REVIEW

Recent advances in multidisciplinary management of hepatocellular carcinoma

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Abstract

The incidence of hepatocellular carcinoma (HCC) is increasing, and it is currently the second leading cause of cancer-related death worldwide. Potentially curative treatment options for HCC include resection, transplantation, and percutaneous ablation, whereas palliative treatments include trans-arterial chemoembolization (TACE), radioembolization, and systemic treatments. Due to the diversity of available treatment options and patients' presentations, a multidisciplinary team should decide clinical management of HCC, according to tumor characteristics and stage of liver disease. Potentially curative treatments are suitable for very-early- and early-stage HCC. However, the vast majority of HCC patients are diagnosed in later stages, where the tumor characteristics or progress of liver disease prevent curative interventions. For patients with intermediate-stage HCC, TACE and radioembolization improve survival and are being evaluated in addition to potentially curative therapies or with systemic targeted therapy. There is currently no effective systemic chemotherapy, immunologic, or hormonal therapy for HCC, and sorafenib is the only approved molecular-targeted treatment for advanced HCC. Other targeted agents are under investigation; trials comparing new agents in combination with sorafenib are ongoing. Combinations of systemic targeted therapies with local treatments are being evaluated for further improvements in HCC patient outcomes. This article provides an updated and comprehensive overview of the current standards and trends in the treatment of HCC.

Core tip: This article reviews the available treatment options for hepatocellular carcinoma. The recent clinical trials of molecular-targeted therapies, as single agents or in combination with other treatments, are reviewed, and some future study directions are addressed. The importance of a multidisciplinary approach to management is highlighted.

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) is increasing, and is currently is the second leading cause of cancer-related death worldwide, accounting for approximately 800000 deaths every year[1]. Clinical management of HCC is tailored according to tumor characteristics, stage of liver disease, and condition of the patients (age, performance status, and presence or absence of comorbidities). The American Association for the Study of Liver Diseases[2] and the European Association for the Study of the Liver (EASL)[3] endorse the use of Barcelona clinic liver cancer (BCLC) staging for the classification and management of patients with HCC. Therapeutic options are stage dependent and can be classified into three categories: curative, palliative, and symptomatic. However, curative treatment options, including resection and percutaneous ablation, are only suitable for early-stage tumors, and are associated with five-year survival rates of up to 75%[4].

Recently, treatment indications have been refined; patients who are not candidates for the first-line therapy for their stage can be shifted to the treatment option for the next BCLC stage (treatment stage migration concept)[3,5]. Trans-arterial chemoembolization (TACE) can be performed at an early stage in patients for whom radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI) cannot be performed because of tumor location (proximity to a gallbladder, biliary tree, or blood vessel), unresectability of the tumor, failed prior curative treatments, or medical comorbidities[6].

The presentations of HCC are variable within each patient. Although the management guidelines for HCC recommend monotherapies as a treatment option, combined or sequential treatment modalities are effective in improving the outcome of patients with HCC. In practice, a multi-modal approach combining various treatments is used, and a multidisciplinary team, where the roles are intertwined and complimentary, should be involved in the management of every case[7,8].

SURGICAL RESECTION

Surgical resection is the recommended treatment for patients with a single nodule, preserved liver function, and good performance status. It is associated with five-year survival rates up to 70%[9] and a 2%-3% perioperative mortality in cirrhotic patients. Some centers report five-year survival rates above 50% in patients undergoing resection for multiple tumors fulfilling Milan criteria (up to three nodules, each ⩽ 3 cm), who are not suitable for transplantation[10], and resection in patients with more advanced stages of HCC has been reported with acceptable outcomes[11].

The minimal critical remnant liver volume for safe resection is approximately 25% (15%-40%) for patients without cirrhosis and 50% (25%-90%) for patients with cirrhotic livers. Preoperative portal vein embolization is occasionally performed when the estimated remnant liver volume is less than the minimal requirement[12], aimed at diverting portal flow, with its content of growth factors, to the non-tumorous lobe to sufficiently increase its size to permit resection. However, the effectiveness of portal vein embolization in cases of HCC with a cirrhotic liver has not been sufficiently tested in large controlled studies[3].

Portal hypertension in cirrhotic patients is considered a relative contraindication for surgical resection, and a hepatic venous pressure gradient > 10 mmHg is reportedly the best predictor of postoperative liver decompensation and poor long-term outcome in compensated cirrhotic patients undergoing resection[2,13]. In practice, resection for patients with significant portal hypertension is still a subject of debate. Similarly, the presence of splenomegaly (major diameter > 12 cm) or esophageal varices with a platelet count of < 100000/mm^3 was correlated with hepatic venous pressure gradient, postoperative decompensation, and poor survival[14]. However, Cucchetti *et al*[15] reported that patients with the same model for end-stage liver disease (MELD) score and extent of hepatectomy had similar outcomes regardless of portal hypertension.

Resection has been refined with the use of the RFA-based resection device, the Habib 4X sealer (a new bipolar RF device designed specifically for liver resection). It releases controlled RF energy between two pairs of electrodes, producing a plane of coagulative necrosis along the intended line of parenchymal resection, avoiding over-coagulation of liver parenchyma. The heat produced seals biliary and blood vessels, resulting in minimal blood loss. With this device, morbidity and mortality rates are superior to other methods of liver resection[16].

Laparoscopic resection, though a more sophisticated surgical procedure, is associated with reduced operative and postoperative morbidities[17]. A recent meta-analysis showed that laparoscopic hepatectomy decreases blood loss, transfusion requirement, postoperative morbidity, recovery time, and hospital stay compared to open hepatectomy, with no difference in recurrence or survival[18]. However, no randomized controlled trials (RCTs) were reported in this meta-analysis.

An important postoperative concern is the high risk of HCC recurrence. Five-year recurrence rates of 68% have been reported after liver resection of very-early-stage HCC. The presence of satellite nodules, cirrhosis, the use of non-anatomic resection, and elevated α-fetoprotein (AFP) levels are independently associated with tumor recurrence[14,19]. Late recurrence can be predicted using molecular biomarkers and gene signatures[20] that are used for the selection of patients amenable to hepatic resection. The 5-gene score, based on combined expression levels of *HN1*, *RAN*,

RAMP3, *KRT19* and *TAF9*, was associated with disease-specific survival[20].

LIVER TRANSPLANTATION

Liver transplantation (LTx) is the best treatment option for patients with decompensated cirrhosis. HCC is the only solid tumor where transplantation plays an important role in management, due to the fact that it allows removal of the primary tumor and treats hepatic insufficiency[21]. The main obstacles for HCC patients amenable to LTx are the organ shortage and the long waiting time for transplantation. Increasing the donor pool by live donation, using bridging therapy, and applying prioritization policies can help overcome this problem[22]. A MELD exception was developed to assign extra points to HCC patients due to their high dropout rate and mortality while on the waiting list. However, no extra points are assigned to patients with compensated cirrhosis and small HCC tumors (< 2 cm) because of the improved survival with local ablation[3]. In practice, LTx is recommended for patients with tumors within the Milan criteria (a single lesion $\leqslant$ 5 cm, or up to three lesions $\leqslant$ 3 cm each)[23]. Restriction of LTx to patients within the Milan criteria results in a five-year overall survival rate of 75%, with a risk of recurrence < 15%[24]. The perioperative mortality and one-year mortality are approximately 3 and $\leqslant$ 10%, respectively. For patients with early-stage HCC, LTx offers the best chance of survival (106 mo), compared with surgical resection (52 mo), RFA (62 mo), PEI (44 mo), and TACE (34 mo)[25].

A systematic review of 90 studies over 15 years, including 17780 patients, identified the Milan criteria as an independent prognostic factor for outcome after LTx, with five-year survival rates comparable to non-HCC patients (65%-78%)[24]. An expansion of the Milan criteria to "up-to-seven" criteria (the sum of the size of the largest tumor and the number of tumors in patients without microvascular invasion) was proposed[23] and externally validated in an independent series[26], but requires larger prospective validation studies[3]. Although listing criteria for LTx currently depend on tumor number and size, the use of molecular markers and gene signatures for determining tumor behavior are under development[27].

The presence of vascular invasion, high AFP level, and transplant waiting time of more than 6 mo, are considered accurate predictive factors for poor survival and recurrence risk. Increased AFP was associated with higher risk of progression and dropout while waiting for a transplant[28,29], and a steady increase of AFP > 15 ng/mL per month was considered the most significant prognostic determinant[30]. In a large French multicenter study, incorporation of AFP in a prognostic score model for post-LTx outcome significantly improved the predictive performance of the Milan criteria in prioritization for LTx[29]. Moreover, adding AFP > 400 to a total tumor volume of 115 cm as a cutoff improved prognosis prediction in an analysis of data of 6478 patients from the Scientific Registry of Transplant Recipients, and performed better than tumor size and number characteristics for predicting post-LTx prognosis[31].

LOCAL ABLATIVE THERAPY

Tumor ablation can be obtained using either chemical (alcohol and acetic acid) or physical (heating or cooling) methods. The first technique used to locally treat HCC was PEI[32], which involves the intra-lesional injection of absolute alcohol. Temperature ablative techniques have advanced, including heating techniques such as RFA[33], microwave ablation (MWA)[34], laser ablation[35], and cryoablation[36].

PEI

PEI is indicated for the treatment of nodular HCC $\leqslant$ 5 cm in diameter, and achieves complete necrosis in 90% of tumors < 2 cm, 70% in those 2- < 3 cm, and 50% in those between 3 and 5 cm[37]. Patient outcome was improved with the use of a specific needle with three retractable prongs, achieving an 80%-90% rate of sustained complete response in tumors < 4 cm[38]. The major limitation of PEI is the high incidence of local recurrence (33%-43%).

RFA

RFA is superior to other local ablative therapies, and is currently the most commonly used ablative method, replacing PEI as the locoregional therapy of choice for early HCC[37]. RFA is considered the standard of care for patients with very early- and early-stage tumors, as well as those not suitable for or that refuse surgery. RFA is recommended as the main ablative therapy for tumors < 5 cm, whereas PEI is recommended in cases where RFA is not technically feasible[3].

In a cohort study, complete ablation was achieved in more than 90% of cases, with a local recurrence rate of < 1% and five-year survival rate ranging from 40% to 70% for lesions < 2 cm in diameter[39]. Three independent meta-analyses, including five RCTs, showed better results regarding local tumor control and survival benefits in patients treated with RFA, compared to ablation with PEI. In addition, patients with tumors 2-5 cm had better survivals if treated by RFA rather than by PEI[40-42].

Some groups have suggested that RFA should be considered as a first-line therapy, even when resection is possible, because it is associated with fewer side effects[39]. The main advantages compared to surgical intervention are that it is less invasive and provides an increased possibility for parenchymal sparing[39,43]. Whether surgical resection for very early HCC is superior to RFA remains controversial. Whereas a Markov model analysis indicated that surgical resection was preferable to RFA in terms of overall survival[44], Peng *et al*[45] reported that RFA was better. A survey in Japan

including 1235 patients with very early HCC ($\leqslant$ 2 cm) who underwent resection and 1315 patients who received RFA showed no significant difference in overall survival between the two groups (one-year, 98% *vs* 99%; two-year, 94% *vs* 95%), over a median follow-up of 37 mo[46]. However, the disease-free survival rate was significantly better after resection than after RFA (one-year, 91% *vs* 84%; two-year, 70% *vs* 58%; *P* < 0.001). Similarly, Wang *et al*[47] suggested that surgical resection was equivalent to RFA in terms of overall survival, and was associated with better disease-free survival.

The size limitation of RFA has been overcome with the use of expandable tipped or cool-tip electrodes, allowing effective ablation of areas $\geqslant$ 5 cm in diameter[48]. However, RCTs with a large sample size are needed before ablation therapy can be confirmed as an alternative to surgery for potentially resectable HCC.

Other ablative therapies
MWA is an alternative to RFA for thermal ablation of HCC. Only one RCT[49] compared the effectiveness of MWA to RFA, which revealed a tendency to favor RFA with respect to rates of local recurrence and complications, likely due to the small volume of coagulation obtained with a single probe insertion[50]. However, newer devices may have overcome this limitation. One advantage of MWA over RFA is that treatment outcome is not affected by the heat-sink effect of vessels in proximity to the tumor[49].

Laser ablation refers to thermal tissue destruction by conversion of absorbed light into heat[51]. The only randomized prospective study comparing laser ablation with RFA reported no significant difference in overall survival rates, with cumulative rates of 91.8%, 59.0% and 28.4% at one, three and five years respectively, without significant complications. However, a significantly better survival rate was reported for RFA in patients with Child-Pugh A stage disease[52].

Cryoablation uses the extreme cold of liquid nitrogen or argon gas to destroy abnormal tissue[53]. Cryoablation showed better local control than RFA or MWA for tumors > 2 cm[54]. A multicenter RCT in China that included 360 patients with one or two tumors < 4 cm in diameter found that cryoablation is safe and as effective as RFA, with a similar five-year survival[55].

TACE

HCC receives 90% of its blood supply from the hepatic artery and only 10% from the portal vein[56]. Thus, the purpose of trans-arterial therapy is to block the blood supply and induce tumor necrosis, without significantly affecting hepatic blood supply[57]. Trans-arterial therapies include TACE, trans-arterial embolization, trans-arterial chemotherapy, and trans-arterial radioembolization[57,58].

TACE is currently the standard of care for patients with compensated liver function and large multifocal lesions without evidence of vascular invasion or extra-hepatic spread[3]. In Japan, TACE is recommended even for HCC patients with vascular invasion if radiologic portal invasion is distal to, or in the second-order branches of, the portal vein[59]. The main contraindications to TACE are extended portal vein thrombosis, diffuse tumor, extra-hepatic spread, and decompensated liver cirrhosis[22,60]. TACE improves survival compared to supportive care or suboptimal therapies[61], observed as an increase in the median survival of patients with intermediate-stage HCC to 20 mo[62]. However, a meta-analysis that included nine trials (six trials assessing TACE and three trials assessing trans-arterial embolization) has shown that trans-arterial therapy does not significantly increase survival in patients with unresectable HCC compared to controls[63].

Proper patient selection is crucial to prevent post-TACE-induced liver failure. Patients with total bilirubin > 3 mg/dL were excluded from TACE in several studies[64,65], and an AFP > 200 ng/mL and a MELD score > 10 were associated with greater risk of mortality[66]. Bolondi *et al*[67] proposed a substaging of intermediate-stage HCC (BCLC-B) patients from B1 to B4, taking into account the tumor burden and Child-Pugh score (A5 to B9). BCLC-B includes disease ranging from variable tumor burden, which can be a multifocal HCC affecting both lobes, extending up to near replacement of the liver, and includes patients with a wide range of liver function impairment (Child-Pugh score from 5 to 9). Substaging revealed decreasing survival for higher B substages, and thus TACE was recommended for early subgroups only[67].

Drug-eluting beads (DEB)-TACE involves the use of embolic microspheres with the ability to sequester and release chemotherapeutic agents in a controlled manner over a one-week period, which subsequently increases the local concentration of the drug with minimal systemic toxicity[68]. A randomized phase Ⅱ study (the PRECISIONV trial) reported that DEB-TACE is a valuable alternative and may be preferred over conventional TACE[69].

Assessment of response to TACE
The use of locoregional options to induce tumor necrosis necessitated a refinement of the conventional criteria to evaluate treatment response. Extent of tumor necrosis has been correlated with outcome after ablation, TACE and systemic therapy. A modification of the response evaluation criteria in solid tumors (modified RECIST) takes into account the degree of tumor necrosis, evaluated by dynamic computed tomography or magnetic resonance imaging[70] and has been adopted by the latest EASL guidelines for evaluating locoregional therapies for HCC[3].

Failure of TACE
There is no established definition for TACE refractoriness, nor is there a consensus for when to consider TACE failure and refer the patient to an alternative

therapy. Despite the absence of solid evidence, however, panels of experts have proposed treatment migration to sorafenib (downward treatment stage migration) for intermediate-stage patients if they demonstrate disease progression or poor tolerance after first or second TACE[71,72]. The current EASL guidelines recommend switching to sorafenib if intermediate-stage patients are non-responsive to at least two cycles of TACE[3].

Repetition of TACE should be considered based on evidence using mRECIST and the risk of adverse events. The response to the first TACE and its effect on the underlying liver disease help in identifying patients at risk of adverse outcome with repeated TACE. Sieghart *et al*[73] conducted a multivariate analysis to investigate TACE repeated for a second or third session and identified three prognostic factors: increase in aspartate aminotransferase by > 25%, increase in Child-Pugh score, and absence of tumor response. These factors were incorporated into an "ART" score, and patients with an ART score of 0-1.5 points benefitted from a second TACE, whereas those with a score ⩾ 2.5 did not[74].

RADIOEMBOLIZATION

Radioembolization, or selective internal radiation therapy (SIRT), has recently emerged as a therapeutic option for intermediate-stage HCC. Unlike TACE, SIRT delivers local radiation to the tumor or liver tissue without causing ischemia. β radiation from radioactive yttrium-loaded glass or resin microspheres is applied to the tumor through the arteries that feed it, so that tumor nodules are treated irrespective of their number, size, or location[75]. The procedure is well tolerated with survival rates similar to TACE. Moreover, it is as safe and effective as sorafenib in patients with more advanced-stage HCC, including patients with portal vein thrombosis and large tumor burden[76-79].

In a study comparing radioembolization to TACE, radioembolization was associated with fewer side effects, better response rate, and longer time to progression (13.3 mo *vs* 8.4 mo), without difference in median survival time (20.5 mo *vs* 17.5 mo)[80]. Another study reported similar safety profile and response rates[76]. However, the cost associated with radioembolization may limit the applicability of this technique.

Stereotactic radiotherapy (SRT) allows the delivery of a high dose of radiation in a single (radio-surgery) or limited number (hypo-fractionation) of sessions, while sparing surrounding structures and healthy tissue[81]. Blomgren *et al*[82] first introduced SRT for liver tumors in 1995, with treatment doses ranging from 15 to 45 Gy, in one to five fractions. In a phase Ⅰ/Ⅱ study using a single dose ranging from 14 to 26 Gy, the treatment was well tolerated in all patients, with no major side effects[83], and the tumor control rate at 6 wk was 98%[84].

The CyberKnife Radio-surgery System is able to deliver very high doses of radiation to both primary and metastatic liver tumors with extreme accuracy, and

treatments can be completed in one to five sessions. Louis *et al*[81] treated 25 patients with CyberKnife stereotactic radiotherapy using respiratory motion tracking, which enables the radiation beam to track tumor movement in real time and allows patients to breathe normally during their treatment sessions. The actuarial one- and two-year local control rates were 95%, and the one- and two-year survival rates were 79% and 52% respectively, with good clinical tolerance. CyberKnife and SRT (though currently still very expensive) offer a local therapy for HCC patients who are not eligible for surgery, embolization, chemotherapy or radiofrequency ablation, without significant complications.

SYSTEMIC CHEMOTHERAPY

HCC is among the most chemoresistant tumors, and until 2007, no systemic chemotherapy was recommended for patients with advanced tumors[3]. Systemic chemotherapy with cytotoxic agents, such as doxorubicin, gemcitabine, cisplatin, 5-fluorouracil or combined regimens for palliative care, was associated with low response rates (< 10%) with only marginal improvements in survival[85]. Moreover, these drugs are poorly tolerated in patients with underlying liver cirrhosis[85-87].

Interferon (IFN) therapy[87], anti-androgens, or tamoxifen[88] used in the treatment of advanced HCC show contradictory results without obvious benefit. A meta-analysis of seven RCTs, including 898 patients, evaluated tamoxifen *vs* conservative management and showed neither anti-tumor effects nor survival benefits for tamoxifen[89]. Subsequent large RCTs reported negative results in terms of survival[90,91].

Cisplatin, IFN, doxorubicin, and fluorouracil (PIAF) used in combination showed promising activity in a phase Ⅱ study[92]. A randomized phase Ⅲ study including 188 patients with HCC was conducted to investigate the effect of PIAF combination compared to doxorubicin alone[87]. The median survival rate of the PIAF group did not significantly differ from the doxorubicin group (8.67 mo *vs* 6.83 mo), and patients treated with the PIAF regimen experienced a significantly higher rate of myelotoxicity.

TARGETED THERAPY FOR HCC

Hepatocarcinogenesis is associated with epigenetic and genetic alterations that eventually lead to uncontrolled growth of hepatocytes. Signal transduction pathways, oncogenes, and growth factors and their receptors are considered new potential therapeutic targets for systemic targeted therapies, limiting widespread systemic toxicity[93]. Several targeted agents are currently in clinical development.

Sorafenib
Sorafenib is an orally administered multikinase inhibitor with antiproliferative and antiangiogenic activity[94]. Sorafenib mediates downregulation of anti-apoptotic

Table 1 Phase III trials of some systemic targeted agents in advanced hepatocellular carcinoma

Ref.	Study design	Patients, *n*	Overall survival, mo
Zhu et al[109] (SEARCH trial)	Sorafenib *vs* sorafenib + erlotinib	358 *vs* 362	Sorafenib: 8.5 Sorafenib + erlotinib: 9.5
Cheng et al[105] (SUN1170 trial)	Sorafenib *vs* sunitinib	544 *vs* 530	Sorafenib: 10.2 Sunitinib: 7.9
Cainap et al[106] (LIGHT trial)	Sorafenib *vs* linifanib	517 *vs* 518	Sorafenib: 9.8 Linifanib: 9.1
Johnson et al[107] (BRISK-FL trial)	Sorafenib *vs* brivanib	578 *vs* 577	Sorafenib: 9.9 Brivanib: 9.5
Llovet et al[108] (BRISK-PS trial)	Brivanib *vs* placebo	263 *vs* 132	Brivanib: 9.4 Placebo: 8.3

proteins, leading to enhanced cytotoxicity of HCC cells to tumor necrosis factor-related apoptosis inducing ligand[95]. Two phase III randomized placebo-controlled trials, the SHARP multicenter trial[96] and the Asia-Pacific trial[97], reported improved overall survival and better outcome for patients who received sorafenib, which was generally well tolerated with mild toxicity. The two most common grade 3 adverse reactions with sorafenib were the hand-foot-skin reaction (8%) and diarrhea (8%). The overall incidence of serious adverse events in the sorafenib and placebo groups was comparable (52% and 54%, respectively).

Based on these findings, sorafenib was approved for treatment of advanced HCC, including patients with unresectable Child-Pugh A or B HCC with performance status 0-2 and vascular invasion or distant metastasis[3], as well as for patients intolerant to TACE or in whom the procedure is technically difficult[98,99]. However, the prognosis for patients with this stage of HCC is still poor, with a median overall survival rate of 6.5-10.7 mo[96]. In addition, Cammà *et al*[100] recently concluded that sorafenib at full dose was not a cost-effective treatment compared to best supportive care in intermediate- and advanced-stage HCC.

Sorafenib is currently being tested as an adjuvant after resection, with local ablation for early-stage HCC, in combination with chemoembolization for inter-mediate stages[101], in combination with erlotinib or systemic doxorubicin in advanced stages. Additionally, sorafenib was effective as a first-line treatment in Child-Pugh B patients with lower survival[3]. In a large retrospective study, the median survival with sorafenib was 5.5 mo compared to 11.3 mo for Child-Pugh A patients[102]. The prospective GIDEON trial confirmed that the median overall survival was shorter in Child-Pugh class B patients (5.2 mo *vs* 13.6 mo in Child A), although the time to progression was similar across subgroups. Serious adverse events were more common in Child-Pugh class B patients[103,104].

Other molecular targeted agents
The antiangiogenic tyrosine kinase inhibitors, suni-tinib[105], linifanib[106], brivanib[107,108], or the combination of sorafenib with erlotinib[109] are not superior to sorafenib in sorafenib-naïve advanced HCC patients, or as a second-line therapy[110] (Table 1). This may be due to the fact that inhibition of a single signaling pathway can induce feedback activation of other pathways. Therefore, combination therapies may demonstrate beneficial synergistic activity[111].

Many molecular-targeted agents other than sorafenib, used in combination or with sorafenib, are in different stages of clinical development, with encou-raging results from phase I - II studies[112-115]. The first phase III study of combination therapy in advanced HCC was SEARCH, a randomized trial testing sorafenib with the epithelial growth factor tyrosine kinase inhibitor erlotinib, which found no survival benefit over sorafenib alone[109].

PREVENTION OF HCC RECURRENCE

Persistence of chronic viral hepatitis in patients treated for HCC is associated with increased rates of recurrence and poor survival, thus control of hepatitis C virus (HCV) replication is an important factor for infected patients. IFN therapy following successful ablation of HCC was shown to be safe and lead to a reduction in recurrence, and patients who continued IFN therapy after tumor ablation had better survival[116]. Long-term, intermittent standard IFN therapy successfully delayed recurrence of HCC after RFA, PEI, and surgical resection[117]. A meta-analysis evaluating the effect of adjuvant standard IFN treatment following resections showed significant improvement in three-year recurrence-free survival (54% *vs* 30%)[118], and other studies have shown similar results[3,119,120]. The use of pegylated-IFN was more effective, and postoperative administration in combination with ribavirin for ≥ 16 wk was associated with reduced recurrence of HCC in patients with HCV infection[121]. Further improvement in prognosis may be expected with the higher efficacy of direct antiviral therapy.

Patients with hepatitis B virus (HBV)-related HCC, even after successful treatment of the initial tumor, usually have multiple recurrences or metastases. High viral load is one of the most important risk factors for HCC development and recurrence following surgical

resection[122]. Similar to HCV, antiviral therapy for HBV following curative HCC ablation improved patient survival and decreased HCC recurrence. In their study, Hann *et al*[123] followed patients for 12 years who underwent local tumor ablation with or without concomitant antiviral therapy with lamivudine. Although initially there was no difference between the treatment groups with respect to tumor size (all ⩽ 7 cm), levels of AFP and albumin, antiviral therapy was significantly associated with increased median survival (36 mo *vs* 16 mo)[123].

No other modality has demonstrated equivalent effectiveness for decreasing recurrence after curative treatment of HCC as antiviral therapy has for viral hepatitis-related tumors. Chemoembolization[124], internal radiation[125,126], immune therapies[127], retinoids[128], and the heparanase inhibitor PI-88[129] have been investigated as methods of reducing postoperative recurrence; however, none can be recommended as a preoperative/postoperative adjuvant/neo-adjuvant therapy for improving prognosis and diminishing the incidence of recurrence following curative therapy.

MULTIDISCIPLINARY TEAM

HCC has diverse presentations that are compounded by the status of liver disease, and the multiple treatment options available make choosing the first line of treatment for a given patient a difficult task. Treatment of HCC patients should be undertaken by a multidisciplinary team that includes all the specialties involved in delivering the different therapies. In addition, simultaneous or sequential multi-modal therapies for patients with HCC show promise for improving patient outcome, further emphasizing the importance of a multidisciplinary approach to HCC management.

The multidisciplinary team should include hepatologists, medical and surgical oncologists, transplant surgeons, diagnostic and interventional radiologists, radiation oncologists, and pathologists[130]. All members should play an active role, as their expertise is required to provide optimal care for patients with HCC. The hepatologist should assess underlying liver disease, identify patients at risk for HCC, and monitor for early detection. Hepatologists are essential for managing liver disease and its complications, arranging for and monitoring treatment, and referring eligible patients for LTx. Oncologists are responsible for assigning systemic or targeted therapy as initial treatment or adjuvant therapy, and for managing associated side effects. The diagnostic radiologist makes and confirms the diagnosis, stages the tumor, its spread and vascular invasion, and assesses the radiologic response to treatment. The interventional radiologist delivers ablative therapy in early stages, and palliative therapy for intermediate-stage tumors. The hepatobiliary surgeon evaluates for and performs resection or transplantation. The pathologist assesses the grade of tumor differentiation,

stage of progression, and evaluates tissue markers. This multidisciplinary team also involves nurses, supportive care specialists, and palliative physicians[130].

MULTI-MODAL THERAPIES

With the multidisciplinary approach, various treatments are being delivered simultaneously or sequentially, as first- or second-line therapies, to improve patient outcome.

Transplantation and locoregional treatment
Patients whose tumors exceed the Milan criteria can undergo locoregional treatment (TACE or RFA) to down-stage the tumor to within the Milan criteria to allow LTx. Two prospective studies showed similar survival after LTx for patients with successfully down-staged HCC compared with those who initially met the Milan criteria[131,132].

Neo-adjuvant therapies for patients while on the waiting list are used in most centers. Systemic and interventional treatments are used to bridge patients in order to control disease and prevent tumor progression when the waiting time exceeds 6 mo[133,134]. Percutaneous treatments are more cost-effective than surgical resection[135]. Moreover, a poor response to TACE before transplantation is an indicator of post-transplantation recurrence[136].

Surgery and sorafenib
Sorafenib following curative surgery in a phase Ⅱ trial including 30 patients resulted in a lower tumor recurrence rate compared to surgery alone (33.3% *vs* 73.6%)[137].

TACE and ablative therapy
Combining PEI with TACE has been shown to be effective for unresectable HCC[138]. The three-year survival rate was longer in patients with large and unresectable HCC treated with a combination of TACE and PEI than with TACE alone (22% *vs* 4%, respectively).

Combining RFA with TACE was evaluated in a RCT for patients with tumors between 3 and 5 cm[139]. The local tumor progression rate was significantly lower with combined treatment compared to RFA only (6% *vs* 39%).

Sorafenib and locoregional treatment
There are more than 20 clinical trials in progress evaluating locoregional treatments combined with molecular-targeted agents, and some have demonstrated promising results[140-142]. A large phase Ⅲ, randomized, placebo-controlled trial (the STORM trial) evaluating sorafenib as an adjuvant therapy after curative treatment (resection or local ablation) is ongoing[143].

Sorafenib and TACE
Following TACE, the tumor microenvironment becomes

Table 2 Clinical studies on combined sorafenib and transcatheter arterial chemoembolization for intermediate and advanced hepatocellular carcinoma

Ref.	Study design	Timing of sorafenib	Patients, *n*	BCLC stage	Child-Pugh class	Primary endpoint results
Kudo *et al*[155]	Sorafenib + TACE *vs* TACE	Sequential	229 *vs* 229	B	A	TTP (5.4 mo *vs* 3.7 mo)
Lencioni *et al*[151] (SPACE trial)	Sorafenib + DEB-TACE *vs* DEB-TACE + placebo	Continuous	154 *vs* 153	B	A	TTP (169 d *vs* 166 d; *P* = 0.072)
Martin *et al*[158]	Sorafenib + DEB-TACE *vs* DEB-TACE	NR	30 *vs* 120	B, C	B	OS (12 mo *vs* 10 mo)
Sansonno *et al*[154]	Sorafenib + TACE *vs* TACE	Sequential	40 *vs* 40	B	A	TTP (9.2 mo *vs* 4.9 mo)
Han *et al*[156] (subgroup analysis of START)	Sorafenib + TACE	Sequential	63	A, B, C	A	TTP (10.6 mo) OS (16.5 mo)
Chung *et al*[150] (subgroup analysis of START)	Sorafenib + TACE	Sequential	63	A, B, C	A	DCR (52%)
Park *et al*[149] (COTSUN Korea)	Sorafenib + TACE	Interrupted	50	B, C	A, B	TTP (7.1 mo) PFS (52% at 6 mo)
Pawlik *et al*[148]	Sorafenib + DEB-TACE	Continuous	35	B, C	A, B	DCR (95%) OR (58%)
Cabrera *et al*[153]	Sorafenib + DEB-TACE or Y-90	Continuous	47	B, C	A, B	At 6 mo DCR (68%) OS (8.5 mo)

BCLC: Barcelona clinic liver cancer; TACE: Transcatheter arterial chemoembolization; DBE: Drug-eluting beads; NR: Not recorded; TTP: Time to progression; DCR: Disease control rate; OR: Objective response; OS: Overall survival; PFS: Progression-free survival.

unbalanced due to increased hypoxia, leading to upregulation of hypoxia inducible factor-1, which in turn upregulates vascular endothelial and platelet-derived growth factors, thus increasing tumor angiogenesis[144,145]. Studies have shown a significant association between poor prognosis after TACE and risk of extrahepatic metastasis with upregulation of vascular endothelial growth factor[146,147]. Efforts to improve the outcome of TACE include the use of adjuvant or concurrent antiangiogenic agents to block the neovascularization[142].

Sorafenib can be used a few days to weeks after the first TACE (sequential introduction) or started prior to the planned TACE and only interrupted for a few days around the time of the procedure (interrupted scheduling). Studies that evaluated the effects of sequential sorafenib treatment after TACE revealed inconsistent results. In phase II studies, sorafenib concomitant with TACE or DEB-TACE was well tolerated and effective in unresectable HCC[148-151]. Synchronous therapy with sorafenib and TACE has also been retrospectively analyzed: the median overall survival for the combined sorafenib and TACE was 27 mo compared to 17 mo for TACE alone[152].

Several prospective controlled studies have evaluated the efficacy of combination treatment[153-158] (Table 2). However, there is a diversity of study designs, including various primary endpoints, patient populations, TACE procedures, timing of randomization and drug administration, which may account for the observed conflicting results[157]. Overall, the results of combined TACE and sorafenib in intermediate- and advanced-stage HCC appear promising. The results of ongoing trials will define the role of this combination in clinical practice, whether it can overcome TACE refractoriness in intermediate-stage HCC patients, and whether it will have an additive role for advanced-stage HCC treatment.

Sorafenib and radioembolization
Several ongoing clinical trials are evaluating the combination of radioembolization and sorafenib in patients with HCC. A retrospective analysis of Child-Pugh class A and B HCC patients who received sorafenib first, followed by yttrium-90, then resumed sorafenib post-treatment, showed that the overall survival was higher than has been previously reported for sorafenib alone[159]. Further prospective studies are being conducted to evaluate this combination.

Sorafenib and systemic chemotherapy
Several combinations of sorafenib with systemic chemotherapeutic agents have been evaluated, including sorafenib with doxorubicin[160], octreotide[161], oxaliplatin[162], 5-fluorouracil[163], S-1 fluoropyrimidines[164], PR-104[165], tegafur/uracil[166], cisplatin and gemcitabine[167], and AVE 1642 (a human monoclonal antibody inhibiting the insulin-like growth factor-1 receptor)[168] (Table 3). Other ongoing phase II trials include the combination of sorafenib with gemcitabine/oxaliplatin[169], modified FOLFOX[170], or capecitabine/oxaliplatin[171].

A randomized, double-blind phase II trial in advanced HCC that compared the efficacy of sorafenib and doxorubicin *vs* doxorubicin plus placebo showed encouraging results (median overall survival 13.7 mo *vs* 6.5 mo; median time to progression 6.4 mo *vs* 2.8 mo; and progression-free survival 6.0 mo *vs* 2.7 mo)[160]. A phase III randomized study of sorafenib plus doxorubicin compared with sorafenib alone (CALGB 80802) is ongoing in patients with advanced HCC[172].

In a systematic review of eight studies with sorafenib combined with other anti-cancer agents for therapy of

Table 3 Combined sorafenib plus systemic anticancer therapy for unresectable hepatocellular carcinoma

Ref.	Chemotherapeutic agent	Type of study	Patients, *n*	Median OS, mo	DCR, %	Median PFS, mo
Abou-Alfa *et al*[160]	Doxorubicin	Multicenter randomized prospective phase II	47 *vs* 49	13.7 *vs* 6.5	62	6.0 *vs* 2.7
Hsu *et al*[166]	Tegafur/uracil	Prospective phase II	53	7.4	57	3.7
Prete *et al*[161]	Long-acting octreotide	Prospective phase II	50	12	76	7
Abou-Alfa *et al*[165]	PR-104	Prospective phase I	14	NR	50	NR
Lee *et al*[164]	S-1 fluoropyrimidines	Prospective phase I	20	10.4	52.9	3.9
Petrini *et al*[163]	5-Fluorouracil	Prospective phase II	39	13.7	48.7	7.5

DCR: Disease control rate; NR: Not recorded; OS: Overall survival; PFS: Progression-free survival.

advanced HCC, the disease control rate was 50%-70%, median progression-free survival was 3.7-7.5 mo, and median overall survival was 7.4-40.1 mo[173]. Xie *et al*[174] performed a systematic review of 21 prospective studies with sorafenib treatment alone (seven studies) or combined with other treatment (14 studies) and found that sorafenib increased overall survival by 2.3-2.8 mo, prolonged the time to tumor progression by 1.4-2.7 mo, and increased disease control rate by 11%-19%. Advanced cirrhosis and combined treatment of sorafenib with 5-fluorouracil drugs were the major risk factors for developing adverse events.

These results are promising, and suggest that sorafenib in combination with some agents (particularly mammalian target of rapamycin inhibitors) is an effective and tolerable treatment option for advanced HCC[171]. However, these trials included small numbers of patients, and although some reported survival advantage over sorafenib alone, combination therapy cannot be recommended for routine practice outside the setting of clinical trials. Large RCTs are needed to establish the efficacy and safety of these combination regimens.

CONCLUSION

Treatment of patients with HCC represents a major challenge in clinical practice. HCC patients require multidisciplinary clinical management and selection of tailored treatments according to disease stage, patient age, and comorbidities. Earlier diagnosis will allow therapies to be more effective, leading to a better prognosis. Several areas in management of HCC still need further evaluation, including the use of neoadjuvant/adjuvant therapies to decrease recurrence after resection or ablation, combinations of local and systemic therapies, combinations of systemic targeted therapies, and second-line therapies. Analysis of the cost-effectiveness of the treatments under investigation should also be an important consideration in future trials.

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