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REVIEW ARTICLE

Re-evaluating transarterial chemoembolization for the treatment of Hepatocellular Carcinoma: Consensus recommendations and review by an International Expert Panel

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Abstract

Patients with unresectable hepatocellular carcinoma (HCC) usually receive transarterial chemoembolization (TACE) or systemic therapies with intermediate and advanced-stage disease. However, intermediate-stage HCC patients often have unsatisfactory clinical outcomes with repeated TACE and there is considerable uncertainty surrounding the criteria for repeating or stopping TACE treatment. In July 2012, an Expert Panel Opinion on Interventions in Hepatocellular Carcinoma (EPOIHCC) was re-convened in Shanghai in an attempt to provide a consensus on the practice of TACE, particularly in regard to evaluating TACE 'failure'. To that end, current clinical practice throughout Asia was reviewed in detail including safety and efficacy data on TACE alone as well as in combination with targeted systemic therapies for intermediate HCC. This review summarizes the evidence discussed at the meeting and provides expert recommendations regarding the use of TACE for unresectable intermediate-stage HCC. A key consensus of the Expert Panel was that the current definitions of TACE failure are not useful in differentiating between situations where TACE is no longer effective in controlling disease locally vs. systemically. By redefining these concepts, it may be possible to provide a clearer indication of when TACE should be repeated and more importantly, when TACE should be discontinued.

The preferred curative treatments for hepatocellular carcinoma (HCC) include liver transplantation, surgical resection or local ablation. These treatments offer the best survival advantages but in practice, most patients either present when the tumour is in an advanced stage or the degree of underlying liver disease precludes these options. Subsequently, treatment algorithms recommend treatment stratification based on the stage of disease. For intermediate-stage patients (1) with unresectable, large/multifocal HCC, most guidelines recommend TACE as a first-line treatment (2–6) whereas for patients with advanced-stage HCC (1)

systemic therapies are the treatment of choice (2). In addition to TACE, there are numerous loco-regional therapies available for unresectable HCC treatment. Potentially curative treatments include percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA), whereas other non-curative treatments include radioembolization and drug-eluting microspheres. Although some of these therapies have been shown to provide benefits in controlled clinical studies, survival benefits have not been proven. These have been reviewed in detail elsewhere and will not be discussed here (7, 8). The only non-curative treatments that improve survival are TACE and sorafenib (9–11).

The widely accepted classification for staging and treatment proposed by the Barcelona Clinic Liver Cancer (BCLC) considers TACE to be the standard of care for intermediate-stage HCC (1). Although this and other guidelines provide clear definitions of when TACE is contraindicated, there is considerable uncertainty around when TACE should be repeated given the variable nature of clinical responses. An additional complication is that compliance for performing TACE according to specific criteria in the various guidelines under well-controlled conditions such as a clinical trial is quite different from that occurring in standard clinical practice.

Expert panel meeting

In July, 2012, the Expert Panel Opinion on Interventions in Hepatocellular Carcinoma (EPOIHCC) meeting was convened in Shanghai bringing together 17 experts from Asia-Pacific. The panel was intended to provide a multidisciplinary approach to optimizing HCC management incorporating input from specialists in gastroenterology, hepatology, surgery, transplant surgery, interventional and diagnostic radiology, medical oncology, radiation oncology and nuclear medicine. The objectives for the meeting were to review current clinical practice with TACE in Asia with respect to clarifying uncertainties around patient selection, scheduling of TACE, evaluation of response, the definition of TACE failure and the evidence for TACE combination therapy from current clinical trials. This is intended to assist clinicians determine the most appropriate treatment strategy in cases where TACE is no longer effective, for whatever reason. To assist with these discussions and to provide a snapshot of current clinical practice in Asia, a premeeting survey was completed by 15 of the expert panel members (Table 1).

Conventional vs. DEB-TACE

Conventional TACE is the primary treatment used most frequently for unresectable HCC and involves embolization of the hepatic artery with the aim of inducing necrosis in large vascularized HCC (7). A chemotherapy agent (most commonly doxorubicin) is mixed into an emulsion with lipiodol and selectively infused via the transarterial route into the tumour, usually in combination with an embolizing agent (most commonly a gelatin sponge or polyvinyl particles). This combination of vessel obstruction and chemotherapeutic agent results in increased exposure of the tumour to the chemotherapeutic agent (12). Using this approach, the lipiodol is selectively retained within the tumour and is thought to magnify the exposure of the neoplastic cells to chemotherapy with additional benefits conferred by obstruction of the feeding arteries. However, tumour response to TACE can be variable and it is considered a non-curative treatment as complete tumour necrosis is difficult to achieve, even with repeated TACE treatments (2, 13). In addition to the highly heterogeneous nature of intermediate HCC, there is also no standard regimen regarding patient selection, treatment schedule or re-treatment strategy, type of chemotherapy or embolizing agent. Efficacy of TACE is most likely related to drug exposure but may also depend on the degree of ischaemia induced. Subsequently, technical proficiency is key in achieving optimal responses to TACE and for preventing complications. Despite this, even with technically perfect TACE procedures, responses are not 100% indicating the paramount importance of tumour-related factors. These include vascularization type, features of the disease and tumour aggressiveness. Superselective TACE may provide benefits in minimizing damage to non-tumourous areas using a microcatheter to selectively (or superselectively) catheterize the hepatic segmental or subsegmental arteries nourishing the tumour (14).

The recently developed TACE with drug-eluting beads (DEB) offers the possibility of more targeted chemotherapeutic delivery with potentially less side effects. The bead's high affinity for the drug results in a gradual release of doxorubicin into the tumour, allowing a longer intratumoural exposure and less systemic exposure of the drug, reducing toxicity (7). A number of recent studies have demonstrated higher tumour concentrations and lower systemic concentrations of doxorubicin compared with intra-arterial doxorubicin used in conventional TACE [reviewed in (7)]. Precision-V, a randomized controlled trial comparing DEB-TACE with conventional TACE recently reported similar tumour response rates but slightly better objective response rates and disease control rates in the DEB-TACE arm, although these were not statistically significant (15). Treatment-related serious adverse events were similar for both groups, but the secondary safety outcomes (incidence and severity of adverse events, liver function parameters and cardiac function) were significantly better in the DEB-TACE group (15). Similarly, a recent retrospective comparison of conventional and DEB-TACE demonstrated significantly better objective response rates (81.6% vs 49.4%) and time to progression (11.7 vs 7.6 months) for the DEB-TACE group (16). There was no statistically significant difference in liver toxicity between groups. Despite these promising results, DEB-TACE uptake in Asia is relatively low compared with

Table 1. EPOIHCC premeeting survey questions and summary of responses

Question	No. of responses
Q1. Do you rely on specific guidelines to advise the use of TACE in HCC?	
Yes	12
No	3
Local/Hospital guidelines	7
AASLD HCC Practice Guidelines	4
NCCN Guidelines	2
APASL Guidelines	4
EASL Guidelines	1
JSH Guidelines	2
KLCSG-NCC Guidelines	3
Other	
Q2. Which TACE regimen do you use routinely in clinical practice?	
DC Beads	5
cTACE-Doxorubicin	13
cTACE-Cisplatin	5
cTACE-Mitomycin	3
Other	
Q3. In your experience, what is the optimal number of TACE procedures required in the treatment of intermediate HCC patients? Please specify average in your practice.	
Q4. How do measure patient response to TACE in clinical practice?	
Response Evaluation Criteria in Solid Tumours (RECIST)	5
Modified RECIST (mRECIST)	11
WHO	0
EASL	1
Other (specify)	
Q5. What is the greatest challenge faced in the application of TACE in intermediate HCC patients?	
Liver Function	12
Vascular Access	7
Tumour Size	5
Tumour Number	5
Evidence	0
Other (specify)	0
Q6. In your opinion, would improved patient outcomes with TACE, mean less procedures and preserve liver function?	
Yes	13
No	2
Q7. For the case of poor response or refractory TACE, would you consider these options?	
Yt-90	8
RFA	3
External beam radiotherapy	5
Other (specify)	5
Q8. Which patients are unsuitable for TACE, what treatment options would you consider in these cases?	
Technical issues	13
Tumour size	12
Liver function	12
In your opinion, there is insufficient evidence to support alternatives	2
Q9. In your opinion, which intermediate-stage HCC patients would potentially benefit from molecular-targeted therapy?	
Patients with tumour >10 cm	6
Patients with vascular invasion	10
Patients who have undergone ≥2 TACE procedures, without satisfactory response	11
Other (specify	4
Q10. In your opinion, is there sufficient evidence to support the use of sorafenib and TACE in combination therapy?	
I do use it in clinical practice currently	3
I do use it but only in special patient populations	10
I do not use it in clinical practice	4

the USA or Europe. Our survey of the EPOIHCC revealed that only 5 of 16 (31%) panellists routinely use DEB-TACE in clinical practice in Asia. This is increased slightly from a 2011 survey of the same Expert Panel where 25% routinely used DEB-TACE.

TACE in Asia

The usage of TACE varies considerably throughout the world as demonstrated by the ongoing GIDEON study. Compared with the USA (44%), Europe (49%) and

Latin America (29%), rates of prior use of TACE in HCC patients are considerably higher in Asia-Pacific (69%) with a reported 84% of Japanese patients receiving TACE prior to the analysed period (17). The number of patients receiving at least 3 TACE treatments prior to this study was also higher in Asia-Pacific and Japan than in other regions. Observations of HCC management patterns from the global BRIDGE study reported that TACE is the most frequently used first recorded treatment in Asia and North America (18). There is now good evidence that TACE prolongs survival compared with best supportive care (19, 20); however, conventional TACE has a wide range of survival rates between clinical series reflecting variations in patient selection and differences in chemoembolization techniques (21–24). Only a limited number of studies report 5-year survival rates for conventional TACE, but these are consistently poorer in Western patients (1–13%) (24, 25) than in Asian patients (24%) (21). A recent systematic review noted a trend since 2000 of studies reporting better survival rates compared with those before 2000, mainly because of better selection of patients (21). Some of the highest survival rates observed are in studies from Japan, which have reported rates of 26% in 2006 (26) and 34% in 2012 (14) primarily through improved patient selection. A recent report on the 5-year overall survival of HCC patients treated with DEB-TACE reported overall survival at 3 and 5 years of 62 and 22.5% respectively (27).

Objectively evaluating treatment response

To objectively evaluate the response to loco-regional therapy, the Response Evaluation Criteria in Solid Tumors (RECIST) (28, 29) and the European Association for the Study of the Liver Criteria (EASL) (30) have been developed. These have gained widespread use internationally despite inherent limitations. RECIST may evaluate unidimensional tumour measurements and does not capture the efficacy of loco-regional therapies in inducing tumour necrosis (31). Although EASL criteria do evaluate response by measuring the extent of tumour necrosis, there is a lack of data supporting correlations with improving survival (7). In 2010, a modification in RECIST (mRECIST) with criteria similar to RECIST was proposed, which includes an assessment of the disappearance or decrease in the intratumoural arterial enhancement in the target lesion (32). Although many clinicians around the world have moved towards mRECIST, the assessment of intratumoural arterial enhancement is relatively subjective and requires validation and correlation with survival. Our survey of the EPOIHCC revealed that 5 of 15 (33%) panellists use RECIST in clinical practice in Asia, whereas 13 of 15 (86%) use mRECIST. Only one respondent indicated that they use EASL criteria. In our 2011 survey, equal numbers of respondents used RECIST and mRECIST. Given the limitations in both criteria, the panel believes that RECIST is still essential for objective assessment. In the months following the EPOIHCC meeting in Shanghai, several publications have considered this controversy in detail. Sato *et al.* directly compared response rates following TACE reported using RECIST and mRECIST in addition to evaluating their variability (33). The CR rate and the response rate obtained using mRECIST (56.9% and 79.7%) were higher than those obtained using RECIST version 1.1 (9.2% and 43.1%) while mRECIST exhibited almost perfect agreement in inter- and intra-observer reproducibility. RECIST version 1.1 exhibited substantial agreement in reproducibility. The authors suggest that mRECIST may be more suitable for tumour response criteria in clinical trials of TACE for HCC as it exhibits higher inter- and intra-observer reproducibility. Although not compared directly to mRECIST, Muenzel *et al.* demonstrated low intra- and inter-observer variabilities for measurements of single target lesions using RECIST, but the high variability in change in Δ sum LD reveals the potential for misclassification of the overall response according to the RECIST guidelines (34). The authors suggest that reproducibility of RECIST reporting can be improved for the case assessment by a single reader and mean results of multiple readers. Shim *et al.* reported good intercriterion agreement between mRECIST and EASL guidelines while a poor correlation was observed between RECIST and mRECIST (35). This study also suggested that mRECIST could more reliably help predict long-term survival in HCC patients treated with TACE than other size-based imaging guidelines. Similarly, a comparison of RECIST1.1, mRECIST, EASL and WHO guidelines suggests that mRECIST provides the highest correlation with survival in HCC patients treated with DEB-TACE while RECIST1.1 is the least useful in predicting survival in these patients (36). An additional study comparing RECIST with mRECIST specifically in patients who received Sorafenib for advanced HCC reported that the majority of patients who had SD according to RECIST had a different prognosis according to mRECIST (37). The authors go on to suggest that for patients with HCC, mRECIST should be used for the standard assessment of treatment efficacy, particularly in patients who are receiving antiangiogenic drugs.

Taking these recent studies into consideration, we acknowledge that mRECIST is widely used in other parts of the world; however, uptake rates are lower in Asia, necessitating an evidence-based assessment of RECIST vs mRECIST prior to widespread incorporation into local practice. Although these recent studies will assist with partial validation of mRECIST as a viable, and potentially, superior response criteria, further prospective evaluation is still necessary. For this reason, we recommend that mRECIST be used in combination with RECIST, wherever possible.

Consensus #1. The panel believes that RECIST is still valuable for objective assessment. We acknowledge that mRECIST is widely used and recent studies are

beginning to address its validation. However, given the continued usage of RECIST in Asia, mRECIST should be used in combination with RECIST wherever possible. Before mRECIST can be widely incorporated for generalized use, EPOIHCC recommends that mRECIST should be more intensively and prospectively studied.

Standardizing TACE protocols

The inherent variability associated with TACE outcomes is primarily related to the heterogenous patient population undergoing treatment; however, variations in the time intervals between treatments and the number of cycles of TACE performed are also likely to be important prognostic factors. Even in the absence of conclusive, predictive biomarkers, it is becoming clearer that the best candidates for TACE are largely asymptomatic patients with preserved liver function without vascular invasion or extrahepatic tumour spread. (38) There are a number of HCC treatment algorithms, which have been proposed as the most widely accepted being the BCLC staging system (1). Recent comparisons of the BCLC and Japanese Society of Hepatology (JSH) guidelines (39) have concluded that they are essentially quite similar in terms of inclusion criteria for TACE and in their absolute contraindications to TACE (40, 41). The EPOIHCC generally supports the use of these criteria. However, we believe that the limitation of TACE to strictly BCLC B patients should be further evaluated. TACE has demonstrated efficacy in patients prior to transplantation (BCLC A), particularly if the waiting time is likely to be more than 6 months (42, 43).

Response to TACE may also be used as a predictor of tumour biology in patients awaiting transplantation (44). TACE also appears to be a safe and effective option in patients clinically excluded from transplantation and who are unfit for surgery or percutaneous ablation (45). At the other end of the TACE spectrum, BCLC C patients with acceptable PS or only partial PVT may also benefit from selective or DEB-TACE treatment. While PVT has been widely accepted as a relative contraindication for TACE, studies have demonstrated little negative impact on hepatic function in cases of PVT and TACE can be safely performed if hepatopedal collateral flow is present (46, 47). In these patients, a superselective approach as well as an adjustment of the chemotherapeutic dosage may minimize liver damage (48). An important recognition is that although the BCLC recommendations are clear, not everybody follows them. In Asia and most of North America, patients with BCLC A-C would probably be considered for TACE. This does not mean that TACE has been recognized as the treatment of choice for those patients, but rather for patients with BCLC A who do not meet the Milan selection criteria for transplantation, and who are unsuitable for resection or local ablation owing to tumour location, TACE remains the only treatment strategy (45). Similarly, patients with ECOG 1 who would be BCLC C could benefit from TACE provided appropriate measures are taken to minimize liver damage.

Consensus #2. Suitable patients for TACE are those that are BCLC A, B or C, ECOG PS <2, Child-Pugh <C. For cases with vascular invasion or metastasis, combination therapy with sorafenib may be tried in practice, but solid evidence from controlled prospective studies is still required to evaluate this approach.

Although most guidelines indicate that the presence of extrahepatic metastases is an absolute contraindication for TACE, in clinical practice, there may be specific situations where patients have extrahepatic progression, but the bulk of disease is within the liver. This will be case specific but if the clinician concludes that the patient is most likely to die from liver disease, in these patients, there may still be a role for TACE, making extrahepatic metastases a relative contraindication only.

Consensus #3. Absolute contraindications for TACE include Child C and poor ECOG status while relative contraindications include extrahepatic disease depending on how extensive.

Multiple TACE cycles can be performed either at regular intervals or based on tumour response (on demand), when there is evidence of insufficient tumour response, tumour recurrence or disease progression. Although it is generally accepted that chemoembolization achieves maximal tumour response when repeated multiple times (49) it is not yet clear whether this results in better survival. In addition, it is also unknown if on demand TACE is preferable to fixed interval TACE. On one hand, TACE repeated at a fixed time, until the planned number of courses has been reached, should provide the greatest opportunity for persistent tumour necrosis. However, repeated chemotherapy insults may cause progressive liver atrophy and vascular damage (50, 51). Alternatively, TACE performed on demand, on the basis of tumour response and patient tolerance, is likely to reduce the degree of liver damage and complications and it allows a proper patient selection at each cycle of TACE (51) but may potentially result in undertreating the tumour. A recent study assessed the clinical impact of TACE repeated on demand on HCC outcome (52). The number of patients submitted to a second and third TACE declined substantially from those initially enrolled; however, similar CR and recurrence rates were observed after the first, second and third TACE procedures. This not only demonstrates the efficacy of repeated on demand TACE procedures but also highlights the declining patient population suitable for repeated TACE. A comparative trial performed conventional TACE in 80 patients from 1986 to 1993 using a fixed schedule of at least three times at 2-month intervals. On demand TACE was performed in a second group of 80 patients from 1993 to 1996, where TACE was used selectively and repeated only when necessary on the basis of follow-up CT or MR imaging (51). Complications of TACE occurred in 19 patients from group 1 and six patients from group 2 ($P < 0.001$) potentially

reflecting the greater number of TACE cycles performed. Similarly, the mean time between the first and the third TACE cycle was significantly different between group 1 (4 months) and group 2 (14 months) ($P < 0.001$). Of note, the 1-year, 2-year and 3-year survival rates were significantly different between the two groups of patients graded as Okuda stage 1: 58, 28, 11% for fixed schedule TACE and 89, 68, 39%, respectively, for on demand TACE ($P < 0.001$). This observation clearly demonstrates the efficacy and tolerability of TACE increase when it is used selectively and repeated on demand (51). A recent systematic review noted that in 63% of studies assessed (reported by 54 studies), TACE was repeated at fixed time intervals until the planned number of courses was reached or death occurred, while on demand TACE was only performed in 27% of studies when there was evidence of unsatisfactory response or recurrence of the tumour (21). Unfortunately, this analysis made no attempt to compare patient outcomes in these two populations.

Consensus #4. TACE should be performed on demand. The decision to repeat TACE should be based not only on tumour response or progression but also on patients' clinical conditions and tolerance, which should be assessed before each new cycle of TACE.

Redefining TACE failure

Key areas of uncertainty not sufficiently addressed by existing guidelines include the criteria for repeating TACE and recommendations about the number of TACE cycles to be repeated before switching to another or no treatment. This latter point relates to the criteria used to determine when to stop TACE treatments, either because TACE is now contraindicated, or because TACE is no longer effective in controlling the disease, referred to generally as TACE failure. The JSH defines TACE failure as the development of an intrahepatic lesion, the appearance of vascular invasion, the appearance of extrahepatic spread or a continuous elevation of tumour markers even though right after TACE (41). In clinical practice, less formal definitions include the treatment of all visible disease in liver without response, being unable to prevent tumour growth and significant toxicities. We believe that an important distinction to make regarding the efficacy of TACE is whether disease progression is characterized by intra or extrahepatic spread. If there is any progression at all, it is clear that TACE is not effective in controlling the disease, but this does not necessarily indicate TACE failure. Technically, the TACE procedure may have been successful, in terms of lipiodol deposition and local tumour necrosis, etc., but patients may still go on to develop metastases. Describing this scenario simply as TACE failure is misleading and scientifically inaccurate. As TACE is a loco-regional therapy, TACE failure should refer to the specific control of the tumour that was planned for treatment. The appearance of subsequent disease is progression of disease and this may, or may not, be caused by TACE failure. This view has recently been proposed by others citing 'progression itself does not seem necessarily to imply the failure of TACE' (53). Untreatable progression, in terms of TACE therapy, may correspond to the development of portal vein thrombosis, extrahepatic metastases or worsening of liver function, for example, despite a clear control of the lesion targeted for TACE.

Consensus #5. As a loco-regional therapy, TACE failure should refer to the specific control of the tumour that was planned for treatment and, therefore, may not be useful in evaluating TACE effectiveness in patients with extrahepatic metastases.

The recent proposal of 'stage progression' from Korea is potentially a useful concept and may provide a surrogate end-point for TACE refractoriness (53). By evaluating 264 patients with intermediate-stage HCC who underwent TACE and designating the development of vascular invasion or extrahepatic spread during follow-up as stage progression (SP), the authors classified the patients according to disease course as: no progressive disease, PD without SP, PD followed by SP, and simultaneous PD and SP. Patients without SP (including both patients with no PD and those with PD but no SP) showed no difference in overall survival (36.6 and 35.8 months, respectively), patients with PD followed by SP had intermediate overall survival (23.9 months) and patients with simultaneous PD and SP had the worst overall survival (12 months). Multivariate analyses of OS indicated corresponding hazard ratios for each patient group. By classifying SP as new vascular invasion or extrahepatic spread, which includes radiological progression of stage from BCLC stage B to stage C, the time from initial treatment to this point can be referred to as 'time-to-stage progression' (TTSP). A further variation in this concept to accommodate the increasing number of cases of SP that develop as the duration of follow-up increases has been proposed as 'SP-free survival' (53). The authors contend that this provides a composite end-point instead of TTSP, which may indicate TACE-refractory HCC. Subsequent analysis indicated that both the development of progression during the first 6 months from the initial TACE and the need for three sessions of TACE during the first 6 months were associated with shorter SP-free survival and thus, TACE-refractory HCC (53).

Consensus #6. Stage progression, defined as the development of vascular invasion or extrahepatic spread during follow-up, may provide a useful surrogate measure of TACE refractoriness, although there are currently limited data regarding this.

Taking this current proposal into consideration along with existing guidelines and the collective clinical experience of the EPOIHCC, the panel agrees that three sessions of TACE in clinical practice (within 6 months) should be adequate for effective tumour control. Sorafenib is recommended for those who have failed TACE or for TACE-refractory patients. By defining TACE

refractoriness more clearly using SP, in intermediate-stage HCC patients who are not eligible for, or who have demonstrated SP after TACE, a switch to sorafenib might be a considered. It should also be noted that TACE, particularly repeated TACE, can result in liver toxicity and chemotherapy-related side effects (50, 51), which may influence retreatment decisions. Recent advances aimed at minimizing the injury to non-tumoural liver tissue include selective (or superselective) TACE (14, 54) and DEB-TACE (15).

Consensus #7. Three sessions of TACE in clinical practice (within 6 months) should be adequate for effective tumour control.

TACE in combination with sorafenib

Transarterial chemoembolization is associated with disturbances of the tumour microenvironment, which result in increased hypoxia, leading to an upregulation in hypoxia-inducible factor-1a, which in turn upregulates vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor (PDGFR) and increases tumour angiogenesis (55–57). Increased angiogenesis may in turn result in tumour-promoting effects and elevations in serum VEGF are a poor prognostic indicator in patients with HCC (58–60). Combining antiangiogenic-targeted agents with TACE to decrease post-TACE angiogenesis may improve the efficacy of TACE therapy as well as improving long-term outcomes. Sorafenib is a potent multikinase inhibitor with antiangiogenic and antiproliferative properties that targets the Raf/MEK/ERK pathway (61) as well as VEGFR-1/2/3, PDGFR-β, KIT, Flt-3 and RET (62). Two landmark phase III trials comparing sorafenib with placebo in patients with advanced HCC reported significant improvements in overall survival establishing sorafenib as the standard of care in advanced HCC patients (10, 11).

Given the success of sorafenib in advanced HCC and the theoretical advantages of combining TACE with sorafenib, a number of ongoing trials are evaluating this combination in intermediate-stage HCC patients. In theory, additional support for either on demand TACE schedules or fixed TACE schedules should be available from recent combination trials of TACE and sorafenib. However, most combination trials have utilized an on demand TACE schedule with only the recent phase II Johns Hopkins University (JHU) and SPACE trials incorporating a fixed schedule of DEB-TACE with concurrent continuous sorafenib administration (63, 64). The JHU trial was a small Phase II study in 35 patients in which DEB-TACE was performed with concurrent continuous sorafenib and reported a disease control rate as evaluated per lesion of 92 to 100%, with an objective response rate of 58% (64). The SPACE trial enrolled 307 patients with intermediate-stage HCC reporting a median treatment duration in the treatment and placebo groups of 4.8 and 6.3 months, respectively, and a HR for TTP of 0.797 (63). Although median TTP reported was similar for both groups, there were considerable differences in TTP at the 25th and 75th percentiles and this study met its primary end-point of improving TTP when sorafenib was added to a regimen of DEB-TACE, compared with DEB-TACE. To eliminate variations in sorafenib administration and type of TACE performed, there is only a single recent European study appropriate for direct comparison. In a small group of patients, this study incorporated a continuous sorafenib schedule with on demand TACE but was stopped prematurely because of safety concerns (65). There are three ways to combine TACE and sorafenib. An interrupted design where sorafenib is stopped around the time of TACE (e.g. START) (66) sequential where several cycles of TACE are performed first and then sorafenib is started (67) or continuous, where both are applied together (e.g. COTSUN, JHU and SPACE) (63, 64, 68). There are currently a substantial number of clinical trials assessing the various combinations of TACE with sorafenib and these have been reviewed elsewhere (8). The outcomes of these combination trials are eagerly awaited and are likely to change the treatment landscape for intermediate HCC patients.

Consensus #8. The combination of sorafenib and TACE may improve the efficacy of TACE therapy as well as improving long-term patient outcomes. However, despite promising initial data, the successful completion of several clinical trials in progress will be essential before recommending the combination of sorafenib plus TACE for patients with intermediate-stage HCC.

Summary

This expert panel meeting was convened to address unresolved issues surrounding the use of TACE in clinical practice in Asia. The palliative nature of TACE frequently necessitates repeated TACE treatments; however, there is still considerable ambiguity surrounding the criteria for repeating TACE, how long TACE should be repeated for, and when it should be stopped and replaced with alternate therapy (or no treatment). The EPOIHCC recommends that a maximum of three sessions of on demand TACE within a period of 6 months should be sufficient for successful treatment. Disease progression during this time may indicate TACE refractoriness and a change in treatment strategy should be considered. By refocusing clinicians on identifying TACE refractoriness rather than the ambiguous concept of TACE failure, patient selection for repeated TACE can be improved leading to important survival advantages.

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