Complications of Image-guided Transcatheter Hepatic Chemoembolization of Primary and Secondary Tumours of the Liver

GUIDO POGGI[1], EMMA POZZI[1], ALBERTO RICCARDI[1], STEFANO TONINI[1], BENEDETTA MONTAGNA[1], PIETRO QUARETTI[2], BARBARA TAGLIAFERRI[1], FEDERICO SOTTOTETTI[1], PAOLA BAIARDI[3], CHIARA PAGELLA[1], CLAUDIO MINOIA[4] and GIOVANNI BERNARDO[1]

[1]Department of Oncology, [3]Consortium for Biological and Pharmacological Evaluations, and [4]Laboratory for Environmental and Toxicological Testing, IRCCS Fondazione S. Maugeri, Istituto Scientifico di Pavia, Italy; [2]Department of Interventional Radiology, IRCCS Policlinico San Matteo, Pavia, Italy

Abstract. *Background: Image-guided transcatheter hepatic chemoembolization (TACE) is accepted worldwide as an effective treatment for patients with unresectable hepatocellular carcinoma (HCC) and for adequate preservation of liver function. Although considered relatively safe, TACE has been associated with several complications. The aim of this study was to determine the prevalence of the complications associated with TACE therapy and to correlate it with certain risk factors, either well-known or not yet evaluated. Patients and Methods: A total of 330 chemoembolization procedures performed in 170 patients (117 males and 53 females) over a period of 64 months were retrospectively analysed. Among the patients, 123 had hepatocellular carcinoma, 10 had intrahepatic cholangiocarcinoma and 37 had hepatic metastases. The variables considered were: tumour histotype, bilioenteric anastomosis, previous or combined treatment with radiofrequency thermal ablation, antibiotic prophylaxis, chemotherapeutic agents, use of new drug-eluting microspheres, comorbidities such as diabetes, patient age and the presence of vascular anatomical variations. Results: A total of 30 complications occurred in 27 procedures. The total complication rate per procedure was 9.1% and approximately 75% of patients had postembolization syndrome. The difference in the prevalence of complications was statistically significant in the group of diabetic patients (13.3%) compared to the remaining patients (6.3%) (p=0.002) and in patients with biliary stents (25%) compared to those without stents (7.75%) (p=0.027). Conclusion: These data show that diabetes mellitus and the presence of bilioenteric anastomosis are risk factors for developing complications after TACE. The use of new drug-eluting microspheres did not increase the risk of complications.*

Correspondence to: G. Poggi, MD, U.O. Oncologia II, Fondazione Maugeri 27100 Pavia, Italy. Tel: +39 0382592675, Fax: +39 0382592026, e-mail: guido.poggi@fsm.it

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Image-guided transcatheter hepatic chemoembolization (TACE) is accepted worldwide as an effective treatment for patients with hepatocellular carcinoma (HCC) in intermediate stage and good performance status (1, 2). In addition, TACE is used as palliative therapy for patients with intrahepatic cholangio-carcinoma or with hepatic metastasis from neuroendocrine tumours, colorectal cancer and uveal melanoma (3-7). Typically, conventional TACE is performed by combining a chemotherapeutic agent, most often doxorubicin, cisplatin and mitomycin, to an ethiodised oil (lipiodol) whose role is to emulsify the drugs and carry them into the lesions. Embolization particles are subsequently used to reduce arterial inflow and to diminish the washout of the chemotherapeutic agents into the systemic circulation in order to prolong the contact time between cancer cells and drugs. New drug-eluting microspheres (DEM) have recently been developed in order to optimise the delivery of chemotherapeutic agents to the tumours. These microspheres may be loaded with many different chemotherapeutic agents so that DEM-TACE may be potentially extended to cure selectively different histotypes. DEM-TACE has also been demonstrated to be safer than conventional TACE in more compromised patients with HCC (8-10). In the near future, it is expected that these technological improvements and the estimated increase of hepatic diseases, especially HCC, will lead to a more extended use of TACE.

Although considered relatively safe, TACE has been associated with several complications. Some risk factors have been associated with an increase in complications after TACE treatment, the most known being a poor hepatic reserve with increased serum bilirubin levels, the presence of significant intrahepatic biliary dilatation and major portal vein thrombosis. Patients who present these risk factors are often denied TACE treatment. However, there are many other less well-known conditions that are potentially related to a high risk of complications after TACE treatment. The present study evaluated the prevalence of complications associated with conventional and DEM-TACE therapy and correlated these with some well-known and other not yet evaluated risk factors.

Patients and Methods

Patients. A total of 330 chemoembolization procedures performed in 170 patients (117 males and 53 females) over a period of 64 months between June 2004 and October 2009 were retrospectively analysed. The patients' age ranged between 39 and 85 years (mean±standard deviation: 68.78±9.05 years). Of the 170 patients, 123 (72.3%) had HCC, 10 (5.9%) had intrahepatic cholangiocarcinoma and 37 (21.8%) had hepatic metastases, from colorectal cancer in 24 patients and other origins (lung, pancreas, breast, gastric, uveal melanoma and small bowel) in the remaining 13 patients. In 130 patients, liver cirrhosis was either confirmed by imaging studies or was well-documented by liver biopsy. Of these patients, 120 (92 %) had Child-Pugh class A and 10 patients (8%) had class B disease. In the HCC group, there were 102 patients in stage B and 21 patients in stage C, according to the BCLC staging system. The main clinical features of the 170 patients are summarised in Table I. The diagnosis of HCC was defined by the European Association for the Study of Liver Criteria, which includes both the radiological criteria alone or in combination with the serum assay of alpha-foetoprotein. Histological or cytological samples of the lesions were obtained in all other patients.

Before TACE, routine laboratory tests and contrast-enhanced abdominal computerised tomography (CT) scans were performed in all patients. Child-Pugh score was estimated for each patient before and after the procedure. Exclusion criteria for TACE included extrahepatic spread, complete portal vein thrombosis, high bleeding risk, oesophageal varices, total bilirubin concentration >3 mg/dl, Child-Pugh stage >B9 and extensive tumour involvement of the whole liver. Liver function tests, complete blood count, INR, serum albumin, amylases, lipases and creatinine levels were measured before and 24, 48 hours and 4 weeks after each session of TACE. Abdominal ultrasound was performed one day after TACE in all patients in order to visualise the gallbladder and the pancreas to exclude early complications related to non-target embolization. Abdominal contrast-enhanced CT or magnetic resonance imaging scans were performed in all patients one month after the last chemoembolization procedure and every three months thereafter. Any problems arising within the early or periprocedural time period or in the late or delayed time period that might be related to the procedure were reported as complications, while mortality was characterised as in-hospital death within 30 days of the procedure, according to the standardisation of terminology and reporting criteria (11)

Table I. *Patient clinical features*.

Variable		Number of patients
Males		117 (68.8%)
Females		53 (31.2%)
Age (mean±standard deviation; years)		68.78±9.05
Hepatic primary		133 (78.2%)
Liver metastasis		37 (21.8%)
Lobar localisation		122 (71.8%)
Bilobar localisation		48 (28.2%)
Pretreatment Child-Pugh score	A5:	101 (78.0%)
(only cirrhotic patients)	A6:	19 (15.3%)
	B7:	5 (4.0%)
	B8:	2 (1.8%)
	B9:	1 (0.9%)
BCLC staging	Stage B:	102/123 (83%)
(only HCC patients)	Stage C:	21/123 (17%)

All patients were informed about the nature of the treatment and gave their consent.

HCCs and liver metastases were treated either with conventional TACE (n=50 procedures, 15.2%) or with DEM-TACE (n=257 procedures, 77.9%) while a few patients were treated with both TACEs either in the same or in non-concomitant sessions (n=23 procedures, 7%). Patients were premedicated with steroids (usually methylprednisolone 40 mg *i.v.* bolus), antiemetic agents, omeprazol and antibiotic prophylaxis. Two different types of prophylactic antibiotics were administered. Before December 2005, routine antibiotic coverage was carried out with 1 g of intravenous amoxicillin-clavunate, administered one hour before the procedure and then, orally or intravenously, every 12 hours, for around five days (n=268 procedures, 81.7%). After December 2005, on the basis of previous experience, more aggressive prophylactic regimens were administered in patients with biliary stents or with a biliary-enteric anastomosis and in patients with diabetes or treated with a combination of TACE and radiofrequency thermal ablation (RFA). They received intravenous tazobactam sodium/piperacillin sodium administered at 4.5 g every eight hours (n=8 procedures, 2.4%) or intravenous ciprofloxacin 200 mg every 12 hours (n=52 procedures, 15.9%), for a mean duration of five days, beginning 24 hours before TACE sessions. After January 2007, 400 mg of oral rifaximin, three times daily, were also administered to all patients (n=200 procedures, 60.6%) beginning 48 hours before the procedure and continued, on the same schedule, for two weeks.

TACE technique. A femoral approach was obtained through a 25-cm-long 5 or 6 F introducer in order to straighten the sharp bending of the elongated iliac arteries. Baseline selective angiography of celiac trunk, common hepatic and mesenteric arteries was performed with a shaped tip catheter prolonging the time of fluorography to obtain diagnostic imaging of the portal system. Conventional TACE was initially performed with infusion of 2-25 ml of iodised oil (Lipiodol; Andre Gurbet, Aulnay-sous-Bois, France) and 20-50 mg of epirubicin hydrochloride emulsion until stasis of arterial flow was achieved or the iodised oil appeared in the portal branches.

Table II. *Complications of TACE.*

Complication	Number of cases (% per procedure)
Complications related to use of chemoembolic agents	
Hepatic	
Liver abscess	4 (1.2)
Biloma	2 (0.6)
Hepatic failure	3 (0.9)
Extrahepatic (due to extrahepatic deposition of embolising material)	
Severe cholecystitis	5 (1.5)
Pancreatitis	4 (1.2)
Pleural effusion	1 (0.3)
Extrahepatic (resulting from systemic effects of the procedure)	
Anaemia	1 (0.3)
Trombocytopenia	4 (1.2)
Allergic reaction	1 (0.3)
Hypertensive crisis	1 (0.3)
Variceal bleeding	2 (0.6)
Complications related to the manipulation of a catheter or guide wire	
Femoral artery pseudoaneurysm	1 (0.3)
Abdominal aortic dissection	1 (0.3)

DEM TACE was performed using either DC Bead 100-300 μm (Biocompatibles, Farnham, Surrey UK) or Hepasphere beads 50-100 μm (BioSphere Medical, Inc., Rockland, MA, USA). DC-Beads were pre-loaded with epirubicin or irinotecan according to the maufacturer's instructions while Hepasphere beads were pre-loaded with epirubicin according to the manufacturer's instructions or with oxaliplatin according to a previous report (12).

The microspheres were injected manually under continuous fluoroscopy assessment with a Luer-Lock syringe through the microcatheter positioned as distal as possible into the right or left hepatic artery, avoiding any dangerous reflux inside the arteries feeding the gallbladder or the gastric wall. Angiographic end point was achieved when stagnant flow in the pathologic area was observed. When combined with TACE, RFA was carried out percutaneously using real-time ultrasound guidance, with an internally cooled needle attached to a 500-kHz radiofrequency generator (Radionics, Burlington, MA, USA) capable of producing 200 W of power. The other RFA system used a multi-tined expandable needle attached to a 460-kHz radiofrequency generator (RITA Medical Systems, Mountain View, CA, USA). The number of insertions of the needle electrode depended on the lesion size.

Statistical analysis. The different prevalence of complications in relation to different variables was assessed with the chi-square test and, in cases of dichotomous variables and expected frequencies less than five, with the Fisher's exact test. Considering the low rate of complications, the TACE treatments were analysed in relation to the presence or absence of complications independently of their nature. Statistical significance was assigned for a p-value of <0.05.

Table III. *Prevalence of complications according to the age group.*

Age class (years)	Number of TACE (%)	Number of complications (%)
≤55	32 (9.7)	3 (9.4)
56-65	64 (19.4)	6 (9.3)
66-75	139 (42.1)	12 (8.6)
≥75	95 (28.8)	9 (10.5)
Total	330 (100.0)	30 (9.1)

Results

The present study analysed 330 procedures of TACE and evaluated the prevalence of complications in relation to different variables. The variables considered were tumour histotype, bilioenteric anastomosis, previous or combined treatment with RFA, regimens of antibiotic prophylaxis, chemotherapeutic agents, new DEM, comorbidity such as diabetes, patient age and the presence of vascular anatomical variations. A total of 30 complications occurred in 27 procedures (in three procedures there were two complications). A total of 330 procedures were performed, therefore the total complication rate per procedure was 9.1%. Complications included acute pancreatitis, hepatic abscesses, bilomas, hepatic failure, cholecystitis, thrombocytopenia, anaemia, hypertensive crisis, allergic reactions, pseudoaneurysm, aortic dissection, pleural effusion and variceal bleeding. Around 75% of patients had postembolization syndrome (fever, pain, nausea) that is not considered to be a complication but rather an expected outcome of embolotherapy. The incidence of all complications is presented in Table II.

A total of 86 TACE sessions (26.1% of all sessions) were performed in diabetic patients. The prevalence of complications in the group of diabetic patients was 13.3% compared to a rate of 6.3% for the remaining patients (p=0.002, statistically significant). There were no differences in the prevalence of complications according to the histotype: 7.2% for HCC and 10.6% for hepatic metastases (p=0.15, no statistically significant). Patients receiving complete prophylaxis containing oral rifaximin (200 procedures, 60.6%) had a higher complication rate than patients who did not receive oral rifaximin (130 procedures, 39.4%), 8.5% and 7.7% respectively, although this difference was not statistically significant (p=0.70). In high-risk patients, a more vigorous antibiotic regimen containing ciprofloxacin or piperacillin plus tazobactam was administered. There were more complications with ciprofloxacin than with amoxicillin plus clavulanic acid, 12.5% and 7.6% respectively, but the difference was not statistically significant (p=0.10, no statistically significant),

while piperacillin plus tazobactam was administered in only 2.4% of all procedures performed so the results were not significant because the sample was too small. By the time DEMs were available, many interventional radiologists preferred to use them instead of lipiodol because of their better pharmacokinetic drug profile but, as yet, there are no conclusive data about their tolerance with respect to lipiodol. The prevalence of complications was compared between the procedures performed with microspheres (257 treatments, 77.9%), with lipiodol (50 treatments, 15.1%) and their combination (23 treatments, 7.0%). The complication rates in these three categories were 8.2%, 10.0% and 4.4%, respectively; these differences were not statistically significant (p=0.48). TACE was performed a few days before RFA in 53 patients. Combining TACE with RFA increases the area of necrosis by reducing the well-known 'heat-sink effect' but it may also add to the risk of complications. In the patients examined, there was no statistically significant difference in the number of complications between the patients treated by TACE with or without RFA (4.7% and 8.85 %, respectively; p=0.16). TACE procedures were also performed with different chemotherapeutic agents: epirubicin (229 treatments, 70.2%), irinotecan (33, 10.1%) and oxaliplatin (64, 19.6%). Therefore, the prevalence of complications was investigated with respect to the drug used, giving rates of 7.85, 7.6 and 10.1%, respectively for the above three chemotherapeutic agents; these differences were not statistically different (p=0.59).

Furthermore, the prevalence of all complications of TACE procedures was compared in patients with and without biliary stents, giving rates of 25 and 7.75%, respectively; this difference was statistically significant (p=0.027).

The presence of vascular anatomical variations did not affect the prevalence of complications; complication rates were 9.7 and 7.2% in patients with and without vascular anatomic variations, respectively (p=0.33). The mean age of patients at the time of TACE treatment was 68.7 years. Approximately 30% of all procedures were performed on very elderly patients (age >75 years). The prevalence of complications in the different age groups was analysed but there was no statistically significant difference among these different patient classes (Table III).

Pain is not considered a complication of TACE but it is normally included in the symptoms of post-embolization syndrome. However, pain is one of the more troublesome symptoms reported by patients, and it may sometimes be a sign of a serious complication. Pain was reported in 250 out of 330 TACE procedures (75.8% of the total). Pain was graded into four classes according to the Common Terminology Criteria for Adverse Events, version 3.0 (13) with G0 class corresponding to the absence of pain. No statistically significant differences of prevalence of pain were detected among TACE with microspheres (74%), TACE with lipiodol (80%) and TACE with both microspheres and lipiodol (83%) (p=0.50). In most TACE procedures, pain was mild (G1), however grade 2-3 pain was reported in 24% and 9% of TACE with microspheres and lipiodol, respectively with the difference approaching statistical significance (p=0.071). The prevalence of pain was also evaluated according to the different classes of drugs used. Pain was reported in 74.2%, 81.1% and 78.1% of procedures, when epirubicin, irinotecan and oxaliplatin were used, respectively. The differences among these three groups were not statistically significant.

Discussion

TACE has been widely used in the treatment of unresectable hepatic tumuors including HCC, intrahepatic colangiocarcinoma and metastatic liver tumours. Although the technique is relatively safe because of the dual blood supply to the liver *via* the hepatic artery and portal vein, TACE has been associated with various complications. (14)

These complications are usually divided into hepatic, extrahepatic complications and due to catheter/guide wire manipulation. Extrahepatic complications comprise the extrahepatic deposition of embolising material and complications resulting from systemic effects of the procedure (11). Some factors have been associated with a high risk of complications after TACE such as a poor hepatic reserve, the presence of significant intrahepatic biliary dilatation or massive portal vein thrombosis. Patients who present portal vein obstruction are at increased risk of hepatic infarction; however some studies have shown that TACE may be performed safely in these patients, provided that they have good hepatic function and adequate collateral circulation (15, 16). A transient deterioration of liver function may occur after TACE. Chung *et al*. reported 20 patients with irreversible hepatic failure after TACE occurring in cases with poor hepatic functional reserve and obstruction of the main portal vein (17). Patients with these risk factors are often not candidates for TACE and were not included in the present analysis. However, there are still many other less known, less studied risk factors and also additional variables that are potentially related to a high risk of complications after TACE and the aim of this study was to evaluate the incidence of complications related to these variables. Overall, this study reported 30 complications occurring in 170 patients who underwent 330 procedures. The incidence of complications per patient was 17.6%, being within the range reported in the literature, while the incidence per procedure was 9.1%, being slightly higher than that reported in other studies (18).

Several variables were investigated that may be related to the incidence of complications and it was found that only two of them, particularly diabetes and the presence of biliary stents, increased the risk of complications. This is the first time that diabetes was evaluated as a predisposing factor for complications after TACE but this is not surprising because diabetes generally increases the risk of infections and predisposition to vascular damage. In the diabetic patients

examined, there were more complications, particularly infections, than in patients without diabetes. As well as diabetes, the presence of biliary stents was another predisposing factor to infectious complications such as hepatic abscesses. Several studies have demonstrated that the presence of a bilioenteric anastomosis is the main risk factor for development of intrahepatic abscesses after TACE treatment, which was also confirmed in the present study. Song *et al*. found a 1.8% incidence of liver abscesses with biliary dilatation alone and a 7.4% abscess rate in patients with biliary stents or biliary-enteric anastomosis (19). Many studies have investigated the incidence of these infectious complications in high-risk patients and the role of different antibiotic regimens in preventing them. Geschwind *et al*. showed that aggressive antibiotic prophylaxis with intravenous tazobactam/piperacillin and a complex bowel preparation is able to provide protection against intrahepatic abscesses in patients who have a history of biliary reconstructive surgery (20). Patel *et al*. treated seven patients having biliary stents with an aggressive prophylactic antibiotic regimen before and after TACE and compared the incidence of complications of these patients with previously reported incidences of patients who received standard prophylaxis. A trend towards a lower rate of abscess formation was found among high-risk patients who received the more aggressive antibiotic prophylaxis, but the difference did not reach statistical significance (21). In the present study, different antibiotic regimens were used with or without bowel decontamination with oral rifaximin but there was no difference in the incidence of complications among these patient groups. Since a more aggressive antibiotic prophylaxis was used in patients at higher risk of complications and there was no difference in the prevalence of complications with respect to patients at lower risk, it is suggested that these antibiotic regimens may have demonstrated their efficacy had they been compared with less aggressive regimens in homogeneous groups of patients; however, only a randomised study may address this issue properly.

Some reports have suggested that the incidences of septic complications are much lower after TACE treatment for HCCs than for metastatic liver tumours (22). This difference between the types of liver cancer has been attributed to the volume of the tumour vascular beds to be embolised, which may determine the relative amount of regional lipiodol retention in the tumour and normal liver tissue. Sakamoto *et al*. reported a higher incidence of biloma in metastatic liver tumours than in HCCs after lipiodol TACE, suggesting that the difference in tumour vascularity between HCC and metastatic liver tumour may be the cause of the difference in the incidence of intrahepatic biloma formation between the two groups (23). In these reports, repeated procedures of TACE over a short period of time or proximal, non-selective, injection sites are also considered risk factors in developing intrahepatic biloma. The present study did not demonstrate a statistically significant difference in the rate of complications between the two histotypes. The low number of repeated TACEs, the longer period of time that elapsed between two consecutive procedures and the more selective technique used may explain these results.

Recent evidence suggests that TACE combined with RFA may have a synergistic effect in treating hepatocellular carcinoma and may provide overall survival rates that are similar to those achieved with surgical resection (24, 25) Although combining TACE with RFA increases the area of necrosis, there was no increase in the rate of complications.

TACE with the now available DEMs may offer a precisely controlled and sustainable release of the chemotherapeutic agent into the tumour bed with significantly lower plasma concentrations of drugs than in conventional TACE (10). Until now there has been only one prospective randomised study comparing doxorubicin-eluting bead embolization with conventional TACE in the treatment of HCC (26). The study showed no statistically significant difference between treatments for the primary safety endpoint. Comparison of the prevalence of complications between the procedures performed with microspheres or with Lipiodol or with both of them also revealed no differences among these three categories. More randomised clinical trials are necessary in order to determine whether DEM-TACE is characterized by fewer local and systemic complications than conventional TACE.

The high prevalence of HCC and prolonged life expectancy in the world population has led to an increasing number of elderly patients being considered for treatment. Many surgical and non-surgical reports suggest that the management of HCC in the elderly should not be different from that in the younger patients because the results are similar between the two groups (27, 28). The present study also confirmed that the treatment of HCC with TACE is well-tolerated in the elderly patients and show no difference in the prevalence of complications among different age groups

Conclusion

The present study showed that diabetes mellitus and the presence of bilioenteric anastomosis are risk factors for developing complications after TACE. The use of new microspheres did not increase the risk of complications. An aggressive antibiotic regimen seemed to reduce the occurrence of complications, although randomised clinical trials are necessary to identify the most appropriate scheme.

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