ISCHEMIC COMPLICATIONS OF TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION IN LIVER MALIGNANCIES

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Abstract

Objective: To determine the frequency, character, methods of treatment, and outcome of ischemic complications after transcatheter hepatic artery chemoembolization (TACE).

Material and Methods: Between 1985 and 1998, 827 sessions of TACE with Doxorubicin mixed with iodized oil, and gelatin sponge particles were performed in 282 patients with primary and metastatic liver cancer. Post-TACE monitoring included clinical observation, US and CT.

Results: Ischemic complications appeared in 13 (4.6%) and included the following: hepatic (n=6) and splenic abscess (n=1), cholecystitis (n=3), and bile duct necrosis (n=3). The treatment was US-guided drainage in 12 cases and systemic antibacterial therapy in 1. No negative influence of these complications on survival of patients was detected.

Conclusion: Serious ischemic complications of TACE occur in about 5% of patients and can be successfully managed without open surgery. These complications do not worsen the survival of patients.

Transcatheter arterial chemoembolization (TACE) is widely applied in palliative treatment of unresectable primary and metastatic cancer of the liver (5, 6). The rationale for TACE is based on a dual blood supply of liver parenchyma from the hepatic artery and the portal vein and the predominantly arterial supply of tumors. The combination of intraarterial injection of a chemotherapeutic agent mixed with iodized oil and arterial embolization allows the achievement of maximal tumor response (2).

However, TACE sometimes brings about ischemic complications such as cholecystitis, pancreatitis, bile duct necrosis, liver and splenic abscess (2, 4, 7–17). The purpose of this retrospective study was to analyze the frequency, severity, methods of treatment and outcome of these complications.

Material and Methods

Between 1985 and 1998, 827 TACE procedures (range 1–12, mean 3.9 per patient) were performed in 282 patients with unresectable primary (n=80) and metastatic (n=202, mainly from colorectal cancer) liver malignancies. The primary tumors were 5 to 30 cm in diameter with 2 to multiple daughter nodules. Tumors 2 to 10 cm in diameter affecting both liver lobes were detected in all cases of metastases.

Angiography and TACE were carried out as follows: The Seldinger technique was used for catheterization of the femoral or axillary artery. Pretreatment celiac and superior mesenteric arteriography using 1.7–1.85 mm (5.0–5.5 F) selective visceral catheters was performed to define hepatic
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<td>Clinical summary of patients with post-TACE ischemic complications</td>
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vascular anatomy, volume and location of the tumor, and portal vein patency. The proper hepatic artery was then selectively catheterized with the same catheter. If both lobes of the liver were affected, the treatment was performed by separate selective right hepatic and left hepatic TACE with a 1- to 2-week interval.

When possible, the tip of the catheter was placed distal to the cystic artery. Intrahepatic injection of 30–80 mg Doxorubicin (Pharmacia-Upjohn) mixed with 10 ml Lipiodol Ultrafluid (Guerbet) was followed by hepatic artery occlusion with 1×1 mm cubes or 1×5 mm torpedoes of Gelfoam (Pharmacia-Upjohn). Then 80 to 160 mg Gentamicin was added to the embolization mixture.

Post-TACE monitoring included clinical observation, laboratory analyses, US and CT.

Results

Serious ischemic complications developed in 13 (4.6%) patients including 11 with liver metastases and 2 with primary hepatic tumors (Table). All complications were symptomatic with local pain, fever, leukocytosis, and were diagnosed by US and/or CT 7–25 days after the first (n=8), second, third (each n=2) and fifth (n=1) TACE.

Liver abscess in the embolized liver lobe occurred in 6 patients (cases 1–6, Table). The lesion was located in the non-tumorous liver parenchyma in 4 patients. Of those, 2 patients developed formation of a solitary abscess with a diameter of 3 cm and 5 cm, while in the each of 2 other patients, 2 abscesses of approximately the same size were revealed. Two remaining patients had a single abscess involving both the tumor nodules and the normal parenchyma.

The treatment included percutaneous US-guided puncture and subsequent drainage by one or two silicon tubes of 3–5 mm diameter with lavage of the abscess cavity by solutions of antiseptics and antibiotics during 8–22 days.

After removal of the drainage tubes the residual cavity decreased slowly and disappeared within 3 months.

Ischemic cholecystitis (n=3) and cholangitis (n=3) were also successfully treated with percutaneous US-guided drainage of the gallbladder or bile ducts, respectively, and systemic antibiotics (cases 7–12, Table, Fig.). Subsequent US and CT investigations showed shrinkage of the gallbladder without formation of gallstones. In the patient with destructive cholangitis (case 10, Table), no bile cysts were seen on subsequent US and CT.

The formation of several small (2–4 mm) splenic abscesses developed in 1 patient (case 11, Table). This complication was successfully managed with 1-week systemic antibiotic therapy. Two months later, US and CT showed normal parenchyma of the spleen.

In the retrospective analysis, there was no correlation of development of infectious ischemic complications with the dose of chemotherapeutic drug and iodized oil, number of procedures, or volume of TACE and the embolized tumor.

At present (October 1999), 6 patients are still alive. Of those, 2 patients, 1 with hepatocellular carcinoma (case 9, Table) and 1 with carcinoid liver

Figure. PTC shows bile duct necrosis with formation of multiple bilomas after TACE (case 10).
metastases (case 6, Table) had remission of disease during 9 and 12 years, respectively. Two other patients with colorectal and gastric cancer metastases, respectively, showed tumor progression at 18 and 60 months post-TACE (cases 7 and 10, Table). Remission for 6 and 7 months was noted in 2 other patients (cases 11 and 12, Table). Seven patients died 14–39 (mean 25.0±7.7) months after TACE (Table).

Discussion

Serious ischemic complications of TACE are relatively rare. According to the literature, their frequency constitutes 3–12% (1, 3, 16). In our group, these complications occurred in 4.6% of patients, or in 1.6% of the procedures.

The cause of necrotic changes in organs adjacent to the liver is the ischemia after inadvertent embolization of arteries, supplying the gallbladder, bile ducts, pancreas and spleen (2, 8, 11–15, 21). However, these aseptic necroses are usually small and do not require invasive treatment (1, 2, 5, 10).

The risk factors for development of post-TACE complications include (6, 14–19, 22) the following: a) non-selective placement of the catheter during TACE; b) high doses of cytostatics and iodized oil used in TACE; c) use of the small-diameter embolic agents; d) liver functional disorders; e) previous surgery on the liver and bile ducts; and f) obstruction of the bile ducts and/or portal vein branches.

The question of preventive application of antibacterial drugs in TACE remains unsolved. REED et al. have urgently recommended supplement of antibiotics in the embolization mixture (20). On the other hand, ALLISON et al., despite of antibacterial therapy, have observed 2 cases of sepsis and 2 liver abscesses in 4 of 57 patients (1), whereas CHUANG & CHARNSANGAVEJ have noted similar complications only in 3 of more than 1,000 patients after embolization without antibiotics (5). On the basis of transcatheter treatment of 61 patients with hepatocellular carcinoma, CASTELLS et al. stated that antibiotic prophylactics are not necessary for TACE (3). Previously, we also found that post-TACE complications arise approximately equally in groups of patients receiving and not receiving antibacterial therapy (26). In our opinion, prophylactic antibacterial therapy should not be used routinely but probably may be indicated in patients with the above-mentioned risk factors.

Liver abscess. The occurrence of gas within the embolized tumor is a frequent finding at subsequent CT. This phenomenon is explained by tumor necrosis, air in the hepatic artery during the procedure, and also vital activity of a gas-producing microflora (5, 22).

The formation of true abscess is rare. CHUNG et al. noted this complication only in 1 of 350 cases, DE BAERE et al. in 4 of 489, and CHEN et al. in 5 of 289 patients after TACE (4, 6, 8).

The clinical and radiologic symptoms of liver abscesses are well known. Surgical (more often in large and multiple abscesses) or percutaneous treatment is usually successful (4, 25). However, in cases complicated by sepsis, the outcome can be fatal (9, 18).

In all our liver abscess patients (cases 1–6), the doses of cytostatic-in-oil used for TACE were within the standard limits, and occlusion of the hepatic artery was performed with relatively large (2 mm) gelatin sponge particles. Prophylactic antibiotics were used in 3 of 4 cases. Nevertheless, ischemic infarction of the liver with formation of abscess occurred. These data confirm the opinion that development of liver abscess after TACE is infrequent but almost unpredictable (9, 12). Iodized oil in the portal vein after TACE and previous biloenteric anastomosis are major risk factors. Also patients with carcinoid liver metastases are more inclined to provoke necrotico-infectious complications (8, 25).

Ischemic cholecystitis. Signs of acute cholecystitis such as local pain at the site of the gallbladder with thickening of its walls is seen on US in 11–45% of patients post-TACE (14, 24). These symptoms are usually resolved after conservative therapy (5, 6, 16). However, it is necessary to take into account, that these patients have a subsequent risk of cholelithiasis. Therefore, if hepatic resection is executed after TACE, the gallbladder also should be removed (14).

Gangrenous post-TACE cholecystitis develops in 1–2% of patients and requires invasive treatment which can vary from open or laparoscopic cholecystectomy to percutaneous US- or CT-guided drainage (16, 23, 27).

The main prophylaxis of this complication is placement of the catheter distal to the cystic artery and avoidance of reflux during TACE (5, 24). However, distal catheterization is sometimes technically impossible because of tortuosity of the hepatic artery or impossibility of identification of visceral arteries (14, 15). Also, reflux of non-contrast particles can be missed even in cases of appropriate placement of the catheter (16).

We performed TACE proximally to the cystic artery in 2 of 3 patients who developed ischemic cholecystitis. In case 7, distal catheterization attempts were unsuccessful even with the use of a microcatheter. In case 8, several hepatic arterial branches
supplying the tumor arose proximal to the cystic artery. In the remaining case 9, probably inadvertent embolization appeared. Treatment with percutaneous US-guided drainage was successful in all 3 patients with ischemic cholecystitis.

**Bile duct necrosis.** It is known, that in contrast to the normal liver parenchyma, the bile ducts do not have any dual blood supply and are fed exclusively from the hepatic artery. Therefore ischemia of the biliary tree of some degree inevitably develops after TACE (14, 15). However, clinical symptoms rarely occur. The risk of ischemic cholangitis with bile duct necrosis and formation of bilomas increases when liquid (ethanol) or small (Gelfoam or Ivalon powder) embolic agents are used (2, 17, 21).

The complication is usually systemically treated with antibiotics (17). Our patients with bile duct necrosis (cases 10–12) had multiple necroses with development of bilomas and rise of blood serum bilirubin level up to 100–150 μmol/l, which made percutaneous biliary drainage necessary.

**Spleenic abscess.** The cause of this complication is inadvertent embolization through arterial collaterals between the liver and spleen or because of unintentional reflux (3). Droplets of iodized oil have sometimes been found in the spleen after TACE. Fortunately, most of these patients show no clinical symptoms. In rare cases of large splenic abscess formation, surgical splenectomy or percutaneous drainage is indicated.

This complication developed in patient 11 with the post-resection recurrent hepatoblastoma and could be provoked by presence of collaterals between the liver and the spleen. Small abscesses located at the upper pole of the spleen resolved after systemic antibiotic therapy.

**Survival.** The survival rate of patients after complicated TACE has not been studied before. The present data showed that the long-term results of TACE in these patients were close to those of patients who had no complications. Moreover, in cases 6, 9, and 10, a 12-, 9- and 5-year survival was achieved.

**Conclusion.** Serious ischemic complications of TACE occur in about 5% of patients and can be successfully treated by percutaneous technique in most cases. The survival rate of these patients is not worse than that of patients who have uncomplicated TACE.

**REFERENCES**


