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REVIEW

Challenges of advanced hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is an aggressive malignancy, resulting as the third cause of death by cancer each year. The management of patients with HCC is complex, as both the tumour stage and any underlying liver disease must be considered conjointly. Although surveillance by imaging, clinical and biochemical parameters is routinely performed, a lot of patients suffering from cirrhosis have an advanced stage HCC at the first diagnosis. Advanced stage HCC includes heterogeneous groups of patients with different clinical condition and radiological features and sorafenib is the only approved treatment according to Barcelona Clinic Liver Cancer. Since the introduction of sorafenib in clinical practice, several phase Ⅲ clinical trials have failed to demonstrate any superiority over sorafenib in the frontline setting. Loco-regional therapies have also been tested as first line treatment, but their role in advanced HCC is still matter of debate. No single agent or combination therapies have been shown to impact outcomes after sorafenib failure. Therefore this review will focus on the range of experimental therapeutics for patients with advanced HCC and highlights the successes and failures of these treatments as well as areas for future development. Specifics such as dose limiting toxicity and safety profile in patients with liver dysfunction related to the underlying chronic liver disease should be considered when developing therapies in HCC. Finally, robust validated and reproducible surrogate end-points as well as predictive biomarkers should be defined in future randomized trials.

Key words: Barcelona Clinic Liver Cancer; Portal vein thrombosis; Modified Response Evaluation Criteria in Solid Tumors; Advanced hepatocellular carcinoma management; Advanced hepatocellular carcinoma second line therapies; Sorafenib

Core tip: Hepatocellular carcinoma (HCC) is an aggressive malignancy, which accounts for great part of all cancer deaths each year. Its management is com-

plex, and although the surveillance performed, many patients have an advanced stage. This comprehends an heterogeneous groups with different clinical condition; sorafenib is the only approved treatment, however affected by many adverse events. No single agent or combination therapies have been shown to impact outcomes after sorafenib failure. Loco-regional therapies as TAE/TACE and TARE have also been tested and at now are under evaluation. This review will focus on patients with advanced HCC and highlights potential and limit of the therapies.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the deadliest malignancies, ranking third as a cause of cancer death in males. Despite the recognition of cirrhosis as the major risk factor for HCC, more than 50% of patients with HCC present an advanced disease at diagnosis[1]. Moreover, increased survival and better care for patients in earlier stages, allow their survival until they reach a more advanced stage.

The concept of "advanced" disease varies considerably analyzing the different staging systems utilized in the past ten years. One peculiarity of HCC is its association with chronic liver disease, especially cirrhosis. This makes prognosis of an individual patient dependent not only on the size, biologic behavior and spread of the tumor, but also on the degree of functional failure of the liver due to the presence of cirrhosis. The role of chronic liver disease in the prognosis of HCC is witnessed by the inclusion of the Child-Pugh score or other aspects linked to liver functions in several staging systems used for HCC (Table 1). In the Barcelona Clinic Liver Cancer (BCLC) staging system[2], advanced HCC is considered as an unresectable HCC with/without 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 performance status 1 or 2, with a liver function defined by a Child Pugh stage not greater than B[3,4].

In this review we discuss several aspects of the management of patients with advanced HCC, focusing on the unmet needs that have emerged in the past few years, specifically since the introduction of sorafenib in clinical practice.

SORAFENIB IN THE TREATMENT OF ADVANCED HCC

The treatment of patients with advanced HCC has been for a long time disappointing for physicians. Curative options such as surgical resection or liver transplantation did not show any efficacy in prolonging overall survival (OS). Trans-arterial chemoembolization (TACE) in patients with advanced HCC due to portal vein thrombosis has been suggested to improve OS compared to patients receiving supportive care, in retrospective studies[5] and in a recent meta-analysis, but is not currently recommended by practice guidelines[6]. Early systemic therapies with hormone analogues (*e.g.,* tamoxifen) or classic chemotherapeutic agents (*e.g.,* doxorubicin) failed when tested in randomized controlled trials[7]. In 2008 the approval of sorafenib in the until then desolated scenario of advanced HCC therapy radically changed the therapeutic approach, opening the era of molecular-targeted therapy. Till now, no additional molecules have yet been added to our pharmaceutical devices. Sorafenib is a multi-kinase inhibitor that suppresses tumor neo-angiogenesis and proliferation, inhibiting the tyrosine kinase activity of vascular endothelial growth factor receptors 1, 2 and 3 and of the platelet-derived growth factor receptor. It also inhibits the serine-threonine kinases Raf-1 and B-Raf[8,9]. The efficacy of sorafenib has been demonstrated in two large independent randomized controlled trials. In the SHARP and Asia-Pacific studies the Authors reported an improvement in OS of almost 3 mo between the sorafenib and placebo arms (10.7 mo *vs* 7.9 mo and 6.5 mo *vs* 4.2 mo, respectively)[10,11]. These results led to the approval of sorafenib for the treatment of advanced HCC. According to the technical schedule, the drug should be administered orally 400 mg b.i.d. until radiological progression or unacceptable adverse events occur.

Therapy is currently recommended in patients with preserved liver function, defined by a Child-Pugh score not greater than A, due to the exclusion of patients with more compromised liver function from randomized controlled trials. This represents a first major problem for sorafenib administration, as only a portion of patients can actually be treated. From the time of sorafenib approval, many field-practice studies have tried to evaluate the efficacy and tolerability of sorafenib in Child B patients, with conflicting results. The GIDEON study is so far the only prospective study that evaluated the impact of liver function in a large cohort of patients (> 3000), with a robust portion of subjects in Child-Pugh B class (666 patients)[12]. In the final analysis, overall adverse events were similarly observed in both Child A and B patients, but

Table 1 Variables included in the most widely used hepatocellular carcinoma staging systems

Staging system	Ascites	Tumor burden	Albumin	Bilirubin	INR	HE	AFP	PVT	EHS	PS	ALP
Okuda	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No
CLIP	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
BCLC	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
GRETCH	No	No	No	Yes	No	No	Yes	Yes	No	Yes	Yes
TNM 7th edition	No	Yes	No	No	No	No	No	Yes	Yes	No	No

AFP: Alpha fetoprotein; ALP: Alkaline phosphatase; EHS: Extrahepatic spread; HE: Hepatic encephalopathy; INR: International normalized ratio; PS: Performance status; PVT: Portal vein thrombosis.

a significant increase in serious adverse events was found in the Child B group. Moreover, Child-Pugh score was confirmed as a strong independent predictor of OS (5.2 mo in Child B *vs* 13.6 mo in Child A). The Authors concluded that sorafenib at full dosage is safe irrespective of the liver function. However, the use of full-dose sorafenib in a Child B patient is still far to be included in the clinical practice, as many physicians fear that the patients are too fragile in this subgroup. Additional trials specifically addressing this issue are ongoing (Sorafenib in First-line treatment of Advanced B Child Hepatocellular Carcinoma, clinicaltrial.gov).

An approach popular in the Hepatology community and potentially applicable to Child B patients is to start sorafenib at lower dosage (*e.g.*, 400 mg/d), ramping up to 800 mg/d in case of good tolerability. In case of poor tolerability, sorafenib should be continued at lower dosage, since data reported from the SOFIA group in 2011 did not show a reduction in OS in patients receiving half-dose sorafenib, whereas they actually had a significant survival advantage with respect to the group receiving full-dose sorafenib[13]. Another rationale for the implementation of a ramp-up strategy could be the lower tolerability profile of sorafenib that seems to emerge from clinical practice. According to those studies, some of the most common adverse events (fatigue, diarrhea, hand-foot syndrome, bleeding, arterial hypertension, elevation of aminotransferase and/or bilirubin) are observed more frequently, in terms of incidence and severity, than reported in the registration trials. This leads to take into consideration a primary issue in sorafenib therapy, *i.e.* that an appropriate quality of life represents an essential goal in a non-curative treatment.

Another hot issue that has emerged from the recent literature is linked to the wide variability in survival and time to progression (TTP) observed in clinical practice. It is a general opinion that sorafenib therapy may be truly effective in a subgroup of patients, while it shows no real benefit in others. Identifying early predictors of response represents therefore a crucial research area, that becomes even more important if we consider the economic burden of the therapy[14]. Numerous studies have explored the role of biochemical markers as prognostic factors or predictors of response. The concentrations of alpha-fetoprotein, alkaline phosphatase, angiopoietin 2, Vascular Endothelial Growth Factor have been linked to improved survival, while soluble c-Kit and Hepatocyte Growth Factor have been proposed as predictive markers infield practice studies[15-17] and in the SHARP trial. Observational studies have also linked the early development of adverse events like arterial hypertension, diarrhea or the hand-foot syndrome to a better response[18-23]. Finally, clinical features such as the presence of macrovascular invasion have been associated with a worse prognosis[21]. However, despite the large numbers of studies and the interesting results, no predictors have reached enough strength to be commonly used in clinical practice, due to the small sample size of most studies or to the lack of external validation of the findings. Therefore, although the aim of tailoring sorafenib therapy still appears exciting, tangible progresses will not be obtained without validation of parameters in large studies. Radiologic parameters also may represent an important tool in the management of sorafenib therapy.

As the majority of HCC develops in patients with chronic liver disease, treatment of the underlying condition and especially management of its complications, is mandatory. HBV infection accounts for about 60% of the total liver cancer in developing countries and for about 23% in developed countries[24,25]. The benefits of antiviral nucleot(s)ide analogue therapy in improving recurrence-free survival and OS after curative treatment of HCC[26] may suggest a possible role in improving outcomes also in advanced HCC, but at this time data on this topic are lacking.

BEYOND SORAFENIB: OTHER PHARMACOLOGIC APPROACHES TO THE MANAGEMENT OF ADVANCED HCC

The discovery of alternative lines of treatment for advanced HCC is an urgent unmet need. Sorafenib therapy is very expensive, and healthcare costs have become one of the main problems confronting governments and patients worldwide[27]. Thus, in countries with limited health resources and a high incidence of HCC, a cost-effectiveness analysis to show the overall advantages of sorafenib is necessary. A

Table 2 Results of studies with molecular targeted therapies as first line in advanced hepatocellular carcinoma

Treatment	Trial	OS	TTP	Ref.
Sorafenib	Phase Ⅲ *vs* placebo (SHARP)	10.7 mo *vs* 7.9 mo, $P < 0.001$; HR = 0.69; 95%CI: 0.55-0.87	5.5 mo *vs* 2.8 mo, $P < 0.001$	[10]
Sorafenib	Phase Ⅲ *vs* placebo (Asia-Pacific)	6.5 mo *vs* 4.2 mo, $P = 0.014$; HR = 0.68; 95%CI: 0.50-0.93	2.8 mo *vs* 1.4 mo, $P = 0.0005$; HR = 0.57; 95%CI: 0.42-0.79	[11]
Sunitinib	Phase Ⅲ *vs* sorafenib (SUN)	7.9 mo *vs* 10.2 mo, $P = 0.0019$; HR = 1.30; 95%CI: 1.13-1.50	4.1 mo *vs* 3.8 mo, one-sided $P = 0.8312$; two-sided $P = 0.3082$; HR = 1.13	[31]
Brivanib	Phase Ⅲ *vs* sorafenib (BRISK-FL)	9.5 mo *vs* 9.9 mo, $P = 0.3116$; HR = 1.07; 95%CI: 0.94-1.23	4.2 mo *vs* 4.1 mo, $P = 0.853$; HR = 1.01; 95%CI: 0.88-1.16	[32]
Linifanib	Phase Ⅲ *vs* sorafenib	9.1 mo *vs* 9.8 mo, P = NS; HR = 1.05; 95%CI: 0.90-1.22	5.4 mo *vs* 4.0 mo, $P = 0.001$; HR = 0.759; 95%CI: 0.64-0.895	[33]
Erlotinib	Phase Ⅲ erlotinib plus sorafenib and eorafenib plus placebo (SEARCH)	9.5 mo *vs* 8.5 mo, $P = 0.408$; HR = 0.929	3.2 mo *vs* 4.0 mo, P = NS; HR = 1.135; $P = 0.18$	[36]

OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression; CI: Confidence interval; HR: Hazard ratio; NS: Not significant.

Chinese study showed that the total cost was $897 for patients in the best supportive care (BSC) group, while in the sorafenib group, the total cost was $19495[27]. Second, sorafenib is often discontinued for patients in whom the disease is progressed after sorafenib treatment[28]. Many compounds and combinations have been explored in phase Ⅱ or even phase Ⅲ studies. Nevertheless, none of these have proven to be more effective than sorafenib as first-line therapy[29,30] nor to be superior to placebo in second-line studies.

First-line treatments

The results of the SHARP trials have been a milestone opening the way to systemic therapy in advanced HCC. Nonetheless, the limited results in terms of survival benefit over placebo indicate that more effective first-line treatments are needed (Table 2). In the phase Ⅲ SUN trial, sunitinib, a multi-kinase inhibitor inhibiting all vascular endothelial growth factor and platelet-derived growth factor receptors, was compared to sorafenib (400 mg) in patients with advanced HCC and the median OS was significantly shorter in the sunitinib arm (7.9 mo *vs* 10.2 mo) while TTPwas not significantly different (4.1 mo *vs* 3.8 mo with sunitinib and sorafenib, respectively)[31]. Of note, sunitinib was associated with severe adverse events, especially bleeding. The trial was prematurely discontinued for futility and safety reasons[31].

Brivanib is a dual inhibitor of Vascular Endothelial Growth Factor and fibroblast growth factor receptors. A randomized phase Ⅲ clinical trial has been conducted to evaluate the role of this drug as first-line therapy. The BRISK-FL study compared brivanib with sorafenib in patients with advanced HCC. This trial failed to meet the primary endpoint of improving OS (with 9.5 mo for brivanib and 9.9 mo for sorafenib) or other endpoints, including objective response rate, TTP (4.2 mo *vs* 4.1 mo) or disease control rates[32].

Linifanib is another multi-targeted tyrosine kinase inhibitor, which has been evaluated as first-line therapy in comparison to sorafenib. Linifanib inhibits members of the Vascular Endothelial Growth Factor and Platelet-derived growth factor receptors families. In the LIGHT phase Ⅲ trial, linifanib was compared to sorafenib for efficacy and tolerability in patients with advance HCC without prior systemic therapy. However, median OS was 9.1 mo on the linifanib arm and 9.8 mo on the sorafenib arm[33], although TTP with linifanib was prolonged as compared with sorafenib (5.4 mo *vs* 4.0 mo, $P = 0.001$). Therefore, this trial failed to meet its primary endpoint and safety results favored sorafenib, as grade 3/4 or serious adverse events leading to discontinuation, dose interruption or reduction were more frequent with linifanib[33].

Erlotinib is an orally active, potent and selective inhibitor of the human epidermal growth factor receptor, and its gene amplification has been reported in HCC[34], although recent large scale results indicate that this occurs in a limited number of cases[35]. This drug was tested in a phase Ⅲ trial, where the efficacy and safety of a first-line treatment with sorafenib and placebo *vs* the combination sorafenib/erlotinib was evaluated in patients with advanced HCC[36]. This trial failed to meet its primary endpoint, *i.e.,* an improvement in OS, the median values of which were 9.5 mo in the sorafenib plus erlotinib arm *vs* 8.5 mo in the sorafenib plus placebo group. Moreover, the median TTP (3.2 mo *vs* 4.0 mo) was not significantly different between the two arms[36]. Withdrawal rates for adverse events were higher in the sorafenib/erlotinib arm. With regard to the drugs combination, a randomized phase Ⅱ trial conducted in Child-Pugh A patients, comparing doxorubicin plus sorafenib or doxorubicin alone, combination therapy led to a longer median TTP (6.4 mo *vs* 2.8 mo, $P = 0.02$), OS (13.7 mo *vs* 6.5 mo, $P = 0.006$) and progression-free survival (6.0 mo *vs* 2.7 mo, $P = 0.006$) were observed[37].

The results of a phase Ⅲ study comparing sorafenib alone *vs* sorafenib plus doxorubicin have been recently presented in abstract form[38]. The addition of doxorubicin to sorafenib resulted in higher toxicity and did not improve OS or progression-free survival. In another phase Ⅱ study, first-line combination therapy with sorafenib and gemcitabine/oxaliplatin did

Table 3 Results of studies with molecular targeted therapies as second line in advanced hepatocellular carcinoma

Treatment	Trial	OS	TTP/PFS	Ref.
Brivanib	Brivanib *vs* placebo (BRISK-PS)	9.4 mo *vs* 8.2 mo, $P = 0.3307$; HR = 0.89; 95%CI: 0.69-1.15	4.2 mo *vs* 2.7 mo, $P < 0.001$; HR = 0.56; 95%CI: 0.42-0.76	[42]
Everolimus	Everolimus *vs* placebo (EVOLVE-1)	7.6 mo *vs* 7.3 mo, $P = 0.68$; HR = 1.05; 95%CI: 0.86-1.27	3.0 mo *vs* 2.6 mo, $P = 0.01$; HR = 0.93; 95%CI: 0.75-1.15	[44]
Ramucirumab	Ramucirumab *vs* placebo (REACH)	9.2 mo *vs* 7.6 mo, $P = 0.14$; HR = 0.87; 95%CI: 0.72-1.05	2.8 mo *vs* 2.1 mo, $P < 0.0001$; HR = 0.63; 95%CI: 0.52-0.75	[45]

OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression; HR: Hazard ratio.

Table 4 Principal ongoing studies in advanced hepatocellular carcinoma with new molecular targeted therapies

Study	Drug	Status
A multicenter, open-label, phase 3 trial to compare the efficacy and safety of lenvatinib (e7080) *vs* sorafenib in first-line treatment of subjects with unresectable hepatocellular carcinoma	Lenvatinib *vs* sorafenib	Active, not recruiting
Study of regorafenib after sorafenib in patients with hepatocellular carcinoma (RESORCE)	Regorafenib *vs* placebo	Recruiting
A study of dovitinib *vs* sorafenib in adult patients with hepatocellular carcinoma as a first line treatment	Dovitinib *vs* sorafenib	Completed (phase 2)
A study of nivolumab *vs* sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma	Nivolumab *vs* sorafenib	Recruiting

not result in longer OS or progression-free survival compared to sorafenib alone, although the primary endpoint (4-mo progression-free survival > 50%) was reached[39]. Conventional cytotoxic chemotherapy has been investigated in a first line, phase Ⅲ trial conducted in Asia and comparing the effects of oxaliplatin/fluorouracil with doxorubicin[40]. Significant benefits of FOLFOX were found on progression-free survival , while OS resulted significant only in a post-hoc analysis (6.5 mo *vs* 4.9 mo). Sorafenib in combination with other chemotherapeutic regimens, *e.g.* gemcitabine/oxaliplatin or capecitabine/oxaliplatin is currently being investigated in phase Ⅱ studies. Although the combination of cytotoxic chemotherapy and sorafenib is still being evaluated in clinical trials, this combination does not appear particularly promising.

Second-line

Patients who fail first-line systemic therapy are considered to have poor prognosis, and second-line trials are warranted[41] (Table 3). Brivanib was also investigated in the BRISK-PS (brivanib-post sorafenib) trial, where brivanib and placebo were compared in patients who progressed on/after or were intolerant to sorafenib. Although TTP was significantly longer in the brivanib arm than with placebo (4.2 mo *vs* 2.7 mo), the primary end point of the study was not reached, as no differences in OS were observed comparing brivanib and placebo (9.4 and 8.2 mo, respectively)[42]. It is possible that imbalances in patients' recruitment, favoring the placebo arm in terms of some parameters associated with a better prognosis, contributed to the failure of the BRISK-PS trial[43].

The human anti-vascular endothelial growth factor Receptor 2 antibody, ramucirumab, has been recently studied in a second-line, phase Ⅲ in comparison to placebo[44]. Median OS for the ramucirumab group was 9.2 mo *vs* 7.6 mo for the placebo group ($P = 0.14$), and thus the primary endpoint of the study was not reached. However, a subgroup analysis showed that patients with elevated alpha-fetoprotein could benefit from this treatment. Therefore, a phase 3, placebo-controlled trial testing ramucirumab as a second-line treatment in patients with elevated basal alpha-fetoprotein is currently recruiting patients (NCT02435433, clinicaltrials.gov, accessed April 25, 2016). Similarly, administration of everolimus to patients who failed sorafenib as a first-line treatment did not result in an improved OS over placebo (7.6 mo *vs* 7.3 mo)[45]. Other mammalian target of rapamycin inhibitors have been tested in phase Ⅰ-Ⅱ trials, but conflicting results have been reported[43].

Ongoing studies

Other compounds are currently under investigation in phase Ⅲ trial, the final results of which have not been yet reported. These include other compounds acting as antiangiogenic agents, including lenvatinib, regorafenib and dovitinib. These are summarized in Table 4. For a more complete discussion of ongoing studies and additional targets refer to a recent comprehensive review[43].

A promising approach has been obtained with the phase Ⅱ study investigating tivantinib, an inhibitor of the Met tyrosine kinase, the receptor for hepatocyte growth factor. In this study, patients overexpressing Met, the target of tivantinib, had a significant benefit over placebo[12]. Remarkably, expression of Met in patients receiving placebo was associated with a more aggressive behavior of the tumor, indicating that Met is both a therapeutic target and a prognostic biomarker. A phase Ⅲ trial comparing tivantinib and placebo as a

second line therapy is currently underway. Along the same lines, a trial comparing placebo and cabozantinib, a dual Met and Hepatocyte growth factor inhibitor, has been undertaken.

One of the most promising areas in the field of HCC is represented by immunotherapy. Expression of PD-1 and CTLA-4 on immune cells is associated with blockade of the anti-tumor immune response, favoring the progression of cancer[46]. In a Phase Ⅰ/Ⅱ study recently presented in abstract form nivolumab, an anti-PD-1 monoclonal antibody, induced tumor size stabilization or reduction in 67% of the patients[47]. In addition, the effects of this treatment were durable, as previously observed in other types of cancer. A phase Ⅲ study comparing the effects of sorafenib and nivolumab in advanced HCC is currently underway (Table 4).

Combination therapy

Sorafenib combined with classic chemotherapy: HCC is considered a poor responder to chemotherapy, which is not routinely used because of adverse events, particularly in patients with advanced cirrhosis. However, shrinkage of the tumor has been reported, although the magnitude of response is lacking consistency. This has led to the possibility to add sorafenib to a chemotherapeutic agent, as above reported, although the toxicity profile of any chemotherapeutic drug to be added to sorafenib should be kept in mind[48,49].

Sorafenib and TACE could be a promising strategies in advanced HCC treatment. The high rate of HCC recurrence after TACE may be due to its enhancement of angiogenesis and upregulation of Vascular Endothelial Growth Factor and platelet-derived growth factor receptors expression, which increases tumor angiogenesis. Therefore, combination of antiangiogenic agents with TACE, could potentially decrease the recurrence of HCC and improve survival. A phase Ⅲ study has been conducted in Japan and Korea using sorafenib in combination with TACE *vs* TACE alone. However, combination therapy failed to show any benefit in terms of TTP (sorafenib *vs* placebo 5.4 mo *vs* 3.7 mo) or OS[50]. The results of the SPACE trial comparing sorafenib and placebo in patients undergoing TACE have been recently published. The combination of sorafenib plus TACE with drug-eluting beads was technically feasible, but the combination did not improve TTP in a clinically meaningful manner[51].

ADVANCED HCC WITH PORTAL VEIN THROMBOSIS

Advanced HCC with portal vein thrombosis (PVT) has a very poor prognosis, and includes a special population of patients at higher risk of liver failure. Reported OS is about 10-24 mo in patients without PVT treated with BSC, compared to 2-4 mo in PVT patients[52,53]. Clinical guidelines recommend sorafenib if PVT is present, but different strategies such as surgery, TACE, external radiation therapy, Trans-Arterial-Radio-Embolization (TARE) and combination therapies are object of several clinical trials. The surgical option, frequently employed in Asia, does not show satisfactory results and it is often technically difficult and not safe (operative mortality rate until 6%) in these patients[54]. TACE is also not recommended in PVT patients, because the injury due to ischemic events may cause serious complications like post-embolization syndrome and liver failure. Therefore TACE should be reserved to those patients with preserved liver function. The results in term of OS are good (from 7.4 mo to 10.2 mo) if compared with BSC, but in general they are not significantly better than those observed during sorafenib therapy[55].

External radiation therapy is largely used in the treatment of cancer, but its role in HCC patients (with or without PVT) is very limited. Today, with newer techniques, a high dose of radiation can be delivered within the tumor, sparing normal liver parenchyma from radiation damage. Two large studies in China and Japan show that OS is longer in patients receiving radiotherapy compared to those treated with sorafenib or surgery[56,57], but these data need to be confirmed in other settings.

Sorafenib is the only drug approved for HCC with PVT. Data from a sub-analysis of the two most important studies in Untied States and Asia show an OS of 8.1 mo *vs* 4.9 mo in control group) and 6.5 mo (*vs* 4.2 mo in control group), respectively. However Jeong *et al*[58], in a smaller study with 33 HCC patients with PVT, shows a percentage of stable disease and disease control rate lower than in the SHARP and Asia-Pacific studies. This data can be easily explained by the fact that in Jeong's study all patients had PVT (first order branches or main trunk), while in SHARP and Asia Pacific trials the percentage of macrovascular disease was much lower (about 36%). It is clear that the presence or absence of PVT negatively influence the prognosis. During treatment, no significant differences in OS have been shown between patients with thrombosis of first order branches and those with thrombosis of the main trunk[58].

TARE is another important tool in the management of HCC with PVT. Some studies reported an OS ranging from 10 to 10.4 mo after treatment[59,60]. Moreover, less adverse events have been reported and in general a better quality of life is shown if compared with TACE. TARE, the efficacy and safety of which has been widely tested in the last decade, is based on the administration of glass or resin microspheres loaded with a radioisotope (usually ^{90}Yttrium) trough catheterization of the hepatic artery. The microspheres deliver a tumoricidal beta-radiation with a mean penetration of 2.5 mm, and a super-selective action towards tumoral tissue. As the embolic action is negligible, the procedure is generally well tolerated.

Table 5 Assessment of target lesion response: Conventional Response Evaluation Criteria in Solid Tumors and modified Response Evaluation Criteria in Solid Tumors assessment for hepatocellular carcinoma following the American Association for the Study of Liver Diseases-Journal of the National Cancer Institute guideline

RECIST	mRECIST
CR: Disappearance of all target lesions.	CR: Disappearance of any intratumoral arterial enhancement in all target lesions.
PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions.	PR: At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.
SD: Any cases that do not qualify for either partial response or progressive disease.	SD: Any cases that do not qualify for either partial response or progressive disease.
PD: An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started.	PD: An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

mRECIST: Modified Response Evaluation Criteria in Solid Tumors; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

TARE efficacy in HCC has been tested in several studies, although most of them were limited to a small number of patients. The largest observational studies reported a median OS in BCLC-C patients similar to that observed in the sorafenib arm of the SHARP trial[59,61]. Additionally, a comparative study TACE *vs* TARE demonstrated the superiority of the latter in prolonging TTP but not in patients with advanced HCC[62]. In a retrospective study, the efficacy of TARE has been compared to that of sorafenib, and no significant differences in OS were found[63]. It should be considered that the study had several limitations, including a small sample size, and imbalance in baseline characteristics between the arms. On the contrary TARE appears to be particularly effective in patients with portal vein thrombosis, with a median OS ranging between 10-18 mo[60,64,65] compared to 8.3 mo in patients with portal vein thrombosis treated with sorafenib in the SHARP study[11]. Similar results showing the superiority of TARE *vs* sorafenib in patients with portal vein thrombosis have also been reported in another recently published study[66]. Moreover, the efficacy of TARE (alone or in combination with sorafenib) *vs* sorafenib alone therapy is being evaluated in at least five ongoing clinical trials. The results will be available in the near future and will probably define the role of TARE in HCC therapy. By now, a good profile of tolerability was reported in the preliminary analysis of SORAMIC trial[67].

IMAGING STUDIES IN PREDICTION AND EVALUATION OF RESPONSE TO THERAPY

In the management of patients with HCC, the role of imaging is crucial, not only to allocate a patient to a specific stage in the BCLC system, but also to check the efficacy of the treatment and to evaluate the progression of disease. Once a diagnosis is made, imaging with computed tomography (CT) or magnetic resonance (MR) scan is performed every 2-3 mo if the patient is receiving treatment with sorafenib[68], the only approved agent for the treatment of advanced HCC[11]. The lesions are usually evaluated applying the Modified Response Evaluation Criteria In Solid Tumors (mRECIST) parameters[69], which have been proposed to improve and replace the previous system, known as RECIST 1.1. Lesion dimension was the only criteria considered by RECIST 1.1, which did not give any information about the viable portion of tumor, measured by the degree of contrast enhancement. While the RECIST 1.1 system is still adopted by some hepatologists, changes on tumor size alone is not considered appropriate to establish a prognosis and to correlate imaging with patients' survival. In fact it has been demonstrated that not all patients who have clinical benefit from antiangiogenic therapy have a dimensional reduction of target lesions.

On the other hand, not all progressive disease at imaging is linked to a shorter survival[11,70]. Conversely, patients who will have benefit from therapy in term of survival, do not immediately show a reduction of tumor size, but more frequently the efficacy of therapy is correlated with some early intralesional decrease in cellularity and vascularization changes[8,70,71]. Recently, a new evaluation criteria called Response Evaluation Criteria In Cancer of the Liver (RECICL) have been introduced[72]. It is based on 2-directional measurement, by contrast enhancement CE-CT or dynamic MR, of tumors showing arterial enhancement, instead of only one measurement as requested in mRECIST. The great advantage these two last criteria, compared to conventional RECIST 1.1, is that both of them evaluate the contrast-enhancing portion of the tumor rather than the whole tumor. For this reason the presence of necrotic areas within the lesions is considered a sign of response. These concepts are summarized in Table 5. Moreover, RECICL criteria also consider the non-enhanced part of a target lesion: this may be useful to investigate hypovascular HCC. Even if progress has been done in order to establish patients response during antiangiogenic therapy, it is not clear how to manage those patients who have no benefit from treatment, because at now there is no approved second-line therapy. Moreover, the concept of "progressive disease" should be refined. In fact, according to mRECIST, there are many types

of "disease progression", including lesion growth, presence of a new lesion, or a distant metastasis. At now, it is still under investigation if these different types of disease evolution have the same significance for patients in terms of prognosis.

The evaluation of the response is a subject of intense discussion, especially since molecularly targeted drugs like sorafenib have been introduced and routinely used in clinical practice. Dimensional parameters, largely used in imaging until now, are no longer appropriate now. In fact, it is clear that the goal for standard chemotherapeutic agent is to reduce tumor dimension, but this rule does not apply to antiangiogenic drugs. The new molecules predominantly act inhibiting angiogenesis, inducing tumor tissue necrosis and this may not have effect on the whole tumor dimension, and tumor size does not necessary decrease after therapy[73]. For this reason, RECIST 1.1 criteria have been overcome by the introduction of mRECIST, based on the evaluation of the viable portion (enhanced part) of a target lesion. Several studies have compared the efficacy of RECIST 1.1, mRECIST and European Association for the Study of the Liver (EASL) criteria in evaluating response to loco-regional or systemic therapies in HCC patients[74,75]. While mRECIST and EASL are considered reliable in assessing response to loco-regional therapies (for example TACE or TARE), there is no general agreement on their appropriateness the in evaluation of response during systemic therapy. In fact, loco-regional therapies often give predictable results, which consist in a well-defined and easy to measure area of necrosis. On the contrary, systemic therapies lead to the appearance of irregular and not homogeneous areas of necrosis, not easily defined and measurable[76,77].

One additional promising method for the evaluation of response to therapy has been introduced by Choi. It was first applied to evaluation of therapy response of GISTs at PET assessment. Its use, based on contrast enhancement CT dimensional (measure of diameter of a lesion) and vascular (density expressed in HU on arterial phase CT) parameters, is currently under evaluation. In particular, according to these criteria, a reduction of 10% in tumor diameter or a reduction of 15% in intralesional density is considered as partial response to therapy[78].

Recently volumetric studies have also been proposed as alternative to mRECIST and EASL, because the actual dimension of a tumor may not be exactly evaluated with simply a mono or bi-dimensional measure[79]. According to recently published studies focused on HCC patients, a 10% increase in volume rate after two months of therapy correlates with a poor prognosis[80,81]. The role of MR diffusion weighted imaging has also been investigated in response assessment. Early variation (at first decrease, and subsequently increase) in apparent diffusion coefficient values after therapy seems to correlate with a better response. Moreover, low pre-treatment apparent diffusion coefficient values seem to be predictive of a good response[82,83]. On the contrary, the results of MR diffusion weighted imaging in HCC patients during therapy (loco-regional, systemic or combination therapies) are controversial and not yet clear because of low reproducibility of this technique.

Perfusion-weighted imaging is a relatively new MR/CT technique for qualitative and quantitative evaluation of the delivery of blood to biological tissues. Recently, attention has been focused on the "mean intralesional transit time", which is the time that a contrast agent takes to go through the tissue volume (*e.g.* liver) from entry to exit[84]. In several studies, this parameter showed not only good correlation with response to therapy, but its baseline value (before starting therapy) seems to be predictive of response. In fact some authors have shown that partial or complete responders had higher mean intralesional transit time levels at baseline examination compared to those with progressive disease[85]. Both diffusion and perfusion techniques are still to be considered "research methods" not applicable in the clinical setting.

When evaluating the response to TARE, it should be considered that radiologic findings are more heterogeneous and variable than in other loco-regional treatments, and identification of residual disease, reactionary changes or complications is crucial to assess tumor response. After TARE the responding tumor can show shrinkage (diameters reduction), "vanishing" (enhancement decrement after contrast agent administration), and necrosis. In addition, various collateral findings can be observed, which could make even more difficult the response evaluation. These include perivascular edema, ring enhancement in case of coagulative necrosis, hepatocyte depletion and hepatic fibrosis[86].

RECIST criteria are not always appropriate in evaluating response after TARE, and criteria which evaluate viable portion of a lesion like EASL and mRECIST are more suitable. In fact, according to Keepke and Seyal, both mRECIST and EASL showed superiority in evaluating objective response to TARE when compared with RECIST[87,88]. On the other hand, other authors compared RECIST, mRECIST, Choi and mChoi criteria, showing that Choi and mRECIST are the most appropriate in assessing response after TARE. In particular, patients who have response according to Choi criteria have significantly longer TTP and OS, while non-responders have worse prognosis[89]. Even if Choi criteria have shown good correlation between imaging and patient outcome, evaluation of tumor density applying a ROI within a lesion is not unanimously accepted, for the excessive inter and intra-observer variability[90]. Moreover, measurements of density could be difficult in hypodense lesions and make this method not reliable.

Volumetric studies also can help the clinician to evaluate response to TARE. This technique is used in order to measure both the whole tumor and the necrotic area. According to Monsky *et al*[91] volumetric

technique is more suitable to evaluate dimension of a necrotic area after TARE. In addition, patients whose change in necrotic area is > 10% has longer survival if compared to patients whose change is < 10%.

PROGNOSIS IN ADVANCED HCC

As described before, advanced HCC is a condition where multiple actors can play a determinant role, resulting in large variability of the disease even in the same BCLC stage.

Portal vein thrombosis

The presence/absence of portal vein thrombosis and its extension, as well as extra-hepatic spread and alterations in liver function, can jeopardize the efficacy of specific treatments. Moreover, the natural history of the disease - even in absence of treatment - is strictly related to these variables. Finally, both natural history and the response to treatment may be influenced by molecular characteristics of the tumor. It is easy to understand how talking of prognosis "in general" for advanced HCC - as well as for all stages of HCC - sounds simplistic.

The natural history of the disease is difficult to evaluate through randomized controlled trials for ethical reasons. Nonetheless, some interesting studies have tried to clarify the prognosis of untreated HCC. A meta-analysis published in 2010 evaluated more than 4000 patients included in the placebo or inactive treatment arms of 30 randomized control trials in order to estimate survival in untreated HCC patients and to evaluate factors related to a different survival[92]. The 1-year survival rate in BCLC B + C patients was 34%, with a pooled estimate 1-year survival of 25% in the subgroup of advanced HCC patients. ECOG performance status, albumin levels, prothrombin activity, portal vein thrombosis and Child Pugh score A emerged as predictors of longer survival in all HCC untreated patients. In the BCLC B + C group ECOG performance status, presence of ascites and an Okuda stage Ⅰ were significantly related with a longer survival. A more recent retrospective cohort study evaluated 320 untreated HCC patients, 39% in advanced stage according to BCLC[93]. The 1-year survival rate for advanced HCC patients was 12%, with a median survival of 6.9 mo. ECOG performance status, INR and alpha-fetoprotein emerged as independent predictors of mortality at multivariate analysis.

Distant metastases

A related emerging issue, analyzed in recent studies, has been the attempt to establish a correlation between progression and survival in patients with HCC. In order to do that, attention has been focused not only on classic OS but also on two new parameters, which were not considered in the past studies on HCC during systemic therapy. The first is TTP, defined as the time from the date of starting therapy to disease progression, evaluated by imaging (CT or MRI). The second is the post-progression survival, which is the time from disease progression to death. Along these lines, four different kinds of progression (progression patterns) have been established: intrahepatic or extrahepatic tumor growth (> 20% increase in tumor size of viable target lesion), new intrahepatic lesion and new extrahepatic lesion (including new metastasis and/or vascular invasion). According to data reported by Lee *et al*[28], patients with only metastatic disease have a better post-progression survival than those with vascular invasion or both of them (respectively 7.7, 3.8 and 3 mo), probably because of a higher rate of liver failure in patient with vascular invasion. TTP also seems to be related with survival: in fact patients with early radiologic progression during sorafenib treatment have a much shorter survival than progressive disease patients at 4 mo (respectively 4.9 and 16.6 mo)[28].

Similar results in term of survival had already been reported by Reig *et al*[94], who showed how the progression pattern may impact on prognosis. In particular the presence of new extrahepatic lesions and/or vascular invasion appear to be correlated to a shorter post progression survival. The purpose of correlating pattern progression with survival is to identify those patients who are eligible for second line treatment, and to appropriately stratify them. In order to do that, the concept of "BCLC upon progression", which evaluates the progression pattern of PD patients, has been introduced. In advanced HCC patients (BCLC-C) two kinds of progressions have been identified: patients who show an increase in size of an existing lesion or a new intrahepatic lesion (probably candidates for second line treatment) and patients who show extrahepatic lesions or vascular invasion, associated with a poor prognosis[94].

BEST SUPPORTIVE CARE

There are currently very few data about BSC in advanced HCC. Although this issue has been neglected, it represents a very important aspect of the care of these patients, as much as in other patients with advanced cancer. According to EORTC "supportive care for cancer patients is the multi-professional attention to the individual's overall physical, psychological, spiritual and cultural needs, and should be available at all stages of the illness, for patients of all ages, and regardless of the current intention of any anti-cancer treatment"[95]. According to BCLC, BSC is the only treatment option in terminal stage HCC. However, the definition of BSC implies its application during every stage of the disease. Despite its importance, BSC is marginally discussed or even only mentioned in all guidelines. The goal of BSC is to improve the quality of life, which is obviously reduced in patient with HCC compared to the general population[96]. BSC should

be performed in order to avoid the complications of cirrhosis (ascites, gastro-intestinal hemorrhage, encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis), but should also be focused to those conditions which are typical of oncologic patients[97]. The most common symptoms reported by HCC patients are sleep disturbances, depression, fatigue, malnutrition, anorexia, pain and psychological issues[98-101].

Unsatisfactory night sleep is reported by 50%-65% of patients with cirrhosis, that actually reduces sleep time, sleep efficacy and REM sleep and increase sleep latency. These pathological changes correlate with the grade of liver dysfunction[102-105]. Insomnia is also reported by 50%-65% of cirrhotic patients and excessive daytime sleepiness is part of the hepatic encephalopathy syndrome[105,106]. Physicians should perform a routine assessment of sleep quality and time and evaluate daytime sleepiness. If the latter is present a treatment for hyperammoniemia should be started or increased. Moreover, sleep and light hygiene practices (regular sleep-wake schedule, exposure to bright light in the morning and not in the evening) should be encouraged. While hypnotics should be used with caution, 25 mg hydroxyzine before sleeping has induced a subjective sleep improvement compared to placebo with a good profile of tolerability[107].

Depression and anxiety are major determinants of an altered quality of life, even after a curative treatment, and are reported in more than 60% of HCC patients. Treatment should include supportive psycho-therapy or behavioral interventions, with particular attention for the relationship between physician and patient and his family. Liver dysfunction modifies pharmacokinetics of antidepressants, which should be introduced at low dosage (1st line citalopram, sertraline)[108,109]. If no improvement is observed in 2 wk, dosage should be increased. A switch to a second line therapy (*e.g.,* paroxetine) should be performed after 4-6 wk of therapy without improvement of symptoms. All psycho-social and spiritual issues are particularly frequent in end-stage disease and require a careful approach, both pharmacological and supportive. Fatigue is very frequent in HCC patients and may be related to multiple causes: depression, sleep disturbances, cachexia, anemia. Exercise, whose level must be related to fatigue, significantly reduces cancer-related fatigue during and after the treatment[110]. Although no specific data are available for HCC, administration of modafinil (a non-amphetamine-based stimulant) has recently shown a significant improvement in fatigue in a trial *vs* placebo involving 631 cancer patients[111].

Malnutrition, anorexia and cachexia are related to the tumor and to the weight loss and muscle wasting observed in cirrhosis. Sarcopenia, that is frequent in alcoholic and cholestatic diseases and may be related to portosystemic shunting, also contributes to malnutrition and cachexia. An adequate energy uptake, exercise and the avoiding of unnecessary diet restriction such as a low protein diet should be recommended. Few and controversial data on parenteral support are available[112]. A randomized controlled trials by Chow *et al*[113] showed that megestrol acetate improved emotional functioning, nausea, vomiting and appetite loss in patients with HCC, while no benefit was observed in OS or quality of life[114]. Numerous studies evaluated the role of oral branched-chain amino acid administration in HCC patients, although very few data are available in the subset of advanced HCC. In general, this kind of treatment seems to improve liver function, and malnutrition (with a significant increase of albumin levels), but no clear effect has been observed on OS[114-117], even though a recent meta-analysis showed an improvement in the 3-years mortality[118]. Although more data are needed to confirm its efficacy, oral branched-chain amino acid supplementation may be considered in HCC patients to improve the liver reserve and quality of life.

Treatment of pain in HCC varies according to the cause. Bone metastases-related pain can be treated with cementoplasty[119] or irradiation. Irradiation can also be used for the treatment of painful lymph nodes and lung metastases. In a recent phase Ⅱ trial by Soliman *et al*[120] liver radiotherapy showed promising results in symptom improvement at one month. In symptomatic treatment nonsteroidal anti-inflammatory drugs should not be used, due to the possibility of hepatorenal syndrome, hepatotoxicity, and gastro-intestinal bleeding. Acetaminophen 2-3 g daily is the first line agent in long-term use, while opioids should be used as second line treatment. Liver participates in degradation and biotransformation to active metabolites of opioids, so a good knowledge of their pharmacokinetics is mandatory. Hydromorphone and fentanyl should be preferred, as they are least affected by renal dysfunction. Treatment should be started with low dose and a 2-3 d titration, with a regular assessment of efficacy and tolerance. Long acting agents should be preferred, possibly in association with a short active drug and paracetamol and/or corticosteroids. A dose increase of 20%-30% must be performed when necessary[121].

Muscle cramps are very frequent in patients with cirrhosis and HCC and may be related to electrolyte imbalance, that must be treated. Many agents showed positive results in muscle cramps treatment in cirrhotic patients, but there is still need of controlled trials. The most interesting agents are taurine, whose synthesis is reduced in cirrhosis leading to a decrease in membrane stabilization, and quinine sulfate[122]. Baclofen is also used by some physicians due to its skeletal-muscle relaxant activity. The drug was reported as effective and safe in a pilot trial including 10 cirrhotic patients[123] and is currently being tested in a randomized controlled trials (Baclofen in the Treatment of Muscle Cramps in Patients With Cirrhosis, ClinicalTrials.gov Identifier: NCT02221570).

CONCLUSIONS AND PERSPECTIVES

The ability to treat earlier stages of HCC and the longer survival of patients with cirrhosis make advanced HCC a common problem facing the Hepatologist. In the past few years a breakthrough step has been the approval of sorafenib as a systemic therapy for this type of cancer. However, we still lack reliable early predictors of the likelihood to respond to sorafenib, to be utilized at the single patient level. Unfortunately, sorafenib has not been followed by approval of other drugs for use in first- or second-line treatment of advanced HCC. Moreover, the role of other approaches to the treatment of the advanced stage, including TARE, conformational radiotherapy, and conventional chemotherapy deserve additional investigation. Attention is being focused on the significance of different types of advanced HCC, *e.g.,* due to the presence of extrahepatic spread or to involvement of the portal vein. Along these lines, the type of progressive disease which leads to migration to an advanced stage plays a yet unknown but probably important role. These lines of information need to be integrated with accumulating data on the molecular heterogeneity of HCC. Collectively, these data will be instrumental to design personalized treatments, considering that HCC is one of the few solid tumors where no molecular-guided therapy exists. Finally, more attention to supportive care needs to be paid by Hepatologists dealing with patients in advanced or terminal stages of the disease, including initiation of supportive treatment and avoiding delay in withdrawing active therapies when unnecessary. Thus, active research in this field will hopefully lead to an even better management of these difficult-to-treat patients.

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