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AIM AND SCOPE

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INDEXING/ABSTRACTING

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EDITORS FOR THIS ISSUE

Chemotherapy for hepatocellular carcinoma: The present and the future

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver. Its relationship to chronic liver diseases, in particular cirrhosis, develops on a background of viral hepatitis, excessive alcohol intake or metabolic steatohepatitis, leads to a high incidence and prevalence of this neoplasia worldwide. Despite the spread of HCC, its treatment it's still a hard challenge, due to high rate of late diagnosis and to lack of therapeutic options for advanced disease. In fact radical surgery and liver transplantation, the most radical therapeutic approaches, are indicated only in case of early diagnosis. Even local therapies, such as transarterial chemoembolization, find limited indications, leading to an important problem regarding treatment of advanced disease. In this situation, until terminal HCC occurs, systemic therapy is the only possible approach, with sorafenib as the only standard treatment available. Anyway, the efficacy of this drug is limited and many efforts are necessary to understand who could benefit more with this treatment. Therefore, other molecules for a targeted therapy were evaluated, but only regorafenib showed promising results. Beside molecular target therapy, also cytotoxic drugs, in particular oxaliplatin- and gemcitabine-based regimens, and immune-check-point inhibitors were tested with interesting results. The future of the treatment of this neoplasia is linked to our ability to understand its mechanisms of resistance and to find novel therapeutic targets, with the objective to purpose individualized approaches to patients affected by advanced HCC.

Core tip: The aim of this review is to make a point on chemotherapeutic options for treatment of hepatocellular carcinoma (HCC) at advanced stage, the most frequent stage of presentation of this neoplasia, still characterized

by an important mortality rate. By now, sorafenib is the only standard treatment, but other options were recently studied and will be soon available for clinicians and patients affected by HCC. The review can be divided in four sections: The first one regards molecular target therapy and are described sorafenib, its open issues, but also other drugs with similar targets that have been evaluated for treatment of HCC. The second and the third parts regard cytotoxic drugs and immunotherapy, respectively, which were evaluated in recent years as possible alternatives or adjuvant to Sorafenib. In the last part of the review, future perspectives are described, in particular for what concerns resistance mechanism of the neoplasia, delivery methods or biological enhancers for drugs already in use, new drugs that will be probably evaluated and molecular targets that could soon become eligible for target therapy hopefully leading to the development of personalized therapy.

INTRODUCTION

According to last EASL-EORTC guidelines, liver cancer is the sixth most common cancer, the third cause of cancer related death, and accounts for 7% of all cancers. Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and is a major global health problem. Its incidence reaches a peak at median age of 70 years, which results to be higher in Japanese population (70-79 years) and lower in Chinese and Black African populations. HCC appears to be more frequent in males than in females (2.4:1)[1].

HCC development is often related to the presence of a chronic liver, which represents one of the most important risk factors for this neoplasia. In particular cirrhosis, which can occur as a consequence of chronic viral hepatitis, excessive alcohol intake, nonalcoholic fatty liver disease or genetic diseases (*e.g.*, hemochromatosis), is a frequent setting for HCC onset as well as a cause of liver dysfunction.

Liver dysfunction, in addition to high heterogeneity regarding the mechanisms of carcinogenesis and to the frequent diagnosis of HCC at an advanced stage despite appropriate screening in particular regarding viral chronic hepatitis, lead to great difficulty in treating this neoplasia, as well as in developing new therapeutic alternatives.

Surgery and liver transplantation (OLT) in fact represent the only radical treatments of this disease, but, as mentioned, are not feasible in case of advanced disease or significant hepatic dysfunction[2]. In particular, according to EASL indications based on

Barcelona-Clínic Liver Cancer (BCLC) classification related on prognostic variables, surgery is proposable in very early stage HCC (stage 0), while OLT is indicated for early stage disease (stage A). More advanced diseases are treated with, in order: Radiofrequency ablation (RFA), transarterial chemoembolization (TACE) or sorafenib, while terminal HCC (stage D) has best supportive care as unique therapeutic option[1]. RFA and TACE are treatment of choice in case of early stage disease (stage A) with associated diseases and in case of intermediate stage disease (stage B) respectively, while other non-surgical approaches as transarterial radiation, percutaneous ethanol injection and microwave ablation are still infrequently used in clinical practice because of partial or less encouraging results compared with TACE and RFA[3,4].

Of particular interest is the approach with TACE, which, in addition to its purely therapeutic indication, has shown utility for its ability to lead to the downstaging of the disease[4,5] and for its neo-adjuvant effect[6]. For this reason, the TACE has been subject to intense technical development, which has led to, in addition to the conventional method Lipiodol-TACE, new approaches such as drug-eluting beads TACE (DEB-TACE)[7], based on doxorubicin and on administration as microspheres, with encouraging results.

In case of TACE resistance or advanced stage HCC (stage C), compatibly with the residual liver function, systemic chemotherapy is indicated, but sorafenib is currently the only standard systemic treatment available[8,9]. In consideration of the frequent approach to advanced HCC, and given the lack of viable alternatives, many efforts in the field of research have been made to optimize the use of sorafenib, for example by using it together with TACE or with hepatic arterial infusion chemotherapy (HAIC), and to evaluate chemotherapy regimens and other small molecules already in use for other types of malignancies or under development. The aim of our review is to evaluate the available options and future possible strategies regarding systemic therapy for HCC.

MOLECULAR TARGETED THERAPY

As previously said, sorafenib is the only standard treatment available for advanced HCC. In the wake of the good results obtained with sorafenib, numerous other small molecules were evaluated for the treatment of this neoplasia.

Sorafenib

The action of sorafenib is expressed on various molecular targets involved in the mechanism of tumor growth and angiogenesis, leading to their inhibition: Serine-threonine kinases Raf-1 and B-Raf involved in RAF/MEK/ERK pathway, RET, FLT-3, the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGFRs) 1, 2 and 3 and platelet-

derived growth factor receptor β (PDGFR-β)[10-13]. The efficacy of this drug in treating Child-Pugh A stage C HCC was demonstrated in two phase III, randomized, placebo-controlled clinical trials: the SHARP trial[8] and the Asia-Pacific study (ORIENTAL)[9]. The SHARP trial compared Sorafenib treatment (400 mg twice a day) to placebo among 602 patients, showing a significant difference in overall survival (10.7 mo *vs* 7.9 mo, *P* < 0.001), time to radiologic progression (5.5 mo *vs* 2.8 mo, *P* < 0.001) and disease control rate (43% *vs* 32%, *P* = 0.002), even if no significant difference was observed in time to symptomatic progression (4.1 mo *vs* 4.9 mo, *P* = 0.77). The observed side effects were diarrhea, weight loss, hand-foot syndrome and hypophosphatemia.

The ORIENTAL trial had a design similar to the SHARP study but was performed on 226 patients from the Asia-Pacific region: The overall survival was significantly increased in the Sorafenib-treated group (6.5 mo *vs* 4.2 mo, *P* = 0.014), even if the overall survival was lower compared to the SHARP study; more encouraging results were observed evaluating the time to progression, which was significantly higher in the Sorafenib group (2.8 mo *vs* 1.4 mo, *P* = 0.0005).

The eligibility criteria for treatment with sorafenib are still relatively restrictive and few data are available regarding its use in the presence of impaired liver function (Child-Pugh B/C) or in elderly patients. Regarding liver function, available data come from retrospective studies[14-18], that evaluated treatment with sorafenib in patients with liver function Child-Pugh B, showing shorter overall survival in these patients, compared with patients with Child-Pugh A. In addition, two studies[15-18] showed an increased incidence of severe adverse events in Child-Pugh B patients, that led to dose reduction or discontinuation of treatment. Thus, in the latest available guidelines there is no clear contraindication about sorafenib administration in patients with Child-Pugh B, but caution is advised due to the increased risk of side effects[19]. Sorafenib treatment in elderly (age > 70 years) was evaluated only in a retrospective study[20], which reported a progression free survival and overall survival similar to younger patients, associated to a higher incidence of some adverse events (neutropenia, malaise and mucositis); anyway, no clear indication about treatment of older patients was given in last guidelines. Beside the evaluation of therapeutic usefulness of sorafenib in single therapy, numerous studies have evaluated its use as adjuvant or neoadjuvant treatment. As previously said, potential down-staging effect was suggested, leading to a possible use of this drug as neo-adjuvant therapy or as bridge-to-transplantation therapy[21]; in particular some studies suggest a possible role of sorafenib in preventing tumor relapse after liver transplantation[22,23], even if available studies were performed on small samples not providing statistically significant results. Unfortunately, the same optimism placed in the use of this drug for a neoadjuvant therapy does not seem to be confirmed regarding its use with adjuvant intent. In 2015, the STORM trial, a randomized, double blind, placebo controlled trial, evaluated sorafenib efficacy as adjuvant after resection or local ablation, but no difference in median recurrence free survival was observed (33.3 mo *vs* 33.7 mo, *P* = 0.26)[24]. A more in-depth discussion should be done about the combination of sorafenib and TACE: Initial encouraging results came from retrospective studies[25,26] that evaluated sorafenib in case of TACE refractory or ineligibility (reduced efficacy of TACE itself, vascular devastation, involvement of complex extrahepatic blood supply routes, vascular invasion, distant metastases)[27]. Despite this, initial randomized trial to evaluate this combination did not confirm the efficacy of TACE + sorafenib. In particular, the SPACE trial[28] showed no difference between TACE + sorafenib *vs* TACE + placebo regarding time-to-tumor progression (169 d *vs* 166 d, *P* = 0.072) and overall survival (554 d *vs* 562 d, *P* = 0.295); a more recent phase III randomized trial from Kudo *et al*[29] with a similar design confirmed those results (time to tumor progression 5.4 mo *vs* 3.7 mo, *P* = 0.252; overall survival 29.7 mo *vs* NE, *P* = 0.072). Recent observational studies[30,31] showed more encouraging results in terms of progression free survival and overall survival respectively, and a systematic review/meta-analysis[32] reported a significant different among TACE + sorafenib *vs* TACE in terms of response rate (OR = 3.59, 95%CI: 1.74-7.39, I^2 = 21%, *P* = 0.0005), disease control rate (OR = 4.72, 95%CI: 1.75-12.72, I^2 = 56%, *P* = 0.002), 1-year overall survival (OR = 3.10, 95%CI: 2.22-4.33, I^2 = 41%, *P* = 0.00001), but further randomized trials are still ongoing with the aim to evaluate the effectiveness of this combination therapy (NCT01004978, NCT01324076, NCT01217034).

To develop novel systemic therapies for HCC, sorafenib was also evaluated as second-line therapy after fluoropyrimidine plus platinum-based chemotherapy[33]: The resulting disease control rate of 58.3%, with overall survival and progression-free survival of 7.1 and 2.3 mo, respectively, without increased incidence of adverse events, suggests a modest efficacy of sorafenib as second-line treatment after other systemic therapies. In consideration of new systemic therapeutic options, great importance has acquired the search for markers of resistance to sorafenib, with the intention to offer a personalized therapy for advanced HCC. An example is represented by c-Jun N-terminal kinase activity, related with the CD133 expression level and inversely correlated with the therapeutic response to the drug[8,34]. Thus, many efforts should be done to identify other markers of poor response to sorafenib, with the aim to give each patient a personalized therapeutic approach, based on the resistance profile of each single HCC and to choose among other drugs that will be hopefully soon available beside Sorafenib.

Brivanib

Brivanib is a small molecule acting as dual tyrosine kinase inhibitor (TKI) of VEGFR and FGFR. The drug, administrated orally (800 mg once daily), was initially evaluated as first line treatment in comparison with sorafenib in the BRISK-FL trial, then as second line treatment in comparison with placebo in patients who complained intolerance or lack of response to sorafenib in BRISK-PS trial. BRISK-FL trial[35] showed no difference regarding overall survival between brivanib and sorafenib (9.5 mo *vs* 9.9 mo, HR = 1.06, 95%CI: 0.93-1.22, *P* = 0.311). Even as second-line therapy, in comparison with BSC, Brivanib failed: BRISK-PS[36] trial showed no significant difference regarding overall survival between the two approaches (9.4 mo *vs* 8.2 mo, *P* = 0.3307). Finally, brivanib, like sorafenib, was tested in a randomized, double-blind, placebo-controlled trial[37] as adjuvant therapy after TACE in comparison with placebo, but even in this case it failed in improving overall survival of HCC patients (19.1 mo *vs* 26.1 mo, *P* = 0.5280). Thus, at this time evidences do not allow to consider brivanib an effective alternative to Sorafenib, but further studies may show better results, if we consider positive data about time to tumor progression (4.2 mo *vs* 2.7 mo; HR 0.56, 95%CI: 0.42-0.76, *P* < 0.001) from BRISK-PS and lack of cross tolerance with Sorafenib.

Sunitinib

Sunitinib is another small molecule acting as multikinase inhibitor which targets VEGFR, PDGFR and c-kit. Only one phase III trial (SUN1170 trial)[38] studied the efficacy of the drug as first-line treatment for HCC, but was discontinued due to adverse events. Anyway sunitinib appeared to be inferior to sorafenib regarding overall survival (7.9 mo *vs* 10.2 mo, *P* = 0.0014). Based on current evidence, sunitinib is not to be considered as a viable therapeutic alternative to sorafenib.

Linifanib

Linifanib is a dual tyrosine-kinase inhibitor targeting VEGFR and PDGFR. LIGHT phase III trial[39] compared the drug to sorafenib as first-line treatment, but overall survival between the two groups was similar (95%CI: 8.3-11.0, HR = 1.046, 95%CI: 0.896-1.221) and linifanib group showed higher rate of adverse events (*e.g.*, hypertension and hepatic encephalopathy).

Erlotinib

Erlotinib is a tyrosine kinase inhibitor targeting EGFR, which was evaluated in combination with sorafenib *vs* sorafenib alone in SEARCH phase III trial[40]. This combination did not lead to an increased overall survival (9.5 mo *vs* 8.5 mo, *P* = 0.408) and was related to potent toxicity.

Everolimus

Everolimus acts inhibiting the mammalian target of rapamycin (mTOR). It was evaluated in comparison with placebo in EVOLVE-1 phase III trial[41] in case of sorafenib failure or intolerance, but it did not increase overall survival (7.6 *vs* 7.3, HR = 1.05, 95%CI: 0.86-1.27, *P* = 0.68).

Ramucirumab

Ramucirumab is a recombinant IgG1 monoclonal antibody able to bind extracellular domain of VEGFR-2. REACH trial[42] failed in showing its efficacy as second-line treatment in comparison with placebo, because overall survival was similar between the two groups (9.2 mo *vs* 7.6 mo; HR = 0.87, 95%CI: 0.72-1.05, *P* = 0.14); however the promising results obtained in patients with alpha-fetoprotein > 400 ng/mL, led to an ongoing trial to verify its usefulness of this drug in this specific population.

Regorafenib

Regorafenib is a multi-target inhibitor acting on VEGFR1-3, TIE2, c-kit, Ret, wild type or V600-mutated B-RAF, PDGFR and FGFR, administered orally and derived from sorafenib. RESORCE[43] trial is a phase III randomized, double-blind trial, that recently evaluated the drug as second-line treatment in comparison with placebo in patients who showed intolerance or failure to sorafenib. Regorafenib was related to positive results in terms of overall survival (10.6 mo *vs* 7.8 mo; HR = 0.63, 95%CI: 0.50-0.79, *P* < 0.0001). Adverse events reported are hypertension (15%), fatigue (9%), diarrhea (3%). It is possible to affirm, on the basis of this trial, that regorafenib appears to be the only alternative currently available regarding systemic therapy for the treatment of advanced HCC in case of progression on sorafenib treatment.

Other small molecules

Other small molecules are currently under evaluation for the treatment of HCC. Some of them act against targets already mentioned as factors involved in angiogenesis (*e.g.*, VEGF), other drugs act on pathways that are already targets of other drugs (*e.g.*, MEK, MET). It is important to emphasize that drugs that act on c-MET may have greater efficacy in cases of HCC with increased expression of the receptor[44,45]. Phase III studies are required to define the clinical utility of these drugs, in particular in comparison with sorafenib; for some of them phase III trial are under way. Table 1 shows a list of drugs under preliminary evaluation.

CYTOTOXIC CHEMOTHERAPY

Historically, traditional chemotherapy agents have not shown great efficacy in the treatment of HCC when used in advanced stage of disease, in particular in case of progression after locoregional therapy. This assessment comes from initial examination of single-arm, open-label studies evaluating the use of some chemotherapeutic, that did not lead in the past years to further evaluation

Table 1 Targeted drugs under evaluation in advanced hepatocellular carcinoma

Drug	Molecular target	Study design	DCR	PFS	OS	TTP	Tolerabilty	Phase III study
Lenvatinib[46]	VEGFR, FGFR, PDGFR,RET, KIT	Phase I/II (first line)	NR	NR	18.7 mo	12.8 mo	Favorable profile	Ongoing (E7080)
Cabozantinib[47]	VEGFR-2, MET, RET	Phase II (second line)	68% at 12 wk	4.2 mo	NR	NR	Favorable profile	Ongoing (NCT01908426 – CELESTIAL)
Tivantinib[48]	c-MET	Phase II (*vs* placebo, second line)	MET low NS MET high 50% *vs* 20%	NR	MET low NS MET high 7.2 mo *vs* 3.8 mo; *P* = 0.01	MET low NS MET high 2.7 mo *vs* 1.4 mo; *P* = 0.04	Severe neutropenia	Ongoing (NCT01755767)
Apatinib[49]	VEGFR2	Phase II (first line)	NR	NR	9.7 mo	4.2 mo	Favorable profile	Ongoing (NCT02329860)
Refametinib[50]	MEK	Phase II (+ sorafenib)	43%[1]	NR	290 d[1]	122 d[1]	High incidence of 3/4 grade adverse events	NR
Foretinib[51]	MET, RON, AXL, TIE-2, VEGFR	Phase I/II (first line)	79%	NR	NR	4.2 mo	Favorable profile	NR
Tepotinib[52]	c-MET	Phase Ib/II (*vs* sorafenib, first line) - Ongoing	NR	NR	NR	NR	Favorable profile	NR
Capmatinib[53]	c-MET	Phase I	NR	NR	NR	NR	Favorable profile	NR
Golvantinib[54]	c-MET	Phase I/IIb (+ sorafenib) - Ongoing	NR	NR	NR	NR	Favorable profile	NR
Emibetuzumab[55]	c-MET	Phase I (monotp *vs* emibetuzumab + erlotinib)	NR	NR	NR	NR	Favorable profile	NR
LY2157299[56]	TGF-β	Phase II (second-line)	NR	NR	36 wk[2]	12 wk[2]	Favorable profile	Ongoing
Pazopanib[57]	VEGFR1-3, PDGFRα-β, c-kit	Phase I	NR	NR	NR	NR	Favorable profile	NR
Axitinib[58]	VEGFR1-3	Phase II (*vs* placebo, second line)	NR	3.6 mo *vs* 1.9 mo; *P* = 0.004	12.7 mo *vs* 9.7 mo; *P* = 0.287	3.7 mo *vs* 1.9 mo; *P* = 0.006	Acceptable profile	NR

[1]Best clinical response was observed in case of RAS mutations; [2]Best clinical response was observed in case of AFP level decrease. DCR: Disease control rate; OS: Overall survival; TTP: Time-to-tumor progression; PFS: Progression free survival; NR: Not reported; NS: Not significant.

of this class of drugs and limiting their use to palliative approaches.

Recently, however, new chemotherapeutic agents, such as oxaliplatin, have shown efficacy in the treatment of cancers of the digestive tract (stomach, colorectal, pancreas). Based on these positive results, some of these drugs have also been evaluated for the treatment of advanced HCC, with promising findings.

Monotherapy regimens
This kind of regimen is indicated in case of worse general conditions or worse tolerance to systemic therapy. Doxorubicin was one of the first chemotherapic drugs used for HCC and showed interesting results[59], but its role is actually related to already mentioned DEB-TACE. Doxorubicin was also evaluated in combination with sorafenib (see below for details).

The interest for doxorubicin is growing again due to the technological advance that allows a targeted release of the drug; this aspect will be discussed in another section of this review. Capecitabine is a drug converted to 5-fluorouracil (5-FU) which acts on DNA synthesis, slowing tumor growth. Currently its role in HCC treatment regards adjuvant therapy after surgery, based on a randomized, controlled trial, placebo-controlled[60], that showed lower recurrence rate (53.3% *vs* 76.7%) and higher time-to-tumor progression (40 mo *vs* 20 mo, *P* = 0.0046); 5-years-overall survival was better in capecitabine group, even if this result did not reach statistical significance (62.5% *vs* 39.8%, *P* = 0.216). From a point of view of safety profile, the drug showed a good tolerability. TS-1 (Titanium-silicate) is a newly developed chemotherapeutic agent that acts on metabolism of 5-FU, increasing its toxicity in neoplastic

cells. Its effect was observed for the treatment of other GI tumors, so it was evaluated as second line treatment for HCC in comparison with placebo in a phase III trial (S-CUBE)[61]. This trial failed in proving the superiority of this drug over placebo, but a subanalysis[62] suggests that better results could be observed in a more specific population, characterized by TNM stage III, IVa or IVb, Child-Pugh liver function class A and low levels of tumor markers. In this subgroup, overall survival was significantly longer (426.0 d *vs* 375.5 d; HR = 0.69; 95%CI: 0.51-0.93, *P* = 0.0156), suggesting that more personalization in therapeutic approach should be aimed. Nonetheless this studies show how the best possible results for the systemic therapy are linked to good liver function and to a not too advanced disease.

Politherapy regimens

As previously said, newly developed chemotherapeutic agents, appear to be a valuable option for HCC. FOLFOX4 regimen (fluorouracil, leucovorin, oxaliplatin) was evaluated in comparison to doxorubicin alone for the treatment of advanced HCC ineligible for surgery or for local treatments in EACH trial (phase III trial)[63]. FOLFOX4 was related to better results in terms of progression free survival (2.93 mo *vs* 1.77 mo, *P* < 0.001), response rate (8.15% *vs* 2.67%, *P* = 0.002), disease control rate (52.17% *vs* 31.55%, *P* < 0.001); beside these positive findings and a good safety profile, no significant difference in terms of overall survival, the primary endpoint of the study, was observed (6.40 mo *vs* 4.97 mo, *P* = 0.07), leading to a formal negativity of the study. Still, an unplanned subsequent analysis performed at 7 mo after the end of the previous study has shown an improvement in terms of overall survival (6.47 mo *vs* 4.90 mo, *P* = 0.04) and significant results regarding overall survival (5.9 mo *vs* 4.3 mo, *P* = 0.0281), but progression free survival, response rate and disease rate control in the Chinese population[64], leading to FOLFOX4 approval by Chines Food and Drug Administration for treatment of advanced HCC ineligible for surgery or local treatment. GEMOX regimen (gemcitabine, oxaliplatin) was firstly evaluated in a large, multicenter, retrospective study (AGEO)[65] for treatment of advanced HCC with notable results: 22% response rate, 66% disease control rate, 4.5 mo progression free survival, 8.0 mo time-to-tumor progression and 11.0 mo of overall survival. Two interesting aspects should be considered: As first, overall survival was related to cirrhosis stage and response to the regimen were associated to overall survival; in particular response to GEMOX led to a better overall survival in comparison with lack of response (19.9 mo *vs* 8.5 mo). As second, this regimen was related to a downstaging effect on the neoplasia, considering that 8.5% of patients became eligible for curative-intent treatments. Attention should be given to possible serious side effects of this regimen (neurotoxicity, thrombocytopenia, neutropenia and diarrhea). Another retrospective study[66] subsequently

evaluated GEMOX as second-line treatment after failure of targeted therapy, reporting an overall survival of 8.3 mo, a 6-mo overall survival rate of 59% and a progression free survival of 3.1 mo. Even this study showed an association between overall survival and performance status, alpha-fetoprotein and BCLC score at diagnosis. Further studies are therefore required, in particular phase 3 trials, to assess the role of this regimen in the treatment of HCC. Some other oxaliplatin-based regimens have begun to be studied in phase II trials for HCC treatment, showing interesting results, such as XELOX[67] (oxaliplatin plus capecitabine), GP[68] (gemcitabine plus cisplatin) and cisplatin plus capecitabine[69]. A meta-analysis study[70] tried to define the efficacy and safety of oxaliplatin-based regimens and to assess the best regimen for treatment of advanced HCC, but it as an important limitation having evaluated only small single arm studies, with the exception of the EACH study; anyway, it suggests that better results could be obtained with GEMOX combination. Given the yet ambiguous and preliminary available data, further efforts are necessary, performing randomized trials on extended samples, to define the role of these regimens for treatment of HCC.

Chemotherapy and sorafenib

The growing interest about chemotherapy for the treatment of HCC, has led to its comparison with the only available standard systemic treatment: Sorafenib.

As previously said, there are no significant data about comparison between sorafenib and chemotherapeutic drugs, being the lack of phase III randomized trials a reason. As a matter of fact, this comparison was evaluated only retrospectively[71] with no significant difference in overall survival (23 wk *vs* 43.6 wk, *P* = 0.105) and progression free survival (11.1 wk *vs* 12.4 wk, *P* = 0.496). More efforts were done to assess a possible synergistic effect of sorafenib plus chemotherapeutic agents. After initial promising data from a phase II study[72], a phase III trial (CALGB80802)[73] was planned to assess the efficacy of doxorubicin plus sorafenib in comparison with sorafenib alone as first-line treatment, but it was interrupted after a planned interim analysis demonstrated a higher toxicity in combination group and because primary and secondary endpoints (overall survival and progression free survival, respectively) were not met. The main difference between this and the previous phase II trial is represented by the use of sorafenib in the control group instead of doxorubicin, suggesting that sorafenib could be the determinant in the therapeutic effect of this combination, with a marginal role of doxorubicin. The GONEXT study[74], a phase II study, evaluated the combination of GEMOX plus sorafenib *vs* sorafenib alone as first-line therapy, with moderately positive results: Response rate (16%), disease control rate (77%), median progression free survival (6.2 mo) e 4-mo progression free survival rate (61%), even if overall survival was similar to the

one reported for sorafenib monotherapy; tolerability resulted to be acceptable. The authors commented results pointing out that primary endpoint was met (4-mo progression free survival > 50%), while other results were encouraging. Another preliminary randomized study[75] evaluated this combination as first-line treatment (6 cycles) followed by maintenance treatment with sorafenib alone: objective response was 26.5%. The median time to progression was 10.3 mo (95%CI: 8.7-11.9 mo) and median overall survival was 15.7 mo (95%CI: 13.0-18.4 mo). Toxicity was manageable. Even this approach deserves further evaluations with phase II and III trials. Another phase-II trial[76] studied SECOX regimen (sorafenib, capecitabine and oxaliplatin) in Asian HCC patients; the primary endpoint was time-to-tumor progression (5.29 mo), while secondary ones were response rate (16%), progression free survival (5.26 mo), overall survival (11.73 mo) and tolerance (good tolerance). Results were thus considerate promising and deserving of further evaluations. It is therefore possible to state that oxaliplatin based regimens plus sorafenib showed results suggesting a synergistic action between these drugs and a possible fundamental role in the future of treatment of HCC.

HAIC

HAIC was introduced in Japan before the advent of sorafenib and Japanese clinical guidelines suggested HAIC plus sorafenib in case of HCC with Vp4 or Vp3 (HCC with invasion of the main trunk or the left and right main branches of the portal vein) even in absence of phase III trials supporting the efficacy of this approach. Available regimens are: IA-call (one-shot intra-arterial injection), LFP (repeated intra-arterial injection of cisplatin with a reservoir catheter system) and 5FU/IFN (5-fluorouracil continuous intra-arterial injection with a reservoir catheter system in combination with subcutaneous interferon administration). The best results from a single regimen came from IA-call, that was related to a response rate of 33.8% in a phase II trial[77]. As previously said, these regimens are often used in combination with sorafenib, but only combination based on IA-call was associated to interesting results in terms of overall survival in comparison with sorafenib alone (9.5 mo vs 7.0 mo; HR = 0.74)[78]. On the other side, no significant difference was observed using sorafenib+LFP (11.8 mo vs 11.8 mo; HR = 1.0)[79].

IMMUNOTHERAPY

Tumor immune escape ad its mechanism brought to a growing interest from scientific community, resulting in development of tumor immunotherapy, that proved to be effective for the treatment of some malignant neoplasia (e.g., melanoma, NSC lung cancer, renal carcinoma). Two immunological pathways are involved in tumor immunotherapy: The first one is related to T cells inhibition caused by the interaction between cytotoxic T lymphocyte-associated-4 (CTLA-4), a transmembrane receptor on T cells, and its molecular ligand B7, that may lead to a protective effect for tumor cells and its inhibition is the target of some immunotherapeutic drugs[80]. The second immunological pathway targeted by immunotherapy is the one started by programmed death receptor 1 (PD-1) and its ligands (PD-L1 and PD-L2). PD-1 is produced by several immunity cells (T cells CD28+/CD4+, B cells, NK cells, etc.) but it's often expressed by tumor cells with an immunosuppressive effect, caused by TCR receptor signal transduction inhibition by PD-1-PD-L1 that results in drop of proliferation and depletion of T-cells[81]. Tremelimumab is a humanized anti-CTLA-4 IgG2 antibody and it was evaluated for the treatment of HCC in patients with chronic HCV infection with encouraging results in terms of response rate (18%), disease control rate (76%) and time-to-tumor progression (6.48 mo); two interesting characteristics of this drug are its long half-life (22 d), which could lead to a more comfortable management for the patient, and its antiviral activity, represented by a drop in viral load[82]. An interesting important clinical aspect is the possible synergistic action of this drug with local treatments (TACE and RFA). This synergy might be explained by immune reaction against the tumor caused by local treatments, which improves the efficacy of immunotherapeutic drug. Only preliminary results[83] are available, but they appear to be promising: 40% of patients reached partial response, 5/7 patients affected by HCV infection showed a drop in viral load, histology evaluation showed immune cell infiltration in tumor and progression free-survival was 7.4 mo; in addition no worsening of safety profile was observed. Nivolumab is a fully humanized monoclonal IgG4 antibody against PD-1, recently studied in a phase I/II study[84] for treatment of patients affected by HCC with intolerance to, or inefficacy of, sorafenib. This study reported extremely positive results: 2/39 patients (5%) showed complete response and 8/39 (18%) showed partial response; 6-mo overall survival rate was 72%. On the other hand a moderate rate of adverse events was observed (71%), but only 17% of patients were affected by grade 3/4 adverse events (elevated AST, elevated ALT, elevated serum lipase). A phase III trial (NCT02576509) to compare nivolumab to sorafenib is ongoing. It is safe to say that tumor immunotherapy is a very promising option among systemic therapies, especially because its targets are completely different from targets of the currently available systemic therapies. Furthermore, its effectiveness may allow a better understanding of the biology of HCC. In the near future it will be interesting to evaluate immunotherapy in comparison with standard treatments, but also in combination with them in consideration of possible synergy as seen in case of Tremelimumab and TACE.

FUTURE PERSPECTIVES

HCC appears to be still a tough opponent, if it is not possible to treat it by surgery or by transplantation. It this therefore necessary to improve medical therapy for this neoplasia to give a chance to patients affected by its more advanced stages. It is important to focus which are directions we should follow regarding research in this field.

Understanding why some drugs had partial results or were able to show improvements only in some groups of patients is very important and could allow us to understand resistance mechanisms of this neoplasia and to develop strategies to overcome them. On the other side, many efforts should be made to find new therapeutic targets and develop new drugs. Certainly, the future of advanced HCC treatment will be represented by personalized therapy based on a deep evaluation of the patients, to find out the better targets of disease to be attacked.

Resistance mechanisms

Not so much data is available about resistance mechanisms of HCC and practical ways to overcome them. Preliminary studies have shown that, as previously said, c-Jun N-terminal kinase activity could be related to sorafenib resistance, but this information did not lead to clinical consequences yet. Resistance could be related to systemic therapy in general or to the single drug. In the first case, altered pathways are fundamental for tumorigenesis, metastatic process and maintenance of stem cell properties; in particular molecules involved in autophagy (osteopontin[85]), apoptosis (Cofilin-1[86] and AKR7A3[87]) and stemness related mechanism of cancer stem stells (NRBP2[88]) seem to play an important role, as showed in some preliminary *in vitro* studies.

Particular mechanisms resulted to be involved in resistance to specific drugs. For example, aberrant expression of non-coding RNA was related to oxaliplatin-resistant profile: 421 differentially expressed mRNAs, 228 up-regulated and 193 down-regulated (fold change > 2, $P < 0.05$) in oxaliplatin-resistant (MHCC97H-OXA), were individuated and appear to be related not only to resistance to oxaliplatin, but also to tumor size, differentiation and poor prognosis[89]. On the other hand, TUC338\RASAL1 pathway was related by Jin *et al*[90] to sorafenib resistance: *in vitro* inhibition by non-coding RNA of TUC338 led to a sensitization to sorafenib and, in addition, to a decrease in proliferative and invasive ability. Of particular interest is the recent hypothesis of the role of tumoral microenvironment in chemotherapeutic resistance: Azzariti *et al*[91] described in their study the resistance to sorafenib induced by hepatic stellate cells, that produce laminin-332, an extracellular matrix protein, that is able to bind α3β1 integrin, if expressed, leading to protection of FAK, a target of sorafenib, from degradation.

New combinations of drug with delivery systems or biological enhancers

Another important field of research is the one regarding the development of new forms of drugs already used to enhance the effect and selectivity for HCC; an example is represented by nanoparticle-mediated targeted drug delivery system[92]. Doxorubicin is an example of drug that could soon have a new role in HCC treatment, as demonstrated by preliminary studies on animal models with modified forms of the drug. Lactosaminated albumin conjugate of doxorubicin showed rapid and selective accumulation in the liver[93], such as mesoporous magnetic nanocomposites wrapped with chitosan gatekeepers[94], that in addition exploit acidic pH of tumoral cells with a selective release of drug at pH 4.0. Even A54 peptide modified Doxorubicin glucolipid conjugate micelles[95] showed high selectivity for hepatic cells, in particular for tumoral ones because of redox-sensitivity.

Moreover the modification of cisplatin by the addition of a pH-sensitive polymer and HCC-targeting peptide, to obtain a higher selectivity to HCC and in particular to its stem cells, that are not sensitive to cisplatin alone, showed promising results[96]. On the other hand, elaboration of sorafenib was targeted to add molecules which could acts as biological enhancers in a synergistic way. Two examples of molecules used with this intent are C2-ceramide[97], a potent inducer of apoptosis in human neoplastic cells, and 2-Deoxyglucose[98], an inhibitor of glycolysis that leads to depletion of ATP.

Other drugs under evaluation

Pre-existing and new drugs were studied for treatment of HCC. Antiangiogenic drugs could have a role, because of important angiogenic activity of this neoplasia; in fact VEGFR is already a target of some drugs previously discussed. Unfortunately, bevacizumab was tested in combination with sorafenib in a phase I/II trial with consequent observation of high toxicity and low efficacy of this combination, that led to the interruption of the study[99,100]. It's necessary to mention drugs that have been studied *in vitro* and *in vivo* with promising results, awaiting for trials on humans. Some examples are ursolic acid derivates[101] and a B5G9[102] (piperazidine derivative of 23-hydroxy betulinic acid), that cause ROS-mediated apoptosis in HCC cells, EMMQ[103] (an indolylquinoline derivative), that causes DNA damage by activating p53 and γ-H2AX, and GL63[104] (a curcumine analogue), which was able to suppress the proliferation of HCC cells by inhibition of the JAK2/STAT3 signaling pathway. Even Valproic Acid[105], a well-known antiepileptic drug, showed potential anti-HCC effect *in vitro* by promotion of epithelial mesenchymal transition of hepatocarcinoma cells *via* transcriptional and post-transcriptional up regulation of Snail.

Another new therapeutic approach regards arginine, which cannot be produced by HCC cells; thus, pegy-

lated arginine diminase (ADI-PEG 20) was tested as arginine-degrading enzyme, with favorable tolerability[106] and encouraging disease control rate and median overall survival[107]; a phase III trial to evaluate this drug is actually ongoing (NCT01287585). JX-594 is a recombinant vaccine virus able to cause virus replication-dependent oncolysis and tumor-specific immunity, after inserting human granulocyte-macrofaghe colony-stimulating factor (hGM-CSF) and β-galactosidase transgenes, with disruption of the viral thymidine kinase gene. This vaccine was tested in a low dose administration *vs* a high dose administration; this last one was related to a better median overall survival (6.7 mo *vs* 14.1 mo; HR = 0.39, *P* = 0.02), while response rate was 15% for both groups[108]. PHOCUS phase III trial in combination with sorafenib is ongoing (NCT02562755).

New molecular targets

The advancement of knowledge of the biology of HCC is gradually allowing us to identify new potential molecular targets, which are an essential part of the development and the activity of this tumor. Rao *et al*[109] recently provided an article in which frequently mutated genes/pathways are described and can be source of inspiration to individuate new future therapeutic targets.

NF-κB has a key role in immune response and resulted to be altered in precancerous cirrhosis tissues and in a subset of HCCs. Ramesh *et al*[110] reported preliminary data about *in vitro* activity of ornithogalum against HCC. The importance of NF-κB in HCC biology and in relation to a potential clinical use, was suggested by Chen *et al*[111]: In his study, pretreatment of sorafenib with RT suppressed the expressions of NF-κB and its downstream proteins induced by radiation through downregulation of phosphorylated extracellular signal-regulated kinase (pERK), with a synergistic effect that could lead to a new role for radiotherapy for the treatment of HCC. Another target that has been evaluated in oncology is telomerase, which appears to be constitutively activated in many tumors. In a recent review by Picariello *et al*[112], inhibition of telomerase activity were evaluated. An interesting new approach is the exploitation of telomerase activity using nucleoside analogues that could be metabolized by telomerase. Acycloguanosyl-thymidyltriphosphate[113], a thymidine analogue pro-drug of Acyclovir, was tested *in vitro* and *in vivo* against HCC, leading to reduced tumor growth, increased apoptosis and reduced proliferation of tumor cells in transgenic and orthotopic mouse models. Further studies are necessary to test this kind of drugs on humans.

Other promising molecular targets are prothymosin-alpha[114], a negative regulator of apoptosis, *NEK2*[115], a critical regulator of centrosome structure and function, and *STARD13*[116], a positive regulator of apoptosis.

CONCLUSION

To date, the treatment of HCC is still a major surgical and medical challenge. This is even more true with regard to cases of advanced disease, treatable only with systemic therapy, which by now has few arrows available in its quiver. Sorafenib is today the only standard systemic treatment, but it presents still unsolved issues; this explains the urgency of finding new alternatives to be proposed to the patient. Molecular therapy has a key role: Many drugs are under development and under evaluation; furthermore another drug from this class, Regorafenib, showed positive results and for sure will be considered by future guidelines for the treatment of HCC; on the other hand, the number of available drugs is likely to increase with the rise of biological weaknesses of this neoplasia. Yet, cytotoxic drugs, in particular modified forms, and immunotherapeutic drugs are making a promising competition to sorafenib, acting on different routes. The future availability of a great number of different options with different mechanisms of action definitely gives much hope regarding the treatment of advanced HCC, in particular in terms of personalized therapy.

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