CIRSE STANDARDS OF PRACTICE GUIDELINES

Quality-Improvement Guidelines for Hepatic Transarterial Chemoembolization

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Introduction

Transarterial chemoembolization (TACE) was first introduced in 1977 by Dr. Yamada, who exploited hepatocellular carcinoma's (HCC) preferential blood supply from the hepatic artery for the delivery of antitumor therapy. His findings on an initial cohort of 120 patients were published in the English literature in 1983 [1]. Conventional transarterial chemoembolization (c-TACE) involves the selective injection of a chemotherapeutic agent, or a combination of different chemotherapeutic agents emulsified, in a viscous carrier (lipiodol), followed by embolic material, into the feeding arteries of the tumor. The aim is to obtain higher intratumoral drug concentrations compared with intravenous therapy, with tumor infarction and necrosis due to vascular occlusion [2]. Commonly the chemotherapeutic drug is mixed with lipiodol, a contrast medium that contains iodinated poppy-seed oil. Lipiodol is routinely used for arterial embolization and after injection by way of the hepatic artery has the characteristic of persisting in tumor nodules for a few weeks or months due to the high vascularity of tumor tissue and the absence of Kupffer cells. Subsequent embolization of the feeding arteries should decrease arterial inflow, decrease washout of the chemotherapeutic agent, and decrease systemic exposure. However, on the basis of recent scientific evidence [3], lipiodol is not able to slowly release chemotherapeutic agents into neoplastic tissue, and some systemic effects may be related to a high level of drug being rapidly released into the systemic circulation.

Recently, to overcome this weakness in c-TACE, preformed microspheres loaded with chemotherapeutic agents have been used in such procedures [4, 5]. This characteristic of the microspheres allows for the delivery of large amounts of drugs to the tumor for a prolonged period of time, thereby decreasing plasma levels of the chemotherapeutic agent and potentially the related risk of systemic effects (e.g., cardiotoxicity) [4, 5]. The rationale for this new TACE technique, known as drug-eluting beads–transarterial chemoembolization (DEB-TACE), is to prolong the contact time between cancer cells and the chemotherapeutic agents and to avoid damage to the hepatic microcirculation that can result in minor systemic effects. Currently TACE is also used for other nonresectable hepatic metastases, e.g., colorectal carcinoma (CRC), and for other liver primary neoplasms, e.g., cholangiocarcinoma [6].

Definitions

Transarterial embolization: Defined as the blockade of hepatic arterial flow with different embolic materials (e.g., particles and gelfoam).

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Conventional transarterial chemoembolization (c-TACE): Defined as infusion of a mixture of chemotherapeutic agents, with or without ethiodized oil, followed by embolization with permanent (polyvinyl alcohol [PVA] particles or spherical embolic agents) or temporary (gelfoam) materials.

Drug eluting beads–transarterial chemoembolization (DEB-TACE): Defined as injection of DEB loaded with chemotherapeutics into the tumor-feeding artery [4], with or without further embolization, using regular (i.e., unloaded) microspheres.

Pretreatment Imaging

All patients should undergo preprocedural abdominal contrast material–enhanced computed tomography (CT) with triphasic acquisitions or magnetic resonance imaging (MRI) to assess liver involvement (number, size, and location of lesions). For hepatic metastases, total-body imaging is required to assess liver-dominant disease. CT or MRI is also indicated for depicting vascular anatomy to plan vascular treatment (e.g., vascular abnormalities and all tumor feeders) by means of maximum-intensity projection postprocessing analysis. Portal vein (PV) patency or thrombosis are also better defined with CT and MRI than with conventional angiography; furthermore, in the latter case, these cross-sectional examinations are able to define the characteristics of thrombosis (e.g., extension and relationship with tumors).

Indications and Contraindications for Treatment

The Barcelona Clinic Liver Cancer (BCLC) tumor staging classification [7, 8] combines the stage of liver disease, tumor stage, clinical performance, and treatment options for HCC. It is also endorsed by the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease. On the basis of the BCLC algorithm, patients in early-stage disease (BCLC stage A) are suitable for curative therapies, such as resection, liver transplantation, and ablative techniques, i.e., percutaneous ethanol injection and radiofrequency ablation; these are undertaken in approximately 30–40 % of patients with HCC [9, 10].

For unresectable intermediate-stage HCC (BCLC stage B or Child-Pugh class A/B with large or multifocal HCC, no vascular invasion, or extrahepatic spread), the current standard treatment is c-TACE [10]. Regarding vascular invasion, some investigators suggest to not consider portal thrombosis an absolute contraindication to TACE because the related risk of parenchymal infarction depends on several specific characteristics, in particular the extent of thrombosis (e.g., contralateral or ipsilateral to the disease, distal or proximal). Recently it has been reported that TACE using less aggressive embolization can also be performed safely with no increase in morbidity or mortality, even in patients with major PV thrombosis [11]. Recently the use of radioembolization has also been advocated in patients with PV thrombosis [12]. However, a detailed explanation of such procedures is not included in the remit of the present review.

General exclusion criteria for TACE based on laboratory assays have not been definitively established despite the fact that a bilirubin level >2 mg/dL, a lactate dehydrogenase level >425 mg/dL, and an aspartate aminotransferase (AST) level >100 IU/L have been reported to be strongly associated with increased postprocedural mortality [13]. Individual abnormalities in the values of these four parameters have not been shown to predict adverse outcomes of TACE [14]. In general, Child-Pugh class C is considered a contraindication for TACE.

Classical indications for c-TACE are not so different from those for DEB-TACE (Table 1). The list of exclusion criteria is more extensive for DEB-TACE because of the lack of related previously published studies due to its limited use in clinical practice [15]. As recently reported by Liapi et al. [15], inclusion and exclusion criteria may be established on the basis of liver disease, tumor status, and patient performance status, and they are also related to drug characteristics and procedural aspects.

Currently TACE is performed for other indications apart from HCC, such as hepatic metastases (e.g., from CRC) or for other primary neoplasms, such as cholangiocarcinoma; however, due to the lack of published data, this document would have limited application.

Patient Preparation

As with any interventional procedure, patients preparing for hepatic transarterial chemoembolization must observe simple pretreatment instructions. These include the following:

1. No food or drink after midnight the night before the treatment.
2. Patients taking medications should routinely check with their physician.
3. If routine medication is allowed the day of the procedure, it should only be taken with a small sip of water.
4. Inform the referring physician of any of the following conditions: asthma, diabetes, and allergies to iodine, shellfish, drugs, or latex.

Table 1 Indications for TACE in HCC patients

Diagnosis	Patients with confirmed diagnosis on the basis of EASL consensus diagnostic criteria for HCC
Tumor status	No extrahepatic localizations
	No main PV thrombosis
	Tumor involvement >50 % of the liver parenchyma
	Patients with HCC not suitable for curative treatments such as resection, liver transplantation, or percutaneous ablation according to BCLC staging classification and treatment schedule
	Ablation is the indicated treatment (early stage); however, if treatment is unfeasible or if patient has declined
	Patients who demonstrate recurrence after potentially curative treatment (resection and percutaneous ablation) who have clearly measurable disease according to modified RECIST criteria or even after transplantation
	In potential transplant recipients, to decrease drop-off rate from the transplant list and limit recurrence
Patient performance status	Eastern Cooperative Oncology Group performance status <3 or Karnofsky score >70
Patient metabolic status	Patients with well-preserved liver function (Child-Pugh class A/B) without encephalopathy and mild or severe ascites
	Serum creatinine <2 mg/dL (177 μmol/L)
	Platelet count >50,000/mm^3
	Prothrombin activity >50 %
Doxorubicin related	WBC >3,000 cells/mm^3; neutrophils >1,500 cells/mm^3; left-ventricular ejection fraction >50 %

5. Peripheral venous access should be obtained before the procedure
6. Patient monitoring during the procedure must be performed with a blood pressure cuff, heart monitor, and pulse oximeter.
7. Premedication before chemoembolization must be standard.
8. Hydration with intravenous administration of 150–300 mL/h normal saline solution is essential before the administration of other premedications, including antiemetics and steroids.

Many centers also administer antibiotics for Gram-negative enteric organisms, even although this practice is not universal or prospectively proven to be beneficial for all patients [16]. In patients without an intact sphincter of Oddi from earlier surgery, sphincterotomy, or biliary drainage, the risk of infection after embolization is significantly increased [17]. The risk of postembolization infection appears to be decreased by the performance of bowel preparation the night before treatment [18]. Patients with neuroendocrine tumor metastases should be premedicated with somatostatin analogues to decrease the severe metabolic reaction that is usually promoted by arterial embolization.

Equipment Specifications and Variations in Technique

c-TACE

The amount of lipiodol emulsion to be injected has been shown to be related to the tumor size. Individualized adjustment of lipiodol dose according to blood supply pattern and tumor diameter, as evaluated using CT scan, has been suggested in a randomized controlled trial [19]. The dose would be approximately 2–3 times the tumor diameter (2–3 mL/cm) in cases of highly vascularized tumors and 1 mL/cm for lesions with poor arterial supply. However, hepatic parenchymal damage or bile duct ischemia have been reported to be caused by the use of large amounts of lipiodol [20].

Regarding chemotherapeutic agents, some basic concepts related to the use of one or multiple drugs and the reported dosage range are listed in Table 2. The most frequently used embolic agents for reversible embolization are gelatin sponge and autologous blood clots.

DEB-TACE

Two products are currently available in Europe: nonbiodegradable PVA microspheres (DC Beads, Biocompatibles, Farnham, Surray, UK) (Hepasphere/Quadrasphere, Merit Medical, South Jordan, UT); both products can be loaded with doxorubicin or other chemotherapeutic agents. Other types of microspheres, such as preloaded doxorubicin or irinotecan microspheres, are still not available for sale in Europe or they are still under clinical investigation.

For DEB-TACE, the dose of doxorubicin is calculated on the basis of body surface (75 mg/m^2) or at a fixed dose of ≤150 mg [5]. The microspheres are loaded with drug according to with the manufacturers' instructions. Irinotecan-loaded beads have also been reported for the treatment of hepatic metastases, mainly from CRC metastases,

Table 2 Practical guidelines for c-TACE

Most commonly used therapy: Monotherapy
Most commonly used chemotherapeutic agent: Doxorubicin
Most commonly used chemotherapeutic agent alone: Doxorubicin
Most commonly used double therapy
Doxorubicin (or epirubicin) + mitomycin C
Doxorubicin (or epirubicin) + cisplatin
Median dosage per session [mg]
Doxorubicin (20–100)
Epirubicin (40–100)
Cisplatin (10–120)

and from cholangiocarcinoma. However, this treatment is still not available in Europe [6].

Procedural Features and Variations in Technique

1. After arterial access is obtained, the standard technique commences with an abdominal aortogram (injection of a total of 3–40 mL contrast agent at 10–20 mL/s) to assess origin, tortuosity, or mural atherosclerotic disease, stenosis, and occlusion of visceral abdominal arteries; however, the introduction of multidetector CT (MDCT) with triphasic technique has made conventional angiography no longer mandatory. Using MDCT, it is possible to assess vascular anatomy with a more panoramic view than is possible using an abdominal aortogram. Furthermore this approach allows for a better evaluation of PV patency.

2. Selective superior mesenteric angiogram: To assess any variant vessels feeding the liver (accessory or replaced right hepatic artery) and to study the patency of the PV in the late phase, 30 mL contrast agent is injected at a rate of 4–5 mL/s.

3. Selective celiac angiogram: To assess normal or variant hepatic branch anatomy (e.g., in the replaced left hepatic artery), 8–12 mL contrast agent is injected at a rate of 4 mL/s.

4. Selective left hepatic arteriogram: To assess the feeding flow to segments II, III, IVA, and IVB, and to investigate any accessory vessels such as the falciform, right, or accessory gastric arteries, 4–8 mL contrast agent is injected at a rate of 2–3 mL/s.

5. Selective right hepatic arteriogram: To assess the feeding vessels to segments I, V, VI, VII, and VIII, and to investigate the origin of the cystic artery, the middle hepatic artery (segment IV) if present, and the supraduodenal, retroduodenal, and retroportal arteries, 8–10 mL contrast agent is injected at a rate of 3–4 mL/sec.

6. Currently TACE can be performed with selective and supraselective catheterization of the hepatic segmental or lobar arteries feeding the HCC lesions to limit injury as much as possible to the surrounding nontumorous liver. For this purpose, the application of microcatheters obviates spasm and ensures antegrade free flow for safe delivery of embolic materials when injected through 1–2 mL Luer-lock syringes.

7. In cases of subcapsular neoplasms previously treated with interventional procedures, or in cases of persistent neoplastic tissue with arterial feeding after interventional treatment, extrahepatic collaterals potentially feeding the tumor should be investigated [21] on the basis of CT scan findings. This enables the avoidance of time-consuming catheterization and the use of an excessive amount of contrast medium during the procedure (Table 3).

8. In cases of celiac artery occlusion, specific maneuvers can be attempted to overcome the obstacle and enable performance of the procedure. These include: (1) transaortic recanalization of the celiac artery and (2) cannulation of the collaterals feeding the hepatic artery (commonly the pancreaticoduodenal arcade) or recanalization in retrograde fashion of the celiac artery [22].

9. All of the vessels feeding the tumor must be highlighted. A microcatheter could be used to select the branches feeding the tumor.

10. Recently the usefulness of cone-beam CT during supraselective TACE for HCC that has not been showed on angiography, or for hypovascular metastases, has been emphasized [23].

11. The traditional procedure aims to achieve cessation of arterial flow for temporary retardation of tumor growth, to decrease wash out, and to increase the contact time of the drug inside tumor tissue. Reversible interruption can maintain the patency of the main feeding arteries, thus avoiding collateral formation, and permits subsequent procedures being performed through the same vessels; it should also decrease the risk of extrahepatic collateralization.

12. The angiographic end point of TACE is usually tumor arterial devascularization.

13. A final angiogram must be performed to depict the devascularized lesion; when using DEB-TACE it must be performed very carefully to avoid particle reflux, which may increase the risk of postembolization syndrome.

14. The suggested scheduled time for consecutive treatment is 3 weeks, even if many centers use imaging control after each treatment, and additional treatment should only be performed if viable neoplastic tissue is still present (i.e., TACE on demand).

Table 3 Potential extrahepatic supply related to specific liver segmentation

Extrahepatic artery	Hepatic segments potentially supplied by extrahepatic collateralization
Right inferior phrenic artery	Dorsal and cranial diaphragmatic surface of segments VI, VII, and VII
Left inferior phrenic artery	Dorsal and diaphragmatic surface of segments II and III
Internal mammary artery	Anterior surface of segments V and VIII
Pericardiophrenic and musculophrenic arteries	Diaphragmatic surface of segments II, III, VII, and VIII
Superior and inferior adrenal arteries	Dorsal surface of segments V and VI
Superior renal capsular artery	Posterior and inferior surface of segment VI
Omental arteries	Anterior surface of segment V
Colic (right or middle) arteries	Inferior surface of segments V and VI
Intercostal artery	Posterior surface of segments VI and VII
Left gastric artery	Dorsal and lateral surfaces of the left lobe
Gastroepiploic and short gastric arteries	Dorsal and lateral surfaces of the left lobe

Medication and Periprocedural Care

Periprocedural medications, including pain medications, antibiotic prophylaxis, intra-arterial lidocaine, corticosteroids, and proton-pump inhibitors, are all administered at the physician's discretion. If necessary, antiemetic medication can be administered with addition of promethazine and/or prochlorperazine based on the sensitivity of the patient.

Postprocedural Follow-Up Care Including Imaging

Many practitioners recommend administration of antibiotics for 3–7 days after chemoembolization to cover Gram-negative enteric pathogens. Data regarding the need for routine antibiotic prophylaxis are mixed, without definitive evidence of benefit [16]. If a patient has a disrupted sphincter of Oddi, it has been suggested that antibiotics should be administered for 14 days [18]. Even with extended administration of antibiotics, data for this group of patients are limited, and the physician should proceed with caution in the setting of any biliary abnormality.

To expedite discharge from hospital, antibiotics administration may be changed from intravenous to oral administration as soon as patients can tolerate a normal diet. Antiemetics should be continued as long as needed. One method preferred by many interventionalists to control pain is to administer narcotics by way of a patient-controlled analgesia pump.

Follow-up imaging should be performed at 4 to 6 weeks after all tumor-bearing areas have been treated. If treatment of both lobes of the liver is planned, imaging between treatment sessions may be performed based on operator preference. Signs of tumor necrosis on CT scan include lipiodol uptake and the absence of arterial-phase enhancement in cases in which it was present before c-TACE [24]. Disappearance of arterial enhancement is the principal determinant of tumor necrosis on MRI [25]. There is a paucity of literature regarding follow-up of lesions after TACE without arterial phase enhancement. Gross enlargement of a lesion or nodular enhancement in the PV, or delayed-phase imaging, has been described as evidence of residual or recurrent tumor after radiofrequency ablation of lesions without initial arterial phase enhancement [26, 27]. Similar findings may be obtained in the setting of residual or recurrent tumor after chemoembolization. Tumor response could be assessed according to EASL or Response Evaluation Criteria in Solid Tumors (RECIST) criteria as evaluated using MRI or CT scan performed at baseline and 1, 3, and 6 months, and annually thereafter. However, interpretation of tumor response based only on dimensions presents several limitations. For this reason some variations in these criteria have been recently proposed (modified RECIST criteria) [28]. The emergence of one or more new lesions is considered as evidence of progression in the overall patient response assessment regardless of the response obtained in target lesions. Patients with HCC require further treatment when new or residual disease is detected [27], so-called TACE on demand, whereas in the past decade several procedures were scheduled at intervals of 2–3 weeks. Before additional chemoembolization sessions, liver function tests and a complete blood count should be performed again to ensure that the patient is still an appropriate candidate.

Outcome

Effectiveness Definitions

Technical success: Defined as successful catheter placement, delivery of the chemotherapeutic drug, and embolization.

Clinical success: According to the Outcomes Working Group of the American Society of Clinical Oncology, the primary end point of any treatment should be survival and quality of life, thus giving a secondary relevance to tumor response rate. Tumor response evaluated on the basis of imaging at scheduled times (RECIST, EASL, and modified RECIST) is defined as (1) complete response, (2) partial response, (3) progressive disease, and (4) stable disease.

HCC

Recently the scientific evidence related to TACE/transcatheter arterial embolism TAE was critically evaluated in a Cochrane review [29]. The investigators concluded that "… there is an absence of evidence of TACE or TAE having a beneficial effect on survival in participants with unresectable HCC." The findings of this review initiated a severe response from a representative of interventional radiologists that was published at the end of 2011 [30]. The investigators of this latter article evaluated all of the bias included in the methodology employed by the investigators of the Cochrane review in their meta-analysis [30]. In this section of our review we do not attempt to present a scientific case supporting the use of TACE for unresectable HCC, but we objectively report on some relevant data from the literature on its use in clinical practice.

c-TACE

Several large case series have shown the efficacy of c-TACE. However, the hypothesis that this procedure provides a statistically significant survival advantage compared with the best supportive care in selected patients with well-preserved liver function is based on two studies published in 2002 [31, 32]. In the first, Llovet et al. [31] showed a statistically significant benefit in survival for chemoembolization using doxorubicin (50–75 mg/m^2) and gelfoam compared with conservative care. In the second randomized controlled trial on 80 patients, Lo et al. [32] reported a marked tumor response in the TACE population with better actuarial survival ($P = 0.002$) in the TACE group (1 year 57 %; 2 years 31 %; and 3 years 26 %) versus the control group (1 year 32 %; 2 years 11 %; and 3 years 3 %), thus indicating a significant survival benefit for patients treated with TACE. Although a survival benefit was shown for c-TACE compared with symptomatic treatment or systematic chemotherapy, in a meta-analysis of randomized controlled trials overall survival at 3 years was found to remain low (30 %) for intermediate HCC patients [33]. No difference between TACE and TAE was reported in these studies. Furthermore, a recent review failed to demonstrate either a survival difference between TACE and TAE or the superiority of one chemotherapeutic agent compared with another [34].

DEB-TACE

At the time of writing this guideline only a randomized trial has been published comparing c-TACE with DEB-TACE for the treatment of cirrhotic patients with HCC. This study evaluated the results obtained from 201 patients with Child-Pugh class A/B cirrhosis and large and/or multinodular unresectable N0, M0 HCCs [35]. At 6-month imaging follow-up, the DEB group showed higher rates of complete response, objective response, and disease control compared with the c-TACE group (27 vs. 22 %, 52 vs. 44 %, and 63 vs. 52 %, respectively); however, the hypothesis of superiority was not met (one-sided $P = 0.11$). The procedure was associated with improved tolerability, a significant decrease in serious liver toxicity ($P < 0.001$), and a significantly decreased rate of doxorubicin-related side effects ($P = 0.0001$). The investigators concluded that DEB-TACE is safe and effective. Furthermore, it offers a benefit to patients with more advanced disease.

Recently a prospective randomized trial [36] evaluated the added role of a chemotherapeutic agent in TACE of intermediate-stage HCC comparing DEB-TACE with bland embolization, a type of TAE using small (50- to 100-μm) microspheres. The investigators randomized a total of 84 patients and they concluded that DEB-TACE presented a better local response, fewer recurrences, and longer time to progression than bland embolization. However, these investigators did not assess the benefit of DEB-TACE compared with bland embolization in relation to survival rate.

Hepatic Colorectal Metastases

c-TACE

In a phase II study published in 1998 [37] involving 30 patients treated receiving c-TACE with a combination of cisplatin, doxorubicin, and mitomycin C, a radiological response, as measured by a decrease in lesion density of ≤ 75 % or a 25 % decrease in the size of the lesion, occurred in 63 % of the cases; a decrease of ≤ 25 % in baseline carcinoembryonic antigen level occurred in 95 % of the cases. Median survival for all 30 patients was 8.6 months after the initiation of chemoembolization and 29 months after the initial diagnosis of liver metastasis. More recently, a study [38] in 463 patients treated with a c-TACE protocol consisting of mitomycin C alone ($n = 243$), mitomycin C with gemcitabine ($n = 153$), or mitomycin C with irinotecan ($n = 67$) reported partial

response (68 patients [14.7 %]), stable disease (223 patients [48.2 %]), and progressive disease (172 patients [37.1 %]). The 1- and 2-year survival rates after chemoembolization were 62 and 28 %, respectively. Median survival from the date of diagnosis of liver metastases was 38 months and from the start of TACE treatment was 14 months. There was no statistically significant difference between the three treatment protocols.

DEB-TACE

Preliminary results in a population prospectively enrolled and treated with irinotecan DEBs showed a decrease >50 % in CEA levels and in lesion contrast enhancement in all patients after 30 days [39]. The same investigators reported 20 patients affected by liver metastases from colorectal cancer in a palliative setting. A high response rate (80 %) was found, with decreased lesion contrast enhancement, in all responding patients [40]. Recently a multicenter multinational single-arm study of metastatic colorectal cancer involving 55 patients who had received DEB-TACE with DEBs loaded irinotecan reported response rates of 66 % at 6 months and 75 % at 12 months [6]. Overall survival in these patients was 19 months with progression-free survival of 11 months [6].

Neuroendocrine Hepatic Metastases

c-TACE

c-TACE has been proven to be effective in symptom relief in ≤90 % of patients, with long-term palliation being achieved with repeated c-TACE sessions, and a reported 5-year survival of ≤83 % [41].

DEB-TACE

There has been only one study on patients with liver metastases from these gastroenteropancreatic tumors [42]. At 3-month follow-up, 80 % of the 20 patients enrolled in the study had partial response, 15 % had stable disease, and 5 % had progressive disease.

Cholangiocarcinoma

c-TACE

A study in 17 patients with unresectable cholangiocarcinoma reported a median survival time of 23 months after c-TACE. The rate of minor complications was 12 %, and one patient had a major complication that resulted in a fatal outcome [43]. More recently Gusani et al. [44] treated 42 patients with unresectable cholangiocarcinoma with the

following chemotherapy regimes: one or more cycles of gemcitabine only ($n = 18$); gemcitabine followed by cisplatin ($n = 2$); gemcitabine followed by oxaliplatin ($n = 4$); gemcitabine and cisplatin in combination ($n = 14$); and gemcitabine and cisplatin followed by oxaliplatin ($n = 4$). Treatment with gemcitabine–cisplatin combination c-TACE resulted in a significantly longer survival time (13.8 months) compared with c-TACE with gemcitabine alone (6.3 months). These investigators concluded that c-TACE is a promising treatment modality for unresectable cholangiocarcinoma [44].

DEB-TACE

Preliminary results were published in 20 patients with unresectable cholangiocarcinoma treated with DEB-TACE (DC beads loaded with 100–150 mg doxorubicin) [45]. A response rate of 100 % was observed using RECIST criteria, and the median survival time was 13 months. The procedure was well tolerated by all patients. One patient developed a hepatic abscess requiring antibiotic therapy [45]. In 2009, Poggi et al. [46] evaluated the feasibility and safety of DEB-TACE (oxaliplatin-eluting microspheres) associated with chemotherapy (oxaliplatin and gemcitabine) in 9 patients. According to RECIST criteria, 44 % (4 of 9) of these patients achieved a partial response, and 56 % (5 of 9) had disease stabilization. The overall survival rate of the 9 patients was higher than that of a historical group of patients treated with chemotherapy alone.

Other Tumors

c-TACE and DEB-TACE have been proposed for the treatment of hepatic metastases from breast cancer, melanoma, thyroid cancer, sarcomas, and other primary tumors [46].

Treatment Complications

Treatment complications can be divided into the four following categories: (1) immediate; (2) periprocedural; (3) long-term on the basis of their onset during the procedure, immediately after the procedure, ≤30 days after the procedure, or >30 days after the procedure; and (4) major and minor (Appendix 1). Complications occur in approximately 10 % of patients. Postembolization syndrome (fever, pain, and increased white blood cell [WBC] count) by itself is not considered a complication but rather an expected outcome of embolotherapy [47].

Major complications are liver failure; abscess with functional sphincter of Oddi; postembolization syndrome requiring extended stay or readmission; abscess with biliary-enteric anastomosis/biliary stent/sphincterotomy; surgical

cholecystitis; biloma requiring percutaneous drainage; pulmonary arterial oil embolus; gastrointestinal (GI) hemorrhage/ulceration; iatrogenic dissection preventing treatment; and death within 30 days [16, 47].

Intraprocedural injury to the hepatic artery, secondary to catheter or guidewire-induced injury of the vessel wall, can be considered an immediate complication. It may only lead to reversible events, such as hepatic artery spasm and inflammatory constriction, but in more severe cases it may lead to thrombosis, dissection, and formation of aneurysms. Hepatic artery damage is more likely to occur in cirrhotic patients with impaired liver function and when a high dose of the chemotherapeutic agent is used. The reported incidence of significant hepatic artery damage is 16 %/artery and 48 %/patient [48]. Periprocedural and long-term complications are probably related to metabolic impairment. Findings from liver function tests often worsen slightly after c-TACE, but the majority of studies have showed a return to baseline function within 1 week. However, a significant number of cases of hepatic failure have been reported [49]. It was found that the dosage of chemotherapeutic agent, the basal bilirubin level, the basal prothrombin time, the basal AST level, and the stage of cirrhosis (Child's score) are significantly associated with the post-TACE increase in bilirubin. Patients with irreversible post-TACE hepatic decompensation present with significantly higher pre-TACE bilirubin levels and longer prothrombin time in the dorsal and lateral surfaces of the left lobe, receive larger doses of drug, and have a more advanced stage of cirrhosis [49]. Hepatic decompensation could be the result of incidental damage caused by the chemotherapeutic agent to the non-tumorous part of the already cirrhotic liver. For this reason, superselective embolization has been suggested to decrease this risk, thus improving survival rates compared with nonselective embolization [49, 50]. Tables 4 and 5 list

Table 4 List of GI complications after c-TACE

Complication	Reported rate (%)	Threshold (%)
Liver failure	2.3	4
Abscess with functional sphinter of Oddi	<1	2
Postembolization syndrome requiring extended stay or readmission	4.6	10
Abscess with biliary-enteric anastomosis/ biliary stent/sphinterotomy	25	25
Surgical cholecystitis	<1	1
Biloma requiring percutaneous drainage	<1	2
Pulmonary arterial embolus	<1	1
GI bleeding/ulceration	<1	1
Iatrogenic dissection preventing treatment	<1	1
Death within 30days	1	2

Table 5 Changes in biochemical parameters after TACE

Biochemical change	Average frequency (%)
>50 % increase in ALT	74
>50 % increase in AST	1.5
>50 % increase in creatinine	45.2
>3-second increase in prothrombin time	58.9
Bilirubin >38 μmol/L	6.5
If pre-TACE level was normal or ≥ twice the basal level	1
If pre-TACE level was abnormal	3
≥25 % decrease in AFP	0.5
≥50 % decrease in AFP	0.5

Table 6 Complications of TACE and their management

Complication	Management
Postembolization syndrome (nausea, vomiting, pain, fever)	Self-limited supportively (acetaminophen, nonsteroidal antirheumatics, etc.)
Hemorrhage	Embolization
Liver abscess	Drainage + antibiotics
Acute hepatic decompensation	Precaution measures: patient selection, superselective treatment
Embolism (pulmonary, cerebral)	Precaution measures: patient selection, (exclusion of relevant tumor AV shunt)
Side effects of chemotherapeutic agents (toxicity)	Supportive medication

complications and potential changes in biochemical parameters after c-TACE.

Reported complications of DEB-TACE include cholecystitis, liver abscess formation, tumor rupture, pancreatitis, pleural effusion, gastric ulcer bleeding, esophageal variceal bleeding, and spontaneous bacterial peritonitis. The list of complications of DEB-TACE is relatively shorter than that for c-TACE. This is mainly because the former technique is a relatively new procedure and is not practiced as widely as the latter one, but it could also be due to the lack of lipiodol [14]. A comparison between complication rates leading to death after c-TACE and DEB-TACE has also been reported by the only randomized study to date [35] that compared the two procedures (Table 6).

Conclusion

C-TACE is considered one of the most effective palliative treatment options for patients with inoperable hepatic

neoplasms. However, the severity of the side effects associated with this type of treatment make it suitable only for selected patients. Approximately 20 % of patients develop acute hepatic decompensation after c-TACE even if, as occurs in the majority of cases, liver function returns to its pretreatment level within weeks. Only a minority of patients eventually develop irreversible liver failure. Recently, DEB-TACE has emerged as a variation of c-TACE with the potential for the selective delivery of large amounts of drugs to the tumor for a prolonged period of time, thereby decreasing plasma levels of the chemotherapeutic agent and related systemic effects. Only future randomized controlled trials focused on long-term survival rates will be able to confirm if DEB-TACE can totally replace c-TACE as the standard treatment for patients with nonresectable hepatic neoplasms.

Conflict of interest   None.

Appendix 1

Minor Complications

A.   No therapy and no consequences.
B.   Nominal therapy and no consequences; includes overnight admission for observation only.

Major Complications

C.   Require therapy and minor hospitalization (<48 h).
D.   Require major therapy, unplanned increase in level of care, and prolonged hospitalization (>48 h).
E.   Permanent adverse.
F.   Death.

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