Abstract. Intrahepatic cholangiocarcinoma account for 13% of annual cancer-related deaths worldwide and for 3% in the USA. Patient with unresectable disease can benefit from palliative therapies such as systemic chemotherapy. However, the only curative treatment for intrahepatic cholangiocarcinoma is complete surgical resection with histologically negative resection margins.

In this report, we describe the case of a 65-year-old woman, affected by unresectable intrahepatic cholangiocarcinoma and previously treated with chemotherapy. After disease progression, because of disappointing results obtained with chemotherapy, we proposed trans arterial chemoembolization with microspheres loaded with oxaliplatin (OEM-TACE) as alternative therapy. No major complications occurred. At the most recent examination, 24 months after the last TACE procedure and 34 months after the initial diagnosis, no residual hepatic disease was found.

Case Report

A 65-year-old woman was referred to our hospital with an unresectable intrahepatic cholangiocarcinoma. One month before admission, surgical removal of the large cholangiocarcinoma had been planned but during surgery the lesion, extending twelve centimeters into the right lobe of the liver, was also infiltrating the lower cava vein, making its removal impossible. On admission to our hospital she reported mild pain in the upper abdominal quadrant and an eight-kilogram weight loss. Laboratory examination revealed mild hepatic dysfunction. The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 67 U/l and 87 U/l respectively; alkaline phosphatase and gamma-glutamyltransferase were 100 U/l and 178 U/l, respectively. Assays for anti-hepatitis C virus (HCV) antibodies were negative while serological examination confirmed the patient to be an asymptomatic carrier of hepatitis B virus (HBV) infection with undetectable HBV DNA viremia. No known risk factors for cholangiocarcinoma were identified in the patient anamnesis, having no known history of primary sclerosing cholangitis, choledochal cyst, hepatolithiasis, previous thorotrast exposure or liver fluke infestation. Serum CA 19.9 was remarkably elevated (1257 U/ml), carcinoembryonic antigen (CEA) level was 38 U/l, and α-fetoprotein was normal. Abdominal computed tomography (CT) showed a huge hypodense large mass in the right lobe of the liver involving the fifth, sixth, seventh and eight segments, with many peripheral nodular lesions.

Every three weeks the patient was treated with six courses of first-line chemotherapy with gemcitabine 1.000 mg/m² on day 1 and oxaliplatin 85 mg/m² on day 2 (GEMOX). However, one month after the last course of chemotherapy, CT scan showed an increase in the size of the main lesion and found new lesions in the right lobe of the liver. The patient was also unresponsive to three subsequent courses of second-line chemotherapy with epirubicin 50 mg/m² and cisplatin 60 mg/m² intravenously (i.v.) day 1, each given every 21 days and 5-fluorouracil (5-FU) 200 mg/m²/day given as a continuous 24-hour i.v. infusion throughout the treatment course (ECF) (1). We decided to perform transcatheter arterial chemoembolization (TACE) using the new drug-eluting microspheres. Such microspheres can load chemotherapeutic agents and deliver them directly into the tumor, achieving high intratumoral concentration and low plasma concentrations. Two kinds of new drug-eluting microspheres are now available: a polyvinyl alcohol-based microsphere (DC Bead™; Biocompatibles UK Ltd.,...
Farnham, UK) and a superabsorbent polymer microsphere (HepaSphere™; Biosphere Medical, Rockland, MA, USA). HepaSphere™ can be loaded with oxaliplatin, an agent effective in the treatment of bile-duct cancer (2). These microspheres increase their volume by fourfold after loading with chemotherapeutic agents, unlike DC Beads™ whose volume decreases. Two sessions of TACE, one month apart, were performed using a 50 mg vial of HepaSphere™ with a diameter ranging from 50 to 100 μm that was preloaded by mixing it for at least 10-15 minutes with 50 mg oxaliplatinum (Eloxatin; Sanofi-Aventis, Paris, France) and was diluted with 5 ml of nonionic contrast medium (iodixanol, Visipaque® 270; Amersham Health; Milan, Italy).

The cycle of treatments obtained the complete devascularization of the lesions (Figure 1A, Figure 1B). One month after the last procedure, the serum level of CA 19.9 dropped to 127 UI/ml and the CEA level was below the normal upper limit of 3 UI/l. PET-CT scan showed a small area of residual uptake of radiotracer (18F-fluorodeoxyglucose) in the larger hepatic lesion. Biopsies of this area showed some microspheres occluding the intratumoral vessels with sclerofibrotic reaction around this area, with a small residual area of tumoral cells (Figure 2A). One further session of TACE with the same protocol was performed. One month after this last session, CA 19.9 was 19 UI/ml and PET-CT scan showed no uptake of radiotracer. No major complications occurred.

Transient abdominal pain with nausea occurred immediately after all three courses of TACE, with mild fever persisting for five days only after the first procedure. The patient was followed up every three month with CT scans and CA 19.9 and CEA levels for the first year, then every six months.

At the most recent examination, 24 months after the last TACE procedure and 34 months after the initial diagnosis, no residual hepatic disease was found. We proposed surgical removal of the necrotic lesion, but the patient declined.

**Discussion**

Cholangiocarcinoma is an uncommon neoplasm with a poor prognosis. It arises from the ductal epithelium of the bile duct tree and is classified into intrahepatic cholangiocarcinoma (IHCC) and extrahepatic colangiocarcinoma (EHCC). The incidence rates of cholangiocarcinoma, especially those of IHCC, are increasing worldwide (3). Even if surgical resection is the only potentially curative treatment, the diagnosis of both IHCC and EHCC most commonly occurs at advanced stages of disease because of an absence of specific symptoms, physical examination findings or laboratory abnormalities in the early stages (4). Survival for patients with unresectable cholangiocarcinoma is reported to be 5-8 months. IHCC is generally present in a more advanced state than EHCC, consequently prognosis is often even worse (5). Systemic chemotherapy has provided disappointing results. Most studies
have used 5-FU alone or in combination with agents such as methotrexate, cisplatin, mitomycin C, etoposide and leucovorin, with poor response rates (6-9). Recent data suggest that gemcitabine, docetaxel and oxaliplatin could be more effective against cholangiocarcinoma (10-13). Because of the poor results with standard systemic therapy, there has been a great interest in other therapies.

The role of TACE in prolonging survival of patients with unresectable hepatocellular cancer is well known (14-15). Recently published reports have focused on the value of TACE and chemoperfusion also in the treatment of unresectable cholangiocarcinoma (16). Burger et al. reported that conventional TACE with lipiodol, epirubicin and embolic agents is far superior to other traditional palliative treatments such as systemic chemotherapy in the treatment of cholangiocarcinoma (5). In the present case, we treated the patient with an unresectable cholangiocarcinoma using new drug-eluting microspheres. Such microspheres, as previously reported by our group (2), can be loaded with oxaliplatin, a chemotherapeutic agent whose activity against cholangiocarcinoma is well known. These microspheres combine the ability for carrying oxaliplatin into the tumor with their capability for embolizing the tumoral feeding arteries. This dual action permits a very high concentration of oxaliplatin in the tumor, improving its efficiency and reducing its systemic side-effects (2).

In conclusion, TACE using HepaSpheres™ loaded with oxaliplatin may be considered a very effective treatment in unresectable intrahepatic cholangiocarcinoma not responsive to systemic chemotherapy.

References


Received May 6, 2008
Revised June 20, 2008
Accepted July 1, 2008