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REVIEW

Evaluation of antiangiogenic efficacy in advanced hepatocellular carcinoma: Biomarkers and functional imaging

Mohamed Bouattour, Audrey Payancé, Johanna Wassermann

Mohamed Bouattour, Audrey Payancé, Department of Hepatology, Beaujon University Hospital (AP-HP - Paris 7 Diderot), 92110 Clichy, France

Johanna Wassermann, Department of Medical Oncology, La Pitié-Salpêtrière University Hospital (AP-HP - Paris 6 Pierre et Marie Curie), 75013 Paris, France

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Correspondence to: Dr. Mohamed Bouattour, Department of Hepatology, Beaujon University Hospital (AP-HP - Paris 7 Diderot), 100 Boulevard du Général Leclerc, 92110 Clichy, France. mohamed.bouattour@aphp.fr
Telephone: +33-1-40875525
Fax: +33-1-40875487

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Abstract

Many years after therapeutic wilderness, sorafenib finally showed a clinical benefit in patients with advanced hepatocellular carcinoma. After the primary general enthusiasm worldwide, some disappointments emerged particularly since no new treatment could exceed or at least match sorafenib in this setting. Without these new drugs, research focused on optimizing care of patients treated with sorafenib. One challenging research approach deals with identifying prognostic and predictive biomarkers of sorafenib in this population. The task still seems difficult; however appropriate investigations could resolve this dilemma, as observed for some malignancies where other drugs were used.

Key words: Hepatocellular carcinoma; Antiangiogenic therapies; Sorafenib; Predictive biomarkers; Prognosis biomarkers; Functional imaging

Core tip: The approval of sorafenib in advanced hepatocellular carcinoma is based on the positive results of two large randomized phase Ⅲ clinical trials. The inter- and intra-individual variability regarding tumor response and clinical outcome highlighted the unmet need of effective biomarkers of response. These biomarkers could be useful for monitoring treatment activity, detecting early resistance to treatment and identifying patients who would more likely benefit from treatment. An overview of prognostic/predictive biomarkers of sorafenib in hepatocellular carcinoma is discussed in this review.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide[1,2]. The incidence of HCC is steadily increasing with about 625000 new cases per year and the disease results in around 600000 deaths yearly over the world[1,2]. Less than 30% of patients diagnosed with HCC are eligible for curative treatment[3] and during the course of the natural evolution of HCC; a significant proportion of patients are candidates for systemic therapies. In recent years, considerable progress has been made in furthering the knowledge of molecular biology of HCC, including better understanding of the role of signaling pathways and angiogenesis[4-8]. These advances have led to the development of targeted therapies in HCC[9-11]. Nevertheless, only sorafenib, a multikinase inhibitor, remains till date the sole approved drug in advanced HCC, based on the clinical benefit observed in properly selected patients enrolled in clinical trials[12,13]. With only three months of survival gain compared to placebo, many practitioners and country health authorities consider the cost-efficacy ratio of sorafenib somewhat insufficient[14-16]. In some emerging countries, the drug is not even approved for patients with advanced HCC. Otherwise, published data and clinical practice highlight a great inter-individual and even intra-individual variation regarding clinical benefit and toxicity[17-22]. For clinicians, there is an unmet need to identify patients more likely to benefit from treatment. Thus, to dispose of predictive markers of response and to support the decision to continue treatment when better outcome has been detected early. Thus, to improve patient management, avoid side effects when sorafenib has proved ineffective, and control health expenses and clinical research. Numerous clinical, plasma and tumor-derived biomarkers have already been studied. Some of them have been proposed as predictive surrogate markers of activity of sorafenib and other antiangiogenic agents. Furthermore, Response Evaluation Criteria in Solid Tumors (RECIST) criteria[23,24] were proposed to evaluate tumor size changes during treatment in patients with cancer. Novel imaging techniques and radiological methods were suggested to strengthen the standard RECIST criteria in HCC to evaluate, directly in patients, the effects of drugs on tumor angiogenesis.

Herein, we review the current knowledge about prognostic/predictive and pharmacodynamics biomarkers for sorafenib and other antiangiogenic agents in advanced HCC and their potential integration into clinical practice. We also discuss the place of functional imaging to evaluate tumor response in advanced HCC. The Tables 1-3 give an overview of different studies of biomarkers in advanced HCC referred to in this review.

BIOMARKERS

Definitions, why biomarkers?

The national institute of health defined "biological marker (biomarker): a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention"[25]. Additionally, Ludwig *et al*[26] defined biomarkers as molecular, cellular or functional quantifiable or quantitative parameters indicative of particular genetic, epigenetic histological or cytological tumor abnormality. Initially, biomarkers were used for risk assessment and screening in cancers and later, to enhance cancer staging, to refine prognosis and to evaluate the response to biological therapy[27]. Biomarkers could then be clinical, biological, molecular or imaging parameters. Identifying prognostic and predictive biomarkers to antiangiogenic therapies is a crucial issue in HCC to be integrated into clinical care in the future. Previously, some predictive biomarkers of anticancer therapy response were identified in the field of oncology. Indeed, the efficacy of anti-epidermal growth factor receptors, such as cetuximab and panitumumab, in metastatic colorectal cancer is limited to proto-oncogene proteins p21(ras) (KRAS) wild-type cancer[28-30]. Other predictive biomarkers are used in clinical practice. For instance, the human epidermal growth factor receptor 2 expression in gastric and breast cancers to predict response to trastuzumab[31-33] and pertuzumab[34]. Moreover, gefitinib and erlotinib showed significant efficacy in patients with specific endothelial growth factor receptor (EGFR) mutations[35,36]. Recently, proto-oncogene proteins B-raf (BRAF) V600 E mutation in patients with metastatic melanoma was proved to be predictive of response to vemurafenib[37]. Regarding HCC, biomarkers should ideally meet at least the following criteria[26,38]: (1) to be easily measurable through minimally invasive procedures, ideally using blood tests; (2) to have a prognostic value in relation to the natural history and the outcome of HCC; (3) to have a predictive value wherein its presence correlates with the clinical response to sorafenib therapy; and (4) preferably not to be detectable in premalignant diseases (*e.g.*, cirrhosis).

Clinical biomarkers

Positive impact of drug-related cutaneous adverse events on clinical outcome was initially reported in patients treated with epidermal growth factor receptor inhibitors for advanced colorectal cancers[29,39], non-small-cell lung cancers[40] and pancreatic cancers[41]. Some retrospective studies have shown in patients with advanced HCC treated with sorafenib a positive association with early skin drug-related toxicities and clinical benefit[42-44] and

Table 1 Association between baseline circulating markers and outcome in patients treated with various treatments for hepatocellular carcinoma

Ref.	Markers	Patients (*n*)	Study design	Treatment	Level values	Clinical impact	Conclusion/comments
Schoenleber *et al*[85]	VEGF-A	1018	Systemic review and meta-analysis including only serum-based studies	Various (surgery, LRT and systemic therapies)	High serum VEGF level	Poorer OS Poorer DFS	Serum VEGF method detection varied among studies Serum VEGF levels seem more reliable than tissue VEGF for HCC prognosis
Poon *et al*[115]	bFGF	88	Prospective	Surgery	High serum level > 10.8 pg/mL	Larger tumor > 5 cm Venous invasion	High bFGF serum level before surgery was shown to be an independent factor of early recurrence. No further studies confirmed these findings
Vejchapipat *et al*[105]	HGF	55	Retrospective	BSC	High level (≥ 1.0 ng/mL	Advanced pTNM stage Poorer prognosis Poorer OS	Although a control group was included, results of this small cohort study need confirmation in larger prospective analysis
Chau *et al*[104]		40	Retrospective	Resection	High portal and serum HGF level (> 699 pg/mL)	Multiple tumor Poorer prognosis	One limit of this study were the feasibility in routine of intraoperative puncture of the portal vein was difficult
Mizuguchi *et al*[106]		100	Retrospective	Resection	High serum level (≥ 0.35 ng/mL)	Postoperative complications Poorer OS	No correlation was observed between HGF level and RFS
Kaseb *et al*[87]	IGF-1	288	Prospective	Various	Low plasma level (26 ng/mL)	High Child-Pugh score High AST level High tumor size Multiple tumor Vascular invasion Poorer OS	The authors proposed that IGF-1 plasma level to be integrated into the BCLC staging system to predict OS for personal management in patients with HCC. This proposal was not yet adopted in clinical practice

BCLC: Barcelona clinic liver cancer; bFGF: Basic fibroblast growth factor; BSC: Best supportive care; DFS: Disease-free survival; HGF: Hepatocyte growth factor; IGF-1: Insulin growth factors 1; LRT: Loco-regional treatment; OS: Overall survival; RFS: Recurrence-free survival; VEGF: Vascular endothelial growth factors.

disease control[44,45] (Table 4). Recently, the Barcelonan group reported the results of a prospective single-arm, monocentric study that assessed the link between early sorafenib-related skin toxicities and outcome in patients with advanced HCC[46]. Added to baseline performance status and barcelona-clinic-liver-cancer staging system[47], early sorafenib-induced skin reactions were an independent predictor of overall survival (OS). Patients who experienced skin adverse events have a better outcome compared to patients without any cutaneous reactions. The time to progression (TTP) was significantly longer in the first group (8.1 mo, 95%CI: 1.6-14.5, *vs* 3.9 mo, 95%CI: 2.08-5.7; $P = 0.016$) as well as OS (18.2 mo, 95%CI: 11.9-24.4, *vs* 10.1 mo, 95%CI: 10.1-13.0; $P = 0.009$)[46]. Accordingly, early skin reactions during sorafenib treatment may indicate antitumor effect and clinical benefit in patients with advanced HCC. These findings support the need to maintain treatment provided that these side effects are well managed.

Arterial hypertension is a frequent side effect observed in patients treated with antiangiogenic agents. The incidence of arterial hypertension in patients treated with sorafenib for advanced cancers was estimated at 23.1%[48]. Previous studies showed a positive link between arterial hypertension due to bevacizumab and outcome in patients with advanced colorectal cancer[49,50] and renal cell cancer[51] or related to axitinib in pancreatic cancer[52]. However, a recent systematic review of all placebo-controlled phase Ⅲ trials with bevacizumab failed to demonstrate any positive impact of drug-related arterial hypertension and clinical benefit [progression-free survival (PFS) and OS] in patients with advanced cancers[53]. Sorafenib-induced arterial hypertension was reported to be predictive of clinical benefit in patients with metastatic renal cell cancer[54]. Estfan *et al*[55] found in a small cohort of patients with advanced HCC that arterial hypertension related to sorafenib correlated with better OS[55]. These results were not reproduced in other retrospective[42] and prospective[46] studies. Thus, no robust data is available to prove the link between an increase in blood pressure during sorafenib treatment and clinical benefit or antitumor activity for HCC (Table 4). In summary, no clinical biomarkers of response to sorafenib were validated in clinical practice. Based on the Barcelonan prospective study, cutaneous adverse events seem to be the best track to explore in patients treated with sorafenib for advanced HCC. These results should be interpreted with caution since no untreated control arm was evaluated in this study.

Circulating biomarkers

Alpha-fetoprotein: Serum alpha-fetoprotein (AFP) is the only biomarker that passed all five phases of

Table 2 Prognostic value of baseline circulating factors in patients treated with systemic therapies including antiangiogenic agents for advanced hepatocellular carcinoma

Ref.	Marker	Patient (*n*)	Study type	Treatment	Levels values	Prognostic value	Conclusion/comments
Kaseb *et al*[86]	VEGF-A	394	Systemic review including only serum or plasma-based studies	Various (AA alone or combined with CT)	High serum or plasma level	Poorer outcome	Plasma VEGF seemed more relevant than serum VEGF as prognostic factor for HCC
Llovet *et al*[63]		490	Prospective phase Ⅲ trial	Sorafenib *vs* placebo	High plasma level (> 101 pg/mL)	Poor OS Better clinical/ demographic parameters	The VEGF level was a prognostic factor for all patient's cohort but surprisingly it did not affect prognosis in patients receiving sorafenib. Moreover, the VEGF level did not predict response
Llovet *et al*[63]	HGF	251	Prospective phase Ⅲ trial	Sorafenib *vs* placebo	High plasma level	Poorer OS	HGF was a prognostic factor for the entire cohort. However, it does not predict response to sorafenib (only a nonsignificant trend)
Miyahara *et al*[112]	Ang2	30	Prospective?	Sorafenib	High serum level	Shorter PFS Progressive disease	The small cohort and the lack of control arm hamper conclusion on the role of Ang2 as predictive of response to sorafenib
Llovet *et al*[63]		490	Prospective phase Ⅲ trial	Sorafenib *vs* placebo	High plasma level (> 6043.5 pg/mL)	Poorer OS Better clinical/ demographic parameters	Ang2 was shown to be a prognostic factor in HCC but did not predict response to sorafenib
Llovet *et al*[63]	c-KIT	245	Prospective phase Ⅲ trial	Sorafenib *vs* placebo	High plasma level (> 11.3 ng/mL)	Trend to a better OS Trend to better TTP Better clinical/ demographic parameters	Soluble c-KIT was shown to be a prognostic factor for HCC. However, it showed only a nonsignificant trend to predict response to sorafenib
Llovet *et al*[63]	IGF-2	254	Prospective phase Ⅲ trial	Sorafenib *vs* placebo	High plasma level (> 797.7 ng/mL)	Better OS Better clinical/ demographic parameters	IGF-2 was shown to be prognostic factor in HCC but did not predict response to sorafenib
Shao *et al*[126]	CEC/ CECP	40	Prospective	Sorafenib + CT	High CECP level	Poorer PFS Poorer OS	The predictive value of CECP was not confirmed in further investigations

AA: Antiangiogenic; Ang2: Angiopoietin 2; CEC: Circulating endothelial cells; CECP: Circulating endothelial cell progenitors; c-KIT: Stem-cell factor receptor; CT: Chemotherapy; HCC: Hepatocellular carcinoma; HGF: Hepatocyte growth factor; IGF-2: Insulin growth factor 2; OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression; VEGF: Vascular endothelial growth factors.

biomarker development as defined by Pepe *et al*[56]. AFP remains a useful prognostic marker and probably a predictive marker of treatment response in HCC (Tables 5 and 6). In a large Chinese retrospective cohort, high serum AFP level correlated with larger HCC size, vascular invasion and low tumor differentiation[57]. Previous studies showed that AFP levels could be useful to predict recurrence after surgery[58,59], liver transplantation[60-62]. The value of AFP as a prognostic marker was reported in several studies evaluating sorafenib in advanced HCC. The SHARP trial[12] is a phase 3, placebo-controlled trial that studied the benefit of sorafenib *vs* placebo in 602 patients with advanced HCC. Llovet *et al*[63] showed in patients included in this study that high baseline AFP plasma levels (> 200 ng/mL) have a negative impact on OS[63]. These findings confirmed previous results reported with sorafenib a small cohort of patients with advanced HCC[64], in retrospective analysis[65]. High baseline serum AFP level (≥ 400 ng/mL) also seemed associated with shorter TTP[63]. Noticeably, in a recent analysis of six prospective phase Ⅱ trials evaluating systemic therapies for patients with advanced HCC, no association between baseline AFP levels and prognosis was observed[66]. More interestingly, some authors evaluated the kinetics of AFP during treatment in HCC as a predictive marker of response or outcome. Previous studies showed a positive correlation between the decrease of AFP plasma levels and objective response and OS in patients with advanced HCC receiving systemic therapies[67,68]. Small series reported the value of baseline and changes in AFP plasma levels to predict response and outcome for patients with advanced HCC treated with sorafenib. Several studies showed consistent correlation between early (varying from 2 to 8 wk) decrease of AFP level more than 20% following sorafenib and objective response[69-73] and better outcome[69-71,73] in patients with advanced HCC. Personeni *et al*[71] showed that early responders, defined by a 20% decrease of AFP 8 wk after sorafenib treatment, had significantly better median OS and TTP compared to non-responders (13.8 mo *vs* 8.2 mo, P = 0.022 and 7.9 mo *vs* 2.4 mo, P = 0.004; respectively)[71]. In a recent study, Nakazawa *et*

Table 3 Treatment-induced changes in biomarkers levels and association with outcome in patients with hepatocellular carcinoma

Ref.	Marker	Patient (*n*)	Study design	Treatment	Marker treatment-induced changes	Impact value	Comments
Llovet *et al*[63]	VEGF-A	490	Prospective phase Ⅲ trial	Sorafenib *vs* placebo	Increase	No association with OS and ORR	The VEGF-A could serve as pharmacodynamic marker of exposure to sorafenib but did not have prognostic or predictive value
Harmon *et al*[93]		37	Prospective single arm phase Ⅱ	Sunitinib	Reversible Increase	Better DCR Better PFS Better OS	Inconsistent results were observed in these trials.
Zhu *et al*[91]	VEGF-C	34	Prospective single arm phase Ⅱ	Sunitinib	Sustained increase	No predictive value	The value of VEGF-A to predict response to sunitinib could be confirmed in larger trial
Harmon *et al*[93]		37	Prospective single arm phase Ⅱ	Sunitinib	Decrease	Better DC Better ORR	The predictive value of VEGF-C was not shown for sorafenib probably because of its limited action against the VEGFR-3
Harmon *et al*[93]	sVEGFR-2/ sVEGFR-3	37	Prospective single arm phase Ⅱ	Sunitinib	Reversible decrease	Better OS (for sVEGFR-2)	The small cohort did not allow a definite conclusion
Zhu *et al*[91]		34	Prospective single arm phase Ⅱ	Sunitinib	Decrease	No predictive value	
Llovet *et al*[63]	Ang2	490	Prospective phase Ⅲ trial	Sorafenib *vs* placebo	No significant change (for sorafenib) Increase (for placebo)	Shorter TTP Shorter OS (for patients who experienced increase)	Ang2 was probably a prognostic biomarker than predictive of response to sorafenib
Llovet *et al*[63]	c-KIT	245	Prospective single arm phase Ⅱ	Sorafenib *vs* placebo	Decrease (sorafenib) no change (placebo)	No predictive value	Tumor expression of KIT was considered as low in HCC, and the role of soluble KIT remains unclear
Zhu *et al*[91]		34	Prospective single arm phase Ⅱ	Sunitinib	Decrease	Better TTP Better OS	
Harmon *et al*[93]		37	Prospective single arm phase Ⅱ	Sunitinib	Decease	Better TTP	
Boige *et al*[98]	CEC	36	Prospective single arm phase Ⅱ	Bevacizumab	Early increase	Better OR Better DCR	CEC level was not associated with prognosis in this study. However, it could predict response to bevacizumab. The rarity of CEC level and non-standardized measurement methods limited the use of CEC as a predictive marker of response to treatment in HCC
Zhu *et al*[91]	CECP	34	Prospective single arm phase Ⅱ	Sunitinib	Decrease	Progression	

Ang2: Angiopoietin 2; CEC: Circulating endothelial cells; CECP: Circulating endothelial cell progenitors; c-KIT: Stem-cell factor receptor; DCR: Disease control; HCC: Hepatocellular carcinoma; ORR: Objective response; OS: Overall survival; PFS: Progression-free survival; sVEGFR: Soluble vascular endothelial growth factors receptor; TTP: Time to progression; VEGF: Vascular endothelial growth factors.

al[74] did not find a significant link between pretreatment AFP levels and tumor response in patients with advanced HCC treated with sorafenib. However, an early increase in AFP levels correlates with poorer outcome with shorter OS and PFS[74].

Japanese groups proposed the lens culinaris agglutinin reactive AFP (AFP-L3), an isoform of AFP, as a good diagnostic and prognostic biomarker for HCC[75-77]. However, scant data is/are available regarding the value of AFP-L3 as predictive of response to antiangiogenic agents in HCC[78].

In summary, available data are not consistent enough to confirm the value of baseline AFP level as a predictive marker of response to antiangiogenic treatment for patients treated for advanced HCC[79].

Des-gamma-carboxy prothrombin: Des-gamma-carboxy prothrombin (DCP) is a prognostic factor for HCC as shown by Japanese research[80]. Changes in DCP plasma level were evaluated in patients treated with sorafenib[73,81,82]. Some studies reported that DCP could be an independent factor of survival in patients

Table 4 Clinical side effects induced by sorafenib in patients with advanced hepatocellular carcinoma and association with outcome

Ref.	Side effect	Patients (*n*)	Study design	Impact on survival	Impact on other parameters	Predictive value
Otsuka *et al*[42]	Skin reaction	94	Retrospective	Better OS	No impact on ORR, DCR, and TTP	No
Vincenzi *et al*[45]		65	Retrospective	Trend to a better OS	Better DCR Better TTP	Early skin toxicity could predict efficacy of sorafenib
Di Costanzo *et al*[43]		65	Retrospective	Better OS	Not reported	Skin toxicity could predict survival
Shomura *et al*[44]		37	Retrospective	Better OS	Better DCR	Skin toxicity could predict efficacy
Reig *et al*[46]		147	Prospective	Better OS	Better TTP	Early skin reaction could predict efficacy of sorafenib and survival
Otsuka *et al*[42]	Arterial hypertension	94	Retrospective	No impact	No impact	No
Estfan *et al*[55]		41	Retrospective	Better OS	Trend to better TTP	

DCR: Disease control rate; OS: Overall survival; ORR: Objective response rate; TTP: Time to progression.

Table 5 Prognostic value of baseline and increase of alpha-fetoprotein for hepatocellular carcinoma in patients who underwent resection or transplantation

Ref.		Patient (*n*)	Study design	Treatment	Level values	Impact value	Comments
Liu *et al*[57]	AFP	2034	Retrospective	Resection (79.2%) NA (20.8)	High AFP levels (> 20 μg/L)	Large tumors (≥ 10 cm) Higher vascular invasion Lower differentiated tumor	This large cohort study showed that High AFP level was associated with poor prognosis and poor clinicopathological features of HCC
Wang *et al*[139]		160	Retrospective	Resection	High AFP level (> 4000 UI/L)	Shorter median TTR	In this study, the value of AFP levels to predict recurrence is limited since only a few numbers of patients (9%) have AFP level higher than the cutoff level
Ma *et al*[58]		108	Retrospective	Resection	High AFP level (> 20 ng/mL)	Lower differentiated tumor Higher vascular invasion Higher postoperative 2-yr recurrence rate Lower 24-mo survival rate	This study demonstrated the negative impact of high AFP levels on surgery benefit and the need to closely screen patients after resection for recurrence
Ikai *et al*[59]		12118	Japanese nationwide Analysis Comparative study	Resection	High AFP level (≥ 20 ng/mL)	Worsen OS after surgery	This large cohort study showed better outcome of patient resected for HCC in the last decade but the persistence of the negative impact of high AFP level on prognosis
Vibert *et al*[60]		153	Retrospective	LT	AFP level increase > 15 μg/L per month	Lower OS Lower RFS Higher recurrence rate	This study showed the negative impact on the outcome of AFP levels increases in patients undergoing LT
Hakeem *et al*[61]		12159	Systemic review	LT	AFP > 1000 ng/mL (based on the majority of study included in the review)	Poorer OS Poorer DFS Higher vascular invasion Poorer differentiated tumor	The authors stressed the poor quality of previous studies and the need for high-quality evidence on outcomes to use AFP levels as a prognostic indicator for patients undergoing LT
Duvoux *et al*[62]		972	Prospective/ retrospective	LT	High AFP level	Tumor recurrence Vascular invasion Poor differentiation	A new score model including AFP level was proposed to select patients for LT

AFP: Alpha-fetoprotein; DFS: Disease-free survival; HCC: Hepatocellular carcinoma; LT: Liver transplantation; NA: Not available; RFS: Recurrence-free survival; TTR: Time to recurrence.

treated with sorafenib[81,82]. These results were not reproduced in other reports[73]. DCP is currently used mainly in Japan and should be investigated more in a western HCC population.

Vascular endothelial growth factors: The vascular endothelial growth factors (VEGF) is one of the potent pro-angiogenic factors implicated in cancer angiogenesis. The activation of the complex VEGF/VEGF receptor (VEGFR) stimulates endothelial cell growth, proliferation, invasion and survival[83]. Circulating VEGF level may be useful in evaluating VEGF expression in HCC tumor[84] and were found suitable for HCC prognosis[85]. The VEGF-A isoform promotes angiogenesis and the dual VEGF-C/VEGF-D isoforms stimulates the lymphangiogenesis through activation of

Table 6 Prognostic and predictive value of baseline or changes of alpha-fetoprotein level for patients with hepatocellular carcinoma treated with antiangiogenic therapies alone or combined with systemic therapies

Ref.		Patients (*n*)	Study design	Treatment	Level values	Clinical impact	Comments
Shim *et al*[160]	AFP	57	Retrospective	Sorafenib	High level ⩾ 400 ng/mL	Shorter TTP	This study suffers from some limits: a retrospective study, a small cohort including only hepatitis B patients, short median follow-up duration, lack of correlation with OS or ORR
Shao *et al*[69]		72	Prospective	Various AA + CT	AFP response (> 20% decrease from baseline within the first four weeks)	Better DCR Better ORR Better PFS Better OS	The magnitude of AFP decline (20% or 50%) from baseline was not clearly defined. Similarly, the time point for evaluation of AFP level was not clear also (4 wk? 7 wk?). Limits: a small number of patients with heterogeneous treatment
Yau *et al*[70]		94	Retrospective	Sorafenib	AFP response (> 20% decrease from baseline within the first six weeks)	Clinical benefit rate Better PFS Marginal better OS	The cutoff value to define AFP response was inconsistent between various studies
Personeni *et al*[71]		85	Retrospective	Sorafenib	AFP response (> 20% decrease from baseline within the first six weeks)	Better DCR Better TTP Better OS	The authors used the landmark method to limit the potential favorable outcome due to tumor features than to AFP response
Køstner *et al*[72]		76	Retrospective	Sorafenib	AFP response (> 20% decrease from baseline within the first four weeks)	Better ORR	No correlation was observed between AFP response and OS probably because of the limited number of patients evaluated and the unusual poor OS seen in all cohort (5.4 mo)
Kuzuya *et al*[73]		48	Retrospective	Sorafenib	AFP response (decrease from baseline within 2 and 4 wk)	Better DCR Better TTP Better OS	Limits of the study: retrospective design and the small number of patients included
Nakazawa *et al*[74]		59	Retrospective	Sorafenib	AFP response (increase from baseline within four weeks)	Progressive disease Shorter PFS Shorter OS	Limits of the study: a small number of patients was enrolled in this and retrospective study. No association between AFP level before treatment and tumor response was observed
Llovet *et al*[63]		491	Prospective Phase Ⅲ trial	Sorafenib vs placebo	High plasma level > 200 ng/mL	Poorer OS	The impact of baseline AFP on survival was observed in both groups of patients treated with placebo or sorafenib
Hsu *et al*[64]		53	Prospective single-arm Phase Ⅱ trial	Sorafenib + mT/U	> 400 ng/mL	Poorer OS?	The prognostic value of baseline AFP level was shown only in univariate analysis and only score CLIP ⩾ 3 was an independent prognostic factor of poor OS
Baek *et al*[65]		201	Retrospective	Sorafenib	⩾ 400 ng/mL	Shorter FFS Poorer OS	Baseline AFP level, tumor size, PS, albumin and bilirubin levels were the independent factor associated with OS in this study
Lin *et al*[66]		156	Systemic review of the prospective phase Ⅱ trials	Various systemic therapies	⩾ 400 ng/mL	No impact	Limits of the study: heterogeneous population
Shao *et al*[119]		45	Pooled analysis of single-arm phase Ⅱ trials	Sorafenib + mT/U and beva + C	> 400 ng/mL	No impact	This study especially focused on the impact of IGF factors on outcome and the small cohort analyzed limits the interpretation of the effect of AFP levels on survival

AA: Antiangiogenic; AFP: Alpha-fetoprotein; Beva: Bevacizumab; C: Capecitabine; CLIP: Cancer of the liver Italian program[161]; CT: Chemotherapy; DCR: Disease control rate; FFS: Failure-free survival; mT/U: Metronomic tegafur/uracil; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PS: Performance status; TTP: Time to progression.

the VEGFR-2 and VGEFR-3 respectively. Several studies showed that high baseline levels of VEGF-A impacts negatively on prognosis in patients with advanced HCC[63,85-87]. Ebos *et al*[88] demonstrated that monitoring of soluble VEGFR-2 (sVEGFR-2) in mouse tumor models could be suggestive of the overall circulating VEGF levels and therefore, a potential surrogate biomarker for VEGF-dependent tumor growth[88]. An inverse link between sVEGFR-2 plasma levels and tumor size was detected. Recently, sVEGFR-1 levels were shown to be associated with more advanced-stage HCC and tumor differentiation and sVEGFR-2 levels to be associated with

poorly differentiated tumor[89]. Llovet *et al*[63] reported changes of plasma VEGF level in patients treated for HCC enrolled in the SHARP study. Compared to baseline level, a significant increase in plasma level of VEGF was observed in the sorafenib group (P = 0.010) and a significant decrease in plasma level of sVEGFR-2 and sVEGFR-3 was seen in the placebo group (P < 0.0001)[63]. The increase of VEGF plasma level found after sorafenib treatment was somewhat surprising since sorafenib showed OS improvement. However, similar findings were observed in patients treated with sorafenib for renal cell carcinoma[90], with sunitinib for advanced HCC[91-93] or renal cell carcinoma[94-96]. Increase of VEGF plasma level could be subsequent to hypoxia induced by the antiangiogenic agents[94]. Noticeably, a reversible increase in the VEGF level induced with sunitinib was also observed in non-tumor-bearing mice suggesting a systemic response that possibly masks tumor-specific changes or any difference in responding patients. Therefore, the increase in VEGF in response to treatment could also occur independently of tumor[97] and might explain the absence of correlation between this change and the outcome in HCC patients treated with antiangiogenic agents[63]. In the SHARP trial, the increase of VEGF-A plasma concentration during sorafenib treatment observed in patients with advanced HCC did not predict OS or tumor response[63]. Similarly, no association between VEGF-A plasma level changes and outcome was observed in patients treated with bevacizumab for advanced HCC[98]. Accordingly, the VEGF-A could serve as a pharmacodynamic marker of exposure to antiangiogenic agents but did not have prognostic or predictive value[85]. Sunitinib induced in patients with HCC, a reduction of VEGF-C (the ligand of VEGFR-3) plasma level that was associated with disease control and tumor response according to the RECIST criteria[23] and Choi criteria[99,100] respectively[93]. Likewise, sunitinib-induced decrease of sVEGFR-3 plasma levels in patients with renal cell cancer and breast cancer correlated with a better outcome[95,101]. Baseline level of VEGF-C may be regarded as a potential predictive biomarker of sunitinib efficacy in patients with advanced HCC[92,93]. However, as sorafenib has limited action against the VEGFR-3[102], the value of this biomarker to predict response in HCC patients could be anecdotal.

In summary, further robust studies are warranted to demonstrate the predictive value of circulating VEGF in patients treated with sorafenib or other antiangiogenic agents for advanced HCC. The plasma VEGF should be assessed more than serum VEGF because it was more reproducible and consistent in estimating the activity of VEGF[86].

Hepatocyte growth factor: The hepatocyte growth factor (HGF) is a strong promoter of hepatocarcinogenesis through the activation of the HGF axis and its receptor MET[103]. Previous studies showed that high serum levels of HGF in patients with HCC negatively associated with OS and outcome[104-106]. In the recent SHARP study biomarkers analysis, patients treated with sorafenib experienced a decrease in a mean plasma level of HGF although; patients treated with placebo have mean HGF concentration increase[63]. Added to circulating stem-cell factor receptor (c-KIT) and angiopoietin 2 (Ang2) concentrations, HGF level was shown to be an independent factor of survival in patients with advanced HCC[63]. Low baseline HGF plasma level trends toward better OS (12.4 mo *vs* 6.3 mo, P = 0.073) and TTP in patients treated with sorafenib for HCC[63]. Noticeably, in contrast to plasma levels, tissue HGF expression carries low prognostic information[107]. Further investigations are needed to identify the role of HGF as a predictor of response to sorafenib in patients with advanced HCC.

Ang2: Ang2, one of the families of angiopoietins, is an angiogenic factor implicated in tumor angiogenesis stimulation and progression in human HCC[108]. Tumor overexpression of Ang2 was associated with vascular invasion, tumor size microvessel density level, poorly prognosis HCC[108,109] and poor differentiated tumor[110]. Preoperative presence of Ang2 in the hepatic vein was also associated with portal invasion and poor outcome in HCC resected patients[111]. In a small uncontrolled cohort of patients treated with sorafenib for advanced HCC, the authors reported that Ang2 could predict the outcome[112]. High Ang2 serum baseline level was associated with PFS but not with OS in HCC patients treated with sorafenib[112]. Llovet *et al*[63] confirmed the negative impact on prognosis of baseline high plasma level of Ang2 in HCC. In patients treated with sorafenib or placebo, median OS was significantly shorter in those with high baseline Ang2 plasma levels compared to those with low baseline concentrations (6.3 mo *vs* 14.1 mo, HR = 2.407; 95%CI: 1.9-3.03; P < 0.001). In the group of patients treated with sorafenib, no significant changes in median Ang2 plasma levels were observed during the treatment. However, concentration increase was reported in the group of patients treated with placebo[63]. Both patient groups treated with sorafenib or placebo that experienced an increase of Ang2 plasma levels during follow-up had shorter OS and TTP[63]. Ang2 seems, therefore, a prognostic factor of HCC aggressiveness but not an adequate predictive factor of sorafenib efficacy. Llovet *et al*[63] suggested that dosing Ang2 plasma levels during treatment with sorafenib could be an attractive option to monitor patients with advanced HCC.

Basic fibroblast growth factor: The basic fibroblast growth factor (bFGF) is one of the identified angiogenic factors with a potent stimulus for HCC growth[113]. Tumor overexpression of bFGF seems mainly implicated in HCC invasiveness than tumor neovascularization[114]. Moreover, a significant correlation between high preoperative serum bFGF level and larger tumor, venous invasion, advanced tumor staging and early recurrence was reported in resected HCC[115]. In the SHARP study,

no difference was observed concerning changes in mean bFGF plasma concentration between sorafenib and placebo in patients with advanced HCC[63].

Stem-cell factor receptor - KIT: The role of stem-cell factor receptor and its soluble forms has not been entirely elucidated in HCC. Soluble forms of KIT were fundamentally implicated in tumor-cell survival and proliferation[93]. Llovet *et al*[63] reported a trend to a positive impact of high baseline soluble c-KIT level on OS and TTP in patients treated with sorafenib. Sorafenib induced a significant decrease in mean plasma levels of soluble c-KIT, unlike the placebo that resulted in no changes in c-KIT concentration[63]. Likewise, following exposure to sunitinib, plasma levels of soluble c-KIT decreased significantly in patients with renal cell carcinoma[95], breast cancer[101] and HCC[91-93]. SHARP biomarker analysis showed a nonsignificant trend of soluble c-KIT in predicting sorafenib response in patients with advanced HCC. In the sorafenib cohort, patients with high baseline soluble c-KIT level showed better median OS and TTP compared to those with low soluble c-KIT level but without reaching significance (10.4 mo *vs* 9.4 mo, P = 0.081 and 6.7 mo *vs* 4.1 mo, P = 0.052; respectively)[63]. In a phase Ⅱ study, Zhu *et al*[91] reported that soluble KIT plasma levels decrease following 14 d of sunitinib treatment in patients with advanced HCC and correlated with better PFS and OS. Similarly, improvement of TTP and trend towards better OS were reported when soluble KIT plasma level decreased from baseline following sunitinib in patients with HCC, metastatic breast cancer and neuroendocrine tumor[93,95,101]. Nowadays, the role of soluble c-KIT in HCC pathogenesis remains unclear since the expression of this protein kinase in HCC tissue appears to be anecdotal[116].

Insulin growth factors: The insulin growth factors (IGF) signaling pathway, including its ligand, IGF-1, and IGF-2, plays a crucial role in carcinogenesis of various tumors[117,118]. In patients with HCC, independently to the tumor stage, low baseline IGF-1 plasma level correlated with poorer OS[87]. In a small cohort of patients with advanced HCC receiving first-line antiangiogenic treatment associated with metronomic chemotherapy, serum levels of IGF-1 could predict treatment efficacy in this population. Indeed, high baseline IGF-1 serum levels before treatment correlate with better OS, PFS and disease control rate[87]. Moreover, high baseline IGF-2 plasma levels associated with a better OS in the placebo group enrolled in the SHARP trial[63]. In this large phase Ⅲ controlled trial, the IGF-2 failed to predict response to sorafenib in patients with advanced HCC[63] confirming previous results observed with other antiangiogenic agents[119].

Circulating endothelial cells and circulating endothelial cell progenitors: In preclinical models, levels of circulating endothelial cells (CEC) and bone-marrow-derived CEC progenitors (CECP) were shown to be potential surrogate markers of angiogenesis[120,121]. High circulating level of CECP in patients with HCC correlates with advanced disease[122]. Previous studies reported levels of CEC and CECP decrease and return to normal values following antiangiogenic therapy in cases of complete remission[123]. Willett *et al*[124] showed that high doses of bevacizumab induce an increase of viable CEC and CECP percentage in a small cohort of patient with rectal cancer. Bevacizumab treatment induced in patients with advanced HCC, an early increase of viable CEC levels that correlated with objective response[98]. In patients with imatinib-resistant gastrointestinal stromal tumor, sunitinib induced early, but not subsequent increase of CEC blood levels that seemed to be correlating with clinical benefit[125]. Otherwise, sunitinib was shown to cause a decrease of CECP level in patients with advanced HCC[91]. Shao *et al*[126] showed that high baseline CECP level, but not CEC level, was associated with poor OS in patients treated with sorafenib combined with metronomic chemotherapy. The value of CEC and CECP levels as biomarkers of angiogenesis and antiangiogenic therapies in HCC needs further prospective analysis. In fact, methods and techniques of measurement were inconsistent, and unreliable results were reported depending on the type of study (clinical or preclinical studies), cancer types, and antiangiogenic agents[98,115,116,121].

In summary, none of the above biomarkers is validated to predict response to sorafenib in patient with advanced HCC. Except the SHARP biomarkers analysis study, the majority of available data was reported from no control arm retrospective studies. Validation through further large, controlled randomized trials are required to confirm the predictive value of such predictive biomarkers so to be integrated with clinical use. Moreover, techniques used to assess drug-induced variation in circulating factors should be standardized for reliable interpretation. An important issue should also be questioned of whether the presence or change in circulating biomarkers could discriminate between treatment benefit and tumor resistance or escape.

Tissue biomarkers

In addition to tissue prognosis markers obtained from tumor samples, some studies tried to identify predictive factors of response and outcome following anticancer agents. Table 7 summarizes studies evaluating tissue biomarkers used as prognostic and predictive of HCC. Abou-Alfa *et al*[127] evaluated the impact of tumor expression of phosphorylated extracellular signal-regulated kinase (pERK) and outcome in patients treated with sorafenib for advanced HCC. A high pretreatment tumor level of pERK correlated with TTP, but the survival impact was not analyzed. Tumor-cell expression and staining levels of pERK using immunohistochemistry analysis were performed in 33 patients. Patients with high pretreatment tumor-cell pERK expression had better TTP compared to those low staining intensity. The

Table 7 Prognostic and predictive value of tissue biomarkers evaluated in hepatocellular carcinoma

Ref.	Marker	Patient (*n*)	Origin of specimen	Method assay	Quantification	Marker level	Clinical impact
Mitsuhashi *et al*[108]	Ang2	46	Resected specimens	RT-PCR and IHC	Quantitative	High tumor Ang2/1 ratio	Tumor portal vein invasion Large tumor Increase MVD Poor OS
Zhang *et al*[109]		38	Resected specimens	RT-PCR	No	High tumor Ang2/1 ratio	Large tumor Portal vein invasion Metastasis
Torimura *et al*[110]		59	Resected specimens (19) and Biopsy (40)	RT-PCR and IHC	Semi-quantitative	High tumor Ang2	Poor differentiated tumor
Abou-Alfa *et al*[127]	pERK	33	Biopsy before sorafenib	IHC	Semi-quantitative	High tumor pERK	Better TTP
Ozenne *et al*[128]		20	Biopsy before sorafenib	IHC	Semi-quantitative	High tumor pERK	No impact
Hagiwara *et al*[131]	JNK	39	Biopsy before sorafenib	IHC and Western Blot	Quantitative	High JNK tumor	Lower ORR Poorer TTP Poorer OS
Peng *et al*[134]	pVEGFR-2	35	Resected specimen before sorafenib	RT-PCR and IHC	Semi-quantitative	Low tumor expression	Poorer OS
Poon *et al*[84]	VEGF	60	Resected specimen	IHC and ELISA	Semi-quantitative	High tumor expression	Advanced HCC stage

Ang2: Angiopoietin 2; ELISA: Enzyme-linked immunoadsorbent assay; IHC: Immunohistochemistry; JNK: C-Jun N-Terminal Kinase; MVD: Microvessel density; ORR: Objective response rate; OS: Overall survival; pERK: Phosphorylated extracellular signal regulated kinase; pVEGFR: Phosphorylated vascular endothelial growth factors receptor; RT-PCR: Real-time polymerase chain reaction; TTP: Time to progression.

authors speculated that tissue expression of pERK could be predictive of response to sorafenib since tumors with higher levels of pERK were associated with more sensitive, or responsive, to sorafenib[127]. Our immunohistochemistry analysis did not confirm these findings[128]. Indeed, immunophenotypical markers (including pERK, VEGF, CD34, CK19, and STAT3) were evaluated in 21 patients treated with sorafenib for advanced HCC. None of these tissue markers was predictive of survival in our population[128]. These inconsistent results could be explained by the significant variability of detection of ERK expression by immunohistochemistry between samples obtained from biopsies compared to their subsequent resected HCC specimens[129] and the potential for rapid dephosphorylation and variable time of tissue fixation[130].

Recently, a Japanese group found in patients treated with sorafenib for advanced HCC, a negative impact of tumor expression of phospho-c-Jun on outcome[131]. Tumor expression of phosphor-c-Jun was associated with low tumor response rate, shorter TTP and OS[131]. These data need further validation since limited samples were evaluated.

Otherwise, previous analysis showed that VEGF expression in HCC tumor was associated with aggressive disease and worse outcome[132,133]. Peng *et al*[134] showed that tumor expression of VEGFR (phosphorylated VEGFR-1 and VEGFR-2) could affect the outcome of patients treated with sorafenib for advanced HCC[134]. Using immunohistochemistry analyzes, low pVEGFR-1 and pVEGFR-2 expressions in previously resected HCC specimens; a subsequent treatment with sorafenib was associated with worse outcome and poorer OS. The authors postulated that high autocrine VEGF signaling activity in tumor tissue could be predictive of response and outcome in patients treated with sorafenib[134]. These results could be hampered somewhat by the retrospective feature of the analysis, the small number of patients included and the low feasibility in clinical practice.

Furthermore, overexpression of "stemness"-related proteins (including c-KIT, K19, and CD34) was shown to be associated with aggressive HCC and poor prognosis[135-138]. Recently, the stem-cell factor, a ligand of c-KIT, was shown to be an independent prognostic factor for HCC after resection[139]. In patients with low tumor expression of stem-cell factor, the median time to recurrence was 24 mo compared to 12 mo in patients with overexpression > 85% of the marker[139].

Microvessel density (MVD) was another tissue biomarker proposed to predict response to antiangiogenic agents. Willett *et al*[124] observed a decrease of tumor MVD following antiangiogenic therapies in rectal cancers and this parameter was suggested as predictive of clinical benefit. However, inconsistent results were reported in an exploratory analysis of a large pivotal trial evaluating the addition of bevacizumab to chemotherapy in patients with metastatic colorectal cancer[140]. The tumor MVD did not predict the survival benefit in this large trial[140]. Noticeably, measurement methods of MVD were not standardized explaining partially the inconsistent results[140]. MVD analysis of HCC tumor tissue was shown to have only prognostic value[141]. The feasibility of tumor MVD expression was very limited in clinical practice hampering its use in predicting response to antiangiogenic agents for HCC.

Some tissue markers of response were evaluated in HCC using other antiangiogenic agents. Tivantinib, a selective MET inhibitor, was evaluated in a second line setting through a randomized, placebo-controlled

phase Ⅱ trial in patients with advanced HCC[142]. In this study, tumor expression of MET influenced treatment benefit. Patients with tumor overexpression of MET clearly benefit from tivantinib treatment. High-MET tumor expression was associated with longer TTP on tivantinib compared to placebo (2.7 mo *vs* 1.4 mo, HR = 0.43, 95%CI: 0.19-0.97; *P* = 0.03) and OS (7.2 mo *vs* 3.8 mo, HR = 0.38, 95%CI: 0.18-0.81; *P* = 0.01). Interestingly, tivantinib did not show any benefit when tumor expression of MET was low[142].

Nowadays, no tissues biomarkers can identify patients who might respond to sorafenib. Tumor analysis data were/was unavailable in large clinical trials, probably because of lack of tumor samples biopsies since HCC diagnosis was frequently made according to imaging features[143,144].

IMAGING FEATURES AND FUNCTIONAL IMAGING

The clinical benefit of sorafenib with OS gain in patients with advanced HCC contrasted largely with a low objective response rate noted in this population. The low response rates could be considered as a sign of lack of antitumor activity in early phases of clinical trials but were favorably balanced by sustained tumor stabilization and small numbers of tumor progression in the waterfall plot activity. Fortunately, the decision to proceed with phase Ⅲ trials was not hampered by the apparent lack of tumor response.

Which response criteria to apply?

The conventional RECIST criteria[23,24] usually used for tumor response evaluation of conventional chemotherapy appear clearly inappropriate to evaluate the response to sorafenib in patients with advanced HCC. Major features were reported following antiangiogenic agents consisting of decreased tumor vascularization[145] and density[146] on computer tomography (CT) scans. The modified RECIST (mRECIST) criteria are a new assessment method proposed by Lencioni and Llovet[145] to overcome the limitations of RECIST criteria. They include vascularization and tumor arterial enhancement changes of the target lesion on CT. Other new criteria including European Association for the Study of the Liver (EASL) criteria and Choi criteria, that evaluated tumor density changes, were also proposed to evaluate tumor response to sorafenib in patients with HCC[100,146-148]. A representative case of discrepancies between these criteria is shown in Figure 1. Several studies used CT-scan evaluation to predict early response to sorafenib and to adjust treatment strategy according to the potential clinical benefit[100,147,149].

Edeline *et al*[147] showed in patients treated with sorafenib for advanced HCC that overall response rate was higher when mRECIST criteria were applied compared to RECIST criteria (22.7% *vs* 1.9%). Interestingly, tumor response assessment according to mRECIST criteria, reclassified 22.6% of patients as responders while they were initially categorized as having stable disease by RECIST criteria[147]. Our group found consistent results when alternative radiological criteria to RECIST were applied[100]. We evaluated early tumor response in 64 patients with advanced HCC treated with sorafenib using RECIST, mRECIST, Choi and EASL criteria[100]. These new criteria identified a higher objective response rate compared to the conventional RECIST criteria (varying from 51% for Choi to 28% and 28% for mRECIST and EASL respectively; compared to only 3% for RECIST criteria). Responder patients according to Choi criteria at the first tumor assessment had better OS compared to non-responders (22.4 mo *vs* 10.6 mo, 95%CI: 0.15-086; *P* = 0.097)[100].

Further evaluations of these new criteria in comparison to RECIST criteria are needed in prospective clinical trials evaluating sorafenib or other antiangiogenic agents for advanced HCC.

In summary, we believe that, combining early reduction of AFP levels following sorafenib initiation with new radiological criteria could be helpful in detecting patients who might benefit from antiangiogenic treatment and to propose better tailor-made strategy management.

Functional imaging

Various functional imaging tools [including contrast-enhanced ultrasound, dynamic contrast-enhanced magnetic resonance imaging (MRI) and dynamic contrast-enhanced CT and positron emission tomography (PET)] were proposed to evaluate the antiangiogenic effects[150] (Table 8). Functional imaging approaches consist of infusion of intravenous contrast agent that enhances vascular and tumor structures and the acquisition of sequential images before, during, and after injection.

Dynamic contrast-enhanced ultrasound

Some small cohort studies evaluated the useful of dynamic contrast-enhanced ultrasound (DCE-US) to predict early tumor response to sorafenib in patients with advanced HCC[151-153]. In a Japanese prospective monocentric study, a total of 37 patients with advanced HCC treated with sorafenib were evaluated using DCE-US, before treatment and on days 7, 14 and 28 of treatment[152]. Significant changes in different US perfusion parameters between responders and non-responders (according to RECIST and mRECIST criteria) were observed at the prescheduled time of the follow-up. Correlation between reduction in tumor blood volume 7 d after treatment initiation and better PFS and OS was found. The authors suggest that DCE-US performed earlier could be useful to identify patients with advanced HCC, who may benefit from sorafenib[152]. Consistent results were obtained in an Italian prospective study that enrolled 28 patients treated with sorafenib and monitored with DCE-US at baseline, days 7, 15 and 30 of treatment[154]. Early decrease of tumor vascularity

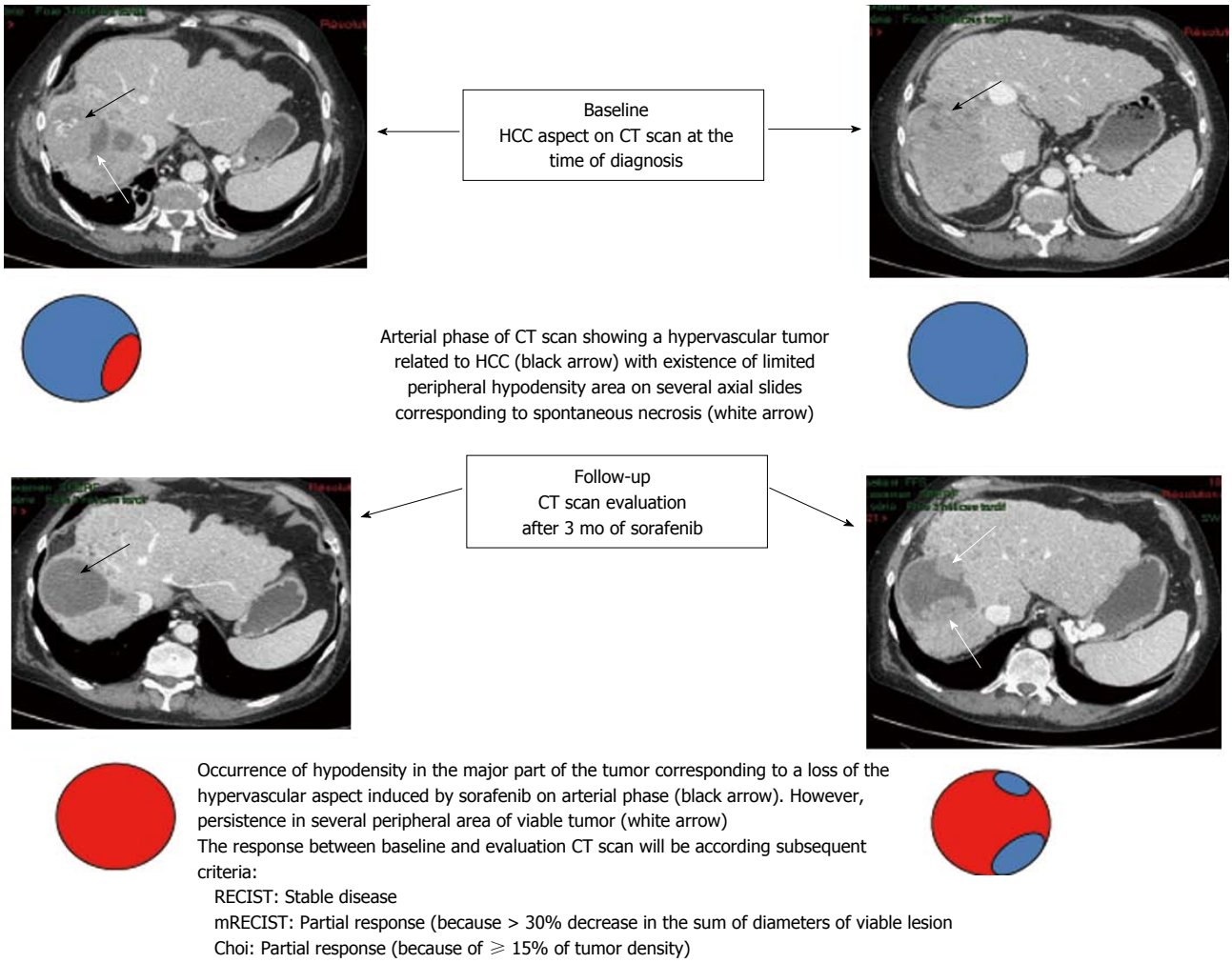

Figure 1 An illustrative case showing discrepancies between subsequent criteria used to assess tumor response in a patient treated with sorafenib for hepatocellular carcinoma. HCC: Hepatocellular carcinoma; CT: Computed tomography; RECIST: Response evaluation criteria in solid tumors; mRECIST: Modified RECIST.

Table 8 Value of functional imaging in patients with hepatocellular carcinoma treated with antiangiogenic agents

Ref.	Imaging tools	Patients (*n*)	Study design	Treatment	Imaging findings and clinical impact	Conclusion/comments
Sugimoto *et al*[152]	DCE-US	37	Prospective	Sorafenib	Tumor vascularity decreases and blood volume within seven days trends towards better PFS and OS	These studies enrolled small cohort of patients hampering adequate interpretation. However, DCE-US remains a promising noninvasive imaging, but operator dependent, to predict response in patients with HCC treated with sorafenib and larger cohort of patients should be evaluated
Zocco *et al*[153]		28	Prospective	Sorafenib	An early decrease in AUC and increase of median transit time was associated with better PFS and OS	
Zhu *et al*[91]	DCE-MRI	34	Prospective	Sunitinib	Decrease in vascular permeability was associated with better disease control	The decrease of vascular permeability induced by antiangiogenic agents seems to be a good predictive of tumor response and clinical benefit. These promising findings should be confirmed by largest cohort of patient
Hsu *et al*[156]		31	Prospective	Sorafenib + mT/U	A ⩾ 40% decrease in vascular permeability with 14 d was associated with better PFS and OS	
Lee *et al*[159]	FGD-PET	29	Retrospective	Sorafenib	SUV < 5.00 correlated with longer PFS and OS	Prospective studies are needed to evaluate the predictive value of the FDG-PET in HCC

AUC: Area under the time-intensity curve; DCE-US: Dynamic contrast-enhanced ultrasound; DCE-MRI: Dynamic contrast-enhanced magnetic resonance imaging; FGD-PET: 18F-fluorodeoxyglucose - positron-emission tomography; PFS: Progression-free survival; OS: Overall Survival; mT/U: Metronomic tegafur/uracil.

occurring during treatment was predictive of tumor response, better PFS and OS.

Dynamic contrast-enhanced magnetic resonance imaging

Dynamic contrast-enhanced magnetic resonance imaging has already been proposed to assess vascular disruption of antiangiogenic compounds in early clinical trials. However, this technique remains considerably more complex than conventional imaging and needs real expertise[155]. Using DEC-MRI, changes in tumor blood flow following VEGFR tyrosine kinase inhibitors were observed in patients with advanced HCC[91,156]. Significant decrease in vascular permeability (K^{trans}) and reverse reflux rate constant between the extracellular space and plasma (K_{ep}) were reported in patients with advanced HCC treated with sunitinib[91]. These changes were associated with better prognosis since the extent of decrease in K^{trans} was significantly greater in patients with partial response or stable disease compared to those with progressive disease or those who died early following sunitinib treatment[91]. DEC-MRI was also evaluated to predict response and benefit in 31 patients with advanced HCC treated with sorafenib plus metronomic tegafur/uracil[156]. In this study, K^{trans} before treatment was significantly higher in patients with partial response or stable disease compared to patients with progressive disease. Following 14 d of treatment, significant change in median K^{trans} was observed in responders compared to non-responder patients (-47.1% *vs* 9.6%; $P < 0.001$). The percentage of K^{trans} change following treatment was an independent predictor of tumor response, PFS, and OS. Better PFS, and OS was seen when a vascular response, defined as $\geqslant$ 40 decrease in K^{trans} at day 14 of treatment, was detected (29.1 wk *vs* 8.7 wk, $P = 0.033$ and 53.0 wk *vs* 14.9 wk, $P = 0.016$; respectively)[156].

Currently, the use of DEC-MRI is limited to clinical research and has not been extended to routine practice. Further studies combining cost-effectiveness are needed to define the place of this innovative tool as predictive of tumor response and clinical benefit with sorafenib in advanced HCC.

^{18}F-fluorodeoxyglucos-PET

Few studies evaluated the prognostic value of ^{18}F-fluorodeoxyglucose-PET (18-FDG-PET) in patients receiving antiangiogenic agents for advanced HCC[157,158]. In a small cohort study, Lee *et al*[159] found that the degree of FGD uptake correlates with outcome in Korean patients with advanced HCC treated with sorafenib. Patients who experienced pretreatment standardized uptake values (SUV) < 5.00 had better PFS and OS compared to those with SUV $\geqslant$ 5.00[159]. Undeniably, such findings should be verified by prospective evaluation in large cohort patients. Finally, no data are/is available regarding the prognostic or predictive value of ^{18}F-fluorocholine, a PET tracer of lipid metabolism, that is supposed to be more sensitive than ^{18}F-FDG for HCC detection[158], in patients receiving antiangiogenic drugs for HCC.

In summary, several studies with antiangiogenic agents have shown the need for additional criteria, beyond RECIST criteria, for early evaluation of antitumor activity and identification of patients who could benefit from these therapies. Furthermore, promising findings of the correlation between biomarkers and radiological response were shown in some studies, warranting further validation in larger clinical trials.

Measurement of tumor hypodensity, intratumor necrosis, and vascular parameters are the main criteria to be explored by dynamic functional imaging. These parameters are not already validated, but they represent prospective radiological investigations of primary interest for the assessment of antiangiogenic therapy effects beyond tumor size.

CONCLUSION

The sorafenib success story in advanced HCC raised new questions regarding the suitable approach to select patients who would likely benefit from treatment, ideally before its initiation. In routine practice, identifying predictive tools and biomarkers of response or early resistance seems to be an unmet need. Nowadays, no one of biomarkers the cited above biomarkers was validated in routine. AFP and some proangiogenic factors, such as VEGF and Ang2, seem to be promising prognostic and predictive biomarkers in HCC. However, there is probably no single ideal biomarker to predict response to antiangiogenic agents.

Controlled-arm prospective studies are required to improve the robustness of result interpretation. New endpoints are necessary for these biomarkers, such as monitoring angiogenesis, predicting early treatment response or even before starting therapy, defining optimum biological dose and identifying early resistance to antiangiogenic agents. Translational research using sequential tumor biopsy analysis while the patient is his own witness could probably be the most reliable method to identify robust biomarkers. Furthermore, advances in functional imaging techniques could allow evaluation of these molecules in real time, by assessing tumor density rather than tumor size. New tumor assessment criteria, particularly in cases of stable disease according to RECIST, should be identified and validated through large prospective cohort analysis. Finally, combining imaging response and efficient circulating biomarkers such AFP or proangiogenic factors (*e.g.,* VEGF or Ang2) could be a practical option and may be helpful to detect patients more likely to benefit from antiangiogenic treatment and to propose better tailor-made strategy management.

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