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TOPIC HIGHLIGHT

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Transarterial chemoembolization and bland embolization for hepatocellular carcinoma

Emmanuel A Tsochatzis, Evangelia Fatourou, James O'Beirne, Tim Meyer, Andrew K Burroughs

Emmanuel A Tsochatzis, Evangelia Fatourou, James O' Beirne, Andrew K Burroughs, Sheila Sherlock Liver Centre, Royal Free Hospital and UCL Institute of Liver and Digestive Health, London NW3 2QG, United Kingdom
Tim Meyer, Department of Oncology, Royal Free Hospital and UCL, London NW3 2QG, United Kingdom
Author contributions: Tsochatzis EA prepared the first draft of this manuscript; all authors reviewed the manuscript for important intellectual content and approved the final version.
Correspondence to: Emmanuel A Tsochatzis, MD, MSc, FEBTM, PhD, Sheila Sherlock Liver Centre, Royal Free Hospital and UCL Institute of Liver and Digestive Health, Pond Street, London NW3 2QG,
United Kingdom. e.tsochatzis@ucl.ac.uk
Telephone: +44-20-7794500 Fax +44-20-74726226
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Abstract

Transarterial chemoembolization (TACE) is the first line treatment for patients with intermediate stage hepatocellular carcinoma but is also increasingly being used for patients on the transplant waiting list to prevent further tumor growth. Despite its widespread use, TACE remains an unstandardized procedure, with variation in type and size of embolizing particles, type and dose of chemotherapy and interval between therapies. Existing evidence from randomized controlled trials suggest that bland transarterial embolization (TAE) has the same efficacy with TACE. In the current article, we review the use of TACE and TAE for hepatocellular carcinoma and we focus on the evidence for their use.

Key words: Cirrhosis; Hepatocellular carcinoma; Mortality; Embolization; Transarterial chemoembolization; Transarterial embolization; Prognosis

Core tip: In the current article, we review the use of transarterial chemoembolization (TACE) and transarterial embolization (TAE) for hepatocellular carcinoma and we focus on the evidence for their use. Apart from their use in intermediate stage hepatocellular carcinoma, we also review the evidence for their use as neo-adjuvant treatment in the pre-transplant setting. We also highlight the fact that there is no conclusive evidence for superiority of TACE over TAE.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the 6th most common cancer worldwide with over 500000 new cases diagnosed each year and the third most common cause of cancer-related death[1]. Its incidence in Europe is 3.6/100000-10.6/100000 persons[2] and rises to 16/100000 persons worldwide[3].

Mortality rates remain high and only 5% of patients survive at 5 years after diagnosis; this is largely due to the fact that diagnosis is most often delayed, with only 15% of patients eligible for surgical procedures such as resection and liver transplantation, 50% for non-surgical therapies and 35% or more for best supportive care at diagnosis[3]. Both the American (AASLD)[4] and European (EASL) Associations for the Study of the Liver[5] have recently published updated guidelines for the management of HCC. These are based on a stratification of patients according to the Barcelona Clinic Live Cancer (BCLC)

classification, which classifies patients according to tumor burden, liver function as assessed by Child-Pugh score, and performance status, into five distinct prognostic categories with different first line treatment recommendations[6].

Intermediate stage HCC or stage B according to BCLC, consists of multi-nodular tumors in patients with Child-Pugh A or B cirrhosis and good performance status[7]. The recommended first line treatment for these patients is transarterial chemoembolization (TACE)[8]. It should be noted that patients with intermediate stage HCC are considered a heterogeneous group with different prognoses and responses to treatment leading to both European and Asian experts identifying the need for further sub-classification[9,10]. This could be based on tumor size and Child-Pugh score[10]. Indeed, in carefully selected patients with preserved liver function intermediate HCCs, hepatic resection could be a more effective therapeutic option than TACE[11]. The future use of molecular signatures and markers might further enhance the classification and prognosis[12].

In the current article, we review the use of transarterial embolization (TAE) with (TACE) or without (TAE) the use of chemotherapeutic agents for HCC focusing on the evidence for their use.

TACE AND TAE

The normal liver receives a dual blood supply from the hepatic artery (25%) and the portal vein (75%). As HCC grows, it increasingly depends on the hepatic artery for blood supply and once a tumor nodule reaches a diameter of 2 cm or more, most of the blood supply derives from the hepatic artery. This unique property of HCC provides the rationale for the use of transarterial therapies. TACE and TAE consist of the selective angiographic occlusion of the tumor arterial blood supply with a variety of embolizing agents, with or without the precedence of local chemotherapy infusion. The occlusion by embolic particles results in tumour hypoxia and necrosis, while the addition of local chemotherapy could have an additive antitumour effect. The efficacy of TA(C)E was established by a meta-analysis published a decade ago that included 6 randomized controlled trials (RCTs), of which only two were positive, and showed improved two-year survival (HR = 0.53; 95%CI: 0.32-0.89: $P = 0.017$)[13]. Patients included in those trials were not staged according to BCLC, as this was not available at that time, and selection criteria differed from current recommendations. More recently our updated meta-analysis, which included nine RCTs also demonstrated a survival benefit of TA(C)E compared to best supportive treatment (HR = 0.705; 95%CI: 0.5-0.99)[14]. A recent Cochrane meta-analysis, including nine RCTs with 645 participants, failed to demonstrate a survival benefit with TA(C)E *vs* best supportive care (HR = 0.88; 95%CI: 0.71-1.10) and concluded that an additional 383 participants would need randomization for a potential benefit to be demonstrated[15]. This meta-analysis was heavily criticized for the exclusion of positive RCTs due to risk of bias and inappropriate inclusion of trials using gelfoam with short follow-up or enrolling patients with early stage HCC[16]. The inconsistency in the results of randomized trials reflects the fact the TA(C)E is not a standardized procedure both in terms of patient selection and the procedure itself.

PATIENT SELECTION AND SURVIVAL

According to current treatment guidelines, TA(C)E is not a curative treatment and should be considered as first line treatment in patients with intermediate HCC. In clinical practice however TACE is frequently used outside these recommendations in a wide range of patients ranging from early HCC to advanced liver disease with ascites. Therefore, the variation in reported survival is likely to be dependent on patient selection as well as TA(C)E schedule and techniques.

A retrospective Italian study compared the results of TACE before and after the implementation of BCLC criteria in 2002; In the 1999-2002 period, there was no significant difference in survival between TACE-treated and untreated patients, while in the 2003-2006 period, TACE-treated patients survived longer ($P < 0.0001$) following the significant increase in Child Pugh class A patients and advanced HCC[17]. Another retrospective Italian study, including 614 elderly and 1104 younger patients with HCC, showed that overall applicability of HCC treatments was unaffected by older age although treatment distribution differed, with elderly individuals being more frequently treated with percutaneous procedures and less frequently with resection or TACE[18]. A retrospective Chinese study that included 1516 patients with HBV-related cirrhosis and BCLC stage B HCC, all of who received TACE as first line treatment, reported 1-, 3- and 5-year overall survival rates of 84%, 29% and 19% respectively[19]. Child-Pugh A liver function and smaller tumor were associated with treatment response. Tumor response after initial TACE, an independent prognostic factor of overall survival, was associated with tumor extent and influenced subsequent treatment[19].

A Spanish cohort study of a highly selected patients, 40% of whom were staged as BCLC-A, reported a median survival of 48.6 mo following TACE with preloaded drug eluting beads (DEB-TACE) after a median follow up of 24.5 mo[20]. Unfortunately, this conclusion was based on projected and not actual data, as at the time point of median survival, less than 15 patients were still at risk of death according to the Kaplan-Meier curve and 35 had died, *i.e.*, there was no adequate follow up for at least 50% of the cohort[21]. A Japanese retrospective study reported the outcomes of TACE in 4966 patients diagnosed between 2000 and 2005 across all spectrums of Child Pugh classes and tumor size; overall median and 5-year survivals were 3.3 years and 34%, respectively[22]. Not surprisingly, the study showed that the survival rate decreased as the tumor number and size increased in all

but one subgroup in both Child-Pugh-A and -B[22].

TA(C)E TECHNIQUES

A systematic review of 175 cohort and randomized trials of transarterial therapies for HCC exposed the huge heterogeneity in the protocols used, with variable use of embolic and chemotherapeutic agents, variable embolization particle sizes, different schedules and indications for repeat sessions and different arterial selectivity for embolization[23].

EMBOLIZING AGENTS

Over the years, a variety of embolizing agents have been used, from gelfoam to polyvinyl alcohol (PVA) particles and more recently drug eluting beads.

Gelfoam, which consists of gelatin sponge particles, was used in the first trials of TACE and is a suboptimal embolizing agent, due to the large size of the particles (1 mm) and the temporary occlusion of the tumor feeding arteries that only lasts for 2 wk[24,25].

PVA particles provide more permanent arterial occlusion and can potentially provide more distal arterial obstruction as their size can be as small as 45-150 microns[25]. A recent study with histopathological analysis of embolized tumors confirmed that smaller PVA particles can reach and occlude more distal arteriolar capillaries and result in slightly better tumor necrosis rate after TACE[26]. Moreover, a non-randomized trial comparing different embolizing agents, demonstrated that the number of TACE sessions was significantly greater for the gelfoam powder group (mean, 2.2) *vs* the PVA group (mean, 1.6; $P = 0.01$), although survival did not significantly differ[27].

Drug-eluting beads (DEBs; Biocompatibles, Surrey, United Kingdom) is a novel system consisting of embolic microspheres preloaded with doxorubicin, that ensure the controlled release of chemotherapy and thus provide a combined local ischaemic and cytotoxic effect[28]. This results in lower systemic doxorubicin concentrations than conventional TACE and higher intra-tumor retention[28]. However, a phase Ⅱ RCT comparing DEB-TACE with conventional TACE failed to demonstrate a superiority of DEB-TACE in tumor response[29]. Drug related adverse events and liver toxicity were lower in the subgroup of patients with Child Pugh class B and bi-lobar tumors, allowing better adherence to treatment protocol and higher objective response rates in this particular subgroup[29]. It should be noted that conventional TACE was not standardized and a variety of embolizing particles and treatment schedules were used, according to the preferences of the treating physician. A RCT comparing TACE with DEBs and TAE with the same particles but without chemotherapy, failed to demonstrate any significant differences in survival or tumor response, further questioning the efficacy of the preloaded chemotherapy[30]. DEBs are more expensive than conventional TA(C)E with as yet unproven superiority. However they do represent an important step towards the standardization of the technique and might increase tolerability in sicker patients[7].

CHEMOTHERAPEUTIC AGENTS

Doxorubicin and cisplatin, followed by epirubicin, are the most commonly used chemotherapeutic agents but none has proven superior to date[23] and the choice usually relies on local protocols and physicians preferences. The dosing of chemotherapeutic agent also varies among centres. The median dose in published trials per session of doxorubicin, cisplatin and epirubicin was 50 mg, 92 mg and 50 mg respectively[23]. There is no consensus if a standard dose for all patients should be used or a dose adjusted to the body surface area or whether the bilirubin level or other measure of liver function is preferable. As already mentioned, patients with more advanced liver disease might benefit from DEB-TACE due to lower systemic chemotherapy concentrations. Higher chemotherapeutic doses did not significantly enhance the anticancer effects and survival compared that with lower doses in a study published a decade ago[31].

FREQUENCY OF TA(C)E SESSIONS

The frequency of TA(C)E has not been adequately addressed to date. From an oncological point of view, chemotherapy should be administered at 3-week intervals in order to fit to the cell cycle[8]. However, such a strategy would carry the risk of increased side effects and indeed patients with an initial good response would not necessarily benefit. A repeat "on demand" strategy of conventional TACE was recently retrospectively evaluated in 151 consecutive patients. Complete response and recurrence rates after first and second TACE were similar, with 64% of patients being submitted to second TACE and 26% to third TACE using an "on demand" policy[32] based on tumor response. We have reported the case of a patient with 10 "on demand" TAE over a 5-year period with repeated radiological response[33].

ADVERSE EFFECTS

The most common adverse effect of TA(C)E is the post-embolization syndrome, which is manifested by abdominal pain, fever and elevated liver function tests in the first 24-48 h post-treatment and only requires supportive measures[34]. Deterioration of liver function with development of ascites and even liver failure occurs in a minority of patients and depends on liver reserve pre-TACE and selectivity of embolisation. Our systematic review reported a median treatment related mortality of 2.4% in 37 trials including 2878 patients[23], however this is influenced by patient selection. A recent Japanese cohort study reported treatment related mortality of 0.38% (19/4966 patients)[22]. However, in the presence of ascites, 17% of patients with develop liver failure post-TACE and tha vast majority of them will die within a year[35]. Other TACE-induced adverse events include the formation of

Table 1 Randomized controlled trials comparing transarterial embolization with transarterial chemoembolization in patients with hepatocellular carcinoma

Ref.	Patients, *n*	Chemotherapy in TACE arm	Embolizing agent	Outcome in survival
Kawai *et al*[41], 1992	289	Doxorubicin	Lipiodol + gerlfoam	NS
Chang *et al*[42], 1994	46	Cisplatin	Lipiodol + gerlfoam	NS
Llovet *et al*[43], 2002	77	Doxorubicin	Lipiodol	NS
Malagari *et al*[30], 2010	84	Doxorubicin-loaded LC beads	BeadBlocks	NS
Meyer *et al*[39], 2013	86	Cisplatin	PVA particles	NS
Brown *et al*[40], 2012	101	Doxorubicin-loaded LC beads	BeadBlocks	NS

TACE: Transarterial chemoembolization; NS: Non-significant; PVA: Polyvinyl alcohol.

liver abscess in the necrotic tumor, bile duct injury and ischaemic cholecystitis[7].

TAE OR TACE

TACE is reported as the preferred transarterial therapy of choice in the literature[1,3] and EASL guidelines[5], despite the fact that this claim is not supported by existing evidence[36,37]. From a pathophysiological point of view, TACE in most centres consists of the chemotherapy and embolization administered at the same time. As hypoxia is a known cause of chemo-resistance, the rational for administering chemotherapy while rendering the tumour hypoxic is questionable[38].

We recently published an updated meta-analysis of five RCTs comparing TACE with TAE, where we found no difference in survival[39]. Since then, a sixth RCT was published in abstract form, also with unequivocal results[40]. All these published RCTs are summarized in Table 1[30,39-43]. The last three RCTs used permanent occluding embolizing particles[30,39,40], as opposed to gelfoam used in the rest[41-43].

In the study by Malagari *et al*[30], 84 patients were randomized to either DEB-TACE or embolization alone using BeadBlocks (100-300 or 300-500 microns diameter). There was no difference in 1-year survival, (86% *vs* 85.3% in DEB-TACE and TAE respectively) despite the fact that the DEB-TACE group had a statistically significant longer time to tumour progression. The RCT performed by our group was a phase Ⅱ/Ⅲ trial of three weekly cisplatin based TACE *vs* TAE with PVA particles (diameter 40-150 microns) as the embolizing agent[39]. The median overall survival and progression-free survival was 17.3 *vs* 16.3 ($P = 0.74$) mo and 7.2 *vs* 7.5 ($P = 0.59$), in the TAE and TACE groups respectively[39]. Finally, the RCT by Brown published in abstract form, compared DEB-TACE with TAE with BeadBlocks and reported no significant differences in progression-free survival (7 mo *vs* 9 mo) and overall survival (16 mo *vs* 14 mo)[40].

These data clearly demonstrate that TAE is equally effective as TACE at a lower cost and with potentially fewer side effects due to the lack of chemotherapy[7]. This lack of additional effect of chemotherapy could be due to the infrequent intervals of TACE of several mo that do not follow the usual oncological chemotherapy principles that target certain cell cycle phases[44]. They could also be attributed to the chemoresistance that results from tumour hypoxia induced by embolization[38]. We therefore advocate that the use of permanently occluding embolizing agent is more important than the use of chemotherapy.

ASSESSMENT OF TREATMENT RESPONSE

Traditionally, tumor response was assessed with the RECIST criteria, which are based on the sum of unidimensional measurements of tumor lesions and therefore require tumor shrinkage in order to document response. Transarterial therapies for HCC exert their therapeutic effect by tumor devascularization and necrosis, which is not always accompanied with reduction in size. In order to address this, EASL advocated the measurement of change in tumor enhancement on contrast enhanced imaging (EASL criteria), while AASLD proposed the modified RECIST criteria (mRECIST), that also assess changes in tumor arterial enhancement.

It was recently shown in a cohort of 160 consecutive patients with HCC that evaluating the largest two lesions is generally the most useful procedure for measuring TACE responses under both EASL and mRECIST[45].

The prognostic implication of treatments response accordnig to mRECIST and EASL compared to RECIST has been assessed in cohort studies. In a cohort of 83 consecutive patients with HCC, we showed that when measured at a single time point after the first transarterial therapy, EASL and mRECIST overall response rates were significantly associated with survival, in contrast with RECIST repsonse rates[46]; EASL response was associated with a 44% risk reduction and mRECIST with a 42% reduction. These findings were confirmed in a cohort of 114 Korean patients with HCC, where both EASL response (HR = 0.21, 95%CI: 0.11-0.40, $P < 0.001$) and mRECIST response (HR = 0.31, 95%CI: 0.17-0.59, $P < 0.001$) after 1-2 TACE sessions were independently associated with survival. Similarly, the use of mRECIST and EASL response criteria 1 mo after initial TACE, better predicted the differences in overall survival between responders and non-responders than conventional RECIST criteria[47].

TA(C)E IN PATIENTS WITH PORTAL VEIN THROMBOSIS

PVT is common in patients with cirrhosis and becomes more prevalent as liver function deteriorates[48]. TACE is generally contra-indicated in patients with PVT, due to concerns that a further decrease to the blood supply of

Table 2 Prognostic scores of survival after transarterial chemoembolization and transarterial embolization

Ref.	Parameters	Cut-off	Comments
Llado *et al*[57]	AFP > 400 ng/mL Tumor volume > 50% Child-Pugh score	Based on regression coefficients	Patients classified in 3 categories
Pinato *et al*[58]	Neutrophil-to-lymphocyte ratio	Significant improvement in survival if NLR stable or normalized post TACE	Radiological response after TACE also associated with survival
Kadalayil *et al*[59]	Albumin < 36 g/dL bilirubin > 17 μmol/L AFP > 400 ng/mL Dominant tumor > 7 cm	4 groups based on HAP scores of 0, 1, 2 and > 2	Validated in an independent dataset
Sieghart *et al*[60]	Increase of AST > 25% Increase of Child-Pugh > 1 Absence of radiologic tumor response	0-1.5 points; ⩾ 2.5 points	Determines prognosis prior to 2nd TACE; validated in independent cohort

TACE: Transarterial chemoembolization; HAP: Hepatoma arterial-embolisation prognostic; NLR: Neutrophil to lymphocyte ratio.

the liver can prove deleterious. Nevertheless, this dogma has been challenged and there are uncontrolled trials and cohort studes that suggest a treatment benefit in selected patients wirth preserved liver function[49,50]. A recent meta-analysis including 8 studies with 1601 patients, concluded that TACE in patients with portal vein thrombosis (PVT) improved the 6-mo (HR = 0.41; 95%CI: 0.32-0.53) and 1-year (HR = 0.44; 95%CI: 0.34-0.57) survival compared with conservative treatment[51]. Nevertheless, studies included in the meta-analysis exhibited significant differences among patient characteristics between the treatment groups, and were ill defined in terms of treatment allocation[51]. Until these results are confirmed in RCTs, they need to be interpreted with extreme caution and decisions should be made on an individual patient basis taking into account the radiological expertise of the treating centers. We would only consider TA(C)E in patients with Child A cirrhosis and segmental PVT.

COMBINATION OF TA(C)E AND PERCUTANEOUS TECHNIQUES

The effectiveness of percutaneous techniques, mainly represented by radiofrequency ablation (RFA), is reduced as tumour size increases. This is partly due ro the increased blood flow in larger lesions resulting in heat loss and thus less effective ablation[7]. Therefore, it seems reasonable to perform RFA after occluding the hepatic arterial flow supplying the tumour with TA(C)E. This would theoretically increase the ablation size of thermal injury as blood flow to and within the tumour is reduced. To date, there have been no large and conclusive RCT assessing dual sequential therapy. In a RCT including 93 patients with tumours less than 3 cm, combination treatment with TACE and RFA did not result in improved survival compared to RFA alone[52], which was a predictable result given the small size of tumours. In another RCT that included 189 patients with tumours < 7 cm, combined RFA and TACE resulted in better overall and tumour free survival than RFA alone[53]. There are only cohort studies that compare TACE and RFA *vs* TACE alone and these have shown promising results that warrant adequately powered RCTs[54,55].

PREDICTION OF TREATMENT RESPONSE AND POST-TREATMENT SURVIVAL

Survival in patients with HCC depends on both the succesful treatment of the tumor but also on the underlying liver function and reserve[56]. Therefore, not surprisingly, survival post transarterial therapies is independently influenced by a combination of tumor and liver function parameters (Table 2).

A simple prognostic score consisting of alpha-fetoprotein (> 400 U/L), tumor size (> 50%) and Child-Pugh score was found to predict the survival of patients treated with TACE and could therefore be used to decide which patients with unresectable HCC should receive this therapy; the authors concluded that TACE should not be administered to patients with one or more positive prognostic factors[57]. Similarly, it was shown that patients with a persistently increased neutrophil-to-lymphocyte ratio post-TACE have a worse outcome[58]. We recently developed and validated a simple prognostic score for post TA(C)E survival, namely Hepatoma arterial-embolisation prognostic (HAP) score, where one point is assigned for each of albumin < 36 g/dL, bilirubin > 17 μmol/L, AFP > 400 ng/mL or size of dominant tumour > 7 cm[59]. This is simpler than previously described scores[57] and only requires calculation at a single time point rather than serial measurements[58].

Similarly, the Assessment for Retreatment with TACE (ART) score was developed and validated in order to guide the decision for retreatment with TACE[60]. The increase of AST by > 25%, an increase of Child-Pugh score of 1 (or ⩾ 2 points) from baseline, and the absence of radiologic tumor response were used to create the ART score. The ART score differentiated two groups (0-1.5 points; ⩾ 2.5 points) with distinct prognosis and a higher ART score was associated with major adverse events after the second TACE[60]. The same authors demonstrated that the sequential assessment of the ART-score identifies patients with dismal prognosis prior to each TACE session[61].

TA(C)E PRE-TRANSPLANTATION FOR PATIENTS ON THE WAITING LIST

Locoregional therapies are increasingly used for patients

on the transplant waiting list despite the lack of conclusive data, in order to prevent further growth of the tumor and thus ensure that the patient remains eligible for transplantation until an organ becomes available[62]. The recent EASL and European Organization for Research and Treatment of Cancer guidelines for HCC recommend neo-adjuvant treatment pre-transplant if the waiting list time is more than 6 mo to prevent dropouts due to tumour progression[5]. This was partly based on a Markov model analysis that did not evaluate waiting list times of less than six month[63]. Percutaneous techniques, although effective, are not routinely used in the pre-transplant setting in our center because of the small, but not negligible risk, of tumour seeding[64].

We recently published our prospectively collected data of patients with HCC treated with TAE on the liver transplant waiting list and we found that pre-transplant TAE significantly reduced post-transplant HCC recurrence in patients within the Milan criteria[65]. We have further demonstrated that the reduced calcineurin-inhibitor exposure in the first month post-transplant is associated with reduced HCC recurrence[66]. Characteristics of tumor response to TACE on the transplant waiting list add a dynamic assessement of tumor biology and were recently suggested as potentially useful in identifying suitable patients for transplantation based on preliminary data from 136 patients[67]. Nevertheless, conclusive data on the effects of TA(C)E on dropout rates are lacking.

TACE COMBINED WITH ANTI-ANGIOGENIC THERAPY

Sorafenib, a multikinase inhibitor with anti-angiogenic activity, became in 2008 the first systemic therapy that showed a survival benefit in patients with HCC[68]. Theoretically, sorafenib could inhibit the growth factors such as VEGF that are synthesized in the tumor tissue in response to the TACE-induced hypoxia and therefore sorafenib may be beneficial as an adjuvant treatment with TA(C)E[69]. Conclusive data from phase Ⅲ trials to support this hypothesis are currently lacking. In a single arm, phase Ⅱ study, sorafenib was administered 3 d after TACE for a total period of up to 24 wk, and resulted in a 6-mo progression free survival of 52% with an acceptable safety profile[70]. Similarly, an interim analysis of the START trial, which is a phase Ⅱ single arm trial, reported an overall response rate of 52% and no unexpected side-effects[71]. Several trials on combinations of TACE with sorafenib but also other agents such as brivanib, sumatinib and thalidomide are registered and currently recruiting[9,70]; a full listing is beyond the scope of these article. Until the results of such RCTs become available, combinations of TACE with targeted therapies should be performed in the context of clinical trials.

CONCLUSIONS-FUTURE DIRECTIONS

TAE and TACE should be regarded as equally effective in the management of patients with HCC; their main indication is in patients with intermediate HCC. However they are increasingly used for patients on the liver transplant waiting list in order to prevent further tumor progression. The absence of chemotherapy may make TAE better tolerated particularly in patients with borderline liver function. Despite its use for over two decades, TA(C)E remains an unstandardized procedure, with variations in the size and type of embolizing particles, choice and dose of chemotherapeutic agent, and interval between procedures. Smaller embolising particles may result in more selective embolisation with less damage to surrounding non tumorous tissue. DEB-TACE, is not more effective than conventional TACE, but might contribute towards the standardization of the technique. The results of various combination trials of TA(C)E with sorafenib and other targeted therapies are eagerly awaited and might further improve survival in this patient group.

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