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TOPIC HIGHLIGHT

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Hepatocellular carcinoma review: Current treatment, and evidence-based medicine

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Abstract

Hepatocellular carcinoma (HCC) is the fifth most common tumor worldwide. Multiple treatment options are available for HCC including curative resection, liver transplantation, radiofrequency ablation, trans-arterial chemoembolization, radioembolization and systemic targeted agent like sorafenib. The treatment of HCC depends on the tumor stage, patient performance status and liver function reserve and requires a multidisciplinary approach. In the past few years with significant advances in surgical treatments and locoregional therapies, the short-term survival of HCC has improved but the recurrent disease remains a big problem. The pathogenesis of HCC is a multistep and complex process, wherein angiogenesis plays an important role. For patients with advanced disease, sorafenib is the only approved therapy, but novel systemic molecular targeted agents and their combinations are emerging. This article provides an overview of treatment of early and advanced stage HCC based on our extensive review of relevant literature.

Key words: Hepatocellular carcinoma; Trans-arterial chemoembolization; Drug-eluting beads; Radiofrequency ablation; Liver transplantation; Chemotherapy; Sorafenib; Radioembolization

Core tip: The article discusses the current evidence based treatment of hepatocellular carcinoma. Specific focus is placed on emerging systemic molecular targeted therapies.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common form of cancer worldwide and the third most common cause of cancer-related deaths. HCC often occurs in the background of a cirrhotic liver[1]. Orthotopic liver transplantation (OLT) is an effective treatment for both HCC and underlying cirrhosis, and is considered the best therapeutic option. Unfortunately, most cases of HCC present in an advanced stage and are not suitable candidates for OLT[2]. In recent years surveillance strategies in patients at a higher risk of HCC have led to the diagnosis of the disease at much earlier stages. Patients in early stages have a much higher chance of curative response with different treatment options[2,3]. Tumor staging plays an essential role in guiding the treatment decisions, but

prognosis is affected by the severity of underlying liver dysfunction. A number of staging systems are available for use in HCC, and there is no worldwide consensus on a preferred system. The Child- Pugh classification system and the model for end-stage liver disease (MELD) score only assess the severity of liver disease and do not include the patient's performance status (PS) or cancer-related symptoms. The only staging system currently in use that addresses each of these concerns is the Barcelona Clinic Liver Cancer (BCLC) classification. This classification links HCC staging with patient's PS and co-morbidities. This allows for an appropriate treatment strategy and defines the standard of care for each tumor stage. The major advantage of the BCLC system is that it can be used to identify the patients with early-stage HCC, who may benefit from curative therapies. This differentiates them from the patients with advanced-stage disease who would benefit more from palliative treatment. American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) have endorsed the BCLC system[4,5]. Several therapies have been proposed for these patients with proven survival benefits in the early-stage of HCC. These therapies comprise the surgical resection, various locoregional treatments including percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), transarterial chemoembolization (TACE) and radioembolization[4-6].

LIVER TRANSPLANTATION

Liver transplantation (LT) is a potentially curative treatment and the best treatment option for the patients with decompensated cirrhosis. Currently LT is recommended for the patients with HCC, whose tumor is within the Milan criteria for HCC (one lesion not larger than 5 cm, or up to 3 lesions with each 3 cm or smaller). This selection criterion results in a 5-year overall survival rate of 75% and a tumor recurrence rate of less than 15%[7-9]. This tumor burden is compatible with early-stage HCC in the BCLC staging system. Priority for assignment to the LT waiting list is based upon the MELD score, which is a good predictor of early mortality in patients with cirrhosis. However, MELD score is not able to predict mortality in the patient with HCC, therefore, a "MELD exception" has been developed to assign extra points to the HCC patients on the basis of the tumor burden. The exception criteria have resulted in an increased number of LTs being performed in the HCC patients; currently 30%-40% of the LTs are performed for HCC[10]. Some centers also consider the patients for LT who exceed the Milan criteria. Transplanting the patients with HCC beyond the established criteria falls into two categories; those whose tumors exceed the Milan criteria at presentation without any prior treatment (expanded criteria), and those who fulfill the Milan criteria after locoregional treatments (downstaging). Currently, however, there is no international consensus regarding these approaches in clinical practice[11,12]. Evidence for listing the patients for LT with tumor burden beyond Milan criteria is poor. Yet, it is clear that some patients with tumor burden beyond Milan criteria may benefit from transplantation. Similarly, studies looking at the LT outcomes in the patients with HCC after downstaging are very heterogeneous and no evidence-based recommendations can be made at this point. Few studies have shown that successful downstaging of HCC can be achieved in carefully selected patients and is associated with excellent post-transplantation outcomes[13]. Success in downstaging has been reported in many studies, although most of these are uncontrolled observational studies[9,14,15]. Multiple modalities including resection, RFA and TACE have been used for downsizing. The largest experience is with TACE and RFA. The two prospective studies showed that survival after liver transplantation in patients with large tumor burden successfully treated by downstaging was similar to survival in patients who initially met the criteria for LT[16,17]. It is essential to consider how expansion of criteria beyond the Milan criteria might affect the survival of candidates for liver transplantation who do not have HCC. In the European Liver Transplant Registry, Organ Procurement and Transplantation Network, and Australia and New Zealand Liver Transplant Registry, 5-year survival for non-HCC was 65%-87%[18]. According to studies based on Markov models using data from the United States, patients outside the Milan criteria would need to achieve 5-year survival of 60% or higher to prevent a substantial decrement to the life-years available to the entire population of candidates for liver transplantation[19,20]. International consensus conference on recommendations for liver transplantation in 2010 recommended that modest expansion of Milan criteria should be considered[18]. Among many proposals, only the University of California San Francisco criteria (one tumor $\leqslant$ 6.5 cm, three nodules at most with the largest $\leqslant$ 4.5 cm, and total tumor diameter $\leqslant$ 8 cm) have been prospectively validated by the proponent group, with outcome data comparable to those from other retrospective studies[17,21].

A minimum observational period of 3-6 mo after downstaging was required before the LT[17]. It has been recognized that tumor size and number are crude measures of prognosis. In future, studies with molecular markers or gene signatures will define tumor biology and these will be incorporated in the eligibility criteria for the transplant listing[22].

SURGICAL RESECTION

Surgical resection is the treatment option for a small number of patients with single nodules, good liver function and no underlying cirrhosis. Surgical resection has an increased risk of hepatic decompensation in the patients with cirrhosis[23,24]. Thus, only patients with well-compensated cirrhosis, Child-Pugh class A, are considered the ideal candidates for surgical resection. Portal hypertension in cirrhotic patients is considered a relative contraindica-

tion for surgical resection according to EASL/AASLD guidelines. In earlier studies Bruix *et al*[4,25] reported that in Child-Pugh A cirrhotic patients undergoing hepatic resection, the presence of portal hypertension based on hepatic venous pressure gradient (HVPG) ⩾ 10 mmHg, to be the best predictor of post-operative liver decompensation and poor long-term outcomes. However, measurement of HVPG is an invasive procedure and requires technical expertise. Some studies have used other surrogate markers of portal hypertension like the presence of esophageal varices or splenomegaly (major diameter > 12 cm) with a platelet count of < 100000/mm^3. Few recent studies have reported comparable postoperative and long-term outcome in patients with and without portal hypertension using these surrogate markers of portal hypertension. These studies demonstrated that cirrhotic patients with both clinically significant portal hypertension and well-preserved liver function have similar short- and long-term outcomes compared with patients without portal hypertension. Overall surgical results depend not only on the presence of portal hypertension but also on the residual liver function, size of segmental resection and the remnant liver volume[26,27]. Moreover with improvement in anesthesia and surgical techniques, specifically laparoscopic resection, results of surgery are much superior[28]. Therefore, the prognostic relevance of clinically significant portal hypertension after hepatic resection in patients with HCC is still a matter for debate. The recent study by Santambrogio *et al*[29] reported that the presence of clinical portal hypertension alone does not influence the post-operative course of cirrhotic patients submitted to hepatic resection. If stringent preoperative selection criteria are met (*i.e.*, Child-Pugh class A patients undergoing resection with a laparoscopic approach and limited segmental hepatic resection) the post-operative mortality rate is very low.

Patients without portal hypertension or with clinically significant portal hypertension and preserved liver function (Child-Pugh A5 class) can undergo hepatic resection without hepatic decompensation and good long-term survival, if limited hepatic resection with enough remnant liver volume is done with laparoscopic approach.

The patients who undergo surgical resection have nearly 70% five-year survival but have a high risk of recurrence. Recurrence rate correlates with the presence of microscopic vascular invasion, which is present in more than 30% of HCC patients without any evidence of macroscopic vascular invasion[30,31]. Early tumor recurrence within two years of surgery is mainly related to local invasion and intrahepatic metastasis. Late recurrence, occurring after two years of surgery, is mainly related to *de novo* tumor formation. Some studies have shown benefit of adjuvant therapies in decreasing the postoperative recurrence rate[32-34].

Though the hepatic resection is not often considered as an option in patients with multiple tumors, some centers have reported optimal results with hepatic resections even in patients with multiple tumors.

Some of the biomarkers (gene signatures or molecular biomarkers) are promising in predicting the late recurrence[35]. These biomarkers are likely to improve selection of candidates for surgical resection with lower risk of recurrence.

At present, surgical resection is recommended in the patients with early-stage disease and preserved liver function. But the surgical option should be weighed against the availability and the response rate of other local ablative therapies like radiofrequency ablation.

RFA

Surgical resection is currently considered the most curative strategy, but in the last decade highly satisfactory results have been obtained with local ablative therapies[36]. RFA is currently considered the most effective local ablative therapy. There has been considerable improvement in the RFA technique like the use of expandable-tipped or cool-tip electrodes. A single electrode insertion can produce a necrotic area of up to 3.0 cm in diameter, thus allowing complete ablation of a 2 cm with necrosis of adjacent 0.5 cm to 1.0 cm margins, achieving tumor free margins like surgical resection.

Local ablation with RFA is considered a standard of care for the patients with very early and early stage (BCLC 0-A) tumors not suitable for surgery. The best results were reported for RFA-treated patients with tumors < 2 cm in diameter who had 5-year survival rates ranging from 40% to 70%. A cohort study of RFA demonstrated that complete ablation of lesions smaller than 2 cm is possible in more than 90% of cases, with a local recurrence rate of less than 1%[37].

RFA has replaced percutaneous ethanol ablation as the locoregional therapy of choice. Three independent meta-analyses, including five randomized controlled trials, have provided evidence for better local control and increased survival benefits in patients treated with RFA compared to ablation with PEI. RFA has also been shown to provide a survival benefit in patients with tumors > 2 cm but < 5 cm, as compared to PEI[38-40]. Consequently, RFA has progressively replaced PEI for patients with small HCC who are not candidates for surgery.

There is no consensus so far whether percutaneous RFA can replace surgical resection as first-line treatment for small tumors. Two RCTs provided conflicting evidence regarding the benefits of RFA *vs* surgical resection. The results from one RCT suggest a benefit for surgery over RFA in patients who met the Milan criteria followed for up to 5 years[41]. Another RCT did not identify a significant difference in survival between RFA and surgery in patients with solitary HCC and a diameter up to 4 cm[42]. At present strong evidence of the superiority or equality of RFA in comparison with surgical resection is lacking, but it is also true that there is no solid evidence that surgical resection is better than RFA for the treatment of small HCC. Studies addressing this issue

Table 1 Surgical resection *vs* radiofrequency ablation

Ref.	5-yr recurrence free survival	5-yr overall survival	1-yr recurrence-free survival	1-yr overall survival	Tumor number	*n* (SR, RFA)	Mean tumor size (cm)	Patients (*n*)	Study design	Year
Hasegawa *et al*[43]	N/A	SR: 71.1% RFA: 61.1%	N/A	N/A	1 (83, 73)	2 (13%, 20%) 3 (3%, 7%)	SR: 2.3 RFA: 2.0	SR: 5361 RFA: 5548	Cohort study	2013
Tohme *et al*[44]	SR: 34% RFA: 28%	SR: 47% RFA: 35%	SR: 66% RFA: 68%	SR: 88% RFA: 86%	1 (78, 78)	2 (20%, 18%) 3 (2%, 3%)	SR: 3.07 RFA: 2.36	SR: 50 RFA: 60	Cohort study	2013
Feng *et al*[42]	N/A	N/A	SR: 90.6% RFA: 86.2%	SR: 96% RFA: 93.1%	1 (62, 57)	2 (38%, 43%)	SR: _	SR: 84 RFA: 84	RCT	2012
Huang *et al*[41]	SR: 51.3% RFA: 28.6%	SR: 75.6% RFA: 54.7%	SR: 85.2% RFA: 81.7%	SR: 98.2% RFA: 86.9%	1 (77, 73)	2 (20%, 26%) 3 (3%, 1%)	≤ 5 _	SR: 115 RFA: 115	RCT	2010
Hasegawa *et al*[45]	N/A	N/A	N/A	SR: 98.3% RFA: 98.5%	1 (84, 72)	2 (12%, 21%) 3 (3%, 7%)	SR: 2.2 RFA: 2.0	SR: 2857 RFA: 3022	Cohort study	2008
Chen *et al*[46]	N/A	N/A	SR: 86.6% RFA: 85.9%	SR: 93.3% RFA: 95.8%		1 (100%, 100%)	≤ 5 _	SR: 90 RFA: 71	RCT	2006
Lü *et al*[47]	N/A	N/A	SR: 82.4% RFA: 78.5%	SR: 91.3% RFA: 93.5%	1 (96, 4)	> 1 (88%, 12%)	3.2 _	SR: 54 RFA: 51	RCT	2006
Chen *et al*[48]	N/A	N/A	N/A	SR: 93.2% RFA: 92.8%		1 (100%, 100%)	≤ 5 _	SR: 65 RFA: 47	RCT	2005

N/A: Not applicable; RCT: Randomized controlled trial; RFA: Radiofrequency ablation; SR: Surgical resection.

have been shown in Table 1[41-48].

It is unlikely that any future RCT will address this issue, because it will require very large sample size to show significant differences between two modalities. RFA is less expensive, less invasive, with lower complication rates and shorter hospital stay than surgical resection. In patients with tumor > 3 cm but < 5 cm in size, the success rate of RFA alone is decreased. In these cases combination with TACE could be considered. Recently, the results of an RCT[49] aimed at evaluating the therapeutic efficacy of combining RFA with TACE for treating intermediate-size (3.1-5.0 cm) HCCs have been published. Local tumor progression rate was significantly lower in the TACE and RFA-treated group than in the RFA-only group (6% *vs* 39%).

RFA should be considered the first option for the treatment of small HCC. However, RFA is size-dependent. RFA can produce a necrotic area of about 4 cm, so it can be effective in HCC measuring up to 3 cm or smaller. In future technical developments allowing achieving ablation areas of 5 cm or more in diameter will make percutaneous thermal ablation an effective alternative to surgery even for tumors measuring 3 cm or more[50].

TACE

TACE is currently considered a standard treatment for the patients with intermediate-stage HCC. Patients with compensated liver function (Child B up to 8 points), with large single nodule (< 5 cm) or multifocal HCC without evidence of vascular invasion or extra hepatic spread are considered candidates for TACE. The recommendation for TACE as the standard of care for intermediate-stage HCC is based on the demonstration of improved survival, as compared with the best supportive care or suboptimal therapies[51]. Llovet *et al*[52] reported a meta-analysis of six randomized controlled trials, comparing TACE with the best supportive care or suboptimal therapies. There was considerable heterogeneity between the individual study designs (including patient populations and TACE technique), as well as the study results, with only two of the six individual studies reporting 2-year survival with a statistically significant improvement[53,54]. TACE has been reported to achieve a partial response in 15%-62% patients, with significantly delayed tumor progression and improvement in median survival from 16-20 mo[52].

Intermediate-stage HCC includes a heterogeneous population of the patients with variable tumor burden and liver function (Child-Pugh class A or B). The risk of TACE-associated complications may be greater in patients with more extensive disease requiring non-selective embolization, with portal vein thrombosis and with poor residual liver function. The patients with Child-Pugh class C and some with Child-Pugh class B should be excluded from TACE. In the studies reported in literature, MELD score has not been used to select patients. Patients with total bilirubin > 3 mg/dL were excluded. TACE benefits should be balanced with risk of treatment-induced liver failure.

There is lack of standardized therapy regimen for TACE. The optimal schedule, choice of antineoplastic agents (*e.g.*, mitomycin, cisplatin, and doxorubicin alone or in combination), embolizing agent (*e.g.*, gelatin sponge particles or polyvinyl alcohol particles) use of iodized oil, or bland embolization *vs* chemoembolization, has not been fully established. From a technical point of view, while there is a general consensus about the fact that TACE should be as selective as possible, more standardization of TACE

protocols is still needed. Selective TACE comprises the injection of chemotherapeutic agents into the segmental or sub segmental branches feeding the tumors. Golfieri *et al*[55] compared the effectiveness of selective or super-selective TACE *vs* standard TACE in determining tumor necrosis in a prospective study of 67 consecutive patients (122 nodules, all < 5 cm). When compared with the standard TACE, selective/super-selective TACE was associated with higher mean levels of necrosis. A direct relationship was reported between the tumor diameter and the mean tumor necrosis level (59.6% for lesions < 2 cm, 68.4% for lesions 2.1-3 cm and 76.2% for lesions > 3 cm). These findings suggest that selective/super selective TACE may determine a higher rate of tumor necrosis than the standard TACE; however, very small nodules (< 2 cm) may not respond as 3-4 cm nodules[56].

The ideal TACE procedure should allow maximum and sustained concentration of chemotherapeutic drug in the tumor, with minimal systemic exposure combined with calibrated tumor vessel obstruction. Lipiodol has been widely adopted in TACE protocols because HCC tumors have great avidity to lipiodol. However there is no data showing that lipiodol allows slow release of chemotherapeutic agents and achieves higher or sustained concentration of chemotherapeutic agents in tumor. One recent survey from multiple eastern and western centers in Europe showed that surgical resection is widely in practice among patients with multinodular, large, and macro-vascular invasive HCC, and provides acceptable short- and long-term results[57,58].

TACE with drug-eluting beads

The recent introduction of embolic microspheres that have the ability to actively sequester doxorubicin hydrochloride from solution and release it in a controlled fashion has been shown to substantially diminish the amount of chemotherapeutic agent that reaches the systemic circulation, as compared with ethiodized oil-based regimens. This significantly increases the local concentration of the drug and the antitumor efficacy[59].

Recently published results from the PRECISION V trial indicate that TACE with drug-eluting beads is a valuable alternative to ethiodized oil-based conventional TACE. Compared with conventional TACE, the TACE with drug-eluting beads (DEB-TACE) with doxorubicin-eluted beads was associated with improved outcomes[60]. At 6 mo, the DEB-TACE group showed higher rates of complete response, objective response and disease control compared with the conventional TACE group. Although the predefined hypothesis of superiority was not met in the overall population, patients with Child-Pugh B, bi-lobar disease and recurrent disease showed a significant increase in objective response. In addition, DEB-TACE was associated with a reduction in serious liver toxicity and lower rate of doxorubicin-related side effects when compared with the standard TACE[60].

In some patients, there is a risk of systemic toxicity of chemotherapeutic agents used in conventional TACE or DEB-TACE. In these patients bland embolization can be performed. Trans-arterial bland embolization achieves tumor necrosis, but much less compared to DEB-TACE[61].

At present TACE is the standard of care for treating patients with intermediate-stage HCC, but due to heterogeneity of the patient population in this stage, all patients do not achieve the same response. DEB-TACE is preferred over conventional TACE. Repetition of TACE with aggressive schedule increases the adverse events. Repeat TACE should be considered based on objective evidence of tumor progression. Patient at risk of adverse outcome should be identified based on response to first TACE and effect on underlying liver disease. Recently describe ART score may help in identifying patients at high risk for poor outcome after repeated TACE[62,63].

RADIOEMBOLIZATION

Radioembolization or selective internal radiation therapy (SIRT) has recently emerged as a therapeutic option for intermediate-stage HCC and its role in unresectable liver disease is still being refined[56,64-66]. In radioembolization, implantable radioactive microspheres are delivered into the arteries that feed the tumor so that tumor nodules are treated irrespective of their number, size or location. Radioembolization is different from the TACE. In TACE, the embolizing particles or drug eluting particles are usually 100-500 μm in size, which cause ischemia of tumor; but in radioembolization the microspheres are usually smaller (35 μm) in diameter and deliver radiation to tumor without ischemia to the tumor or liver tissue. Currently, the most popular radioembolization technique uses microspheres coated with Y^{90} b-emitting isotope (TheraSphere and SIR Sphere). The safety of Y^{90} radioembolization has been documented in phase I and phase Ⅱ clinical investigations[67]. A few observational studies and retrospective analyses have reported the efficacy of radioembolization in the treatment of HCC[68,69]. Median survivals for intermediate stage HCC, however, vary widely (between 7 and 27 mo) between phase Ⅱ studies, depending on the PS, extent of the disease and the degree of hepatic functional reserve. Salem *et al*[70] reported a large prospective study in 291 patients treated with glass-based Y^{90} microspheres (TheraSphere) showing that liver function and portal vein thrombosis were main predictors of survival. Recently, a comparative analysis of radioembolization or TACE reported fewer side effects, better response rate and longer time to progression (13.3 mo *vs* 8.4 mo) in radioembolization group, but median survival time was not different (20.5 mo *vs* 17.5 mo)[68]. In another similar study by European Network on radioembolization with Y^{90} resin microspheres. Sangro *et al*[69] reported similar safety profile and response rates. Results of RCTs would provide the highest level of evidence, but based on these studies, it has been estimated that more than 1000 patients would be required to confirm the statistical equivalence or superior-

ity of one treatment over other. Moreover, the relevant cost associated with radioembolization may limit a wide use of this technique. At present radioembolization appears to be safer in more advanced stage HCC including portal vein thrombosis and large tumor burden[69,71,72].

HCC TREATMENT AS A BRIDGE TO TRANSPLANT

Patients with HCC receiving LT within Milan Criteria have a low rate of recurrence and excellent long-term survival.

In recent years, waiting time for LT has progressively increased and despite priority for HCC within the Milan criteria, a significant rate of dropout from the waiting list occurs due to tumor progression. Hence treatment of HCC in patients awaiting LT has become routine, primarily in an effort to prevent tumor progression, reduce dropout rate and to decrease the post-transplant HCC recurrence.

The risk of dropout for HCC within the Milan criteria correlates with the length of waiting time and initial tumor characteristics. In patients initially presenting with solitary HCC < 2 cm, risk of progression is low and only tumors > 2 cm receive priority on waiting list. Hence most transplant centers observe rather than treat these lesions until they grow to 2 cm. The cumulative dropout rates at 6 and 12 mo for patients with single HCC > 3 cm or with 2-3 nodules have been reported 12% and 56% *vs* 0% and 10% with solitary HCC ≤ 3 cm. These patients are often considered for treatment while awaiting LT.

Chemoembolization, radiofrequency ablation and ethanol injection all are effective in controlling tumor growth; however, there is no high level evidence that these modalities are effective in stopping tumor progression in patients on the waiting list, reducing dropout rate or decreasing post-transplant recurrence. TACE has been widely used, as a bridge to transplant but there is no evidence-based data to support this practice. TACE has not been shown to decrease the dropout rates on waiting list[14,73], but most of the studies addressing this issue were heterogeneous in patient selection, TACE-related protocols and had variable waiting time on LT list. It is unlikely that well-designed RCTs will address this issue in the future. Nevertheless, particularly in the United States, where continued waiting list priority depends on maintaining HCC within Milan criteria, use of nonsurgical HCC treatment will likely continue in an effort to prevent tumor progression and waiting list dropout.

TACE alone or combination with other treatments is recommended to bridge patients to transplant specifically when the waiting list time is more than six mo.

TARGETED SYSTEMIC CHEMOTHERAPY

Hepatocarcinogenesis is the result of genetic alterations affecting multiple signaling cascades resulting in uncontrolled growth of the hepatocytes. Systemic targeted therapies focus on the critical steps of the carcinogenic pathways, limiting widespread systemic toxicity. No single dominant or pathognomic pathway exists in the hepatocarcinogenesis. Overexpression of multiple signaling pathways have been implicated in the pathogenesis of HCC including Vascular endothelial growth factor (VEGF), epidermal growth factor, Ras mitogen-activated protein kinase (MAPK), insulin-like growth factor receptor, hepatocyte growth factor/c-MET, PI3K/PTEN/Akt/mammalian target of rapamycin (mTOR) and Wnt/β-Catenin pathways[74-79]. Targeted molecular agents may block one or more steps in a targeted pathway or potentially more than one pathway to provide suitable results. Currently, sorafenib is approved for the treatment of HCC and represents a paradigm shift in the systemic treatment of HCC, and many new molecular therapies are under investigation.

Sorafenib

Multiple cellular kinases are involved in the development and progression of the HCC by promoting angiogenesis, cellular differentiation, proliferation and survival. Sorafenib is an oral bi-aryl urea, which inhibits multiple cell surface and downstream kinases involved in tumor progression. Cell surface tyrosine kinases inhibited by Sorafenib include VEGF receptor- (VEGFR-) 1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor- (PDGFR-) β, RET, c-KIT and FMS-like tyrosine kinase-3. Sorafenib also inhibits Ras/MAPK pathway, this pathway involves extracellular signal-regulated kinases and multiple intracellular serine/ threonine kinases including Raf-1 (C-Raf) and B-Raf (wild and mutant-types). Ras/MAPK pathway activation could be due to the mutational activation of *Ras* oncogene or over expression of surface tyrosine kinases. Overexpression of these kinases is important in HCC proliferation and angiogenesis[80,81]. Two phase Ⅲ randomized placebo-controlled trials, the SHARP trial conducted mainly in America and Europe[82] and a similar trial conducted in Asia[83] reported improved overall survival with sorafenib. In the SHARP trial, the median overall survival was 10.7 mo with sorafenib and 7.9 mo with placebo. In the Asian study, the median overall survival was 6.5 mo with sorafenib and 4.2 mo with placebo. Sorafenib was generally well tolerated; toxicities were mild to moderate in severity, predominantly including diarrhea, fatigue, and hand-foot skin reaction.

These two, phase Ⅲ trials have established sorafenib as the preferred systemic therapy for advanced HCC although the role of sorafenib in intermediate HCC is less clear. Moreover, only small numbers of patients with Child-Pugh B have been included in clinical trials, so it is not possible to assess efficacy and safety of sorafenib in this group of patients. Various phase Ⅲ trials reporting the overall survival in patients with advanced HCC treated with sorafenib, sunitinib, erlotinib, linifanib and brivanib are shown in Table 2.

Table 2 Phase Ⅲ clinical trials of systemic targeted agents

Ref.	Year	Patients (*n*)	Overall survival (mo)
Llovet *et al*[82] (SHARP trial)	2008	Sorafenib: 299 Placebo: 303	Sorafenib: 10.7 Placebo: 7.9
Cheng *et al*[83] (NCT00492752)	2009	Sorafenib: 150 Placebo: 76	Sorafenib: 6.5 Placebo: 4.2
Zhu *et al*[100] (SEARCH trial)	2012	Sorafenib: 358 Sorafenib + Erlotinib: 362	Sorafenib: 8.5 Sorafenib + Erlotinib: 9.5
Cheng *et al*[99] (SUN1170 trial)	2013	Sorafenib: 544 Sunitinib: 530	Sorafenib: 10.2 Sunitinib: 7.9
Cainap *et al*[101] (LIGHT trial)	2013	Sorafenib: N/A Linifanib: N/A	Sorafenib: 9.8 Linifanib: 9.1
Johnson *et al*[95] (BRISK-FL trial)	2013	Sorafenib: 578 Brivanib: 577	Sorafenib: 9.9 Brivanib: 9.5
Llovet *et al*[94] (BRISK-PS trial)	2013	Brivanib: 263 Placebo: 132	Brivanib: 9.4 Placebo: 8.3

Sorafenib has also been used in combination with other systemic chemotherapeutic agents with a goal to improve efficacy. Sorafenib in combination with doxorubicin[84], octreotide[85] and oxaliplatin[86], tegafur/uracil[87], cisplatin and gemcitabine[88] and AVE 1642 (a human monoclonal antibody inhibiting the insulin-like growth factor-1 receptor)[89] has been used. All of these studies report some survival advantage over sorafenib alone. But most of the studies looking at the combination of sorafenib with other systemic therapies have small sample size. Large randomized double-blind studies are needed to establish the role and toxicity profile of these combination regimens.

Other chemotherapeutic agents

Sunitinib: Sunitinib is a multi-kinase blocker that targets VEGFR and PDGFR. Sunitinib was used in phase Ⅱ clinical trials for HCC treatment, which led to an open-label phase Ⅲ trial comparing it with sorafenib[90]. A total of 1073 patients were randomized to receive either sorafenib (544) or sunitinib (529). This trial was terminated early due to increased side effects and futility concerns.

Linifanib: Linifanib is a multi-kinase inhibitor targeting VEGFR and PDGFR along with other kinases. It was found to be effective in the treatment of the HCC with an acceptable safety profile in a single arm phase Ⅱ clinical trial[91].

Brivanib: Brivanib is a selective inhibitor of fibroblastic growth factor receptor and VEGFR. It showed somewhat promising results in the phase Ⅱ trials as first line (median overall survival: 10 mo) and second line (median overall survival: 9.5 mo) treatment agent for HCC[92,93]. Brivanib was tried in a phase Ⅲ BRISK-PS trial as a secondary treatment agent (failed prior systemic treatment due to side effects or progression of the disease) for the treatment of HCC. The median length of overall survival was 9.4 mo for brivanib recipients *vs* 8.2 mo in the placebo group, which was not statistically significant (P = 0.33)[94]. Another phase Ⅲ trial, BRISK-FL, compared brivanib with sorafenib as first line treatment agent for HCC[95]. Median survival was 9.5 mo in the brivanib group compared with 9.9 mo in the sorafenib group, which was not statistically significant. Sorafenib was better tolerated than brivanib leading to lesser discontinuation rate (33% *vs* 43% respectively).

Tivantinib: Tivantinib is an oral MET receptor tyrosine kinase inhibitor. When added to sorafenib, it had synergistic effect against HCC as noted in a phase I clinical trial[96]. In a randomized, placebo-controlled, double-blind, phase Ⅱ trial, tivantinib was used as a second line agent for the treatment of HCC in previously unresectable HCC who progressed or could not tolerate the first line systemic therapy[97]. The patients were randomly assigned to receive tivantinib (n = 71) or placebo (n = 36). Time to progression of HCC was longer in tivantinib group (1.6 mo) than the placebo group (1.4 mo) (HR = 0.64; P = 0.04). The subgroup of patients who received tivantinib and expressed high tissue MET levels (n = 22) had even longer median time to progression of HCC (2.7 mo). A randomized, double-blinded, controlled phase Ⅲ study (METIV-HCC trial) is currently underway to determine the efficacy and safety of tivantinib plus sorafenib *vs* sorafenib alone in the patients with previously unresectable cancer as a first line treatment agent.

Everolimus: Everolimus is an inhibitor of mTOR. A phase Ⅰ/Ⅱ single arm trial using everolimus in advanced HCC patients (unresectable) with and without prior systemic therapy for HCC showed that the median progression free survival of 28 patients was 3.8 mo (95%CI: 2.1-4.6) and overall survival was 8.4 mo (95%CI: 3.9-21.1)[98]. And phase Ⅲ clinical trials of systemic targeted agents is shown in Table 2[82,83,94,95,99-101]. A randomized, double blind, placebo control phase Ⅲ trial (EVOLVE-1) is underway to assess the role of everolimus in unresectable HCC patients who failed prior treatment with sorafenib.

Sorafenib and TACE combination

As previously discussed, TACE works by blocking the hyper-vascular arterial blood supply of the tumor with the help of an embolic agent and injecting the chemotherapeutic drug. As a result of TACE, a hypoxic environment is created around the surviving tumor cells. Hypoxia stimulates the expression of VEGF and hence the neovascularization of the surviving cells. Sorafenib appears to be a good choice to block the neovascularization at that stage. A phase Ⅲ trial comparing linifanib to sorafenib as a first line targeted agent has recently been reported[101]. Recently Gadani *et al*[102] presented their results of a retrospective analysis of 19 patients with Child-Pugh class A and B patients with HCC. Most of the patients were Child-Pugh class A (n = 16) and BCLC stage C (n = 13).

Various studies have looked at the combination of

TACE with sorafenib, where sorafenib was introduced few days to weeks after the first TACE (sequential introduction) or it was started prior to the planned TACE and only interrupted for few days around the procedure (interrupted scheduling). There has been reluctance to use combination of TACE and sorafenib due to fear of increased toxicity. In a prospective study patients with unresectable HCC received a combination of sorafenib (started 2-4 wk prior to TACE) and TACE with LC beads[103]. The authors reported safety of concurrent sorafenib and transarterial therapy but without clear benefit of survival.

The efficacy of combination treatment has been assessed in few prospective studies. In a prospective, placebo controlled, randomized, double-blind study Sansonno *et al*[104] randomized 31 patients with Child-Pugh class A and BCLC-B HCC to receive conventional TACE plus sorafenib and similar number of patients to receive TACE plus placebo. Sorafenib was added 30 d after the first TACE procedure and the patients received more than one TACE procedures. The median time to progression was 9.2 and 4.9 mo in the TACE plus sorafenib and the TACE plus placebo groups respectively.

In another study Kudo *et al*[105] did not find a difference in overall survival or time to progression benefit with TACE plus sorafenib combination compared with TACE plus placebo. But this effect was likely due to the fact that sorafenib was started late after the first TACE procedure (> 50% of the patients starting it more than 9 wk post-TACE) and there were significant dose reductions and multiple dose interruptions. The START trial[106] was conducted to assess the combination of sorafenib with conventional TACE procedure. One subgroup analysis of the Chinese patients (n = 62) in the START trial was recently published[107]. Patients with unresectable HCC were enrolled and they received conventional TACE and sorafenib 400 mg twice a day. Sorafenib was continued until 4 d prior to the next TACE and was resumed 4 d after TACE procedure for safety reasons. The preliminary results of START indicate concurrent sorafenib and TACE therapy is safe and effective with no unexpected side effects. Similar results were produced in another subgroup analysis of the START trial in Asia-Pacific region, without any un-expected side effects[108]. Currently DEB-TACE has shown superiority over conventional TACE. DEB-TACE in combination with sorafenib has been studied in clinical trails (SPACE, and TACE-2 trials)[109,110]. Recently reported data from the randomized phase Ⅱ SPACE trial suggest that DEB-TACE in combination with sorafenib met the predefined primary endpoint of improving time to radiologic progression compared with DEB-TACE in combination with placebo[109]. The results of ongoing phase Ⅲ trials will determine whether there is a role to implement this combination in clinical practice.

The results of concurrent TACE and sorafenib in intermediate stage appear promising but at present it is difficult to recommend combination therapy. There are uncertainties regarding dose, frequency and duration of sorafenib when used in combination with TACE.

Sorafenib and radio-embolization

Several on-going clinical trials are looking at the combination of radio-embolization and sorafenib in patients with HCC. Recently Gadani *et al*[102] presented their results of a retrospective analysis of patients with Child-Pugh class A and B patients with HCC. The patients were on sorafenib prior to yttrium-90 treatment, which was resumed post- treatment. The overall survival of the patients was higher than the previously reported studies that only used sorafenib. Further prospective studies are being conducted to evaluate the combination of radiation therapy and sorafenib.

CONCLUSION

Management of HCC depends on the tumor stage, liver function reserve, and patient performance status (BCLC stage), and requires a multidisciplinary approach for optimal treatment. LT and hepatic resection are the only curative options in early stage of disease. There have been significant advances in local ablative and transarterial therapies. In the early stage HCC, RFA is equivalent to surgical resection in well-selected patients. Drug-eluting beads have improved the efficacy and safety of conventional TACE. Radioembolization with use of resin or glass sphere appear promising. Molecular studies of HCC have identified aberrant activation of different signaling pathways, which represent key targets for novel molecular therapies. For patients with advanced disease, sorafenib is the only approved therapy, but novel targeted agents and their combinations are emerging.

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