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New challenges in clinical research on hepatocellular carcinoma

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ABSTRACT

This is an updated review of screening, early diagnosis and treatment of hepatocellular carcinoma, focusing on the advancements occurred in the last years and highlighting the challenges in clinical research.

Hepatocellular carcinoma (HCC) is nowadays the sixth most frequent cancer worldwide with up to 740,000 new cases diagnosed each year, and it is the third most prevalent cause of cancer-related-death worldwide (1). This neoplasm usually appears linked to an underlying liver disease, being one of the most relevant causes of death in patients diagnosed of liver cirrhosis (2,3). In the last years, important advancements in terms of diagnosis, staging and treatment of HCC, improving the management and outcome of the disease, have been made (4-7). Despite the fact that these improvements have absolutely changed natural history of HCC, there are several areas that still need

further advancements.

The aim of this document is to discuss some controversial aspects, which in our opinion constitute real challenges in clinical research of HCC.

Key words: Hepatocellular carcinoma. BCLC. Sorafenib. TACE. AFP.

IMPROVING EARLY DIAGNOSIS

From the basis that the only possibility to offer and apply treatments with curative intention is being able to diagnose HCC at early stages, when there are not cancer related symptoms. Since this option is only feasible if screening is performed in population at risk, scientific guidelines recommend performing abdominal ultrasonography (US) in every patient with liver cirrhosis. Despite the recommendation of HCC screening by the Spanish guidelines (4), one registry study performed in Spain which included 62 and 705 patients diagnosed of HCC within a period of time of 4 months showed that just 47% of HCC patients were diagnosed in the setting of surveillance and less than a half were diagnosed at early stage (8).

This data shows that early diagnosis, a key issue to be able to significantly reduce HCC-related mortality, is one of the most relevant issues that deserve further efforts from scientific community. Aiming to evaluate which were the causes of screening program fail in the United States of America, Singal et al evaluated 1,005 patients included in the HALT-C prospective study. A third part of patients did not adhere to an adequate screening program and, in 70% of cases that were diagnosed at an advanced stage, the main reason was the absence of detection in US (9).

With the aim of improving detection rate, it is crucial to establish formative programs in order to certify the capability of being able to carry on this activity and it is necessary to use up-to-date ultrasonography scans in order to perform an optimal liver exploration. Tumor markers could be a useful tool to overcome theoretical limitations of US: its evaluation is not subjective, does not depend on the operator and it may be reproducible, as well as it is relatively cheap and a tool easy to access in areas with low monetary income. Regrettably, different tumor markers evaluated in early stage HCC scenario have shown a low diagnostic accuracy (10-13) and its association with

ultrasonography does not improve its performance and increases the cost of screening programs (14). A recent study has proposed a microRNA panel detected in plasma samples for the early diagnosis, but there is a need of external validation of its efficacy (15).

Another relevant aspect is choosing an optimal population in whom the screening program is cost-effective. The decision of entering into surveillance is based on the risk of developing HCC, life expectancy and the cost that should be assumed. More than 30 years ago (and based in patients with chronic kidney disease in whom the decision was if they were entered on dialysis program) it was determined that an intervention was cost-efficient if it permitted increasing survival 100 days with a cost of \$50,000/year of life gained (16). These considerations are outdated: life expectancy of patients with liver cirrhosis is difficult to predict, and nowadays it is more challenging as there is an available and effective treatment for hepatitis C virus (HCV) infection. In addition, the assumed cost is not updated, and the most important issue, the actual costs of screening programs are very difficult to determine; besides the cost of screening techniques and subsequent studies needed to confirm diagnosis, also is important to consider the social impact risen by the implementation of a screening program (for instance, days of labor absenteeism), as well as economical and emotional impact of false positives and potential complications derived from screening and confirmation techniques (17).

Based on the assumptions previously described, surveillance is cost-efficient if HCC incidence in patients with underlying liver cirrhosis exceeds 1.5% and if it is over 0.2% in patients with chronic liver disease but who have not developed cirrhosis. Accordingly, surveillance is recommended in every patient with cirrhosis whatever the etiology, as well as in non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3, and in those patients with chronic HBV infection who present an increased risk of HCC (incidence of HCC in Asian or African adults with an active HBV infection, with or without family history of HCC, clearly exceeds this point [18]). Nevertheless, many authors have recently showed that the risk of developing HCC is not homogeneous and have suggested different tools to predict it. Regarding patients with chronic HCV infection, liver elastography seems to be a useful tool in order to stratify

patients at risk of developing HCC (19,20). It is worthy to highlight that in those cases of HCV-related cirrhosis, the achievement of sustained virological response does not rid the risk of developing HCC after treatment (21) and therefore these patients should remain under surveillance. In those patients with HBV-related chronic infection, age, male sex, an increased liver stiffness, alcohol consumption and an increased viral load are associated with an increased risk of HCC (18,22-24). Among patients with alcoholic cirrhosis, low platelets count and age older than 55 years identifies the patients at high risk of HCC development (25). Finally, information about risk of developing HCC among those patients with non-alcoholic fatty liver disease (NAFLD) is scarce, particularly in those who have not developed cirrhosis yet. In addition, screening in this population is complicated by obesity and application of potentially curative treatments may be limited by the frequently associated comorbidities. Accordingly, no recommendation can be raised about screening programs in this group of patients.

Noninvasive diagnosis by imaging technics has been progressively refined, allowing a definitive diagnosis of HCC without any biopsy in a great amount of patients. Nevertheless, in those nodules under 2 cm, sensitivity of imaging techniques is about 50-60% (26-28) so in about 40-50% of cases a biopsy is mandatory. Some new strategies have been recently evaluated in order to increase sensitivity of noninvasive criteria. The presence of intralesional fat, hypointensity in venous-phases and the presence of a pseudocapsule have been analyzed. Unfortunately, these parameters do not significantly increase the diagnostic accuracy of MRI (29). Diffusion weighted imaging have shown a potential utility for HCC, but until now there are no prospective studies showing a relevant increase of the diagnostic accuracy (30,31). Organ specific contrast media have been also investigated (32). Despite the fact that retrospective studies have described promising results (33,34), there are no prospective studies showing a better performance comparing to conventional MRI contrast media.

REFINING PROGNOSTIC ASSESSMENT AND THERAPEUTIC DECISION

Once the diagnosis is established, prognostic evaluation is a crucial step in management of HCC. Taking into account that, in most cases, HCC raises in patients with underlying cirrhosis, and the fact that the severity of liver dysfunction determines

therapeutic options and survival regardless of HCC, it is mandatory to consider both liver function and tumoral extent. In addition, the presence of cancer-related symptoms evaluated in an appropriate way with validated scales such as ECOG performance status (35) have shown a very important prognostic value and, as well as liver dysfunction, determines the applicability of different therapeutic options. Success of any staging system is based on the ability of linking the disease stage with the recommended treatment option. Multiple staging systems have been suggested during last 30 years; most of them do not take into account the presence (or not) of cancer related symptoms or evaluate tumoral extent roughly (36). Among all staging systems proposed until now, the most relevant and successful one has been Barcelona Clinic Liver Cancer (BCLC) staging system. Since its former publication in 1999 (37), BCLC classification has been continuously refined to its last version in 2014 (38), it has been externally validated (39-42) and because of its very well known predictive ability and its utility for clinical decision making, this staging system is the recommended one by the most relevant scientific societies (5,6,43,44). A new staging system called Hong Kong Liver Cancer (HKLC) staging has been recently published. It was built based in a cohort of 3,856 patients treated in Hong Kong (45). The main singularity proposed by this group is the acceptance of surgical treatment in intermediate/advanced stage patients. However, HKLC classification has several and important limitations (46). One of the most important one is the fact that it has been constructed in a retrospective way and, because of this, those patients selected for surgical resection instead of TACE present certain peculiarities, which determine good prognosis, while those patients treated with TACE lack those favorable profile, inducing an important bias towards surgical resection (47).

The intermediate stage (BCLC-B) is formed by a heterogeneous group of patients. Aimed to refine the prognostic evaluation in this stage, Bolondi et al. have proposed a sub-classification of this intermediate stage in 4 subgroups attending to tumor stage, presence or not of cancer related symptoms and severity of liver dysfunction (48).

This sub-classification includes patients with a severe liver dysfunction. These patients, as it is clearly defined in the BCLC staging system, should be evaluated for liver transplantation and in those decompensated patients, the presence of HCC may

become a contraindication criterion if tumor extent exceeds the criteria accepted for enlistment. Furthermore, they suggest not taking into account the presence of cancer related symptoms measured by ECOG-Performance status, issue that is clearly contradictory and inconsistent with studies published by the same authors showing the prognostic importance of having an impaired performance status (ECOG PS 1) in patients treated with chemoembolization (49). Another drawback is that, while in the BCLC staging system those solitary tumors without cancer related symptoms and with no dissemination must be considered as BCLC A, Bolondi proposes classifying these patients as BCLC B. Finally, this sub-classification has not been externally validated in European patients (50).

Despite the advantages of the BCLC system, there is room for further prognostic evaluation refinement. In this regard, several genetic expression profiles with prognostic significance have been suggested (51-57). However, to date, it has not been shown that the presence of a specific molecular pattern allows a concrete therapeutic decision.

Furthermore, the use of genetic information is clearly limited because of tumoral heterogeneity in HCC (58,59). Similarly, although some tumoral markers (mainly AFP), have shown an indisputable prognostic power (60-64), there is no consensus in terms of determining a pathological cutoff value, and these markers do not have enough strength to evaluate patients in an individual way and in most clinical scenarios, they do not induce a change in therapeutic approach (7). Therefore, one of the current challenges in clinical research is to try to integrate gene expression data in the current evaluation systems and basing the survival prediction and treatment indication in the molecular profile of the patient.

IMPROVEMENTS IN THE TREATMENT OF INTERMEDIATE-ADVANCED HCC

BCLC-B and BCLC-C stages have experienced many changes in last years, and are in those stages where the research has been most active. Based on two positive randomized-controlled trials and a latter meta-analysis, chemoembolization (TACE) is considered the first-line treatment in intermediate stage (65-67). However, this treatment has been evolving during last years and there are many aspects still to be

investigated (68). For instance, which is the best chemotherapeutic and/or embolic agent is still under debate. One of the greatest advances in this field was the development of polyvinyl-alcohol spheres loaded with doxorubicin; these spheres slowly and selectively release intratumoral chemotherapy, minimizing adverse events related to systemic distribution of chemotherapy (69) and allowing a homogeneous and calibrated embolization.

Despite de fact that previous studies have shown an excellent radiological response (70) and promising overall survival (71,72), randomized trials have not been able to confirm in a definitive way advantages in terms of radiological response and overall survival using these spheres comparing to conventional TACE with lipiodol (73,74). Other relevant aspects are evaluating which is the best therapeutic scheme (fixed schedule or on demand taking into account the treatment response), how response must be assessed, or the most important aspect, when treatment failure and other therapeutic approaches should be considered. Recently, intractable progression concept has arisen and it is being now suggested. This concept is defined as the progression associated to a relevant tumor load, a not so important progression but linked to liver dysfunction, worsening of performance status or a technical contraindication (75,76). Based on this concept of intractable progression, various indexes have been recently generated, aimed to objectively decide when to interrupt TACE because of inefficiency or uselessness. Most of these indexes consider radiological response and liver function worsening as the main parameters for assessing TACE failure (77,79). Unfortunately, these indexes have not been externally validated and many of them are derived from cohorts of patients who initially were bad candidates for TACE. The main inconvenient of TACE is that the majority of patients develop disease progression despite good initial response. Aimed to decrease or delay tumor progression after TACE, the association of molecular agents with antiangiogenic effects such as sorafenib or brivanib with TACE has been evaluated; regrettably, this strategy has failed in demonstrating improvement in response rate, time to progression or overall survival (80,81).

One of the most promising treatments is radioembolization using Yttrium-90 spheres (82). Many prospective studies in different stages of HCC have shown safeness and

radiological response, with an overall survival comparable to those treated with TACE or sorafenib (83-87). All this promising data is the rationale for conducting randomized clinical trials comparing radioembolization in combination or not with sorafenib *versus* sorafenib. Table I describes those main studies that are ongoing evaluating effectiveness of radioembolization in HCC.

The HCC field that has experienced the most relevant advancements is systemic treatment. Progresses in the understanding the molecular alterations associated with tumor progression (88-90) have permitted the development of multiple agents acting specifically at level of the disrupted molecular pathways. Many molecular agents have been studied, but the only one that showed efficacy in terms of overall survival and time to progression has been sorafenib, as was revealed by two phase III, randomized-controlled studies (91,92). Those results have been prospectively confirmed in different clinical trials in which sorafenib was the control arm (93-97) as well as in multiple prospective studies in real life clinical practice (98-100). Furthermore, sorafenib is able to maintain its efficacy despite the etiology of liver disease, the baseline status of neoplasm, the presence or absence of cancer related symptoms or previous therapies (101).

Despite the success of sorafenib at advanced stage, there are still many aspects to be clarified. One of the most relevant issues is to identify those patients in whom sorafenib is inefficacious, and thus, to avoid the exposure of patients to an unnecessary toxicity. Nowadays there is enough evidence to discourage the use of sorafenib in patients with an advanced liver dysfunction (classified as Child-Pugh C) (99,102,103). In those patients Child-Pugh B, pharmacokinetic profile is not substantially modified and there is no evidence about a relevant increase of adverse events, but the impact on tumor progression may not lead to survival improvement because of liver dysfunction (99,104), and that is the reason why treating patients with such liver dysfunction must be individualized (105). Furthermore, some biomarkers and clinical characteristics at baseline or during the treatment have suggested being able to predict response to sorafenib. Biomarkers such as AFP, vascular endothelial growing factor (VEGF), angiopoietin-2 (ang-2), hepatocitary growing factor or c-Kit have shown a prognostic ability in patients with advanced HCC (63). Regrettably, as

previously highlighted, there are no validated cutoffs for defining pathological values and, therefore, the use of these biomarkers does not contribute to the therapeutic decision. Much more interesting is the identification of some adverse events as predictors of favorable response. In that sense, developing diarrhea (106), arterial hypertension (AHT) (107) or dermatological adverse events (108-110) are associated with better outcomes. For instance, in a recently published prospective cohort, those patients who develop early dermatological adverse events within the first 60 days under sorafenib presented a longer median overall survival comparing to those who did not develop this adverse event (18.2 *versus* 10.1 months respectively; $p < 0.009$) and the occurrence of dermatological adverse events was identified as an independent prognostic factor for survival in the multivariate analysis with time-dependent variables. This association highlights the need of a close follow up of patients with the aim of adjusting doses if adverse events appear and, thus, avoiding unnecessary interruptions. The potential basis for the relationship between side effects and treatment efficacy is the genetic polymorphisms. In that regard, the impact of genetic polymorphisms of tumor necrosis factor alpha (TNF- α), interleukin-6 and nucleotide binding protein 3 (GNB3) in inflammatory/immunological syndromes is very well known. For instance, G308A of TNF- α is associated with AHT, increased risk of coronary disease and a higher predisposition for vein thrombosis; C857T TNF- α is associated with psoriatic arthritis; IL-6 and C825T of GNB3 polymorphisms play a role in development of AHT. On the other hand, it is well known that hypoxia induced by sorafenib treatment may induce a proangiogenic compensatory response. Accordingly, there are several trials aimed to identify potential polymorphisms in genes associated with angiogenic response (VEGFA, ANGPT2 and PLA2G12A) that could allow us to recognize different patient's profiles in order to adjust treatment (111-113).

Finally, in those patients with an HCC in intermediate/advanced stage treated with sorafenib, the type of radiological progression has been identified as a statistically significant independent predictor of the post-progression survival (100,114). In that regard, the development of a new extrahepatic lesion or vascular invasion is the type of progression associated with the poorest prognosis.

The positive result of sorafenib was the demonstration of the usefulness of molecular therapies in HCC and it opened the door for assessing the potential efficacy of multiple pathways blockade, in the same way as it is done in other neoplasms. Until now, no other agent evaluated in phase 3, randomized-controlled trials in first (sunitinib, linifanib, brivanib) (93,94,115) or second line (brivanib, everolimus, ramucirumab) (116-118) alone or combined with sorafenib in first line (erlotinib) (95) has shown any benefit when compared with sorafenib.

The negative results of these clinical trials must make us to speculate why these agents, efficient in other neoplasms, have failed in HCC. First lesson we have learned is that many of them are too toxic for patients with cirrhosis. Therefore, before planning phase 2-3 trials, phase 1 trials in patients with cirrhosis in order to be able to determine the maximum tolerated dose is mandatory. Another learned lesson is that results coming from phase 1-2 trials are not informative enough to be able to predict efficacy in terms of survival. For instance, the clinical trial evaluating a combination of chemotherapeutic agents (PIAF) showed objective response but without impact in survival (119), or those clinical trials with sorafenib in which, despite the absence of objective response, increase of survival was pointed out (91,92), or, recently, clinical trials with linifanib (115) or brivanib (116) in which, despite an improvement in time to radiological progression, these studies were not able to demonstrate survival benefit. In addition, these trials have several selection biases, particularly those clinical trials evaluating second line agents. In the trial design and target population selection, it is mandatory to register those events appeared during sorafenib therapy. As discussed above, the pattern of radiological progression has a statistically significant impact on post-progression survival (100,114). In addition, second-line trials recruit patients who, despite sorafenib failure, have a preserved liver function and good general condition (ECOG-PS 0-1), and in many cases had presented adverse events linked to good prognosis (110). Therefore, this population probably presents a disease with a less malignant behavior. Finally, some trials have shown a potential efficacy in a specific population according to a concrete molecular profile (120). Taking into account the preliminary data, enrichment of these trials with those patients with such molecular profile is completely justified.

Despite the dispiriting results of the last five years, nowadays there are several ongoing clinical trials evaluating different agents that have shown promising results in preliminary studies (Table II). Among the different approaches, immune checkpoints blockade has disclosed promising results, as long as treatment with these molecules has shown an objective radiological response with an acceptable security profile. The potential benefit of this approach should be confirmed in larger, randomized trials (121,122). All these efforts will allow, in an immediate future, increasing therapeutic options for our HCC patients at advanced stage.

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Table I. Ongoing trials evaluating radioembolization efficacy in HCC, according to the website www.clinicaltrials.gov (accessed on September 15th 2015)

<i>PI</i>	<i>Trial</i>	<i>Starting Year</i>	<i>Phase</i>	<i>Patients</i>	<i>PS</i>	<i>Primary endpoint</i>	<i>Identifier</i>
Acoba J	TARE + sorafenib	2014	1	BCLC B or C	≤ 1	Security	NCT02288507
Salem R	TACE vs. TARE	2009	2	Not surgical or suitable for ablation HCC	≤ 2	TTP	NCT00956930
Defreyne L	DEB-TACE vs. TARE	2011	2	Not surgical or suitable for ablation HCC	> 1	TTP	NCT01381211
Kaseb A	TARE + sorafenib	2013	2	BCLC C	≤ 1	Toxicity	NCT01900002
Chow PKH	TARE vs. sorafenib	2010	3	BCLC B or C	≤ 1	Overall survival	NCT01135056
Salem R	TARE + sorafenib vs. sorafenib	2012	3	Advanced HCC	≤ 1	Overall survival	NCT01556490
Mazzaferro	TARE	2013	3	Advanced HCC with	≤ 1	Overall survival	NCT01887717

HCC: Hepatocellular carcinoma; PI: Principal investigator; PS: ECOG performance status; TARE: Transarterial radioembolization; TACE: Transarterial chemoembolization; DEB-TACE: Drug eluting beads TACE; BCLC: Barcelona Clinic Liver Cancer; TTP: Time to progression.

Table II. Ongoing trials evaluating different molecules in advanced HCC according to the website www.clinicaltrials.gov (accessed on September 15th 2015)

HCC: Hepatocellular carcinoma; PS: ECOG performance status; BCLC: Barcelona Clinic

<i>Trial</i>	<i>Starting year</i>	<i>phase</i>	<i>Patients</i>	<i>PS</i>	<i>Primary endpoint</i>	<i>Identifier</i>
Nivolumab	2012	1	Advanced HCC	≤ 1	Dose and toxicity	NCT01658878
Tivozanib	2013	1b/2	BCLC C or D	≤ 2	PFS	NCT01835223
Resminostat + sorafenib	2013	1/2	Advanced HCC	≤ 1	Toxicity. TTP	NCT02400788
BBI608 + sorafenib	2014	1b/2	Advanced HCC	≤ 1	Dose and toxicity	NCT02279719
y BBI503 + sorafenib						
Donafenib	2014	1b/2	Advanced HCC	≤ 2	Security	NCT02229071
MSC2156119J	2014	1/2	Advanced HCC C-MET+	≤ 1	Dose and toxicity	NCT02115373
MSC2156119J vs. sorafenib	2014	1/2	BCLC C MET+	≤ 2	Toxicity	NCT01988493
Dalantercept + sorafenib	2014	1b/2	Advanced HCC	≤ 1	Security and tolerability	NCT02024087
TKM-080301	2014	1/2	Advanced HCC	≤ 1	Dose and toxicity	NCT02191878

Liver Cancer; OS: Overall survival; TTP: Time to progression; PFS: Progression free survival; MET: *Hepatocyte growth factor* (HGFR) receptor.

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