Review Article

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Current status of multimodal & combination therapy for hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world. Surgery offers the only hope for cure. However, the potentially curable method is only possible for a small proportion of those afflicted, for the rest, palliative treatment is indicated. Despite all the treatment options when used as monotherapy, patients with HCC have a poor long term prognosis. In this setting, multimodal and combination therapy has emerged as an alternative treatment modality for HCC. Studies have looked at various forms of combination therapy, including neoadjuvant/adjuvant/downstaging therapy for surgery and the combined modality of non-operative therapies. The novel molecular targeted therapies are also being used as combination regimens for surgery or other non-operative therapies. Some forms of combination therapies, including downstaging therapy for surgery, salvage transplantation, and molecular targeted therapy have been shown to provide survival benefits for well selected patients, and need to be encouraged in the future. And others such as pre-operative bridging therapy for liver transplantation, adjuvant therapy for hepatic resection and combination of local and regional therapies have also shown some benefits in preliminary results, which need confirmation in further studies. In conclusion, multimodal and combination therapy is an encouraging treatment modality for HCC. Future research should continue to unravel the role of combination therapy with properly selected patients and appropriate end points.

Key words Adjuvant therapy - hepatectomy - hepatocellular carcinoma - liver transplantation - neoadjuvant therapy

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, and the third most common cause of cancer-related death[1]. Surgery gives the best chance of cure with complete extirpation of the tumour. However, this potentially curable method is possible only in a small proportion of patients, for the remaining, palliative treatment is indicated, which includes local ablative therapy (LAT), transarterial chemoembolization (TACE), systemic chemotherapy, immunotherapy, radiotherapy or molecular targeted therapy. Despite all the treatment options when used as monotherapy, patients with HCC have a poor long term prognosis. In this setting, multimodal and combination therapies have emerged as alternative treatment modalities for HCC[2]. In this review we discuss the various forms of combination therapies for HCC.

Neoadjuvant therapy for resection

Because of the graft shortage of liver transplantation (LT), resection remains the mainstay of treatment for HCC. However, recurrences after resection, in particular intrahepatic recurrence, are common. In order to prevent tumour recurrence after resection, non-operative therapies are employed preoperatively in the setting of resectable HCC, which should be recognized as pre-planned combined therapies.

Several randomized controlled trials (RCTs) have shown a marked treatment-related survival benefit of TACE as a palliative therapy for unresectable HCC. Some centers have used it as a neoadjuvant therapy for resectable HCC. Although some retrospective series have shown a survival benefit of using TACE before resection[3]. With respect to the role of TACE as a neoadjuvant therapy for resection, the four recent systematic reviews failed to demonstrate any overall or disease-free survival (OS or DFS) benefit[4-7]. Further, a lower resection rate and longer operative time with pre-operative TACE were noted in a RCT which included 108 patients with resectable HCC (>5 cm)[8]. Many histopathologic studies of resected specimens after TACE have demonstrated partial or complete necrosis of lesions[4]. However, none of these confirmed the correlation between the amount of tumour necrosis and the recurrence rate. On the contrary, it is speculated that the partial tumour necrosis induced by neoadjuvant TACE may causes the remaining tumour cells to be less firmly attached and more likely to be dislodged into the bloodstream during liver resection[9]. Based on the currently available evidence, TACE as neoadjuvant therapy before resection cannot be recommended for a resectable HCC. More RCTs are necessary to address this issue and more novel procedures need to be exploited.

Downstaging therapy for resection

While patients with HCC can be resected primarily, a neoadjuvant treatment is usually not recommended, but some locoregional therapies (LRTs) with original aim at palliation can give a chance of achieving tumour necrosis and shrink in tumour size. Theoretically, these treatments could be attempted as a downstaging therapy prior to resection for patients with unresectable HCC. TACE, radiotherapy, chemotherapy and immunotherapy have all been tested as downstaging agents in monotherapy or combination regimens. With such a downstaging strategy, 8-18 per cent of unresectable HCC were reported suitable for resection[10]. However, no definite factors were identified to predict the responders to downstaging therapy. In general, most surgeons agree that patients with good liver function are not qualified for primary resection because the local extent of the tumour can be considered for downstaging therapy. Although it is not well known whether the outcome of downstaging resection is comparable to those of primary resection, considering the lack of alternative potentially curative options in these patients, the downstaging strategy is relatively well accepted by most groups. Several issues however, remain necessary to address, such as the optimum time interval after downstaging treatment to surgical resection and the best choice of downstaging regimens. It has been noted that even after successful resection following downstaging therapy, these patients are associated with a high rate of recurrence. The five-year survival rates were about 50 per cent[10-12]. It is urgent to find better treatment regimen to improve the effects of this strategy.

Adjuvant therapy for resection

Despite curative resection, prognosis of HCC remains poor due to the high rate of tumour recurrence. Adjuvant therapy is attempted sequentially to prevent or delay the recurrence. Currently, the role of adjuvant therapy after curative resection is widely investigated, which includes virustatic drugs, systemic chemotherapy, intra-arterial approaches and immunotherapy.

Hepatitis B/C virus (HBV/HCV) infection is the major risk factor for development of HCC. It was assumed that effective control of hepatitis virus after resection in patients with active hepatitis virus infection may reduce the risk of tumour recurrence. A meta-analysis[13] indicated that the post-operative antiviral therapy, interferon in particular, may reduce recurrence and mortality in patients with HBV/HCV related HCC, subgroup analyses have further demonstrated that post-operative antiviral therapy can reduce recurrence of pure HCV-associated HCC, regarding HBV-related HCC, the current data demonstrate only a trend of superiority in late recurrence but without significant differences. A non randomized prospective trial study from Japan concluded that although lamivudine therapy after radical therapy for HBV-related HCC was no beneficial considering recurrence rate and survival, there may be a benefit to improve remnant liver function, thus decreasing the risk of liver failure and increasing the chances of receiving available treatment modalities for recurrent HCC[14]. Interferon in addition to its antiviral

property also has anti-proliferative effect. Two meta-analysis showed a significant beneficial effect of interferon after curative treatment of HCC in terms of both survival and tumour recurrence, however, a proportion of 8-20 per cent of patients cannot complete the procedure because of side-effects[15,16]. Although the results of adjuvant interferon therapy are encouraging, more randomized studies are necessary to address the issues such as the role of interferon in HCC from different tumour aetiology and different pattern of recurrence (the primary or second recurrence), and the side effects of interferon also should be considered carefully.

Due to the chemoresistance of HCC and the toxicity of chemotherapy regimens, there have been very few studies on adjuvant systemic chemotherapy for HCC. A randomized controlled study[17] which included 160 patients who underwent curative resection reported that systemic chemotherapy after curative resection for HCC provided no benefit in recurrence-free survival at 5 years. They also noted a higher occurrence of more advanced disease at the time of recurrence in patients receiving adjuvant therapy. Two recent systemic reviews have also concluded that systemic chemotherapy does not improve overall or disease-free survival after resection of HCC[5,7].

Adjuvant intra-arterial approaches (including intra-arterial chemotherapy/ embolization/ radioembolization) make sense, as intrahepatic recurrence is frequently the only site of recurrence after hepatic resection. Studies regarding adjuvant TACE after curative resection have shown conflicting results. A recent systemic review comprised six randomized controlled trials assessing the benefit of adjuvant TACE/ TAC showed no robust evidence to support the routine use of adjuvant TACE/TAC after curative resection[5]. Recently, the survival benefit of adjuvant TACE after resection in patients with HCC involving the portal vein has been confirmed by two RCTs and a retrospective study[18-20]. Another retrospective study concluded that post-operative TACE can only prolong the survival of patients with risk factors for residual tumour (tumours with a diameter more than 5 cm, multiple nodules, and vascular invasion)[21]. It suggested that adjuvant TACE may be beneficial in a subset of HCC patients. The benefit of adjuvant therapy with intra-arterial ^{131}I-lipiodol was also demonstrated by several trials[22,23]. However, its routine use as an adjuvant therapy after curative resection is not recommended because of the small samples. Other radioisotopes including rhenium-188 radioconjugate, Yttrium - 90 microspheres and phosphorus-32 glass microspheres have also been used in unresectable HCC with encouraging results, which are potentially useful options in the setting of adjuvant therapy for HCC[24].

Hui *et al*[25] conducted a randomized study to evaluate the effects of adjuvant immunotherapy with cytokine-induced killer cells for HCC after radical resection, which enrolled 127 HCC patients with solitary tumour, resection margin >1 cm and showed a significantly higher disease free survival rates in treatment group, but no difference in overall survival. Peng *et al*[26] used autologous tumour vaccine for HCC after curative resection, also showed promising results. These strategies of adoptive immunotherapy opened a new field for HCC treatment in the setting of adjuvant therapy, but need more data to confirm the efficacy and safety.

Based on the above evidence, it is reasonable to adopt virustatic therapy in patients with active hepatitis virus infection after resection, and intra-arterial approaches as adjuvant therapy for resection may prolong the survival in selected patients, but systemic chemotherapy is not recommended as an adjuvant therapy in HCC.

Pre-operative bridging therapy for liver transplantation

Liver transplantation (LT), which offers the theoretical advantage of removing both the tumour and the organ at risk to develop future malignancy, has been proved to be the best treatment for early-stage HCC. However, shortage of organs often lengthens the time of waiting for a graft[27,28]. Patients listed for LT face the risk of progression of HCC which may lead to dropout from the waiting list or worsened post-LT prognosis. To improve the survival, some non-surgical therapy protocols are pre-planned as neoadjuvant treatment for patients awaiting LT. In this context, some LATs and intra-arterial approaches are widely accepted for bridging therapy before LT.

Currently, several LATs have been developed, including intratumoural injection of ethanol or acetic acid, and thermal ablation with radiofrequency, laser, microwaves or cryosurgery. The role of LAT as a bridging therapy during the waiting time for LT has also been widely investigated. The general goal of LAT is to coagulate the tumour and control tumour growth during the waiting time and decrease the dropout from

the waiting list, and to improve the post-transplant outcome by reducing the risk of post-operative recurrence. Many histological data from explanted liver specimens in patients who underwent radiofrequency ablation (RFA) has shown a favourable efficacy profile with pathological complete necrosis in more than half of cases[29-31]. However, discouraging result was noted by Diaz-Sanchez *et al*[32]. This discrepancy may be explained by heterogeneity in the ablation technique, the interval of pre-operative treatment to transplantation and different criteria of patient selection. Several studies were conducted to show whether the histological response can be transformed into decreasing of dropout rate and improving post-LT outcomes. Some of these have shown favourable outcome, especially in patients who need to wait more than a few months for LT[30,33-37]. Diaz-Sanchez *et al*[32] suggested that treatment of HCC before LT in patients with a waiting list time of less than 6 months does not appear to influence survival or tumour recurrence. Lao *et al*[38] recently reported that use of pre-transplant therapy for HCC in patients with about one year waiting time, within Milan/UNOS criteria, was associated with a decreased HCC recurrence after transplantation. One study showed that the use of any type of ablation had a minimal effect on dropout rate of T2 patient (decreasing from 10.1 to 8.0% at 180 days after listing)[39]. Similar results were also reported in other studies[40,41]. The geographic differences, different criteria used for inclusion and exclusion of waiting list, different diagnosis and treatment protocols and wide range of waiting time might all or in part contribute to the variance. Unfortunately, there is no RCT available for comparing patients who underwent LT for HCC with or without LAT to address this issue.

Due to the favourable outcomes of TACE in patients with intermediate-stage and unresectable HCC, it was postulated as a rational bridging therapy prior to LT[42-44]. TACE has been shown to provide complete necrosis of the treated HCC nodules in about 30 per cent of cases at the examination of the explanted liver[32, 45]. In a study, eight HCC patients (mean target lesion size 32 ± 15.4 mm) received pre-transplantation chemoembolization with drug-eluting beads (DEB) achieved complete necrosis in 77 per cent of lesions[46]. With regard to the impact of TACE on dropout rates, a dropout rate of 8.6 per cent (2.9 and 12.1 for the Milan criteria group and the UCSF-expanded group separately) after a median waiting time of 9 months, was reported[45]. However, some studies have found no impact on this endpoint[39,47,48]. The issue of benefits with respect to the post-transplantation recurrence and long-term outcomes was also addressed by many studies. The study of Millonig *et al*[45] showed a marked survival benefit according to pathologic response (with a 5-year survival rates of 85.1% and 63.9% for complete and partial response). Some other studies also concluded that pre-operative TACE had no influence or bad effects on post-operative survival[49-51]. Radioembolization with Yttrium-90 microspheres before transplantation was recently reported to offer comparable tumour responses with less liver and little systemic toxicity[52]. Further studies are needed to evaluate it as a bridging therapy for patients with advanced HCC who are on the waiting list for LT.

A new systemic, molecularly targeted therapy, sorafenib, was recently tested and demonstrated efficacy in delaying tumour progression. Vitale *et al*[53] conducted a Markov model analysis to evaluate the cost-benefit ratio of sorafenib as a neoadjuvant therapy for HCC patients meeting the Milan criteria and awaiting LT, and demonstrated that sorafenib neoadjuvant therapy was cost-effective by comparison with no therapy for T2-HCC patients waiting for LT, particularly for median times to LT under 6 months.

In summary, although RFA has been widely accepted as a safe treatment for small HCC in cirrhotics awaiting LT and an effective option in inducing tumour necrosis, there is no clear evidence to recommend this procedure as a standard care for all patients in the waiting list. Based on the available evidence, it is recommended that for HCC within the Milan criteria, within 6 months waiting time pre-transplant therapy is not necessary; for T2 patients, RFA can be used as a bridging strategy if they likely to wait longer than 6 months; for T1 patients with a longer waiting time, decision should be made according to the prediction of tumour response, the delay before transplantation, and possible complications. Concerning TACE, although not much survival benefit was gained, in a population close to the Milan criteria, it was safe and associated with a lower dropout rate, and may reduce the post-operative recurrence. Further, these forms of bridging therapy can select out patients with rapidly progressive disease and so those who undergo transplantation may have more favourable outcome. In this condition, we would recommend TACE as a bridging therapy before LT in patients close to the Milan criteria expected to wait more than six months for a graft. The data on some novel forms of neoadjuvant therapies such as

molecularly targeted therapy are scanty, further studies are needed.

Downstaging therapy for liver transplantation

In the treatment of HCC, some LRTs have shown efficacy to decrease the tumour burden, thus for patients who are initially outside the accepted listing criteria for LT, the application of such treatments aiming to downstage tumours seems appropriate. The effectiveness of downstaging could be used as a selection strategy for LT other than morphological criteria alone[54]. TACE and RFA have been most frequently used for this purpose.

In the study of Chapman *et al*[55] 23.7 per cent of patients with advanced (American liver tumour study group stage III/IV) undergoing TACE prior to LT, were successfully downstaged to stage II disease. Recently, most reports have demonstrated that downstaging can be successful in more than half of patients[56-62], and not associated with a high risk of tumour recurrence[58,59]. Favourable survival benefits, following successful downstaging were also demonstrated by several groups[55-57,59,60]. The post-transplant 5-year overall survivals have been reported at more than 50 per cent which was substantially better than non-downstaged patients[57]. Ravaioli *et al*[60] reported a 3-year disease-free survival rates of 71 per cent in 32 patients who obtained successful downstaging and received LT which was comparable to the patients initially listed by Milan criteria. An intention-to-treat survival of 87.5 and 69.3 per cent at 1 and 4 years after downstaging was reported by Yao *et al*[59]. Such outcomes were obviously better than published controls in patients with such advanced tumours[44,48]. However, it is difficult to compare these results and define an objective therapy strategy, because of the different criteria used to include patients in downstaging strategy and subsequently listed for transplantation. In general, patients who are decided to enter the downstaging programme should have well defined and acceptable chances of good response to these treatments and a comparable outcome after transplantation to non-HCC recipients and with limited adverse effect. Unfortunately, there are no suitable markers to predict patients who are likely or unlikely to well respond to these treatments. Recently, it was noted that mean alpha-foetoprotein (AFP) levels were significantly higher in the non-downstaged group than in the downstaged group[57]. It suggests that in addition to tumour size, number and major vascular invasion revealed by radiological studies, several biological markers may help to prioritize the assessment of tumour biology[37,39,56]. The criteria to enter a downstaging strategy have been described by several groups[55,56,59-61,63], the most accepted criterion was proposed with an upper limit at 8 cm in diameter, and recently Toso *et al*[64] have proposed an upper limit at 250 cm^3 in total tumour volume. Multifarious end-points of successful downstaging were also reported by different groups[54-56,59]. Recent studies have reached a consensus that only patients whose tumours have demonstrated complete ablation or met the Milan criteria should be considered for LT. Some investigators suggest excluding patients with an AFP remaining above 400 ng/ml after treatment[59,64]. While it is clear that the time interval between downstaging and transplantation may be a double edged sword, on the one hand it may be privilate exclusion patients with bad biology and on the other hand may allow the progression of tumours. It has been defined a minimum observation time of 3 months, and a mean waiting time of at least 6 months between included in the waiting list after downstaging and the date of transplantation. Based on the currently available clinical evidence, it appears reasonable to attempt downstaging treatment in well selected patients and subsequently implement transplantation for successful downstaging ones with a rational observation time.

Hepatic resection and salvage transplantation

For patients evaluated as resectable, a resection as a bridging procedure before LT has been suggested, and two different settings were proposed. First, resection was used as a primary therapy, and LT can only be performed for patients who develop recurrence and/or liver failure, which should be recognized as a rescue therapy; second, for selected patients with high recurrence risk based on resection pathology, LT can be performed immediately even in the absence of proven recurrent disease[65,66], which can be recognized as pre-planned combined therapies. The essence of the two approaches is to use resection as a first-line treatment and to restrict LT to selected patients to limit the use of liver grafts. However, it is argued that resection is associated with a high tumour recurrence rate and with a considerable risk of losing the opportunity of LT.

Although some groups have noted a significantly increased perioperative mortality (26.8 versus 2.1%) in secondary transplantation than primary transplantation[67], most of the recent studies have shown comparable results

both in terms of perioperative complications and long-term survival[68-71]. Recently a few retrospective studies directly comparing liver resection and transplantation for considered transplantable and resectable patients demonstrated similar overall long-term survival[71-74]. On the other hand, in an intention-to-treat analysis by Baccarani *et al*[75], LT was found to be superior to resection for small HCC in cirrhotic patients. In this series patients listed for transplantation were always treated with TACE while waiting for a donor and there were only two dropouts for reasons of tumour recurrence with a mean of <4 months waiting time. The optimal initial treatment for such patients depends on not only the survival outcome but also the availability of liver grafts. Resection was suggested as the initial treatment and transplantation as a salvage treatment in case of tumour recurrence or liver failure because of several potential advantages besides comparable outcomes. This strategy can save liver graft because some patients who may survive long-term without tumour recurrence or liver failure after resection, can postpone the time of LT and the natural history of HCC predicted on the basis of the histological profile of the resected specimen can be used as a selection tool for LT. A proportion (34%) of patients underwent hepatic resection for early HCC surviving without necessity of LT for 5 years was reported by Facciuto *et al*[76]. Despite the higher tumour recurrence rate associated with hepatic resection, up to 70 per cent of recurrence is also eligible for LT[70,76,77]. The optimal candidates for this strategy and the criteria of salvage transplantation remained unestablished. Two patterns of recurrence of HCC have been noted, on the basis of the genomic data it has been clearly shown that recurrence of HCC in the liver appearing more than 2 years after resection is nearly always *de novo*[78]. Therefore, It has been suggested that patients who develop HCC that meets Milan criteria more than 2 years after resection could be considered eligible for priority equivalent to primary HCC[79]. In another study, in 75 per cent patients the histological features of both primary and recurrent tumours were exactly the same[74]. It suggested that the natural history of HCC can be predicted on the basis of the histological profile of the resected specimen, which may be used as a selection tool for LT.

In summary, many studies have shown that primary resection with salvage transplantation is associated with a favourable results. Considering the superiority of saving liver grafts and revealing the nature of HCC, this strategy should be encouraged.

Combined modality of non-operative therapies

Although hepatic resection and LT are the only potentially curative therapy, only a minority is eligible for such therapies because of advanced disease and/or concomitant hepatic decompensation. The major progress of multimodal treatment leads to an exploration of combined modality of non-operative therapies for advanced HCC.

Combination of local and regional therapies: TACE and LAT have shown survival benefits for patients with unresectable HCC. Both treatments, however, have inherent limitations that rebate their effects. TACE is usually difficult to achieve complete necrosis of the target lesion and ablation efficacy is significantly limited by lesion size. Current treatment strategies aim to combine these treatments to improve the effects. A meta-analysis performed by Wang *et al*[80], including 10 RCTs and 595 patients, evaluated the benefits of TACE combined with RFA/PEI for patients with unresectable HCC in comparison with those of monotherapy, and showed an improvement in 1-, 2-, and 3-year overall survival [odds ratio (OR) = 2.28, 4.53, 3.50, respectively]. A randomized study which included 37 patients with solitary HCCs (diameter 3.1-5.0 cm) also concluded that in patients with intermediate-sized HCC, RFA combined with TACE was more effective than RFA alone for extending the ablated area and decreasing the local tumour progression rate with fewer treatment sessions[81]. Several investigators recognized that the stage of HCC plays a role in the benefits of this combination strategy[82,83]. Recently, RFA combined with TACE has been recommended for tumours >3 cm by Japan Society of Hepatology (JSH)[84]. TACE with drug (doxorubicin)-eluting beads (DEB) has also been conjoinedly used with RFA in a western group, who demonstrated a complete response of the target lesion in 60 per cent patients with single HCC ranging 3.3-7.0 cm[85]. Based on the current evidence, the conclusion on TACE plus LAT in treating unresectable HCC across the spectrum of patients with various prognostic factors remains to be clarified. Other local/regional treatments were recently introduced to provide local control of disease which can be delivered in conjunction with each other for advanced-stage patients in the future[86-88].

Systemic therapy with combined agents: A variety of combination regimens of chemotherapeutic agents, including doxorubicin, 5-fluorouracil (5-FU), capecitabine, cisplatin, oxaliplatin,

gemcitabine, mitoxantrone, epirubicin, rinotecan and novel chemotherapy agents, have been studied in HCC. Although a 6-39 per cent response rate was documented[89-94], most of these have not shown survival benefit, and more important was the lack of large randomized phase III studies to confirm the results. Combination of chemotherapy and immunotherapy has also been investigated. Especially, combinations of interferon and different chemotherapy agents have been tested extensively and shown promising activity with a 16.8-25 per cent response rate[95-97]. However, most of these failed to show any survival benefit in randomized phase III studies and were associated with frequent toxicity. Other systemic approaches, such as hormonal therapy (tamoxifen, anti-androgen), thalidomide, octreotide have also been examined in combination with each other and have shown limited activity and no survival benefit in HCC[98]. Based on the current evidence, even using agents in combination, systemic therapy except novel molecular targeted agents is not recommended in HCC because of their marginal activity and frequent toxicity in cirrhotic liver.

Combination of locoregional and systemic therapies: Although many systemic therapies have failed to demonstrate improved survival in patients with advanced HCC, the successful clinical development of molecularly targeted agents and the initial encouraging results of combination therapy have led to a resurgence of interest in combination therapy of locoregional approach and systemic agents.

While LAT has been well accepted as a radical cure for small HCC[99], the role of systemic agents as adjuvant therapy is being investigated, and some of these have shown a marked inhibition of the recurrence rate and improvement of survival[100-103]. Kudo *et al*[104] reported a significantly reduced recurrence rate and improved survival (5-yr survival rate: 83 vs 66%) with long-term interferon maintenance therapy after curative RFA therapy in HCV-related HCC. Immunotherapy such as interferon was reported to reduce the recurrence and improve the survival of HCC patients after TACE[105]. However, some other investigators have shown that adding interferon to intra-arterial infusion chemotherapy did not show any additional beneficial effects in terms of tumour response rate or survival[106,107]. Autologous cytokine-induced killer (CIK) cells combined with TACE and RFA have also demonstrated limited feasibility and safety for the treatment of HCC patients[108,109]. Based on the current data, there is no robust evidence to show the survival benefits with any form of combination of locoregional and systemic therapies, which needs more experience to address this issue.

Molecular targeted therapy for combination

Improved understanding of the mechanism of hepatocarcinogenesis and the successful clinical development of sorafenib in HCC have provided a new alternative of using these molecular targeted agents combined with other locoregional and systemic therapies or in the setting of adjuvant therapy after curative treatment.

Due to the complexity of hepatocarcinogenesis and heterogeneity of HCC, the combination of multiple targeted agents that inhibit different pathways in hepatocarcinogenesis is an area of active investigation. In a phase II study, the combination of bevacizumab and erlotinib in patients with advanced HCC showed significant, clinically meaningful anti-tumour activity with a 25 per cent response rate and 15 months of overall survival rate[118]. A randomized international phase III study comparing sorafenib plus erlotinib versus sorafenib plus placebo as first-line treatment in advanced HCC is ongoing. Other molecular targeted combination therapies are also at an early stage of investigation[111,112].

Several combination regimens of molecular targeted agents and chemotherapy agents are also investigated. In a phase II study, Hsu and colleagues[113] evaluated the safety and efficacy of bevacizumab plus capecitabine in the advanced HCC, and a 9 per cent overall response rate and 52 per cent disease control rate were observed. Abou-Alfa and colleagues[114] reported a 4 per cent response rate by using sorafenib and doxorubicin in patients with advanced HCC in a randomized, double-blinded, phase II study which included 96 patients with advanced HCC. Zhu and colleagues[115] completed a phase II study that used bevacizumab in combination with gemcitabine and oxaliplatin in advanced HCC, and showed a 20 per cent of overall response rate.

Considering the treatment with TACE elicits the secretion of growth factors, such as vascular endothelial growth factor (VEGF) from hypoxic cells at the periphery of the treated lesion, there is a strong rationale to combine TACE with molecular targeted agents such as sorafenib to enhance efficacy. Dufour and colleagues[116] reported a significant decrease of the concentration of plasma VEGF in a phase I study

evaluating the safety and efficacy of continuous administration of sorafenib after TACE in patients with HCC, unfortunately there were no data concerning the survival benefits. In a study from China, 30 HCC patients with lung metastasis were treated by the combination of TACE and sorafenib, the metastatic lesions in the lung were diminished in 6 cases and stable diseases achieved in 8 cases[117]. A prospective, randomized, double-blind, multi-center, phase III clinical study on TACE combined with sorafenib versus TACE plus placebo in patients with hepatocellular cancer before LT is ongoing[(118)]. The value of sorafenib in the adjuvant setting after potentially curative treatment (surgical resection or local ablation) is also being assessed in an ongoing phase III RCT setting (STORM)[119]. The outcomes of these trials are eagerly awaited, because these have the potential to revolutionize the treatment of HCC.

We know that geographic variations exist in the incidence and aetiology of HCC. Esnaola *et al*[120] demonstrated that 65 per cent of patients in Japan had severe cirrhosis in the adjacent liver compared with 52 and 23 per cent of patients in France and the United States, respectively. With the increase of effective treatment options for HCC, the most appropriate therapy depends largely on the tumour extent and functional status of the underlying liver. Clinical practice guidelines for HCC have been published in different regions[121-123]. It is widely accepted that in patients with advanced cirrhosis and tumour extent within the Milan criteria, LT is clearly the best option, while patients with well preserved hepatic function, liver resection is the most appropriate and effective treatment, palliative treatment such as TACE is recommended for very late stage. As LT is constrained by the graft shortage, investigation has increasingly focused on downstaging therapy and salvage transplantation in some regions. However, there is a lack of standard guidelines of combination therapy for HCC. The major risk factors for HCC are HBV/HCV infection and alcoholic cirrhosis. The epidemiology of HCC is characterized by marked demographic and geographic variations. Some authors have noted distinct gene events depending on different risk factors[124,125], which suggest that HCC with different risk factors may represent different forms of the disease. It is rational to consider different therapeutic strategies for patients with different risk factors, and these preliminary findings indicate the need for a more detailed study of ethnic variability in the pathogenesis of HCC.

In conclusion, some forms of combination therapies, including downstaging therapy for HR and LT, salvage transplantation, and molecular targeted therapy, have been shown to provide survival benefits for well selected patients, and should be encouraged in the future. Others such as pre-operative bridging therapy for LT, adjuvant therapy for HR and combination of local and regional therapies have also shown some benefits in preliminary results, which need further studies. However, some strategies like neoadjuvant therapy for HR, systemic chemotherapy after HR and a variety of combination regimens of chemotherapeutic agents are not recommended based on current evidence. Overall, multimodal and combination therapy is an encouraging treatment modality for HCC. Future research should continue to unravel the realistic role of combination therapy with properly selected patients and appropriate end points.

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