2). In both studies, sorafenib also improved OS over placebo irrespective of baseline serum alanine aminotransferase/aspartate aminotransferase, alpha-fetoprotein (AFP), and bilirubin levels. [9, 10] Notably, in the SHARP trial, hepatitis B virus (HBV) surface antigen positivity was associated with a longer median OS but shorter TTP in patients treated with sorafenib; however, DCR was similar in sorafenib- and placebo-treated groups.

It is interesting to note that in the SHARP trial, patients positive for HCV antibody derived more benefit from sorafenib treatment than patients with other etiologies [8] (Figure 1). Consistent with this notion, preclinical data suggest that sorafenib may inhibit Raf-dependent HCV replication and HCV-induced increases in vascular endothelial growth factor (VEGF) expression. [11, 12] However, in a small clinical study in 33 HCV-infected patients, viral load was not reduced during treatment, even among those who showed a tumor response; notably, VEGF levels were not measured. [13]
| Study Phase N | Treatment Schema | Patient Population | Efficacy Results | Safety Results |
|--------------|------------------|--------------------|------------------|---------------|
| Llovet [7]   | Phase 3          | 400 mg BID continuous SOR vs PBO | CP: A, 97%; B, 3% (BCLC stage: B, 17%, C, 82%)<br>ECOG PS: 0, 54%; 1, 38%; 2, 8%<br>Hepatitis virus status: HBV, 18%; HCV, 28% | Median OS: 10.7 mo SOR vs 7.9 mo PBO; HR 0.69 (95% CI 0.55-0.87; P<.001) | Gr 3/4 drug-related AEs (SOR vs PBO):<br>HFSR: 8% vs <1%; Fatigue: 4% vs 3-4% (P<0.001) |
| CHENG [6]    | Phase 3          | Randomized 2:1 to CP: A, 97%; B, 3% (BCLC stage: C, 96%)<br>ECOG PS: 0, 26%; 1, 69%; 2, 5%<br>Hepatitis virus status: HBV, 73%; HCV, 8% | Median OS: 6.5 mo SOR vs 4.2 mo PBO (HR 0.68 [95% CI 0.50-0.93]; P=0.014) | Median TTP: 2.8 mo SOR vs 1.4 mo PBO (HR 0.57 [95% CI 0.42-0.79]; P=0.005) | Gr 3/4 drug-related AEs (SOR vs PBO):<br>HFSR: 11% vs 0%; Fatigue: 3% vs 1% |
| Lencioni [15]| Phase 4          | Prospective, non-interventional study of pts with unresectable HCC treated with SOR | CP: A, 61%; B, 23%; C, 2% (BCLC stage: A, 7%; B, 19%; C, 54%; D, 6%<br>ECOG PS: 0, 40%; 1, 43%; 2, 9%, 3-4, 3%<br>HCC etiology: HBV, 37%; HCV, 32%; alcohol, 29% | Median OS by initial dose: 400 mg/d: 7.1 mo (95% CI 5.8-8.1)<br>800 mg/d: 9.3 mo (95% CI 8.6-10.2) | Median TTP by initial dose: 400 mg/d: 3.6 mo (95% CI 2.8-4.1)<br>800 mg/d: 4.5 mo (95% CI 4.1-5.1) | Drug-related serious AEs: 9% (SOR discontinuation: 28%) |

AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; BID, twice daily; CI, confidence interval; CP, Child-Pugh; CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; GIDEON, Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and Of Its Treatment with Sorafenib; gr, grade; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HFSR, hand-foot skin reaction; HR, hazard ratio; OS, overall survival; PBO, placebo; PD, progressive disease; PR, partial response; pt, patient; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SHARP, Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol; SOR, sorafenib; TTP, time to progression

Table 1. Key phase 3 and phase 4 trials evaluating the safety and efficacy of sorafenib in advanced HCC
BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; MVI, macroscopic vascular invasion; OS, overall survival; TACE, transarterial chemoembolization.

Figure 1. Median survival in the SHARP trial population overall and by subgroups. [8] *Includes 1 sorafenib-treated patient with BCLC D. **Resection/local ablation, percutaneous ethanol injection, or radiofrequency ablation.

Figure 2. Median survival in the AP trial population overall and by various subgroups. [9]

ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HBV, hepatitis B virus; MVI, macroscopic vascular invasion; OS, overall survival; TACE, transarterial chemoembolization.
3. Understanding sorafenib efficacy and safety in advanced liver disease

The Global Investigation of Therapeutic DEcisions in Hepatocellular Carcinoma and Of its Treatment with SorafeNib (GIDEON) was initiated in 2009 as a global, prospective, post-marketing non-interventional study to further evaluate the safety of sorafenib in patients with unresectable HCC and CP B liver function. This study of more than 3000 patients was designed to assess a variety of patient subsets under real-life practice conditions. [14] At a second interim analysis in 2011, grade ≥3 AEs and drug-related serious AEs were similar across BCLC stages and were consistent with those reported in the SHARP and AP trials (i.e., hand-foot skin reaction [HFSR], diarrhea, fatigue). [15, 16] The GIDEON data are consistent with those from another study by Abou-Alfa and colleagues, who observed comparable AE rates in CP A and CP B patients with the exception of all-grade elevated bilirubin levels (67% vs 86%, respectively), grade ≥3 hyperbilirubinemia (14% vs 53%, respectively), and grade ≥3 encephalopathy (3% vs 13%, respectively). [17]

In both the GIDEON second interim analysis and the study by Abou-Alfa, patients with CP B status exhibited shorter median OS compared with patients with CP A, supporting the prognostic significance of this classification. [17, 18] Nonetheless, data suggest that CP B patients derive benefit from sorafenib. A retrospective study compared the outcomes of 148 patients with unresectable HCC treated with sorafenib to those of a similar cohort of 78 patients receiving best supportive care (BSC). [19] Sorafenib significantly extended the median OS over BSC in patients with CP A (11.3 vs 6.4 months, respectively; \(P=0.01\)) and patients with CP B (5.5 vs 1.9 months, respectively; \(P=0.02\)). An ongoing randomized phase 3 trial (BOOST, NCT 01405573) comparing sorafenib plus BSC to BSC in patients with CP B will further explore efficacy outcomes in this population; this study is estimated to be completed in March 2014.

4. Trials comparing sorafenib to other potential first-line agents in advanced HCC

The American Association for the Study of Liver Diseases (AASLD) recommends sorafenib for the treatment BCLC stage C disease, [20] and it remains the only approved systemic treatment for unresectable HCC. Although several other targeted therapies have been investigated, to date, none have improved on the outcomes of sorafenib in randomized controlled trials. Cheng and colleagues compared sunitinib and sorafenib in 1073 patients with advanced HCC similar to those in the SHARP and AP trials. [21] Although TTP was comparable, sorafenib-treated patients experienced significantly longer OS (10.0 vs 8.1 months; \(P=0.002\)) than sunitinib-treated patients, possibly due to greater sunitinib-related toxicity, and the trial was terminated early. Employing a non-inferiority statistical design, a recent trial comparing first-line brivanib to sorafenib in advanced HCC (BRISK-FL; N=1155) did not meet its primary OS objective. [22] A phase 3 study evaluating linifanib and sorafenib in CP A patients with advanced HCC (N=1035) failed to show an advantage for linifanib in this setting. [23] OS was 9.8 and 9.1 months in sorafenib- and linifanib-treated patients, respectively. Although secondary end-
points of TTP and overall response rate favored treatment with linifanib, sorafenib was better tolerated in this study population.

| Agent   | Molecular Targets                                                                 |
|---------|----------------------------------------------------------------------------------|
| Sorafenib | BRAF, mutant BRAF, CRAF, FLT3, KIT, PDGFRβ, RET, VEGFR1, VEGFR2, VEGFR3 [70]   |
| Sunitinib | CSF1R, FLT3, PDGFRα, PDGFRβ, RET, VEGFR1, VEGFR2, VEGFR3, KIT [71]             |
| Brivanib  | FGFR1, VEGFR [72]                                                               |
| Linifanib | CSF1R1, FLT3, KIT, PDGFRβ, VEGFR1, VEGFR3 [73]                                   |
| Dovitinib | CSFR1, FGFR1, FGFR2, FGFR3, FLT3, KIT, PDGFRβ, RET, TrkA, VEGFR1, VEGFR2, VEGFR3 [74] |
| Nintedanib | FGFR1, FGFR2, FGFR3, FGFR4, PDGFRα, PDGFRβ, VEGFR1, VEGFR2, VEGFR3 [75]     |

CSF1R, colony-stimulating factor 1 receptor; FGFR, fibroblast growth factor receptor; HCC, hepatocellular carcinoma; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

It is remarkable that despite significant overlap in molecular target specificity — particularly the VEGF receptors (Table 2) — none of these agents have, as yet, demonstrated superior OS benefit compared with sorafenib. One explanation may be that a unique molecular activity of sorafenib accounts for its consistently improved benefit. For example, among these agents, sorafenib is the only reported inhibitor of BRAF; overexpression of Raf1 has been detected in 49-100% of HCC biopsies and is an independent risk factor for death [24, 25] (Table 2). It is also possible that tolerance of sorafenib is a factor in improving OS or that the clinical trial designs (e.g., dosing, patient criteria) were suboptimal for demonstrating comparator activity. Two additional agents, dovitinib and nintedanib (BIBF1120), which have significant activity against fibroblast growth factor receptor, are currently being evaluated as first-line agents in phase 2 trials (NCT01232296, NCT01004003).

5. Addressing HCC management dilemmas: Ongoing studies

The introduction of sorafenib has unveiled a number of new challenges in the real-world setting. Patient management is complicated by the concurrence of underlying hepatic dysfunction. Given the complexity of managing both liver cancer and hepatic impairment, the value of a multidisciplinary approach to HCC care has become increasingly apparent. Patients may have undergone or be candidates for procedures such as TACE, surgery, or radiofrequency ablation. Questions remain as to whether sorafenib use is safe and beneficial in these settings and when it should be used in the continuum of care. Similar questions arise in the
context of transplantation. Compounding these scientific quandaries is the fact that these patients may initially be seen by surgeons or interventional radiologists, who typically do not prescribe oncology medications. By the time patients are evaluated by an oncologist or hepatologist, clinical deterioration may prohibit the initiation of sorafenib therapy. Moreover, while institutional standards exist with respect to implementation of these procedures, substantial regional variations occur, making clinical trial design difficult. Significant challenges persist in defining appropriate response guidelines (e.g., RECIST) for specific therapies [26] and in defining the role of sorafenib in the treatment of patients with HCC progression.

5.1. Combination with locoregional therapy

The rationale for combining sorafenib with TACE is to mitigate the VEGF surge in response to hypoxemia associated with embolization of the hepatic artery supplying the tumor. [27, 28] Because increased circulating VEGF post-TACE has been linked to more aggressive disease, [29] blocking angiogenesis following embolization is hypothesized to improve outcomes and provides rationale for further studies.

Two large placebo-controlled studies evaluated the efficacy and safety of sorafenib combined with TACE. The first trial (N=458) evaluated sorafenib in Japanese and Korean patients with unresectable HCC, good performance status (88% ECOG PS 0), preserved liver function (100% CP A), and prior radiologic response to TACE. [30] The median time from TACE to initiating treatment with sorafenib was 9.3 weeks. This interrupted sequencing did not significantly prolong OS or median TTP (5.4 and 3.7 months in the sorafenib and placebo groups, respectively). Hypothetically, the delay between TACE and sorafenib initiation and the relatively low daily dose of sorafenib (median 386 mg, range 112-794.5 mg) may have contributed to the lack of superiority for combined treatment. Notably, significant differences in outcomes were observed among patient groups stratified by geographic region, likely reflecting regional variations in HCC treatment.

Sorafenib may exert its greatest benefit when administered before or concurrent with TACE treatment. The second trial, Sorafenib or Placebo in combination with transarterial chemoembolization with doxorubicin-eluting beads for intermediate-stage HCC (SPACE), examined this strategy. This global phase 2 study randomized 307 patients (CP A, ECOG PS 0) with intermediate-stage HCC to TACE with doxorubicin-eluting beads (DEB-TACE) plus sorafenib or placebo. DEB-TACE was administered 3-7 days after initiating sorafenib or placebo and subsequently on the first day of cycles 3, 7, and 13, and every 6 cycles thereafter. [31] While TTP was similar between the DEB-TACE/sorafenib and DEB-TACE/placebo arms, interpretation of the results is limited by the study design (scheduled DEB-TACE treatments are not routinely employed in clinical practice) and challenges inherent with assessing response to locoregional therapies. A third, single-center, phase 2 randomized controlled study (N=80) examined TACE with or without sorafenib exclusively in HCV-infected patients. [32] In this study, in which sorafenib was administered 30 days after TACE, TTP was significantly delayed in the sorafenib-treated group (9.2 months vs 4.9 months; \(P=.001\)). This result is interesting in light of the SHARP trial results in which patients with HCV may have derived more benefit from sorafenib treatment than patients with other HCC etiologies.
Several additional trials are currently recruiting patients to evaluate the combined use of LRT and sorafenib. A phase 3 (N=412) TACE-2 trial (NCT01324076) is examining the benefit of initiating sorafenib treatment 2-5 weeks prior to DEB-TACE. Patients may undergo further TACE based on their clinician’s evaluation. Another phase 3 (N=400) trial, ECOG 1208 (NCT01004978), will also evaluate initiating sorafenib prior to TACE, with TACE treatment occurring every 4 weeks with up to 4 courses of treatment. In this trial, the TACE protocol may use conventional chemoembolization comprising doxorubicin hydrochloride only or DEB-TACE. Finally, the phase 3 (N=400) STOP-HCC trial (NCT01556490) is evaluating the use of radioembolization followed 30 days later by sorafenib (R. Salem, personal communication). The large number of trials assessing the combination of LRT with sorafenib attests to the perceived potential of this approach. However, the wide variations in trial design underscore the difficulties in evaluating the true benefit of this combination. Variations in the timing of sorafenib dosing and the type of LRT (conventional TACE, DEB-TACE, or radioembolization) and frequency employed, coupled with a lack of reliable standardized methods for evaluating response, make trial design and treatment decision-making very challenging.

5.2. Is there a potential role for adjuvant sorafenib?

Despite intervention with potentially curative resection or ablation, HCC recurrence remains at 15-20% annually, with the 5-year recurrence rate reaching 80-90%. [33] Addressing residual disease and preventing or delaying recurrence remain key unmet needs; proven adjuvant therapies do not yet exist. A phase 3 randomized, double-blind, placebo-controlled study of sorafenib as an adjuvant treatment after surgical resection or local ablation (STORM: NCT00692770) is underway. If sorafenib can substantially delay HCC recurrence, survival may be impacted in a clinically meaningful way.

5.3. Could neoadjuvant sorafenib facilitate surgery or transplantation?

Liver transplantation is the accepted best curative option for HCC patients meeting the Milan criteria. However, organ availability is limited, and in one study, dropout while on the waiting list was found to be the sole prognostic factor in patients selected for orthotopic liver transplantation (OLT). [34] Sorafenib may represent a potential “bridge” option for patients awaiting OLT. Evaluating the benefit of sorafenib treatment in the transplant setting faces many of the same hurdles as for TACE, especially with respect to when it should be used in the continuum of care. Using a sensitivity analysis, one study showed that neoadjuvant sorafenib improved survival over no therapy, providing a cost benefit in T2-HCC patients waiting for liver transplant for ≤6 months; however, further safety assessments in the pre-transplant population are needed. [35]

In a pilot cohort study (N=33) of patients undergoing liver transplantation for HCC, overall death rates were similar between sorafenib-treated patients and controls (20% vs 9%, respectively; *P*=NS). [36] Despite the small sample size, the incidence of post-transplant biliary complications (67% vs 17%, respectively; *P*=.01) and acute cellular rejection (67% vs 22%, respectively; *P*=.04) were significantly higher in the sorafenib group than in controls. Notably, in this study, sorafenib was continued until the day of transplant. Some practitioners recom-
mend that sorafenib be discontinued before a surgical procedure due to potential risks for bleeding, impaired wound healing, and liver dysfunction in the perioperative period. [37] However, limited notice of organ availability challenges the ability to implement defined and controlled pre-transplant regimens. Consequently, patients may be required to remain off therapy for a protracted period of time, with the impact on HCC recurrence unknown.

In another study, investigators reviewed 59 consecutive HCC patients (10 treated with sorafenib and 49 controls) who underwent liver transplantation at a single center and concluded that pre-transplant sorafenib did not increase the rate of surgical complications. [38] The frequency of post-transplant AEs, including biliary complications, strictures, wound infection, and bleeding, was similar in both groups.

Two case reports describe successful outcomes associated with sorafenib followed by curative treatment for HCC. In one report of two patients with locally advanced HCC with portal vein thrombosis (PVT), neoadjuvant sorafenib administered for 10 and 12 months, respectively, produced sufficient tumor shrinkage to reverse PVT, normalize alpha-fetoprotein (AFP), and enable curative surgical resection. In both patients, sorafenib was stopped one week prior to surgery without post-operative complications. [39] However, in the SHARP and AP trials, response rates were <5%; therefore, chances of consistently downsizing HCC are very slim, and multimodality therapies need to be studied in this setting. In another report, a patient with relapsed HCC following hepatic resection was treated for 5 months prior to salvage transplant without complications. Three months after transplant (at the time of the report), the patient had normal liver function and no evidence of recurrence. [40]

5.4. Sorafenib in the post-transplant setting

Only a few small studies have addressed treatment options for post-transplant HCC recurrence. Preliminary data from a phase 1 trial show that sorafenib treatment in high-risk HCC patients post-transplant is feasible, with no dose-limiting toxicities to date; 12 patients have received sorafenib (200 mg once daily [QD] escalating thus far to 400/200 mg QD) for a median 167 days (range 21-170 days) and 3 patients experienced HCC recurrence. [41]

In a retrospective case-controlled study of 17 patients outside Milan criteria who underwent OLT, adjuvant or palliative sorafenib was administered to 5 and 6 patients, respectively. Patients treated adjuvantly demonstrated significantly improved disease-free survival at 6 months (100% vs 37.5%, \(P=.034\)), 12 months (66.7% vs 9.4%, \(P=.026\)), and 18 months (68% vs 0%, \(P=.011\)). All 5 patients treated with adjuvant sorafenib were alive at 24 months, while OS for patients treated with palliative sorafenib was 66.7% at 12 months (vs 40% for controls, \(P=.248\)) and 50% at 18 months (vs 20%, \(P=.17\)). [42]

In a single-center retrospective analysis of 24 patients with HCC recurrence post-transplant, treatment with sorafenib (N=8) for disseminated disease outside the liver produced a mean OS of 6.7 months (95% confidence interval [CI], 4.8-8.6). [43] These data require confirmation through further study with larger cohorts and a more rigorous trial design. A randomized phase 2 trial (N=356) of sorafenib versus placebo in high-risk patients after liver transplant.
(NCT01624285) is ongoing; 2-year recurrence-free survival (RFS) is the primary endpoint, with secondary endpoints of OS, safety, and RFS at 1 year.

5.5. Potential for combination with other targeted systemic therapies

Although sorafenib significantly improves OS in patients with advanced HCC, patients ultimately experience disease progression. Disease progression may result from the lack of inhibition of, or compensatory activation of, alternate signaling pathways that promote tumor regrowth. Adjunct treatment with other systemic agents may provide additive or synergistic effects. Table 3 summarizes several phase 2 and 3 trials examining combinations of sorafenib with inhibitors of HMG-CoA reductase, mTOR, and angiopoietins-1 and -2 in the first-line setting. SEARCH (Sorafenib and Erlotinib, a rAndomized tRial protocol for the treatment of patients with Hepatocellular carcinoma) (N=720) compared the efficacy of sorafenib plus the epidermal growth factor receptor inhibitor erlotinib with sorafenib alone. This trial did not achieve its primary endpoint of a 33% improvement in OS (9.5 vs 8.5 months, \( P=0.204 \)). [44]

5.6. Sorafenib benefit in portal hypertension remains controversial

Preliminary data suggest a beneficial effect of sorafenib on portal hypertension (PHT) in patients with cirrhosis and HCC. [45, 46] Increased splanchnic circulation combined with increased hepatic vascular resistance and hyperperfusion are the principal mechanisms leading to PHT. Angiogenesis is crucial in mediating increased splanchnic blood flow, and the ability of sorafenib to inhibit angiogenesis may account for the observed effects. This finding may be most relevant in patients with an HCV etiology due to a higher frequency of coexisting cirrhosis and PHT, but additional studies are needed to confirm a benefit in this setting.

5.7. Optimization of sorafenib therapy and patient selection

Prognostic HCC staging may be used for (1) predicting survival; (2) guiding therapy decisions; and (3) stratifying patients in clinical trials. Unlike other cancers, risk factors and underlying chronic liver disease (CLD) in HCC patients may have a greater impact on OS than tumor biology. This syndrome of “two diseases” directly affects patient survival, which in turn influences prognostic stratification in clinical trials and clinical decision-making. Therefore, HCC staging systems generally consider multiple prognostic factors related to CLD status and tumor stage.

The CP score is the standard assessment for classifying liver function in HCC patients. BCLC tumor staging, which also serves as a treatment algorithm, is most commonly used in the US and Europe. BCLC staging is endorsed by the AASLD and the European Association for the Study of the Liver and is most commonly used in therapeutic decision-making and in clinical trials. The prognostic power of the BCLC and other staging systems may potentially be improved by incorporating criteria based on plasma concentrations of biologic factors related to liver reserve and tumor biology.
| Study phase | Study identifier | Title | Secondary agent | Secondary agent target | Primary/secondary outcome measures |
|-------------|------------------|-------|-----------------|------------------------|-----------------------------------|
| Phase 3     | NCT01075555      | Randomized Phase III Trial Sorafenib-Pravastatin Versus Sorafenib Alone for the Palliative Treatment of CP A Hepatocellular Carcinoma | Pravastatin | HMG-CoA reductase | OS/PFS, TTP, QOL |
| Phase 2     | NCT01005199      | Sorafenib Alone or in Combination With Everolimus in Patients With Unresectable Hepatocellular Carcinoma. A Randomized Multicenter Phase II Trial. | Everolimus | mTOR | PFS/OR, DS, PFS, TTP, OS |
| Phase 2     | NCT01687673      | Phase II Trial of the Combination of Temsirolimus and Sorafenib in Advanced Hepatocellular Carcinoma | Temsirolimus | mTOR | TTP/RR, PFS, OS, TTF |
| Phase 2     | NCT01418729      | Phase-II, Multicenter, Randomized, Double-Blind, Parallel-Group Trial to Compare the Efficacy and Safety of Sorafenib Plus Pravastatin Against Sorafenib Plus Placebo in Patients With Advanced Hepatocellular Carcinoma | Pravastatin | HMG-CoA reductase | OS/TTP, TTSP |
| Phase 2     | NCT00872014      | Phase 2 Open-label Multi-Center Study to Evaluate the Efficacy and Safety of AMG 386 and Sorafenib as First Line Therapy for Subjects With Advanced or Inoperable Hepatocellular Carcinoma | AMG386 angiopoietins -1 and -2 | - | PFS/OR, DCR, OS, TTP |

CP, Child-Pugh; DCR, disease control rate; DS, disease stabilization; OR, objective response; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RR, response rate; TTF, time to treatment failure; TTP, time to progression; TTSP, time to symptomatic progression

Table 3. Prospective ongoing clinical trials evaluating sorafenib in combination with other agents in the first-line setting.
In clinical studies, plasma levels of angiopoietin-2, VEGF, hepatic growth factor (HGF), insulin-like growth factor (IGF)-1, and IGF-2 have shown prognostic value. In the SHARP study population, 10 plasma biomarkers implicated in HCC pathogenesis were measured in 491 patients at baseline and 305 patients after 12 weeks of treatment. VEGF and ang2 were found to be strong, independent predictors of survival. Similar results were demonstrated in other studies in which elevated expression of angiopoietin-2 and upregulation of its mRNA in HCC tissues were associated with advanced pathologic features and poor outcome. Elevated HGF was also found to be indicative of poor prognosis, though its significance was not retained in multivariate modeling. Kaseb et al have found that integrating plasma IGF-1 as an indicator of liver reserve and VEGF as a measure of tumor burden improves the prognostic stratification of BLCL stage C patients. These results represent promising steps in improving patient stratification but will require further validation.

Biomarkers predicting response to sorafenib have yet to be identified. In the SHARP analysis, low baseline HGF or high baseline s-c-KIT levels were independent predictors of survival in sorafenib-treated patients but showed only a non-significant trend as predictors of response. In another study, an AFP response (>20% decline over baseline) at 6 weeks was associated with improvements in clinical benefit and PFS, and marginally improved OS. Ueshima et al reported that a ≥2-fold increase in serum des-γ-carboxyprothrombin (DCP) at 2 weeks was observed in HCC patients with significantly extended TTP (P=.029). However, the use of this marker is confounded by the fact that chronically elevated DCP levels are associated with poorer prognosis. Finally, preliminary data indicate that reductions in carbonic anhydrase-9 at 1 month after initiating sorafenib may be associated with delayed disease progression (P=.031). Identifying and validating predictive biomarkers of response to sorafenib has been challenging, at least in part, because markers explored to date are not directly affected by sorafenib, and their levels often reflect a combined measure of tumor response and liver reserve.

Studies suggest that AEs occurring during sorafenib treatment may provide prognostic and predictive information. In a single-center prospective study of 40 Asian, predominantly HBV-positive patients with unresectable HCC, the presence of any AE was associated with longer OS than the absence of an AE (21.5 vs 7.6 months, respectively; P=.014) and was also predictive of stable disease (hazard ratio [HR] 0.345 [95% CI 0.991-0.120]; P=.048). In a retrospective study of 112 sorafenib-treated patients with advanced HCC, the onset of diarrhea was an independent predictor for prolonged OS (14.1 vs 7.1 months, P=.011, HR 0.41; P=.001), whereas, the occurrence of HFSR was not associated with prolonged OS or TTP. In contrast, in a retrospective study of 65 sorafenib-treated patients, multivariate analysis found that those developing any-grade HFSR or a rash within 1 month of initiating treatment demonstrated a markedly reduced risk of progression (median TTP, 8.1 vs 4.0 months for patients without skin toxicity; P=.006).
6. Perspective in the management of sorafenib-treated patients with HCC

When sorafenib treatment is initiated, several factors may be considered regarding dose selection, including age, ECOG PS, and status of underlying liver disease. Sorafenib should be continued until unacceptable toxicity or lack of clinical benefit is documented; this latter endpoint is challenged by the suboptimal tools available to assess response in HCC [24] and therefore relies heavily on the discretion of the treating physician. If a patient demonstrates radiologic progression only, sorafenib may be continued at least until symptomatic progression. In a recently published nonrandomized study (N=36), Miyahara et al found that metastatic tumor growth rates increased in patients who discontinued sorafenib after radiologic progression, but remained unchanged in patients who continued sorafenib. Survival beyond first radiologic progression was also significantly longer in patients who continued sorafenib. [63] In the SHARP trial, both clinical and radiologic assessments were performed; OS did not correlate with radiologic response, and patients continued sorafenib until both clinical and radiologic progression. It is important to note that symptomatic progression may be related to tumor growth and/or deteriorating liver status.

Management of side effects is critical for promoting uninterrupted treatment. It is well known that sorafenib is associated with skin reactions, diarrhea, and fatigue, but with proactive management and diligent follow-up in the early months of therapy, long-term treatment is feasible. HFSR often contributes to early discontinuation of sorafenib. In one study, the median onset of HFSR-associated symptoms was 18.4 days after initiating therapy (range 3-56 days). [64] A recent meta-analysis of 24 trials in patients with solid tumors reported a 9% incidence of high-grade HFSR in sorafenib-treated patients. [65] Prophylactic measures may minimize the onset and intensity of HFSR. A large, randomized, controlled phase 2 study (N=868) demonstrated that prophylaxis with urea-based cream over a 12-week period significantly reduced the incidence of all grades of HFSR compared to BSC in sorafenib-treated patients (56% vs 74%; P<.0001). [66] Other interventions may include removing hyperkeratotic tissue; applying emollients, creams, and exfoliating agents; limiting exposure to hot water; and protecting the feet with soft, well-fitting shoes and cotton socks [65, 67]; as well as sorafenib dose reduction or interruption until resolution to grade 1 or 0. [68, 69]

7. Conclusion

Sorafenib is an orally active multikinase inhibitor approved for the treatment of advanced, unresectable HCC. In randomized, double-blind, placebo-controlled, multicenter trials, sorafenib monotherapy prolonged median OS and delayed median TTP. With its acceptable safety profile and demonstrated survival benefit, sorafenib remains the only standard of care systemic therapy for unresectable HCC. However, additional trials of new molecules or combination therapy including sorafenib are needed to improve the outcomes of patients with unresectable HCC. Critical to HCC management is the establishment of surveillance programs
to facilitate identification and referral in earlier-stage HCC, as well as the introduction of novel approaches to reducing the size of HCC tumors to increase the utilization and success of curative options such as resection or transplantation.

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References

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10. Lyon, France: International Agency for Research on Cancer; 2010. Available at: http://globo-can.iarc.fr/. Accessed July 19, 2013.

[2] El-Serag HB. Epidemiology of hepatocellular carcinoma. Clin Liver Dis 2001; 5: 87-107, vi.

[3] Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009; 27: 1485-1491.

[4] El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007; 132: 2557-2576.

[5] Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362: 1907-1917.
[6] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, 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.

[7] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378-390.

[8] Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012; 57: 821-829.

[9] Cheng AL, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. Eur J Cancer 2012; 48: 1452-1465.

[10] Raoul JL, Bruix J, Greten TF, Sherman M, Mazzaferro V, Hilgard P, et al. Relationship between baseline hepatic status and outcome, and effect of sorafenib on liver function: SHARP trial subanalyses. J Hepatol 2012; 56: 1080-1088.

[11] Himmelsbach K, Sauter D, Baumert TF, Ludwig L, Blum HE, Hildt E. New aspects of an anti-tumour drug: sorafenib efficiently inhibits HCV replication. Gut 2009; 58: 1644-1653.

[12] Mee CJ, Farquhar MJ, Harris HJ, Hu K, Ramma W, Ahmed A, et al. Hepatitis C virus infection reduces hepatocellular polarity in a vascular endothelial growth factor-dependent manner. Gastroenterology 2010; 138: 1134-1142.

[13] Cabrera R, Limaye AR, Horne P, Soldevila-Pico C, Clark V, Morelli G, et al. The antiviral effect of sorafenib in hepatitis C-related hepatocellular carcinoma. Aliment Pharmacol Ther 2013; 37: 91-97.

[14] Lencioni R, Marrero J, Venook A, Ye SL, Kudo M. Design and rationale for the non-interventional Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and Of its Treatment with Sorafenib (GIDEON) study. Int J Clin Pract 2010; 64: 1034-1041.

[15] Lencioni R, Venook A, Marrero J, Kudo M, Ye SL, Nakajima K, et al. Second interim results of the GIDEON (Global Investigation of therapeutic Decisions in HCC and Of its Treatment with sorafemib) study: Barcelona-Clinic Liver Cancer (BCLC) stage subgroup analysis. European Multidisciplinary Cancer Congress (ECCO-ESMO); September 23-27, 2011; Stockholm, Sweden.

[16] Marrero J, Lencioni R, Kudo M, Ye S, Nakajima K, Cihon F, et al. Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib (GIDEON) second interim analysis in more than 1,500 patients: Clinical findings in patients with liver dysfunction. J Clin Oncol 2011; 29(15s May 20 suppl): 4001.
[17] Abou-Alfa GK, Amadori D, Santoro A, Figer A, De Greve J, Lathia C, et al. Safety and efficacy of sorafenib in patients with hepatocellular carcinoma (HCC) and Child-Pugh A versus B cirrhosis. Gastrointest Cancer Res 2011; 4: 40-44.

[18] Marrero J, Venook A, Kudo M, "Ye S, Nakajima K, Cihon F, et al. Second interim analysis of GIDEON (Global Investigation of therapeutic DEcisions in unresectable hepatocellular carcinoma and Of its treatment with sorafeNib): subgroup analysis by initial sorafenib dose. Presented at the 62nd Annual Meeting of the American Association for the Study of Liver Diseases, November 4-8, 2011; San Francisco, CA. Abstract 2192.

[19] Pinter M, Sieghart W, Huckle F, Graziaidei I, Vogel W, Maieron A, et al. Prognostic factors in patients with advanced hepatocellular carcinoma treated with sorafenib. Aliment Pharmacol Ther 2011; 34: 949-959.

[20] Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022.

[21] Cheng A, Kang Y, Lin D, Park J, Kudo M, Qin S, et al. Phase III trial of sunitinib (Su) versus sorafenib (So) in advanced hepatocellular carcinoma (HCC). J Clin Oncol 2011; 29(15 May 20 suppl): 4000.

[22] Johnson P, Qin S, Park JW, Poon RT. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results form the phase 3 BRISK-FL study. 63rd Annual Meeting of the American Association for the Study of Liver Diseases; November 9-19, 2012; Boston, MA. Abstract LB-6.

[23] Cainap C, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, et al. Phase III trial of linifanib versus sorafenib in patients with advanced hepatocellular carcinoma (HCC). J Clin Oncol 2013; 31(suppl 4): 249.

[24] Chen L, Shi Y, Jiang CY, Wei LX, Wang YL, Dai GH. Expression and prognostic role of pan-Ras, Raf-1, pMEK1 and pERK1/2 in patients with hepatocellular carcinoma. Eur J Surg Oncol 37: 2011; 513-520.

[25] Hwang YH, Choi JY, Kim S, Chung ES, Kim T, Koh SS, et al. Over-expression of c-raf-1 proto-oncogene in liver cirrhosis and hepatocellular carcinoma. Hepatol Res 2004; 29: 113-121.

[26] Riaz A, Memon K, Miller FH, Nikolaidis P, Kulik LM, Lewandowski RJ, et al. Role of the EASL, RECIST, and WHO response guidelines alone or in combination for hepatocellular carcinoma: radiologic-pathologic correlation. J Hepatol 2011; 54: 695-704.

[27] Sergio A, Cristofori C, Cardin R, Pivetta G, Ragazzi R, Baldan A, et al. Transcatheter arterial chemoemoblization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. Am J Gastroenterol 2008; 103: 914-921.
[28] Wang B, Xu H, Gao ZQ, Ning HF, Sun YQ, Cao GW. Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter arterial chemoembolization. Acta Radiol 2008; 49: 523-529.

[29] Shim JH, Park JW, Kim JH, An M, Kong SY, Nam BH, et al. Association between increment of serum VEGF level and prognosis after transcatheter arterial chemoembolization in hepatocellular carcinoma patients. Cancer Sci 2008; 99: 2037-2044.

[30] Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011; 47: 2117-2127.

[31] Lencioni R, Llovet J, Han G, Tak WY, Yang J, Leberre MA, et al. Sorafenib or placebo in combination with transarterial chemoembolization (TACE) with doxorubicin-eluting beads (DEBDOX) for intermediate-stage hepatocellular carcinoma (HCC): Phase II, randomized, double-blind SPACE trial. J Clin Oncol 2012; 30(4 suppl Feb): LBA154.

[32] Sansonno D, Lauletta G, Russi S, Conteduca V, Sansonno L, Dammacco F. Transarterial chemoembolization plus sorafenib: a sequential therapeutic scheme for HCV-related intermediate-stage hepatocellular carcinoma: a randomized clinical trial. Oncologist 2012; 17: 359-366.

[33] Kudo M. Adjuvant therapy after curative treatment for hepatocellular carcinoma. Oncology 2011; 81(suppl 1): 50-55.

[34] Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999; 30: 1434-1440.

[35] Vitale A, Volk ML, Pastorelli D, Lonardi S, Farinati F, Burra P, et al. Use of sorafenib in patients with hepatocellular carcinoma before liver transplantation: a cost-benefit analysis while awaiting data on sorafenib safety. Hepatology 2010; 51: 165-173.

[36] Truesdale AE, Caldwell SH, Shah NL, Argo CK, Al-Osaimi AM, Schmitt TM, et al. Sorafenib therapy for hepatocellular carcinoma prior to liver transplant is associated with increased complications after transplant. Transpl Int 2011; 24: 991-998.

[37] Di Benedetto F, Tarantino G, Montalti R, Ballarin R, D’Amico G, Berretta M, et al. Sorafenib before liver transplantation for hepatocellular carcinoma: risk or give up. Transpl Int 2011; 24: e97; author reply e98-99.

[38] Frenette C. Sorafenib prior to liver transplant does not result in increased surgical complications. Presented at the 62nd Annual Meeting of the American Association for the Study of Liver Disease; November 4-8, 2011; San Francisco, CA. Abstract 562.

[39] Irtan S, Chopin-Laly X, Ronot M, Faivre S, Paradis V, Belghiti J. Complete regression of locally advanced hepatocellular carcinoma induced by sorafenib allowing curative resection. Liver Int 2011; 31: 740-743.
[40] Kim R, Menon N, Aucejo F. Safe use of sorafenib in a patient undergoing salvage liver transplantation for recurrent hepatocellular carcinoma after hepatic resection. Med Oncol 2011; 28: 1044-1047.

[41] Siegel AB, El-Khoueiry AB, Finn RS, Blanke CD, Hidalgo R, Brown RS. Phase I trial of sorafenib in high-risk hepatocellular carcinoma (HCC) patients after liver transplantation. J Clin Oncol 2012; 30(suppl 34): 280.

[42] Teng CL, Hwang WL, Chen YJ, Chang KH, Cheng SB. Sorafenib for hepatocellular carcinoma patients beyond Milan criteria after orthotopic liver transplantation: a case control study. World J Surg Oncol 2012; 10: 41.

[43] Pfiffer TE, Seehofer D, Nicolaou A, Neuhaus R, Riess H, Trappe RU. Recurrent hepatocellular carcinoma in liver transplant recipients: parameters affecting time to recurrence, treatment options and survival in the sorafenib era. Tumori 2011; 97: 436-441.

[44] Zhu AX, Rosmorduc O, Evans J, Ross P, Santoro A, Carrilho FJ, et al. Search: A phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with hepatocellular carcinoma (HCC). Ann Oncol 2012; 23(suppl 9): 11.

[45] Hidaka H, Nakazawa T, Kaneko T, Minamino T, Takada J, Tanaka Y, et al. Portal hemodynamic effects of sorafenib in patients with advanced hepatocellular carcinoma: a prospective cohort study. J Gastroenterol 2012; 47: 1030-1035.

[46] Pinter M, Sieghart W, Reiberger T, Rohr-Udilova N, Ferlitsch A, Peck-Radosavljevic M. The effects of sorafenib on the portal hypertensive syndrome in patients with liver cirrhosis and hepatocellular carcinoma--a pilot study. Aliment Pharmacol Ther 2012; 35: 83-91.

[47] Llovet JM, Pena CE, Lathia CD, Shan M, Meinhardt G, Bruix J, et al. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma. Clin Cancer Res 2012; 18: 2290-2300.

[48] Kaseb AO, Abbruzzese JL, Vauthey JN, et al. I-CLIP: improved stratification of advanced hepatocellular carcinoma patients by integrating plasma IGF-1 into CLIP score. Oncology 80: 373-381, 2011

[49] Kaseb AO, Hassan MM, Lin E, Aloia TA, Abdalla EK, Hassan MM, et al. V-CLIP: Integrating plasma vascular endothelial growth factor into a new scoring system to stratify patients with advanced hepatocellular carcinoma for clinical trials. Cancer 2011; 117: 2478-2488.

[50] Schoenleber SJ, Kurtz DM, Talwalkar JA, Roberts LR, Gores GJ. Prognostic role of vascular endothelial growth factor in hepatocellular carcinoma: systematic review and meta-analysis. Br J Cancer 2009; 100: 1385-1392.

[51] Kaseb AO, Morris JS, Hassan MM, Siddiqui AM, Lin E, Xiao L, et al. Clinical and prognostic implications of plasma insulin-like growth factor-1 and vascular endothel-
lial growth factor in patients with hepatocellular carcinoma. J Clin Oncol 2011; 29: 3892-3899.

[52] Yu Q, Stamenkovic I. Angiopoietin-2 is implicated in the regulation of tumor angiogenesis. Am J Pathol 2001; 158: 563-570.

[53] Moon WS, Rhyu KH, Kang MJ, Lee DG, Yu HC, Yeum JH, et al. Overexpression of VEGF and angiopoietin 2: a key to high vascularity of hepatocellular carcinoma? Mod Pathol 2003; 16: 552-557.

[54] Scholz A, Rehm VA, Rieke S, Derkow K, Schulz P, Neumann K, et al. Angiopoietin-2 serum levels are elevated in patients with liver cirrhosis and hepatocellular carcinoma. Am J Gastroenterol 2007; 102: 2471-2481.

[55] Llovet J, Pena C, Shan M, Lathia C, Bruix J. Plasma biomarkers as predictors of outcome in patients with advanced hepatocellular carcinoma: results from the randomized phase III trial. Presented at the EASL Annual Meeting; April 22-26, 2009; Copenhagen, Denmark.

[56] Yau T, Yao TJ, Chan P, Wong H, Pang R, Fan ST, et al. The significance of early alpha-fetoprotein level changes in predicting clinical and survival benefits in advanced hepatocellular carcinoma patients receiving sorafenib. Oncologist 2011; 16: 1270-1279.

[57] Ueshima K, Kudo M, Takita M, Nagai T, Tatsumi C, Ueda T, et al. Des-gamma-carboxyprothrombin may be a promising biomarker to determine the therapeutic efficacy of sorafenib for hepatocellular carcinoma. Dig Dis 2011; 29: 321-325.

[58] Bertino G, Ardiri A, Malaguarnera M, Malaguarnera G, Bertino N, Calvagno GS. Hepatocellular carcinoma serum markers. Semin Oncol 2012; 39: 410-433.

[59] Reig M, Boix L, Forner A, BCLC Group, Hospital Clinic. Forner 1, and BCLC Group, Hospital Clinic. Serum carbonic anhydrase 9 is a valuable biomarker to predict the outcome in patients with hepatocellular carcinoma treated with sorafenib. Presented at the International Liver Cancer Association Annual Meeting; September 1-3, 2011; Hong Kong, China.

[60] Song T, Zhang W, Wu Q, Kong D, Ma W. A single center experience of sorafenib in advanced hepatocellular carcinoma patients: evaluation of prognostic factors. Eur J Gastroenterol Hepatol 2011; 23: 1233-1238.

[61] Bettiger D, Schultheiss M, Knuppel E, Thimme R, Blum HE, Spangenberg HC. Diarrhea predicts a positive response to sorafenib in patients with advanced hepatocellular carcinoma. Hepatology, 2012; 56: 789-790.

[62] Vincenzi B, Santini D, Russo A, Addeo R, Giuliani F, Montella L, et al. Early skin toxicity as a predictive factor for tumor control in hepatocellular carcinoma patients treated with sorafenib. Oncologist 2010; 15: 85-92.
[63] Miyahara K, Nouso K, Morimoto Y, Takeuchi Y, Hagihara H, Kuwaki K, et al. Efficacy of sorafenib beyond first progression in patients with metastatic hepatocellular carcinoma. Hepatol Res 2013 Apr 2 (Epub ahead of print).

[64] Lee WJ, Lee JL, Chang SE, Lee MW, Kang YK, Choi JH, et al. Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. Br J Dermatol 2009; 161: 1045-1051.

[65] Zhang T, Ding X, Wei D, Cheng P, Su X, Liu H, et al. Sorafenib improves the survival of patients with advanced hepatocellular carcinoma: a meta-analysis of randomized trials. Anticancer Drugs 2010; 21: 326-332.

[66] Ren Z, Zhu K, Kang H, Lu M, Qu Z, Lu L, et al. A randomized controlled phase II study of the prophylactic effect of urea-based cream on the hand-foot skin reaction associated with sorafenib in advanced hepatocellular carcinoma. J Clin Oncol 2012; 30(May 20 suppl): 4008.

[67] Anderson R, Jatoi A, Robert C, Wood LS, Keating KN, Lacouture ME. Search for evidence-based approaches for the prevention and palliation of hand-foot skin reaction (HFSR) caused by the multikinase inhibitors (MKIs). Oncologist 2009; 14: 291-302.

[68] Autier J, Escudier B, Wechsler J, Spatz A, Robert C. Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor. Arch Dermatol 2008; 144: 886-892.

[69] Lacouture ME, Wu S, Robert C, Atkins MB, Kong HH, Guitart J, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. Oncologist 2008; 13: 1001-1011.

[70] Wilhelm S, Chien DS. BAY 43-9006: preclinical data. Curr Pharm Des 2002; 8: 2255-2257.

[71] SUTENT® (sunitinib malate) [prescribing information]. New York, NY: Pfizer Labs; 2012.

[72] Bhide RS, Cai ZW, Zhang YZ, Qian L, Wei D, Barbosa S, et al. Discovery and preclinical studies of (R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yl)-oxy)-5-methylpyrrolo [2,1-f] [1,2,4]triazin-6-yloxy)propan-2-ol (BMS-540215), an in vivo active potent VEGFR-2 inhibitor. J Med Chem 2006; 49: 2143-2146.

[73] Albert DH, Tapang P, Magoc TJ, Pease LJ, Reuter DR, Wei RQ, et al. Preclinical activity of ABT-869, a multitargeted receptor tyrosine kinase inhibitor. Mol Cancer Ther 2006; 5: 995-1006.

[74] Lee SH, Lopes de Menezes D, Vora J, Harris A, Ye H, Nordahl L, et al. In vivo target modulation and biological activity of CHIR-258, a multitargeted growth factor receptor kinase inhibitor, in colon cancer models. Clin Cancer Res 2005; 11: 3633-3641.
[75] Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res 2008; 68: 4774-4782.
