REVIEW

Transarterial chemoembolization: Evidences from the literature and applications in hepatocellular carcinoma patients

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Abstract

Transarterial chemoembolization (TACE) is the current standard of care for patients with large or multinodular hepatocellular carcinoma (HCC), preserved liver function, absence of cancer-related symptoms and no evidence of vascular invasion or extrahepatic spread (*i.e.*, those classified as intermediate stage according to the Barcelona Clinic Liver Cancer staging system). The rationale for TACE is that the intra-arterial injection of a chemotherapeutic drug such as doxorubicin or cisplatin followed by embolization of the blood vessel will result in a strong cytotoxic effect enhanced by ischemia. However, TACE is a very heterogeneous operative technique and varies in terms of chemotherapeutic agents, treatment devices and schedule. In order to overcome the major drawbacks of conventional TACE (cTACE), non-resorbable drug-eluting beads (DEBs) loaded with cytotoxic drugs have been developed. DEBs are able to slowly release the drug upon injection and increase the intensity and duration of ischemia while enhancing the drug delivery to the tumor. Unfortunately, despite the theoretical advantages of this new device and the promising results of the pivotal studies, definitive data in favor of its superiority over cTACE are still lacking. The recommendation for TACE as the standard-of-care for intermediate-stage HCC is based on the demonstration of improved survival compared with best supportive care or suboptimal therapies in a meta-analysis of six randomized controlled trials, but other therapeutic options (namely, surgery and radioembolization) proved competitive in selected subsets of intermediate HCC patients. Other potential fields of application of TACE in hepato-oncology are the pre-transplant setting (as downstaging/bridging treatment) and the early stage (in patients unsuitable to curative therapy). The potential of TACE in selected

advanced patients with segmental portal vein thrombosis and preserved liver function deserves further reports.

Core tip: Transarterial chemoembolization (TACE) represents the standard of care for patients with large or multinodular hepatocellular carcinoma (HCC). However, TACE is a heterogeneous technique varying in terms of chemotherapeutic agents, devices and schedule. In order to overcome these drawbacks of conventional TACE (cTACE), drug-eluting beads have been developed. Unfortunately, despite its theoretical advantages, definitive data in favor of its superiority over cTACE are still lacking. TACE represents the standard-of-care for intermediate-stage HCC, in competition with other therapeutic options (surgery and radioembolization). Other fields of application are the pre-transplant setting and the early stage (in patients unsuitable to curative therapy).

INTRODUCTION

Transarterial chemoembolization (TACE) is the current standard of care for patients with large or multinodular hepatocellular carcinoma (HCC), preserved liver function, absence of cancer-related symptoms, and no evidence of vascular invasion or extrahepatic spread [*i.e.*, those classified as intermediate stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system][1,2]. Furthermore, in clinical practice, many patients in the early stage (*i.e.*, single nodule or up to 3 nodules under 3 cm) carrying contraindications to curative approaches - liver resection, liver transplantation (LT) or radiofrequency ablation (RFA) - are treated with TACE.

The rationale for TACE is that the intra-arterial injection of a chemotherapeutic drug such as doxorubicin or cisplatin followed by embolization of the blood vessel will result in a strong cytotoxic effect enhanced by ischemia[3]. The embolization end point is usually defined as stasis in the second- or third-order branches of the lobar hepatic artery and injection should be continued until near stasis is observed in the artery directly feeding the tumor (*i.e.*, the contrast column should clear within 2-5 heartbeats)[4].

TACE is a very heterogeneous operative technique and varies in terms of chemotherapeutic agents, treatment devices and schedule. Such heterogeneity explains the great range in terms of efficacy outcomes: a recent systematic review reported mean overall survival (OS) times of 3.422 up to more than 40 mo, with a median of 16.5 mo[5]. The best outcomes in terms of OS reported so far are 48 mo in a series published by the Barcelona group[6].

INDICATIONS

Patients should present a relatively well preserved liver function, defined as Child-Pugh (CP) ≤ B7 stage without ascites according to European Association for the Study of the Liver (EASL) guidelines[2] or only CP A according to the more conservative American Association for the Study of Liver Diseases (AASLD) guidelines[1].

Absolute contraindications to TACE are generally related to decompensated cirrhosis or impaired portal blood flow[1,2]. Other absolute contraindication, supported by the expert opinion, is represented by extensive tumors massively replacing both entire lobes, whereas a tumor size ≥ 10 cm, the bile-duct occlusion and untreated varices at high risk of bleeding constitute relative contraindication rather than absolute ones[5]. Main absolute and relative contraindications to TACE are reported in Table 1.

Although the adverse events associated with TACE are generally transient and easily manageable, they are very common with 35%[7] to 100%[8] of treated patients experiencing post-embolization syndrome (defined by the occurrence of abdominal pain, fever and nausea). Treatment-related deaths are expected in less than 2% of cases if proper selection of candidates is in place[9].

Therefore, TACE appears as a safe treatment in selected candidates, as defined by current guidelines.

TREATMENT SCHEDULE

Current evidence suggests that one cycle of TACE may not be sufficient for effective treatment of intermediate-stage HCC. On the other hand, there is evidence suggesting that repeating TACE prolongs survival; however, current guidelines do not specify the criteria for treatment repetition. In particular, it should be noted that in bilobar tumors, the two hepatic lobes usually have to be treated in separate treatment sessions 2-4 wk apart.

There are no solid data to suggest that "on-demand" TACE (*i.e.*, number of sessions on the basis of tumor response after each TACE cycle) is more or less effective than scheduled TACE (pre-defined number of sessions regardless of "at interim" response or safety evaluations) for improving patient survival. In fact, although scheduled strategy is more concordant with the general principle of oncologic therapy, which uses standard chemotherapeutic sessions based on the

Table 1 Absolute and relative contraindications to transarterial chemoembolization
Absolute contraindications
Decompensated cirrhosis (Child-Pugh ≥ B8)
Extensive tumor with massive replacement of both entire lobes
Severely reduced portal vein flow
Technical impediments to hepatic intra-arterial treatment
Relative contraindications
Kidney failure
Severe cardiopulmonary comorbidities
Tumor size ≥ 10 cm
Untreated varices at high risk of bleeding
Bile-duct occlusion

cell cycle, however, there is evidence suggesting that the repetition of TACE with an aggressive schedule increases the incidence of adverse events[10]. Therefore, the experts in the field propose the on-demand repetition with longer intervals between treatments, rather than a regular predefined schedule[5,11]. This has been recently confirmed by Terzi *et al*[12] in a series of 151 patients treated with on-demand conventional TACE (cTACE). In their analysis, a second TACE course was administered to 65% of patients who experienced a recurrence after the complete response and to only 41% of patients non responder to the first course. Therefore, the results of this study demonstrate that only approximately half of the patients with incomplete response or recurrences were eligible for repeated TACE, mainly because of tumor burden growth and liver function impairment[12]. These findings stand for an on-demand strategy to be "tailored" according to individual patients' characteristics.

REPEATED TACE: IS IT POSSIBLE A SCORE FOR ALL SEASONS?

What remains to be definitively established is the maximum number of repeated TACE procedures that should be administered before switching to another therapeutic option or stopping treatment. Applying TACE procedures up to 3 to 4 times per year[11] and switching in absence of response to at least 2 sessions[5] has been recommended in absence of definitive evidence of an optimal retreatment strategy because more intensive regimens might induce liver failure in an unacceptable proportion of patients. A review of cohort and randomized controlled trials (RCTs) reported a mean number of TACE courses of 2.5 ± 1.5 per patient[13], but in the common clinical practice an even greater number of repeated sessions is undertaken.

To help the hepatologists to select appropriate candidates for starting or repeating TACE, several prognostic indices were introduced in the past, but none of them were universally accepted since they resulted difficult to implement or insufficiently discriminatory[14,15]. More recently, a number of other scores and nomograms have been proposed, particularly: the hepatoma arterial-embolization prognostic score published by Kadalayil *et al*[16] in 2013, based on albumin, bilirubin, alpha-fetoprotein (AFP) and tumour size; the assessment for retreatment with TACE (ART) score proposed by Sieghart *et al*[17] in 2013, considering aspartate transaminase and CP increase after the first session together with tumor response; the ABCR score published by Adhoute *et al*[18] in 2014 on the basis of AFP and BCLC stage at baseline together with CP increase and tumor response after TACE; the inflammation based index score, that combines C-reactive protein and serum albumin, proposed by Pinato *et al*[19] and applied to TACE patients in 2015. Other proposed scores and nomograms are reported in Table 2[20-22].

Unfortunately, none of these new prognostic systems have been unequivocally confirmed in clinical practice[23-26]. In fact, all these efforts, although properly conducted, suffer from overfitting: a phenomenon occurring when a model maximizes its performance on some set of data but its predictive performance is not confirmed elsewhere due to random fluctuations of patients' characteristics in different clinical and demographical backgrounds. The very fact that so different scores keep on being proposed confirms and gives proof of this concept. When a model is built, as in the case of the aforementioned studies, the score is tested in a different but "plausibly related" cohort and that is called external validation; unfortunately, external validation has been found to show sufficient power to detect clinically important changes in performance only when substantial sample sizes are available, that is not common in clinical research[27]. With smaller series, as in the case of most of the above reported papers, the sole external validation may lead to an overestimation of the performance of the model. In attendance of larger multicenter series and more reliable statistical tools (for instance bootstrap sampling or internal validation)[28], an unequivocally accepted prognostic system able to guide the decision of TACE repetition remains an unmet need. The detailed list of the proposed scoring systems for HCC patients undergoing TACE is reported in Table 2.

USEFULNESS OF DRUG INJECTION

Robust data in favor of a clear superiority of conventional TACE over transarterial embolization (TAE) are lacking[29]. A RCT comparing cTACE, TAE and best supportive care (BSC) was prematurely terminated due to the superiority of cTACE over BSC (see below)[30]. Unfortunately, this prevented the possibility to verify the efficacy of TAE, which could be hypothesized based on the trend observed in OS[30]. Similarly, no difference in terms of survival rates was reported between cisplatin-based TACE and TAE in a small Chinese RCT[31]. On the other hand, the added value of the chemotherapeutic agent (doxorubicin) in drug-eluting bead (DEB)-TACE over bland TAE has been recently demonstrated in a Greek RCT, which found an increase in time to progression (TTP) from 36.2 ± 9 wk up to 42.4 ± 9.5 wk ($P = 0.008$) in

Table 2 Proposed scoring systems for hepatocellular carcinoma patients undergoing transarterial chemoembolization

Ref.	Variables considered	Aim
Lladó *et al*[15]	AFP (> 400 UI/L), tumor size (> 50%) and CP score	Treatment selection
Kadalayil *et al*[16]	Albumin < 3.6 g/L, bilirubin > 17 μmol/L, AFP > 400 ng/mL and dominant tumor size > 7 cm	Treatment selection
Sieghart *et al*[17]	Increase of AST by > 25% and of CP score from baseline, tumor response	Treatment repetition
Adhoute *et al*[18]	BCLC, AFP (> 200 ng/mL), increase in CP score by ≥ 2 from baseline and tumor response	Treatment repetition
Pinato *et al*[19]	Normalization of CRP and serum albumin after TACE	Treatment repetition
Hucke *et al*[20]	Albumin level, tumour burden (reference: up-to-7 criteria) and CRP(≥ 1 mg/dL)	Treatment selection
Xu *et al*[21]	PVT, tumor number, tumor capsule, AFP, AST and ICR	Treatment selection
Sciarra *et al*[22]	CD34 and VEGF staining[1]	Treatment selection

[1]Assessed in tumor biopsy. AFP: Alpha-fetoprotein; CP: Child-Pugh; AST: Aspartate transaminase; BCLC: Barcelona Clinic Liver Cancer; CRP: C-reactive protein; TACE: Transarterial chemoembolization; PVT: Portal vein thrombosis; ICR: Indocyanin retention test; VEGF: Vascular endothelial growth factor.

DEB-TACE patients[32]. Another investigation assessed the degree of necrosis in explanted livers after epirubicin DEB-TACE versus TAE and found tripled complete necrosis rates (77% *vs* 27% of lesions) in the DEB-TACE group[33].

There is no consensus on the optimal chemotherapeutic agent to use in TACE. Worldwide, the most popular anticancer drug injected is doxorubicin. In cTACE, the dose of doxorubicin typically ranges from 30 to 75 mg/m^2 (to a maximum of 150 mg) mixed with 5 to 20 mL of lipiodol, followed by mechanical embolization with an embolic agent, as Gelfoam[4]. In DEB-TACE, the planned dose of doxorubicin should depend on the extent of the liver tumor burden: as a general rule, for disease within the Milan criteria each single treatment should include a planned dose of up to 75 mg doxorubicin loaded into one vial of DC Bead, whereas for disease beyond the Milan criteria, the dose should be of up to 150 mg loaded into two vials of DC Bead[4].

DEB-TACE *VS* CTACE

Ideally, the injected chemotherapeutic should be retained in the tumor and be gradually released to avoid systemic toxicity. However, even if suspended in lipiodol as in the case of cTACE, its selective injection is associated to significant passage into the systemic circulation. Other important limitation of conventional TACE has been the lack of standardization of the technique. In fact, the emulsification of the drug and lipiodol is prepared extemporaneously and hence is operator-dependent (not standardized) and is unstable. Therefore, to overcome the major drawbacks of cTACE, non-resorbable embolic microspheres loaded with cytotoxic drugs (DEBs) have been developed. In fact, DEBs are able to slowly release the drug upon injection and increase the intensity and duration of ischemia while enhancing the drug delivery to the tumor[4].

The first report on the efficacy of DEB-TACE was the phase Ⅱ study by Varela *et al*[34]. In this pivotal paper, 27 CP A HCC patients received two DEB-TACE (500-700 μm particles) sessions at 2-mo intervals: objective response rate was 66.6% (whereof 26% were complete responses). Serial blood samples were obtained in 13 patients to determine doxorubicin maximal concentration and area under the curve, which resulted significantly lower in DEB-TACE patients as compared to an historical cohort of cTACE patients (*P* = 0.00002 and *P* = 0.001, respectively). Furthermore, DEB-TACE was well tolerated with only two cases of severe adverse events (namely, liver abscesses)[34]. These results were confirmed by Poon *et al*[35], who used the highest dose possible of doxorubicin (150 mg). In both studies, none of treated patients presented doxorubicin-related systemic toxicity (alopecia, bone marrow toxicity, dyspnea or pulmonary embolism)[34,35].

In light of successive clinical and in-animal studies[36,37], use of 100-300 μm beads is actually recommended, based on the demonstration that such small particles are delivered inside the tumor or in close proximity to the tumor margins and thus are ideal for drug delivery or precise embolization[4].

Despite the promising results of these preliminary studies and the aforementioned theoretical advantages of DEB-TACE, a clear superiority of one technique over the other is still lacking.

The comparison between cTACE and DEBs has been object of 12 studies (whereof 4 RCTs)[38-49] and 3 recent meta-analyses[50-52] (Table 3). In the most recent meta-analysis, a significantly better objective tumor response rate was found for DEB-TACE than for conventional TACE [odds ratio (OR) = 1.84, 95%CI: 1.02-3.33; *P* = 0.04], but Mantel-Haenzel OR for 3-year survival (reported in 4 studies) was non significant (0.77, CI: 0.55-1.06, *P* = 0.11)[50]. With regard to toxicity, either overall and severe adverse events were similar in both groups, with post-embolization syndrome occurring most commonly[50,51].

Although a clear superiority of DEB-TACE is still lacking, new micro-particles have been recently introduced in the clinical practice. As previously mentioned, small diameter beads have been shown to inflict pan-necrosis of the target lesion since smaller bead diameters achieve a more distal embolization, thus also obstructing collateral channels[35-37]. Therefore, smaller particles have been recently tested with promising results[53-55], but broader cohort studies and RCTs are warranted to validate such findings.

Table 3 Studies comparing conventional and drug-eluting beads transarterial chemoembolization in hepatocellular carcinoma patients

Ref.	Arm	Drug	Sample size	Study design	Region
[1]Nicolini *et al*[38]	DEB-TACE	Doxorubicin	22	R	Italy
	cTACE	Epirubicin	16		
[1]Frenette *et al*[39]	DEB-TACE	Doxorubicin	35	R	United States
	cTACE	Doxorubicin	76		
Song *et al*[40]	DEB-TACE	Doxorubicin	60	R	South Korea
	cTACE	Doxorubicin or Epirubicin/Cisplatin	69		
Sacco *et al*[41]	DEB-TACE	Doxorubicin	33	RCT	Italy
	cTACE	Doxorubicin	34		
van Malenstein *et al*[42]	DEB-TACE	Doxorubicin	16	RCT	Belgium
	cTACE	Doxorubicin	14		
Lammer *et al*[43]	DEB-TACE	Doxorubicin	93	RCT	Europe
	cTACE	Doxorubicin	108		
Golfieri *et al*[44]	DEB-TACE	Doxorubicin	89	RCT	Italy
	cTACE	Epirubicin	88		
Ferrer Puchol *et al*[45]	DEB-TACE	Doxorubicin	47	P	Spain
	cTACE	Doxorubicin	25		
Dhanasekaran *et al*[46]	DEB-TACE	Doxorubicin	45	R	United States
	cTACE	Doxorubicin/Cisplatin/Mytomicin-C	26		
Wiggermann *et al*[47]	DEB-TACE	Epirubicin	22	R	Germany
	cTACE	Cisplatin	22		
Recchia *et al*[48]	DEB-TACE	Doxorubicin	35	P	Italy
	cTACE	Doxorubicin	70		
Megìas Vericat *et al*[49]	DEB-TACE	Doxorubicin	30	R	Spain
	cTACE	DOxorubicin	30		

[1]Study conducted on transplanted patients. DEB-TACE: Drug-eluting beads transarterial chemoembolization; cTACE: Conventional transarterial chemoembolization; R: Retrospective; RCT: Randomizes controlled trial; P: Prospective.

APPLICATIONS OF TACE IN HEPATO-ONCOLOGY

Intermediate stage

The recommendation for TACE as the standard-of-care for intermediate-stage HCC is based on the demonstration of improved survival compared with best supportive care or suboptimal therapies in a meta-analysis of six RCTs[56]. However, there was considerable heterogeneity between the individual study designs (including patient populations and TACE technique) as well as the study results, with only two[30,57] of the six individual studies that reported 2-year survival rates showing a statistically significant improvement compared with conservative management (relative risk of death after 2 years: 0.53, $P = 0.017$). Results from other two meta-analyses confirmed that TACE improved survival outcomes compared with conservative management, however, both meta-analyses also concluded that there were other treatment options (such as TAE or ethanol injection) as effective as, if not superior to, TACE for the treatment of unresectable HCC[58,59]. Furthermore, intermediate-stage HCC includes a heterogeneous population of patients varying widely in terms of tumour burden, liver function and disease etiology[11]. In fact, it should be noted that the previously mentioned studies included patients with HCC described as "unresectable" rather than those with HCC classified as intermediate according to the BCLC schema.

Overall, the expected survival for untreated intermediate HCC is 16 mo, whereas after TACE increased up to 20 in the first studies[56]. However, these studies compared TACE to BSC and not to other treatment modalities such as surgery. Several reports on expanding criteria for resection in HCC have been published in the last years. In fact, two retrospective studies[60,61] and, above all, a RCT[62] explored the comparative effectiveness of surgery (partial hepatectomy) with respect to cTACE for intermediate patients. In the Chinese RCT, median survival was 41 mo (range 1-50 mo) after surgery *vs* only 14 mo (range 5-47 mo) after TACE ($P < 0.001$). However, it should be noticed that in both study groups, median tumor size was beyond 7 cm, a value representing a suboptimal indication to TACE[62]. This may explain the relatively poor outcomes observed in TACE patients, that resulted very far from the most recent studies in the field[6,63].

On the other hand, besides the attempt to expand criteria for radical treatments, also the recently developed new loco-regional techniques have challenged the assumption of TACE as standard of care for BCLC B patients. Transarterial radioembolization (TARE) with yttrium 90 has gained increasing attention for intermediate and advanced patients in the last years[64-66]. Salem *et al*[67] retrospectively compared data from 245 patients (122 who received chemoembolization and 123 who received radioembolization) and reported longer TTP following radioembolization than chemoembolization (13.3 mo *vs* 9.4 mo, $P = 0.047$) but similar median OS (17.5 mo *vs* 17.2 mo, $P = 0.42$) in BCLC B patients. Therefore, in this landmark paper by the Chicago group, TARE resulted in longer time-to-progression and less

toxicity than chemoembolization[67]. Post-hoc analyses of sample size indicated that a randomized study with > 1000 patients would be required to establish equivalence of survival times between patients given the different therapies, a cohort not easy to collect in the clinical practice[67,68]. Other retrospective reports and a small RCTs confirmed the non significant superiority of one technique over the other[69-71].

In conclusion, in absence of further solid data provided by large RCTs, TACE remains the standard of care for intermediate HCC patients, with surgery and TARE as competitive options in case of compensated cirrhosis (CP A) or more advanced tumor burden, respectively.

Early stage
The EASL and AASLD guidelines recommend that the first option for HCC patients within Milan criteria should be hepatic resection or LT[1,2]. Nevertheless, some patients may be poor surgical candidates and the alternative is a variety of loco-regional ablation techniques. Of these, RFA is considered the treatment of choice for these patients, recently reported to be as effective for small HCCs (BCLC 0) as surgical resection[72-74]. However, some tumors with a subcapsular or dome location and tumors adjacent to intestinal loops or the main bile duct may be unsuitable for RFA and in such cases TACE can be used as therapy. Recently, Hsu *et al*[75] investigated the clinical outcomes of Milan-in HCC patients undergoing RFA (n = 315) or cTACE (n = 215). In the univariate survival analysis, the RFA group had a significantly better long-term survival than the TACE group (the 1-, 3-, and 5-year survival rates were 93%, 89%, and 72% for RFA, and 63%, 55%, and 43 % for TACE, P = 0.048), but after propensity-score matching (selecting 101 patients from each treatment arm) such a difference was lost (1-, 3-, and 5-year survival rates were 85%, 60%, and 41% for RFA, and 86%, 55%, and 36% for TACE; P = 0.476)[75]. However, patients undergoing TACE had a significantly higher cumulative recurrence rate than patients undergoing RFA (P = 0.023), hence, this study indicates that TACE and RFA lead to comparable long-term survival but differ in recurrence rate for HCC patients within the Milan criteria[75]. In subgroup analysis, patients with a smaller total tumor volume (< 11 cm^3, equivalent to a single nodule 2.8 cm in diameter) were found likely to benefit more from RFA with respect to TACE[75]. A probable reason for these results is that RFA has a less satisfactory effect on medium tumors (3.1-5 cm in diameter) and multiple tumors[76-78].

Following the conclusions of this paper, Kim *et al*[79] have recently compared the two treatments in 287 very early (BCLC 0) HCC patients (122 and 165 patients treated with cTACE and RFA, respectively). In this study, RFA and TACE did not differ significantly in terms of mean survival (80.0 ± 2.3 mo and 72.1 ± 3.2 mo, respectively; P = 0.079), but objective response rate (100% and 95.9% in the RFA and TACE group, respectively; P = 0.013) and median TTP were

significantly in favor of RFA (27.0 ± 3.8 mo after RFA and 18.0 ± 2.9 mo after TACE; P = 0.034)[79]. Therefore, although the study by Kim *et al*[79] does not strongly support the superiority of RFA over TACE as no statistically significant difference was noted in terms of OS, however, RFA led to better tumor responses and was associated with delayed tumor progression compared with TACE.

The aforementioned study suggests RFA as first-line treatment for unresectable early/very early HCC patients, whereas TACE may be considered a viable alternative when RFA is not feasible.

Downstaging/bridging
TACE is the most used treatment for patients in waiting list for LT[80].

The aims of bridging treatments include decreasing the waiting list dropout rate before transplantation, reducing HCC recurrence after LT and improving post-transplant overall survival.

TACE has been extensively used in the past as a bridging treatment to LT and a number of studies have shown that it is an effective therapy in terms of adequate tumor necrosis achievement at explant analysis with complete tumor necrosis rates ranging between 27% and 57% in patients within Milan criteria[81,82].

These results are certainly of interest, considering that RFA leads to superior complete necrosis rates (between 50% and 78%) in single HCCs up to 3 cm, but significantly poorer outcomes in larger or multiple neoplasms (necrosis rate between 13% and 43%)[83-85].

The effectiveness of TARE has recently been evaluated by Riaz *et al*[86], who studied 38 nodules in 35 patients treated with radioembolization before LT. In this study, at explant analysis, 23 of the 38 target lesions (61%) showed complete tumor necrosis; in particular, complete tumor ablation was detected in 89%, 65%, and 33% of lesions smaller than 3 cm, between 3 and 5 cm, and larger than 5 cm, respectively[86]. The same Group retrospectively compared effectiveness of TACE and TARE in T3 HCC patients (*i.e.*, beyond conventional criteria): down-staging rate was 58% after TARE *vs* 31% after TACE (P < 0.05)[87].

In conclusion, no definitive recommendation can be made for one type of loco-regional therapy over others in the pre-transplant setting. However, on the basis of the aforementioned studies, RFA could be considered as the first-line treatment for single lesions up to 3 cm, in which complete tumor necrosis has been shown in more than 50% of cases at explant analysis[83-85]. TACE should be preferred for treating lesions > 3 cm because its effectiveness appears to be better in well-vascularized tumors with large feeding arteries.

Advanced stage
Advanced HCC (*i.e.*, BCLC stage C) is characterized by an Eastern Cooperative Oncology Group performance status of 1-2 and/or the presence of portal vein thrombosis (PVT) or extrahepatic metastases. According

to current guidelines, advanced HCC patients can only receive sorafenib while it is generally accepted that TACE is not recommended in cases of macroscopic portal vein invasion because of the potentially increased risk of liver failure[1,2]. Recently, however, some prospective controlled trials have shown the survival benefit of TACE over BSC in advanced HCC patients with PVT[88,89]. Therefore, the clear effects and safety of TACE in these patients remain controversial. A recent meta-analysis of 8 studies (whereof 3 prospective) has summarized the published results on this regard: TACE resulted potentially suitable and safe for advanced HCC patients with PVT with a low rate of fatal complications[90]. Furthermore, for selected patients (those with established collateral circulation and good liver function), TACE treatment prolonged survival[90]. However, the results of this meta-analysis should be interpreted with caution because all the included studies were conducted in Asia (hence, it is uncertain the applicability of these findings to Western settings) and patients with better liver function tended to be selected into the TACE group, whereas those decompensated tended to be treated with BSC. Moreover, sorafenib, and not BSC, is the reference standard treatment for advanced-stage HCC, hence, direct comparisons between the two therapies are needed.

The only head-to-head comparison between the two treatments published so far, is a retrospective European study delivered by the Vienna group[91]. By the way, even in this well written paper, an underlying selection bias can be detected, as thrombosis of the main trunk of portal vein (well-known as at poorer prognosis) was more frequently present in the sorafenib group than in the TACE group (25% *vs* 3%). Median TTP was similar between the two treatment groups ($P = 0.737$) as well as median OS (9.2 mo, 95%CI: 6.1-12.3 mo after TACE *vs* 7.4 mo, 95%CI: 5.6-9.2 mo in patients treated with sorafenib, $P = 0.377$)[91]. Interestingly, in the Austrian study, TACE achieved promising outcomes (median OS of 14 mo) in selected advanced patients (CP A and segmental PVT), a result confirmed in other retrospective reports[92]. However, in the TACE group, 13 patients experienced severe adverse events and 4 treatment-related deaths, thus pointing out serious concerns on the safety of TACE in this setting[91].

Therefore, TACE might be a reasonable alternative for selected advanced patients (segmental PVT and CP A) who do not have access or are intolerant/unsuitable to sorafenib or TARE, but the particular attention to be paid to the safety profile restricts this therapeutic opportunity to highly-experienced centers.

Combined regimens

A meta-analysis of 10 randomized trials and 18 observational studies including 2497 patients showed that the combination of TACE with other treatments, such as ethanol injection, external radiotherapy and high-intensity focused ultrasound, result in better survival outcomes and similar side effects than TACE

alone[93]. However, for each combination, the number of studies were mostly inadequate to provide a definitive recommendation, thus further well-organized randomized trials are needed to confirm these findings.

TACE is associated with local and systemic increase in vascular endothelial growth factor, since embolization interrupts blood supply to the tumor, inducing hypoxia and necrosis[94]. These observations suggest that an antiangiogenetic agent (namely, sorafenib) may counteract TACE-induced angiogenesis, thus improving the post-procedural outcomes[95,96]. Two important RCTs have explored the feasibility and the efficacy of the combined regimen, without finding any definitive evidence in favor of the association of sorafenib with TACE[97,98]. However, since other smaller RCTs and retrospective studies provided discordant results, combined regimens between antiangiogenetic agents and TACE remain an interesting field of research in hepato-oncology[99-102].

CONCLUSION

TACE covers a broad spectrum of therapeutic indications in hepato-oncology and, if the proper selection of candidates is followed, represents a safe and effective treatment. Further studies are needed to correctly expand treatment indications and define the more appropriate combined regimens with other loco-regional therapies or systemic drugs.

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