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REVIEW

Advanced hepatocellular carcinoma and sorafenib: Diagnosis, indications, clinical and radiological follow-up

Stefano Colagrande, Francesco Regini, Gian Giacomo Taliani, Cosimo Nardi, Andrea Lorenzo Inghilesi

Stefano Colagrande, Francesco Regini, Gian Giacomo Taliani, Cosimo Nardi, Dipartimento di Scienze Biomediche, Sperimentali e Cliniche, Università degli Studi di Firenze-Azienda Ospedaliero-Universitaria Careggi, 50134 Florence, Italy
Andrea Lorenzo Inghilesi, Dipartimento di Medicina Sperimentale e Clinica, Università degli Studi di Firenze-Azienda Ospedaliero-Universitaria Careggi, 50134 Florence, Italy
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Correspondence to: Stefano Colagrande, MD, Dipartimento di Scienze Biomediche, Sperimentali e Cliniche, Università degli Studi di Firenze-Azienda Ospedaliero-Universitaria Careggi, Radiodiagnostica 2, Largo Brambilla 3, 50134 Florence, Italy. stefano.colagrande@unifi.it
Telephone: +39-055-7947189
Fax: +39-055-431970
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Abstract

Advanced stage hepatocellular carcinoma (HCC) is a category of disease defined by radiological, clinical and hepatic function parameters, comprehending a wide range of patients with different general conditions. The main therapeutic option is represented by sorafenib treatment, a multi-kinase inhibitor with anti-proliferative and anti-angiogenic effect. Trans-arterial Radio Embolization also represents a promising new approach to intermediate/advanced HCC. Post-marketing clinical studies showed that only a portion of patients actually benefits from sorafenib treatment, and an even smaller percentage of patients treated shows partial/complete response on follow-up examinations, up against relevant costs and an incidence of drug related adverse effects. Although the treatment with sorafenib has shown a significant increase in mean overall survival in different studies, only a part of patients actually shows real benefits, while the incidence of drug related significant adverse effects and the economic costs are relatively high. Moreover, only a small percentage of patients also shows a response in terms of lesion dimensions reduction. Being able to properly differentiate patients who are responding to the therapy from non-responders as early as possible is then still difficult and could be a pivotal challenge for the future; in fact it could spare several patients a therapy often difficult to bear, directing them to other second line treatments (many of which are at the moment still under investigation). For this reason, some supplemental criteria to be added to the standard modified Response Evaluation Criteria in Solid Tumors evaluation are being searched for. In particular, finding some parameters (cellular density, perfusion grade and enhancement rate) able to predict the sensitivity of the lesions to anti-angiogenic agents could help in stratifying patients in terms of treatment responsiveness before the beginning of the therapy itself, or in the first weeks of sorafenib treatment. This would bring a strongly desirable help in clinical managements of these patients.

Key words: Modified Response Evaluation Criteria in Solid Tumors; Diffusion weighted imaging; Barcelona clinic liver cancer; Advanced hepatocellular carcinoma; Sorafenib; Advanced hepatocellular carcinoma second line therapies; Perfusion weighted imaging; Response evaluation; Hepatocellular carcinoma follow-up; Response

Evaluation Criteria in Solid Tumors

Core tip: Advanced stage hepatocellular carcinoma comprehends a wide range of patients with different general conditions. The main therapeutic option is represented by sorafenib. Although the treatment has shown a significant increase in mean overall survival, only a part of patients actually shows benefits. Differentiating responder from non-responder patients is a pivotal challenge for the future. In particular, finding parameters quantitatively describing perfusion grade, and then able to predict the sensitivity of the lesions to anti-angiogenic agents could help stratifying patients in terms of responsiveness before the beginning of the therapy itself. This would bring a great help in management of these patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) represents the fifth most prevalent tumor worldwide and the third cause of cancer related death[1]. The feasibility of treatments and the linked prognosis largely vary because of the tumor characteristics that present wide variability in terms of local and extra-hepatic burden. Moreover, the differences in molecular features and aggressiveness of the tumor significantly influence the natural history of the disease. Finally, the management of HCC is also complicated, in the majority of patients, by its development on a background of a cirrhotic liver, that can compromise the viability of the appropriate treatment[2].

Advanced HCC represents a major problem, as a considerable portion of HCC is diagnosed at this stage despite the wide use of ultrasound for surveillance in patients with increased risk[3]. This stage of disease is related to a poor prognosis and is reported to be associated with a survival rate of about 25% at 1 year[4,5]. Unfortunately, patients with advanced HCC are not suitable for curative therapeutic strategies like surgery, loco-regional treatments or orthotopic liver transplant. Moreover, HCC has a significant resistance to classic radio- or chemotherapy, that represent the standard of care in the majority of advanced tumors. Although the setting changed with the introduction of the multi-kinase inhibitor named sorafenib in 2008 for the treatment of advanced HCC, relevant issues in the management of this disease are still open. In particular, this therapy owns a wide variability in the prolongation of the survival of these patients. Furthermore, sorafenib therapy has some significant side effects and is very expensive.

On this background, the aim of this review is to remind the main problems related to diagnosis, staging and treatment allocation in case of advanced HCC, the principal indications of sorafenib, how to evaluate and to predict the response to treatment and when a second line therapy is suitable.

DIAGNOSIS, STAGING AND TREATMENT ALLOCATION

The development of radiological techniques has radically changed the approach to the diagnosis of HCC in the past decade. According to the American HCC guidelines, in 2005 a diagnosis of HCC without biopsy could be made in presence of a mass > 1 cm showing characteristic arterial enhancement, observed in two different imaging modalities, either biphasic computed tomography (CT) or magnetic resonance (MR)[6]. In the following years the diagnostic accuracy of a single tomographic contrasted technique has been largely validated. The last American guidelines published in 2011 made possible the diagnosis of HCC in a cirrhotic patient when a nodule > 1 cm shows arterial enhancement and portal/delayed phase "washout", with the use of a single tomographic exam (CT or MR)[7]. Future guidelines may probably include the use of organ-specific contrast agents (CA), that have shown a high sensitivity in the detection of new HCC lesions and of post-surgical disease recurrence as well as a good potential in hypo-vascular HCC diagnosis[8-10]. This additional radiological advancement, which has been included in Japanese guidelines[11] and is currently used in clinical practice, might further reduce the diagnostic role of liver biopsy in HCC in the next years.

Many staging systems have been developed for HCC, and so far there is no international consensus for the use of a favored one. The barcelona clinic liver cancer (BCLC) is the staging system most widely endorsed in HCC evaluation[12]. It was developed in 1999 and refined during the following years[3,5,6,13,14]. Considering different parameters such as the tumor burden, the hepatic function and the presence of disease-related systemic symptoms, the BCLC individuates five different stages of disease and suggests the appropriate first line therapeutic strategy. Moreover, it considers the impact of treatment on overall survival (OS), linking the stage with the prognosis[3].

According to BCLC, advanced stage (BCLC-C) is defined by the presence of unresectable HCC with extra-hepatic spread (metastases or lymph nodes involvement) and/or vascular invasion (portal or segmental invasion) and/or systemic symptoms, defined by an Eastern Cooperative Oncology Group[15] performance status 1 or 2, with a liver function defined by a Child Pugh[16] stage not greater than B. It is easy to understand

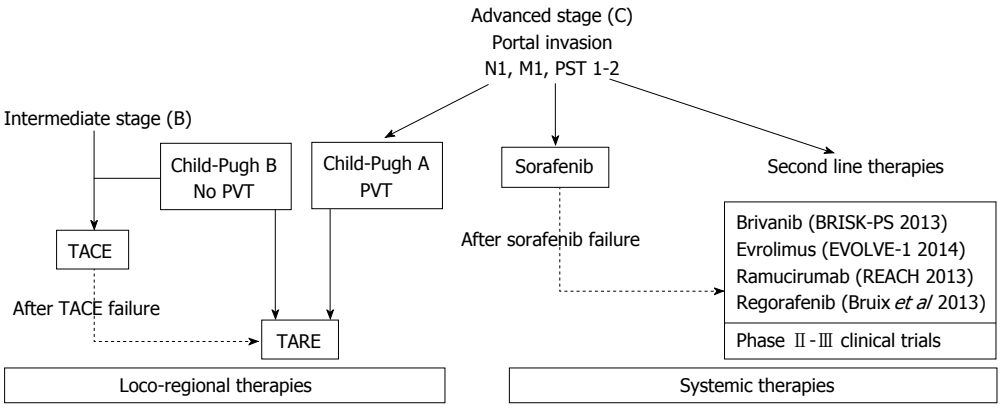

Figure 1 Main therapeutic options for advanced hepatocellular carcinoma treatment. TACE: Trans-arterial chemo-embolization; TARE: Trans-arterial radio embolization; PST: Performance status; PVT: Portal vein thrombosis.

how advanced stage HCC includes a heterogeneous population of patients, with different prognosis. For instance, the grade of liver function is significantly related to prognosis: patients with a Child Pugh B class have a shorter median survival (5 mo) than patients with more preserved liver function (7 mo)[5,17]. This stage of disease has been considered untreatable until 2008, when sorafenib has proven his efficacy in prolonging the survival of these patients in two different large studies[17,18]. Since then, sorafenib has become the suggested therapy for advanced HCC in the BCLC algorithm (Figure 1).

Despite its wide use, the definition of advanced HCC by the BCLC and the allocation of sorafenib show some minor flaws.

The first one is represented by the treatment of intermediate HCC, a stage of disease that includes a heterogeneous group of clinical presentations. Trans-arterial chemo-embolization (TACE)[3,5] is the recommended primary therapy for this stage, but some authors suggest its use also in selected BCLC-C patients with a better liver function[19,20]. Conversely some others consider TACE not safe in patients with so advanced disease and recommend this treatment only in patients with Child-Pugh A cirrhosis and segmental portal vein thrombosis[21]. Besides, the BCLC does not lead to a clear therapeutic indication for patients who cannot afford or have failed TACE. This problem has been partially solved through the introduction of the concept of "treatment stage migration": if patients are not candidates for first-line therapy as per stage, they can be shifted to the treatment option for a more progressed BCLC stage[3,5]. Translated in clinical practice, sorafenib should be administered also in intermediate HCC patients who can't afford or have failed the treatment with TACE. At the same time TACE may be considered a suitable alternative for advanced stage HCC patients who are not compliant with oral therapy or could not have access to sorafenib[22]. In the last years even the combined use of sorafenib and TACE for intermediate and/or advanced HCC has been evaluated in different studies[23-25]. However, data published so far about safety and efficacy of this therapeutic regimen is controversial and a precise validation is still needed.

The second problem is related to the notion that BCLC defines as "advanced HCC" any patient presenting an Eastern Cooperative Oncology Group performance status of 1-2. In clinical practice, it means that patients could be excluded from potentially curative treatments if they are "restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.*, light house work, office work"[15]. In our judgment, this approach could seriously limit the clinical benefit in this particular kind of patients. It should be stressed that every therapeutic choice, especially in this kind of patients, deserves a multidisciplinary approach, as every disease represents an unique case.

A relatively new promising therapeutic option for intermediate/advanced HCC is represented by trans-arterial radio embolization (TARE). Differently from TACE, its main effect is not related to a mechanic obstruction of the arteries that feed the tumor: by the use of yttrium-loaded glass or resin particles a localized beta radiation of the mass can be obtained[26] (Table 1). Although there are some absolute contraindications, represented by a tumor burden over 75% of liver parenchyma and lung or gastrointestinal uncorrectable shunts[26] (that may lead to development of a radiation induced pneumonia), TARE has emerged as a safe treatment option and showed survival rates similar to TACE and sorafenib in studies published so far[27,28]. In particular this therapeutic option may be considered an interesting alternative to TACE, especially in patients with portal vein thrombosis[29]. However, data from randomized control trials are needed in order to confirm the therapeutic role of TARE for HCC in clinical practice.

SORAFENIB TREATMENT

Sorafenib still represents the only approved therapy for advanced HCC[5]. It is a multi-kinase inhibitor with anti-angiogenic and anti-proliferative effect. It acts by inhibiting the serine-threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular

Table 1 Main loco-regional therapies in advanced hepatocellular carcinoma treatment

Loco-regional therapies
TACE is the most common used loco-regional treatment in patients with unresectable HCC, without macrovascular invasion or extrahepatic spreads (BCLC stage B)
The use of TACE in advanced HCC is controversial: some authors affirm its better efficacy in term of survival benefit, than the best supportive care in HCC with extrahepatic spreads and macrovascular invasion. Some other ones recommend to be careful and suggest its use only in selected patients with Child A cirrhosis and segmental portal vein thrombosis
TACE can be a valid alternative for advanced HCC patients who are not compliant with oral therapies or have severe side effects or could not have access to sorafenib because of health authorities or high cost
In advanced HCC, TARE shows survival rates similar to sorafenib and TACE, especially in patients with portal vein thrombosis
TARE contraindication: important arterial shunt to gastrointestinal tract or lung, any contraindication to catheterization

TACE: Trans-arterial chemo-embolization; TARE: Trans-arterial Radio Embolization; HCC: Hepatocellular carcinoma; BCLC: Barcelona clinic liver cancer.

endothelial growth factor receptors 1, 2, and 3 and platelet-derived growth factor receptor β[30-32]. Sorafenib, according to technical schedule, can be prescribed in patients with preserved liver function (Child-Pugh A) and it should be orally administered at 800 mg/die (400 mg twice a day). The therapy should be carried on until disease progression or unacceptable adverse effects (AE) occur[33]. Fatigue, diarrhea, hand-foot syndrome, bleeding, arterial hypertension and hepatic toxicity (represented by the elevation of transaminase and/or bilirubin) are some of the most frequent AE observed during treatment, and can compromise the quality of life during a therapy that in any case is palliative[34,35]. Sorafenib treatment cost varies from about 2600 to 5300€ per month, depending on the dose (400 mg/die *vs* 800 mg/die), with a mean cost about 4079 United States dollars per month[36].

Although sorafenib is the only drug which has indication for advanced HCC, only a few patients obtain a real benefit from this therapy. In general, the outcome and the extent of therapy is also linked to liver function: Child B patients have lower survival than Child A ones[37].

In the two largest studies published so far, "SHARP" and "Asia-Pacific", the main objective tumor response ratio according to Response Evaluation Criteria in Solid Tumors (RECIST) was only 2%-3% in the sorafenib group patients, and a stable disease was observed in 34%-43% of patients, with an OS only three months longer than placebo group[17,18]. In fact, in the first of these phase Ⅲ studies conducted comparing sorafenib (at 800 mg/die) and placebo with a double blind fashion on a total of more than 600 patients with advanced HCC[17], this drug showed a significant improvement in terms of OS (median OS 10.7 mo *vs* 7.9 mo of the placebo control group) and of time to progression, but the number of partial responses in the treatment group was low (7 out of 299)[17,38,39].

The increase in median OS was confirmed also in the second of the two abovementioned studies, conducted in China, Taiwan and South Korea on 226 advanced patients: mean OS was 6.5 mo in the treatment group against a 4.2 mo in the placebo arm[18]. Unfortunately the development of AE can reduce the compliance to therapy and worsen patient prognosis: in the SHARP study the incidence of AE was 70%-85% (*vs* 43%-60% in the placebo groups) but severe effects were observed in 9.4%-14.6% of patients[17]. The median duration of treatment was 5.3 mo (range, 0.2 to 16.1) and 176 of the patients in the sorafenib arm discontinued the study because of AE[17]. In both studies the most common significant AE causing a drug dose reduction (from 800 to 400 mg/die) were Hand-Foot Syndrome (10%-11% of patients) and diarrhea (5%-7%)[18].

Recent studies suggest that a dose reduced regimen of 400 mg/die could be equally effective in prolonging OS[40]. This data should advise the use of a "softer" regimen in patients who are more likely to develop AE during sorafenib treatment (*e.g.*, Child B7, elder patients). In those cases sorafenib could be started at reduced dose, *e.g.,* 400 mg/die, and "ramped up" to 600 or 800 mg/die if the patient shows a good profile of tolerability. Post-marketing clinical studies showed that only a portion of patients actually benefits from sorafenib treatment (Figure 2), and an even smaller percentage of patients treated shows partial/complete response on follow-up examinations (Figure 3), up against relevant costs and an incidence of drug related AE probably higher (24%-28% of severe AE) than reported in the SHARP and Asia Pacific studies[17,35,41].

Because of the problems related to the poor effectiveness of sorafenib and because of its cost, many studies tried to compare sorafenib to other commonly used treatments for unresectable HCC. Although, according to BCLC, TACE has no indication for advanced HCC, a study comparing this two different therapeutic options reported similar benefits from TACE and sorafenib in advanced stage HCC[42].

Association therapy of TACE and sorafenib has been investigated in some recent works that showed good results in term of safety and efficacy in BCLC-B patients[24,43], but its therapeutic role in BCLC-C patients is still unclear. In fact, most of the studies have shown that association therapy may improve time to progression, but it does not seem to improve OS if compared to TACE alone[44-47]. Conversely, Bai *et al*[48] have found some benefits in terms of OS, in patients treated with sorafenib plus TACE. This combination finds its theoretical physiological basis on the anti-angiogenic effect of the drug, in contrast with the physiological release of angiogenic factors consequent to the arterial iatrogenic obstruction[30]. Nevertheless the results about this kind of treatment are still uncertain[44].

In a recent study sorafenib has also been compared to TARE: median OS was similar in the two groups[49].

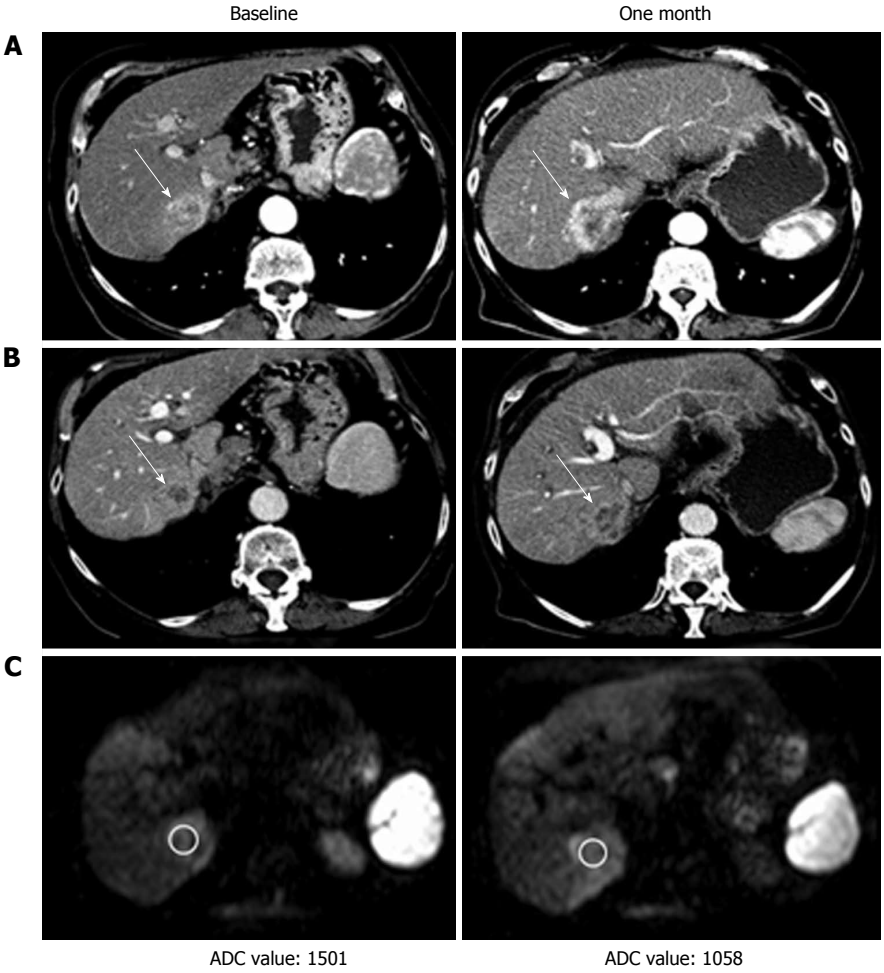

Figure 2 Computed tomography and magnetic resonance imaging examination at baseline and one month after the start of sorafenib therapy of patient showing progressive disease. A: Arterial phase computed tomography (CT); B: Venous phase CT; C: Magnetic resonance imaging diffusion weighted imaging. ADC: Apparent diffusion coefficient.

The extension of portal invasion resulted to be an important prognostic factor for the good result of TARE since patients with partial portal invasion of a branch of the vein had better prognosis than those who had disease extended to the main trunk[50]. The association of TARE and sorafenib has been investigated and showed good results in terms of safety, although data about OS with this combined therapy are still being investigated[51]. The physiological basis to combine these two therapies is that sorafenib seems to decrease the risk to develop a new lesion or distant metastasis, while TARE is more efficient in controlling primary hepatic lesion.

Ravaioli *et al*[52] reported two cases of advanced disease HCC that became suitable to liver transplantation after TARE treatment. TARE ability to downstage tumor has also been reported by other authors[53].

Over against its apparent simplicity, the treatment with sorafenib owns relevant open issues that can make the management problematic for the clinician. In fact, to reach a real benefit for the patients and to obtain a proper allocation of the money resources, it is crucial to identify a suitable method to evaluate response and hopefully early predictors of response and survival.

BIOCHEMICAL RESPONSE EVALUATION PARAMETERS

According to reported data we deduce that sorafenib therapy does not improve the prognosis in all advanced HCC patients and a part of responders have not such an important benefit to justify an expensive and rich in terms of AE therapy. Therefore, one of the primary objectives is to identify some biomarkers that may predict the efficacy of sorafenib treatment and may help the clinicians to select possible responder patients.

To clarify this point, many studies have focused on serum anti-angiogenic factors concentration; in particular, in the SHARP study, Llovet *et al*[17] found that low baseline concentration of vascular endothelial growth factor-A (VEGF-A) and high baseline concentration of Ang-2 correlated with a better OS in both arms of the study (sorafenib and placebo group). These data suggest that VEGF-A and Ang-2 are independent prognostic factors, but they have not a straight correlation with sorafenib therapy efficacy[54]. Similar results were shown in another study on patients treated with sorafenib and metronomic tegafur/uracil[55].The possible role of some cytokines

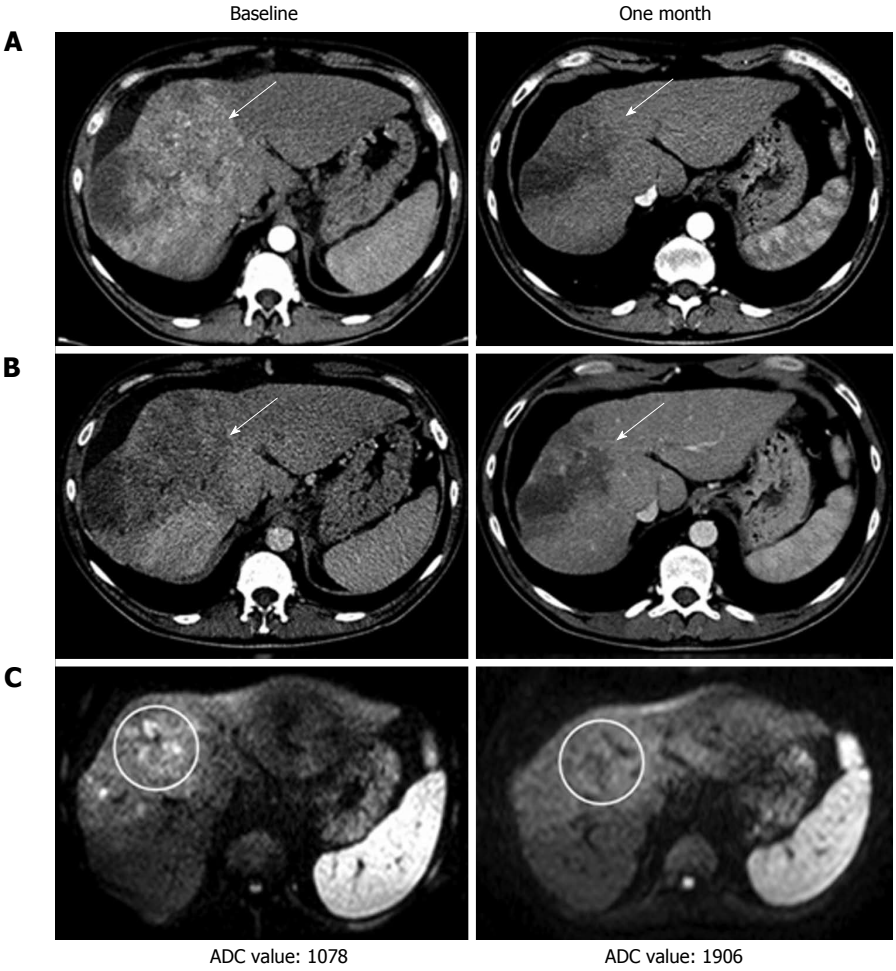

Figure 3 Computed tomography and magnetic resonance imaging examination at baseline and one month after the start of sorafenib therapy of a patient showing partial response. A: Arterial phase computed tomography (CT); B: Venous phase CT; C: Magnetic resonance imaging diffusion weighted imaging. ADC: Apparent diffusion coefficient.

[interleukin 6 (IL-6)/IL-8] as predictive biomarker of sorafenib treatment efficacy has also been evaluated, but no significant results have been found[56]. Some interesting, but preliminary results have been found using insulin-like growth factor-1 (IGF-1) baseline serum concentration: high IGF-1 blood levels seem to correlate with a better OS during anti-angiogenic therapy[57]. In the last years, great interest was devoted on serum alpha-fetoprotein (AFP) levels in HCC patients during systemic therapy: high basal levels of AFP generally correlate with a poor prognosis, both in intermediate and advanced HCC[54]. Personeni *et al*[58] analyzed a cohort of 85 patients treated with sorafenib and individuated a significant association between the decrease of > 20% in AFP in the first 8 wk and OS. Similar results have been found in other studies[59,60]. An important problem in the use of AFP as a biomarker is the difficulty in establishing a reference of percentage decrease (relatively to baseline values) as a cut-off to assess a response to therapy; in fact, an accepted worldwide threshold has not been defined, and the choice of this cut-off differed in the various studies, usually between 20% and 50%. Moreover, measuring the early change in AFP level seems to be a valid predictive factor only for patients who have higher baseline AFP serum level. For this reason, some authors suggest that only patients with pre-treatment AFP level > 200 microg/L are suitable for this analysis[61]. Despite the key role of AFP in diagnosis and follow-up of HCC, the effectiveness in outcome prediction during anti-angiogenic treatment is not clear yet, and needs to be evaluated in future.

In general, countless field-practice studies have analyzed the possible role of other biochemical and clinical parameters in early evaluation of response to sorafenib[40,62-67], *i.e.*, aspartate transaminase, alkaline phosphatase basal and on-going levels, as well as the development of AE such as hand-foot syndrome or diarrhea have been related to a significantly prolonged OS, that represents the ultimate goal of treatment in patients with advanced HCC.

IMAGING RESPONSE EVALUATION PARAMETERS

Evaluation by imaging is another important tool and is usually performed every 2-3 mo during sorafenib

treatment[68] by dynamic imaging (CT or MR contrast enhanced scan), applying the modified RECIST (mRECIST)[69].

The introduction of the mRECIST radically changed the approach to treatment response evaluation. While RECIST 1.1 is principally based on lesion dimensions without any consideration for tumoral vitality, mRECIST introduced the evaluation of the actual vital part of the lesions, which is the one that shows contrast enhancement at CT or MR.

Although the efficacy of mRECIST in tumor response evaluation in comparison with old RECIST 1.1 during sorafenib treatment has been recently confirmed by different studies[70,71], these criteria, based on vital lesions size measurements in time, still have some limitations. In fact, since sorafenib mainly operates through an anti-angiogenic effect, considering only the diameter of the vital portion is inadequate for a proper response evaluation. Some other parameters, able to quantitatively assess intralesional vitality or vascularization, are necessary to integrate mRECIST in order to make tumour response evaluation more reliable. It is proven that not all tumour progressions at imaging translate into a decreased OS and some improvements in prognosis have been shown in absence of tumour burden reduction[17,72]. This means that, even considering the increase in median OS, only a part of patients actually shows appreciable benefits, and those whose life expectancy is increased by the treatment are difficult to individuate since they rarely show a decrease in terms of lesion size/conspicuity. In other terms, the response does not correlate, at least initially, with a change in lesion dimension, but more probably it brings some intralesional decrease in cellularity and/or vascularization changes[30,72,73].

In this direction, the analysis of new radiological parameters in evaluation of response to sorafenib has shown promising results, and many attempts to evaluate different tumoral characteristics, such as intralesional perfusion and cellular density, have been performed so far.

Perfusion weighted imaging (PWI) is a relatively new MR/CT technique for qualitative and quantitative evaluation of the delivery of blood to biological tissues[74]. The importance of local changes in blood flow, angiogenesis and capillary permeability in cancer progression and treatment motivate the researchers' increasing interest in PWI. The primary mechanisms for the cancer lesions enhancement are the filling of the vasculature with CA enhanced blood, and the diffusion of this CA from the blood into the extravascular-extracellular interstitial spaces; these phenomena are increased by tumoral angiogenesis. An increase in blood flow leads to a more rapid CA filling of the vessels, with faster changes in signal intensity/density while a greater blood or extravascular-extracellular volume will increase the fraction of the voxel to be filled with CA[74,75]. In tumoral lesions the level of peak enhancement and the rate of passage of the extravasated CA back to the vessels, with a return of signal intensity/density to its baseline values, is altered. In order to use image signal intensities to track and analyze enhancement dynamics, in PWI it is necessary to form a temporally resolved series of images (multiple acquisitions on the same area) that tracks the signal/density changes in different times after the CA administration, in analogy to tracer studies in nuclear medicine[75,76]. CT PWI parameters evaluation have shown significant changes during sorafenib treatment, in particular with a reduction in intralesional mean transit time as possible consequence of the anti-angiogenic effect of the drug[68,76].

Simple parameters, which indirectly correlate with intralesional vascularization have also been elaborated: Ronot has recently presented that in follow-up during sorafenib treatment the use of CHOI criteria, based on intralesional density on arterial phase CT acquisition, has shown promising potentials in terms of tumor response evaluation, comparable to those of mRECIST, although with minor reproducibility[71].

Studies on perfusion changes during therapy were also developed in ultrasonography. Contrast enhanced ultrasound, a technique which is now available in a large number of centers, and that can be repeated more than once in the first weeks from the beginning of therapy has shown, despite some major limits (such as operator dependency and partial liver volume exploration) some promising results in early response evaluation during sorafenib treatment, since it is able to evidence changes in target lesions enhancement during treatment[77].

The role of MR diffusion weighted imaging (DWI) in response assessment has been evaluated as well with controversial results[78-80]. This MR technique is based on water diffusion, which is the inconsistent and random microscopic motion of molecules caused by thermal energy, also known as Brownian motion. Even the more basic DWI principles description is beyond the aim of this review. It is sufficient to know that DWI indirectly describes the cellular density and the architectural changes of a tissue[81,82]. In fact, if within a tissue or a tumor several cells and many architectural barriers are present (as fibrosis, edema, any type of disorders or derangements), water molecules have difficulties in free movements and so "diffusion" is low (and, in general, signal intensity increases). On the contrary, if the cellular density is low and environment homogeneous, water molecules freely move, "diffusion" is easy and in general signal intensity decreases[81]. DWI technique could then be able to show some intralesional changes that are not evident on standard CT/MR scans. As regards to early assessment by DWI, in general, some studies conducted on different tumoral lesions have shown that apparent diffusion coefficient (ADC) changes in the first few weeks of treatment may precede dimensional reduction since, early after the start of treatment, changes in cellularity and necrosis may occur[83-85]. Conversely to what has been observed in solid cancers during chemotherapy treatment[86], Schraml *et al*[79] found an unexpected decrease in

Table 2 Main systemic therapies in advanced hepatocellular carcinoma treatment

Systemic therapies
The only drug approved for the treatment of advanced HCC. Patients treated with sorafenib have longer OS then placebo group in the two largest studies
The efficacy of this treatment is linked to liver function: Child B patients have much lower survival than Child A ones (5.5 mo *vs* 11.3 mo). Child C patients have very poor prognosis and seem not to be suitable for sorafenib therapy (1.6 mo)
Patient treated with sorafenib has longer survival than those treated with sunitinib. No difference in OS has been found comparing sorafenib treatment to brivanib
Some combination therapies have been proposed, but none of these has shown superiority compared to sorafenib alone
At now there is no therapeutic plan approved as second line in advanced HCC pretreated with sorafenib
Some drugs as capecitabine, brivanib, sunitinib, everolimus have been tested in monotherapy, moreover some combination therapies as erlotinib with sorafenib, and gemcitabine with oxaliplatin have been evaluated as second line options, but all of them have not given significant results
Many studies are still in progress and some interesting, but preliminary results have been obtained in patients with high expression of c-met in treatment with brivanib

HCC: Hepatocellular carcinoma; OS: Overall survival.

HCC mean intralesional ADC values in the first 3-4 wk of sorafenib therapy (maybe due to some micro-hemorrhagic intralesional injury), with a subsequent increase at 3 mo evaluation[79].

Also in case of DWI, the main limitation remains the large variability of data (both in different acquisitions and in different centers and scanners), which reduces the reproducibility of this technique[87,88]. However it has also been demonstrated that timing of imaging is relevant: changes in ADC could precede changes in tumor size but may even disappear after a certain time because of repair mechanisms such as edema decrease and necrosis organization[89,90]. The early changes in intralesional ADC described by Schraml *et al*[79] in advanced HCC could be expression of some intralesional temporarily changes, preceding an eventual dimensional reduction and expressing a possible sensitivity to sorafenib action[79].

Until now, none of the aforementioned radiological technique has been positively tested in a large number of patients, but the good results obtained so far are suggestive for a possible integration of some of these parameters to standard follow-up and response evaluation.

Even more important would be the prediction of the response based on pre-treatment examinations. This continues to be controversial. From a general point of view, tumors with necrotic areas, often surrounded by hypoxic but viable cells, were shown being less sensitive to ionizing radiation[91], more prone to aggressive behavior and probably less sensitive to cytotoxic agents[92]. In case of HCC, on the contrary to what reported for other solid tumors, higher ADC values on DWI baseline images could be related to a minor cellular density and a higher vascularization, and this could be somehow an index of treatment sensitivity (particularly in case of anti-angiogenic drug such as sorafenib itself), while low levels of intralesional ADC could correlate with a worse prognosis a poor response to treatment, as shown by some studies, since they could be expression of a poorly vascular lesion with high cellular density[80]. In these terms also a CT/MR pretreatment evaluation could give some additive information about tumor cellular density and vascularization, and maybe help stratifying patients in terms of anti-angiogenic therapies sensitivity.

Data available in this field are still limited and controversial, but more researches will certainly be made, as being able to identify patients with high probability of response before or shortly after the start of the therapy is strongly desirable.

Even if the first encouraging results will be confirmed in a larger scale, the addition of CT/MR perfusion parameters evaluation to a routinely liver study and then the quantitative evaluation on a per patient basis is not possible yet. The main problems related to perfusion studies are some technical difficulties and the acceptable, but suboptimal reproducibility of these parameters, particularly with MR; while the greatest limitation in DWI use is the mentioned large standard deviation of the measurements and then the low reproducibility[93,94].

SORAFENIB FAILURE AND SECOND-LINE THERAPIES

As already mentioned, no other systemic treatment other than sorafenib have, so far, shown the capability to improve the OS in patients with advanced HCC.

Despite the results in terms of survival during treatment, only a very small percentage of patients actually shows benefits in terms of radiological staging[17,18], so it is still discussed whether sorafenib treatment should actually be prolonged also in case of tumor progression at first follow-up examinations[56,95]. Anyway, even in case of evident benefits from the treatment, most of the patients experience a loss of efficacy of the drug during time[96].

There is then a strong request from clinicians for an established second line therapy to propose to patients when sorafenib cannot be administered or has to be interrupted due to AE or loss of efficacy (Table 2).

Metronomic capecitabine has been largely used as second line treatment in patients showing progressive disease after sorafenib treatment mainly because of its high tolerability[97].

In the randomized controlled trial that compared brivanib *vs* placebo as second-line therapy after sorafenib failure[98], the improvement of time to progression observed in brivanib arm did not translated in an increased OS[72]. An interesting phase Ⅲ trial comparing sunitinib with sorafenib has shown similar results in terms of time to progression between the two drugs, but

with worse results for sunitinib in terms of survival[99]. The use of brivanib and the combination of erlotinib with sorafenib have also been tested but failed in phase Ⅲ trials[72,100-102].

From ongoing studies, the most promising results come from the observation of a significantly better outcome in patient with high expression of c-met treated with tivantinib[103]. From these data, a large phase Ⅲ trial in second line is currently ongoing.

Although, it has been demonstrated that HCC patients who respond to TACE usually have poor response to a subsequent sorafenib treatment[104], as we mentioned above the possible role of the synchronous use of both therapies is also being investigated[105].

CONCLUSION

Advanced stage HCC is a category of disease defined by clinical, functional and radiological parameters, comprehending a wide range of patients with different general conditions, but with poor prognosis and life expectancy.

Since 2008 the main option for this stage of disease is represented by systemic treatment with sorafenib, that mainly shows an anti-angiogenic effect.

Although the treatment has shown an increase in OS in different studies, only a part of patients actually shows some benefits with a little percentage of partial response, while the incidence of drug related significant AE and the economic costs are high.

Being able to properly differentiate responder from non-responder patients as early as possible is then a pivotal challenge and could spare several patients a therapy often difficult to bear, directing them to some other second line treatment, at now under investigation.

For this reason, some supplemental parameters as biochemical and radiological prognostic factors are being searched for. In particular, finding some parameters quantitatively describing perfusion grade, and then able to predict the sensitivity of the lesions to anti-angiogenic agents could help in stratifying patients in terms of treatment responsiveness before the beginning of the therapy itself.

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