**Name of journal:** **World Journal of Gastroenterology**

**ESPS Manuscript NO: 5390**

**Columns: TOPIC HIGHLIGHTS**

WJG 20th Anniversary Special Issues (1): Hepatocellular carcinoma

**Chemotherapy for advanced hepatocellular carcinoma in the sorafenib age**

Miyahara K *et al.* Chemotherapy for advanced hepatocellular carcinoma

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**Received:** September 4, 2013  **Revised:** January 2, 2014

**Accepted:** February 26, 2014

**Published online:**

**Abstract**

The kinase inhibitor sorafenibis the only systemic therapy proven to have a positive effect on survival of patients with advanced hepatocellular carcinoma (HCC). After development of sorafenib and its introduction as a therapeutic agent used in the clinic, several critical questions have been raised. Clinical parameters and biomarkers predicting sorafenib efficacy are the most important issues that need to be elucidated. Although it is difficult to know the responders in advance using conventional characteristics of patients, there are specific serum cytokines and/or gene amplification in tumor tissues that have been reported to predict efficacy of sorafenib. Risk and benefits of continuation of sorafenib beyond radiological progression is another issue to consider because no other standard therapy for advanced HCC as yet exists. In addition, effectiveness of the expanded application of sorafenib is still controversial, although a few studies have shed some light on combinational treatment with sorafenib for intermediate-stage HCC. Recently, over 50 relevant drugs have been developed and are currently under investigation. The efficacy of some of these drugs has been extensively examined, but none have demonstrated any superiority over sorafenib, so far. However, there are several drugs that have shown efficacy for treatment after sorafenib failure, and these are proceeding to further studies. To address these issues and questions, we have done extensive literature review and summarize the most current status of therapeutic application of sorafenib.

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**Key words:** Biomarker; Molecular targeted therapy; Clinical trial; Hepatic arterial infusion chemotherapy; Hepatocellular carcinoma; Sorafenib

**Core tip:** Sorafenib is the only systemic therapy proven to have a positive effect on survival and to be well tolerated in patients with advanced hepatocellular carcinoma (HCC). We summarize the most current status of sorafenib therapy, focusing on (1) safety and efficacy of sorafenib for advanced HCC; (2) biomarkers predicting efficacy of sorafenib; (3) expanded application for the treatment of non-advanced HCC; (4) sorafenib efficacy beyond radiological progression; and (5) novel therapeutics and hepatic arterial infusion chemotherapy.

**Miyahara K**, **Nouso K, Yamamoto K.** Chemotherapy for advanced hepatocellular carcinoma in the sorafenib age.

**Available from:**

**DOI:**

**INTRODUCTION**

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide and is associated with the second lowest 5-year survival rate of all tumor types[1]. For patients diagnosed at early stages, potentially curative treatments are available, such as radiofrequency ablation, resection, and liver transplantation; and patients at intermediate stages may be treated with transcatheter arterial chemoembolization (TACE). However, for disease that is diagnosed at an advanced stage or progresses after locoregional therapies, sorafenib is the choice of treatment.

Sorafenib, which is an oral multi-kinase inhibitor, suppresses tumor angiogenesis and proliferation by inhibiting the activity of such targets as vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor (PDGF) receptor, mast/stem cell growth factor receptor (c-KIT), rearranged during transfection (RET), Fms-like tyrosine kinase 3 (FLT-3), and the proto-oncoprotein, c-RAF[2,3]. In addition, sorafenib also has been shown to induce apoptosis as direct effects on tumor cell[4]. The safety and efficacy of sorafenib in patients with advanced HCC was demonstrated in two phase III randomized, double-blind, placebo-controlled trials, the Sorafenib HCC Assessment Randomized Protocol (SHARP) and Asia-Pacific (AP) trials[5,6], thereby establishing sorafenib as the standard systemic therapy for advanced HCC[7,8].

HCC is often resistant to chemotherapy, and the potential for liver failure accompanying this disease has complicated the therapies that are employed. However, there is currently no systemic therapy other than sorafenib, although many clinical trials are on-going. The aim of the present review is to summarize recent clinical evidence and present a current status of sorafenib in therapeutic treatment of HCC.

**STATUS OF SORAFENIB IN CLINICAL GUIDELINES**

Sorafenib is recommended as a treatment in patients with (1) extrahepatic lesions, (2) macrovascular invasion; or (3) those who do not response to TACE/arterial injection chemotherapy, when the liver function is Child-Pugh (CP) -A, in a consensus-based treatment algorithm for HCC (JSH Consensus 2010)[9]. The recommendation was based on the results demonstrated in SHARP and AP trials (Table 1). Patients recommended for sorafenib in this algorithm overlap with those recommended according to the European Association for the Study of the Liver (EASL), the European Organization for Research and Treatment of Cancer (EORTC)[10], the American Association for the Study of Liver Diseases (AASLD)[8], and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline[11]. The EASL-EOTC, AASLD, and NCCN guidelines indicate sorafenib as an option for CP-B patients; whereas, no clear evidence, based on randomized controlled trials, has been presented on safety of sorafenib in CP-B patients.

The recent report in Global investigation of therapeutic decisions in HCC and of its treatment with sorafenib (GIDEON), which is a global, non-interventional, surveillance study, has presented data from sorafenib treatment of patients with liver dysfunction[12]. In the study, CP subgroups showed similar incidence of all grade of adverse events (AEs) [84.0 (CP-A) *vs* 88.6% (CP-B)] and time to progression (TTP) [4.7 (CP-A) *vs* 4.4 mo (CP-B)]. In contrast, serious AEs were more common in CP-B (60.4%) than CP-A (36.0%) patients. The finding that severity of AEs is associated with poor liver function provides a certain warning to the use of sorafenib for the CP-B patient, even if the treatment efficacy is consistent irrespective of liver function.

**CLINICAL CHARACTERISTICS AND EFFICACY OF SORAFENIB**

Clinical characteristics at baseline that might affect responses to therapy have been examined. Subgroup analyses of SHARP and AP trials, in which patients with well-preserved liver function had been enrolled, demonstrated the baseline status related to outcomes during sorafenib treatment[13-15]. In both analyses, the patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 1 or 2, aspartate/alanine transaminase (AST/ALT) elevation, or macroscopic vascular invasion (MVI) had similar hazard ratios with the total population [hazard ratio (HR) of 0.69 in SHARP; 0.68 in AP]. These findings provide an opportunity for patients with these statuses to be treated with sorafenib, but it should be noted that high ECOG PS, AST/ALT elevation, or presence of MVI themselves were associated with short OS. Sorafenib treatment for patients with prior local therapy, prior TACE, or extrahepatic spread (EHS) also resulted in longer median OS than placebo, except for those with prior hepatectomy in the AP trial. However, careful interpretation of these results is needed because the studies did not aim to show the differences between these subgroups, and statistical confirmation had not yet been performed.

**BIOMARKERS FOR PREDICTING OUTCOMES OF SORAFENIB TREATMENT**

Predictive biomarkers are expected to advance the potential of personalized medicine in cancer treatment. Biomarker research for predicting the efficacy of sorafenib is a growing field, and a few candidate markers in plasma, serum, and tissue have been reported (Table 2). Llovet *et* *al*[16] reported results of sub-analysis in the SHARP trial, examining expression of 10 molecules in plasma of HCC patients. Plasma c-KIT and hepatocyte growth factor (HGF) were suggested as possible predictors of response to sorafenib, although the association was not statistically significant. In other preliminary studies, angiogenesis-related cytokines in serum, including angiopoietin-2, were reported to correlate with treatment response[17]. Several candidates for tissue markers, such as FGF3/FGF4[18], αB-crystallin[19], JNK[20], and pERK[21], have been proposed. Amplification of FGF3/FGF4 was observed only in objective responders, but not in patients with stable or progressive disease. Frequency of FGF3/FGF4 amplification remains below a few percent in HCC[22-24]; however, FGF3/FGF4 amplification might represent a promising therapeutic target, and it provides a novel insight for molecular-based therapy in HCC. Various molecules thought to have potential to be novel markers or therapeutic targets have been identified on the basis of basic research observations[4,25-28] (Table 2), but none of them has been verified in clinical studies. Candidate biomarkers should be validated in prospective clinical trials, in order to assess their potential to lead to personalized therapy.

**CONVENTIONAL TUMOR MARKERS DURING TREATMENT WITH SORAFENIB**

Conventional tumor markers for the diagnosis of HCC, *i.e.*, α-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), have been reported to show contrasting behavior after administration of sorafenib. Early AFP decrease correlates with beneficial efficacy of sorafenib in patients with HCC[29-31], as observed in other therapies. However, DCP increases with sorafenib administration, regardless of the treatment response[29]. Interestingly, a few reports have shown that elevation of DCP[32,33] and NX-DCP, which is a vitamin K-specific phenotype of DCP[34], is associated with a highly therapeutic effect of sorafenib. These markers are expected to be used for monitoring HCC patients undergoing treatment, rather than as predictive biomarkers.

**ADVERSE EVENTS AND EFFICACY OF SORAFENIB**

Various adverse events were frequently observed during sorafenib therapy (Table 3). Adverse events of molecular-targeted agents sometimes associate with a favorable effect on prognosis[35-46]. Regarding sorafenib therapy, development of skin toxicities[47,48] and arterial hypertension[49] in some trials correlated with longer time to disease progression or longer survival in patients with HCC, and similar correlations were seen in those with renal cell carcinoma[50,51]. However, this correlation has not been identified in randomized controlled trials, and validation might be difficult if there are agents for preventive care being administrated, such as preventive and therapeutic skin care, systemic analgesics for pain, vitamin B6, *etc*., for hand-foot skin reaction[52]. Furthermore, haphazard continuation of chemotherapies with side effects requires careful management, as these may sometimes lead to dangerous conditions.

**EFFICACY OF SORAFENIB IN NON-ADVANCED HCC**

Sorafenib is recommended for treatment of advanced HCC in clinical algorithms, as described above, but the utility for early or intermediate stages of HCC remain unclear. Intermediate-stage HCC with multiple nodules and without major vascular invasion or extrahepatic spread is commonly treated by TACE. Ischemic injury after TACE induces up-regulation of VEGF[53], which is associated with poor prognosis[54,55]. However, combination with sorafenib, which inhibits angiogenic factors, including VEGF receptor, could theoretically reinforce the efficacy of TACE.

Several clinical trials evaluating effects of TACE with sorafenib in treatment of intermediate-stage HCC are being conducted (Table 4). Two single-arm phase II trials have shown promising efficacy[56,57]. A randomized placebo-controlled study of sorafenib or placebo in combination with TACE for intermediate-stage HCC (SPACE) successfully demonstrated that sorafenib prolongs TTP after TACE, although improvement of OS or time to untreatable progression (TTUP) was not observed[58]. In a randomized phase III trial in patients who responded to TACE (post TACE study), sorafenib did not significantly prolong TTP after TACE, compared to placebo[59]. In this study, a long lag time of > 9 wk prior to administration of sorafenib may also have contributed to the absence of a positive effect of sorafenib. In response, a trial titled Transcatheter Arterial Chemoembolization Therapy in Combination with Sorafenib (TACTICS, NCT01217034) is currently being conducted, with a stipulated lag time (3−21 d).

Furthermore, sorafenib is under evaluation as an adjuvant therapy for the prevention of recurrence following surgery or local ablation. The trial is a phase III, randomized, double-blind, and placebo-controlled study, titled Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of HCC (STORM trial; NCT00692770). The results from this study will provide more information about whether sorafenib has efficacy for HCC at early stages and reduces the risk of recurrence.

**CONTINUATION OF SORAFENIB AFTER RADIOLOGICAL PROGRESSION**

In general, tumor progression implies resistance to the therapy being employed, and it is thus a motivation to change therapy regimen. However, in contrast to typical cytotoxic agents, sorafenib seldom induces an objective response (2%−3%)[5,6]; this modest response would make it difficult for physicians to decide whether to continue or discontinue sorafenib treatment. Several reports speculate about sorafenib efficacy beyond radiological progression. Sorafenib administration beyond first radiological progression was seen to continuously suppress tumor growth[60], and long-term treatment was associated with prolonged survival regardless of therapeutic effect[61]. Interestingly, the SHARP trial was designed to continue sorafenib after radiological progression, if symptomatic progression was absent[5]. Hence, it is reasonable to consider continuing sorafenib at the time of radiological progression when patients will tolerate the therapy and have no symptomatic disease progression or liver dysfunction in the present status, with no other effective therapy.

**HEPATIC ARTERIAL INFUSION CHEMOTHERAPY**

Before the development of molecular targeted therapies based on evidence from randomized controlled trials, hepatic arterial infusion chemotherapy (HAIC) had been used to treat advanced HCC with vascular invasion and/or multiple intrahepatic lesions. The protocol of HAIC is not standardized. The most frequently used regimens in Japan are (1) continuous infusion of 5-fluorouracil plus low-dose cisplatin combination therapy (termed low-dose FP, for fluorouracil and platinum); (2) continuous intra-arterial infusion of 5-fluorouracil plus systemic interferon therapy (5-FU plus IFN), or one-shot infusion of cisplatin (one-shot CDDP). The response rates of HAIC were reported to be 24.5%−38.5% in low-dose FP[62-68]; 21.5%−63% in 5-FU plus IFN[69-77]; 3.6%−33.8% in one-shot CDDP[78-81], which were higher than that of sorafenib; but the survival benefit of these therapies are controversial. The lack of evidence based on randomized controlled trials in most of the regimens is a serious criticism of the importance of HAIC in HCC treatment. Trials evaluating the efficacy of HAIC in combination with sorafenib are currently on-going: Comparing Efficacy of Sorafenib *vs* Sorafenib in Combination with Low-dose FP in Patients with Advanced HCC (SILIUS Phase III trial; NCT01214343); and Randomized Phase II Study of Sorafenib and Hepatic Arterial Infusion Chemotherapy with Cisplatin *vs* Sorafenib for Advanced HCC (UMIN000005703).

**NOVEL THERAPEUTICS FOR ADVANCED HCC**

After the successful result of sorafenib in the SHARP and AP trials, more than 50 reagents are currently under evaluation in phase I to IV trials (www.clinicaltrials.gov.). Recently, phase III studies have been reported to evaluate the survival benefit of sunitinib, brivanib, linifanib, and the combination of sorafenib plus erlotinib over sorafenib monotherapy; however, there have so far been no agents showing survival improvement or alleviation of AEs[5,6,82-86]. Linifanib shows longer TTP and similar OS compared to sorafenib, but linifanib is inferior to sorafenib in safety[86]. Brivanib, as a second-line therapy after failure by, or intolerance to, sorafenib, shows longer TTP but similar OS relative to placebo[85]. The failures in these trials point to the difficulty of both improving the OS and alleviation of the AEs concurrently in advanced HCC.

For effective use of molecular-targeted agents, clinical trials to investigate new agents in combination with predictive markers are on-going. These include c-MET inhibitor (tivantinib; ARQ 197) and monoclonal antibody against glypican-3 (GC33). For patients with c-MET-high tumors, TTP was found to be longer with tivantinib than for those with placebo in a randomized phase II trial (2.7 *vs* 1.4 mo, *p* = 0.03)[87]. For patients treated with GC33, TTP was longer in patients with GPC3-high tumors than in those with GPC3-low tumors in a phase I trial (26.0 *vs* 7.1 wk, *p* = 0.033)[88]. The efficacy of these surrogate markers are being evaluated in randomized, placebo-controlled phase III (NCT01755767) and II (NCT01507168) trials.

**CONCLUSION**

We have reviewed current status of chemotherapy for advanced HCC. Sorafenib has been established as a standard therapy prolonging survival in patients with advanced HCC, but it only provides a small treatment response. To compensate for the modest effect on tumor regression, new molecular-targeted drugs and their biomarkers for prediction of treatment efficacy are being investigated. In addition, several novel therapeutics in combination with HAIC are being evaluated in clinical trials. The development of these markers and therapeutics in the near future will improve prognosis of advanced HCC and provide novel insights into molecular-based therapy for HCC.

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**P-Reviewers:** Aghakhani A, Eghtesad B, Grassi G, Ishikawa T, Kakizaki S, Kim SH, Tsai JF **S-Editor:** Ma YJ **L-Editor:** **E-Editor:**

**Table 1 Overall survivals in sorafenib treatment**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Clinical trial** | **Sorafenib** |  | **Placebo** |  | ***P*** |
| ***n*** | **Median OS (mo)** | **95%CI** |  | ***n*** | **Median OS (mo)** | **95%CI** |  |
| SHARP[5] | 299 | 10.7 |  9.4–13.3 |  | 303 | 7.9 | 6.8–9.1 |  | < 0.001 |
| AP[6] | 150 |  6.5 | 5.56–7.56 |  |  76 | 4.2 | 3.75–5.46 |  | 0.014 |

CI: confidence interval; OS: overall survival; AP: Asia-Pacific.

**Table 2** **Biomarkers for predicting outcomes with sorafenib**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Year** | **Obtained from** | **Biomarker** |
| [Llovet *et al*](http://www.ncbi.nlm.nih.gov/pubmed?term=Llovet%20JM%5BAuthor%5D&cauthor=true&cauthor_uid=22374331)[16] | 2012 | Plasma | HGF*,* c-KIT |
| Miyahara *et al*[17] | 2011 | Serum | Angiogenesis-related cytokines1 |
| Arao *et al*[18] | 2013 | Tissue | FGF3/FGF4 |
| Huang *et al*[19] | 2013 | Tissue | αB-Crystallin |
| Hagiwara *et al*[20] | 2012 | Tissue | JNK |
| Abou-Alfa *et al*[21] | 2006 | Tissue | pERK |
| Shan *et al*[25] | 2012 | Cell line | Nanog |
| Blivet-Van Eggelpoël *et al*[26] | 2012 | Cell line | EGFR, HER-3 |
| Chen *et al*[27] | 2012 | Cell line | SIRT1 |
| Tai *et al*[28] | 2011 | Cell line | STAT3 |
| Liu *et al*[4] | 2006 | Cell line | Mcl-1, eIF4E |

1These include angiopoietin-2, follistatin, granulocyte colony-stimulating factor, hepatocyte growth factor, leptin, platelet-derived growth factor-BB, platelet endothelial cell adhesion molecule-1, and vascular endothelial growth factor. HGF: hepatocyte growth factor; c-KIT: also known as SCFR (mast/stem cell growth factor receptor); FGF: fibroblast growth factors; JNK: c-Jun N-terminal kinase; pERK: phosphorylated extracellular signal regulated kinase; EGFR: epidermal growth factor receptor; HER-3: also known as ErbB3; STAT3: signal transducer and activator of transcription 3; Mcl-1: myeloid cell leukemia-1; eIF4E: eukaryotic translation initiation factor 4E.

**Table 3 Incidence of drug-related adverse events of sorafenib treatment**

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse event, %** | **SHARP[5]** | **AP[6]** | **GIDEON (second interim analysis)[89]** |
|  | **(*n* = 297)** | **(*n* = 149)** | **(*n* = 1571)** |
| Any adverse event | 80 | 82 | 64 |
| Diarrhea  | 39 | 26 | 25 |
| Hand-foot skin reaction | 21 | 45 | 24 |
| Fatigue  | 22 | 20 | 14 |
| Rash ⁄ desquamation | 16 | 20 | 12 |
| Anorexia  | 14 | 13 |  9 |
| Hypertension  | 5 | 19 |  7 |
| Alopecia  | 14 | 25 |  7 |
| Nausea  | 11 | 11 |  6 |
| Weight loss | 9 | NA1 | 5 |

1NA: not available; this adverse event was observed in < 10% of patients in AP trial. Incidence of all grades of adverse events was shown. Adverse events in ≥ 5% of the total population in GIDEON study were listed.

**Table 4** **Clinical trials for evaluating the effect of transcatheter arterial chemoembolization with sorafenib in intermediate stage of hepatocellular carcinoma**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Acronym****(NCT number)** | **Reported year** | **Trial phase** | **Study design** | ***n*** | **TACE** | **Outcomes** |
| Pawlik *et* *al*[56] | - | 2011 | II | single-arm (TACE plus sorafenib) | 33 | DEB/scheduled | Disease control rate = 100%, per lesion. Objective response = 58%, per lesion |
| Park *et al*[57] | - | 2012 | II | single-arm (TACE plus sorafenib) | 50 | conventional1/on demand | Median TTP = 7.1 mo6-mo PFS rate = 52% |
| Kudo *et al*[59] | post TACE study | 2011 | III | TACE plus sorafenib *vs* TACE plus placebo | 458 | conventional1/1 or 2 sessions | Median TTP = 5.4 (Sorafenib)/3.7 (placebo) mo. HR [sorafenib] = 0.87; 95%CI: 0.70−1.09; *p* = 0.252 |
| Lencioni *et al*[58] | SPACE | 2012 | II | TACE plus sorafenib *vs* TACE plus placebo | 307 | DEB/scheduled | Median TTP = 169 (Sorafenib)/166 (placebo) d. HR [sorafenib] = 0.79; 95%CI: 0.588−1.080; *p* = 0.072 |
| Kudo *et al*2 | TACTICS (NCT01217034) | currently recruiting participants | II | TACE plus sorafenib *vs* TACE alone | 2283 | conventional1/on demand | Time To Untreatable Progression4 |
| Meyer *et al*2 | CRUK-TACE-2 (NCT01324076) | currently recruiting participants | III | TACE plus sorafenib *vs* TACE plus placebo | 4123 | DEB/1 session | PFS4 |
| Kauh *et al*2 | (NCT01004978) | currently recruiting participants | III | TACE plus sorafenib *vs* TACE plus placebo | 4003 | conventional1 or DEB/scheduled | PFS4 |

1Conventional TACE indicated transcatheter arterial chemoembolization with gelatin foam and lipiodol; 2The information of the trial can be accessed at ClinicalTrials.gov; 3Estimated Enrollment; 4Primary Outcome Measures. DBE: Drug-eluting beads; NCT: National clinical trial; PFS: Progression-free survival; TACE: Transcatheter arterial chemoembolization; TTP: time to progression.