Irinotecan drug eluting beads used as a treatment of advanced intra hepatic cholangiocarcinoma

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ABSTRACT

This report describes a 74-year-old male with unresectable intrahepatic cholangiocarcinoma (ICC). However surgical procedure is the only curative treatment, it often seems to be ineffective because of the aggressive behaviour of the disease. The role of systemic chemotherapy in the ICC is undefined with a median survival between 6.43 to 12.17 months obtained by using the combination chemotherapy of gemcitabine with cisplatin. In the present case, we performed a targeted treatment using drug eluting beads (DEB) with irinotecan (IRI) administered as transarterial-chemoembolization (TACE). After one session, the tumour vascularity decreased significantly at the one month evaluation on computed tomography (CT) scan of the liver. This case report suggested that minimally invasive transcatheter DEB embolization could be a promising, safe and effective treatment for selective patients with unresectable ICC.

CASE REPORT

Introduction:

Cholangiocarcinoma is a rare malignant tumour which carries a dismal prognosis, with low survival times. It is the second cause of primary liver cancer after hepatocellular carcinoma (1, 2), and composed of cells that arise from the biliary tract. Chronic biliary tract inflammation is known to be a risk factor for the development of ICC, such as primary sclerosing cholangitis, infection, or hepatolithiasis. Histologically, ICC is mostly well-differentiated adenocarcinoma, arising from a malignant transformation of epithelial cells (cholangiocytes) and classification is based on location divided into three categories (intra-hepatic tumours, extra-hepatic tumours, and distal locations). These different forms are distributed as follows: about 5-10% for intra-hepatic form, 60–70% for hilar tumours and 20–30% for common bile duct tumours (3). The Liver Cancer Study Group of Japan has suggested a classification using macroscopic features which are mass forming, periductal infiltration, intraductal growth, or mixed form (4, 5).

Treatment options are determined by the local extension, the vascular invasion, presence of metastasis, and the liver function. Although surgical complete resection remains the only curative treatment for ICC, most of the patients have advanced disease at the time of the diagnosis and are not eligible for surgical management. Adjuvant chemotherapy can be performed in case of unresectable ICC, but it efficacy remains controversial with no benefit in term of survival and tumor recurrence (6).

Recently, TACE using DEB with doxorubicin has been proposed as an alternative therapy for carcinoma (7). Drug eluting beads are an embolic microsphere product that is capable of being loaded with anthracycline drugs such as IRI just before administration in a TACE procedure. Advantages of this procedure are to stop arterial workflow for the tumour

(ischemic step, tissue necrosis), to minimize systemic toxicity of the chemotherapy, and to offer the possibility of controlling the release and dose of the drug into the tumour bed (8). IRI is an active drug used frequently in the treatment of advanced colorectal cancer of first and second line. A recent study of the chemoembolization of rat colorectal liver metastases with IRI-DEB showed significant anti-tumoral activity (9).

We present a case of DEB with IRI administered by TACE in a patient with unresectable ICC.

Case report:

A 74-year-old male with history of myocardial infarction and sigmoiditis underwent an abdominal ultrasonography for right upper quadrant pain, which identified multiple liver lesions without bile duct dilatation (Fig. 1). A CT scan examination demonstrated nodular, diffuse and heterogeneous liver lesions with peripheral hypervascular appearance (Fig. 2). The greatest lesion was located within the segments IV and V; measuring 86 mm x 74 mm. A targeted liver biopsy was performed in the greatest lesion and microscopic analysis showed an ICC. Based on the CT scan results, multidisciplinary staff discussion confirmed the resectable approach was impossible. Patient was qualified for palliative systemic chemotherapy treatment with iterative sessions using the combination of gemcitabine with cisplatin (GEMZAR protocol) (10). However, this therapy not induced positive response and the greatest lesion in a new CT scan examination (5 months after initial CT scan) measured 100 mm x 74 mm.

A multidisciplinary approach decided to perform a DEB with IRI in a TACE, offering the patient another therapeutic strategy.

After explaining the benefits and risks of the TACE, we received the complete consent from the patient to proceed. Before TACE, patient received i.v. hydration, antibiotic prophylaxis, 500 mg of hydrocortisone, and antiemetic drug.

Procedure:

A 5-French desilet was inserted in the right femoral artery under local anesthesia. Prior to embolization, angiography of the hepatic and mesenteric artery was performed to map liver vascular anatomy, check for arteriovenous shunts, and identify arterial feeders of the tumor, which demonstrated many hypervascular nodular lesions (Fig. 3) in both lobes of the liver. The liver invasion of the biggest lesion was over 30%. Catheter was placed in the right hepatic artery with the use of a 2.7 Fr microcatheter (Progreat, Teruno) and injection of the load beads was performed.

DEB with the cytotoxic agent (Irinotecan 100 mg) was previously loaded by an experienced pharmacist two hours before the treatment, with 15 ml of drug eluting bead (size ranging from 200-400 microns). At the end of the injection, liver angiography control demonstrated the treatment's efficacy and the tumor's devascularization (Fig. 4). Patient presented a post embolization syndrome during three days (pain, fever, nausea and vomiting).

One month after TACE, a control CT was done and revealed significant decreased vascularity of the liver lesions in the liver's right side (Fig. 5). Clinical evaluation demonstrated an increase in ascitis of 20%, which was attributed to the advanced state of the hepatic dysfunction.

DISCUSSION

Cholangiocarcinoma is a rare hepatic malignant tumour for which surgical resection is the only chance for cure, with results depending on patient selection and careful surgical technique. Chemotherapy, radiation therapy or combination therapies remain as the only treatment for inoperable patients. However, these are uniformly ineffective in patient's survival. To date, chemotherapy has had limited impact on the course of this disease. This is mainly due to the heterogeneity of the tumour with different presentations and also to the absence of significant activity of the evaluated drugs. Recently, a number of phase II trials using newer chemotherapeutic agents (Gemcitabine and Capecitabine, Irinotecan with 5Fluoro-uracil) suggest better activity and report improved progression-free survival (PFS) (11, 12). Additional data are awaited for targeted therapies including anti VEGF/R (Vascular endothelial growth facor receptors) and multiple RTK inhibitors (Receptor of the Tyrosine Kinase), such as the Sunitinib, Lapatinib, Sorafenib.

TACE is generally accepted as an effective palliative treatment for patients with unresectable HCC and adequate preservation of liver function. Embolic agents have been used to reduce arterial inflow and drug washout and to maximize contact time between the drugs and the tumour (13). The justification of TACE as a palliative treatment for HCC has been strengthened by recent randomised trials and meta-analysis of previous smaller randomised trials (14), and the goal is to deliver maximum concentration of chemotherapeutic agents within the tumour, to make it highly selective with the use of its arteries feeding, reducing the substance concentration in peripheral blood, combined with tumoral vessel obstruction and giving the patient another therapeutic option (15). DEB is a new product specifically designed for TACE. DEB microspheres can be loaded with IRI, a topoisomerase 1 inhibitor. This novel device aims for the combined induction of ischaemia and cellular lysis, which can be achieved more simply using only one step allowing tumoral vessel obstruction and sustained controlled release of the chemotherapeutic agent locally within the tumour. This present case that described TACE of DEB with IRI in one patient with ICC was promising with excellent results at the CT (figure 4) at one month and stability on biological and clinical tests. Although TACE with IRI- DEB was feasible, efficient and well tolerated, the follow-up was too short to define more detailed conclusions. After we obtained this good result, we believe it is suitable to follow the investigation with the IRI as a new palliative treatment of ICC.

TEACHING POINT

TACE with IRI- DEB was feasible, efficient and well tolerated, and we believe it is suitable to follow the investigation of Irinotecan as a new palliative treatment of unresectable ICC.

ABBREVIATIONS

ICC = Intrahepatic cholangiocarcinoma
DEB = Drug eluting beads
IRI = Irinotecan
TACE = Transarterial-chemoembolization
CT = Computed tomography
Fr = French

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FIGURES

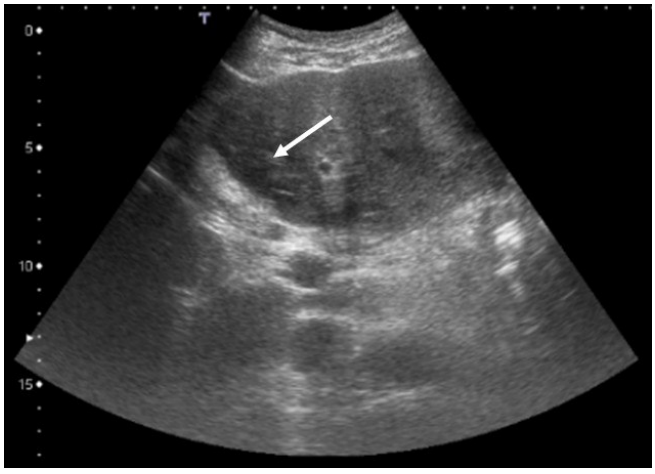

Figure 1: Grayscale ultrasound of the liver demonstrates multiple liver lesions (arrow).

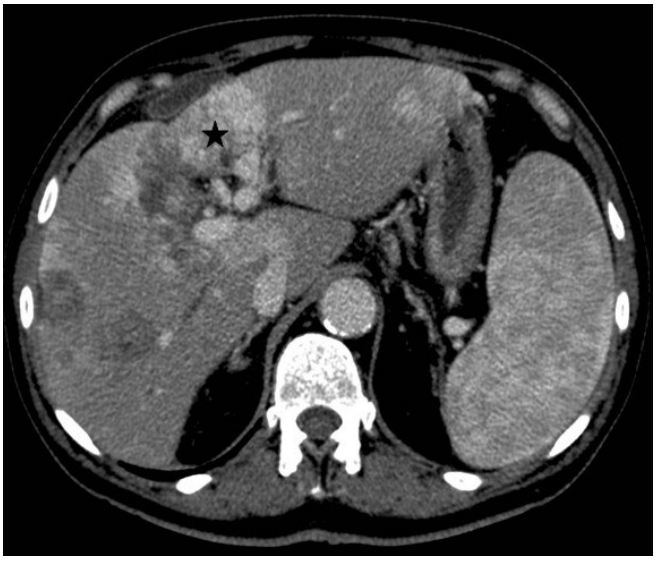

Figure 2: Contrast enhanced CT scan in the arterial phase demonstrates nodular and heterogeneous liver lesions with peripheral hypervascular appearance (black star).

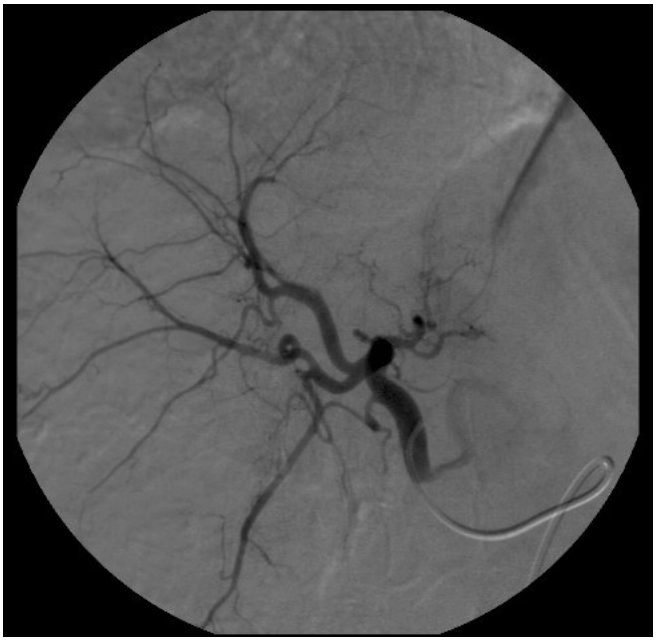

Figure 4: Selective angiography of the right hepatic artery after DEB's injection.

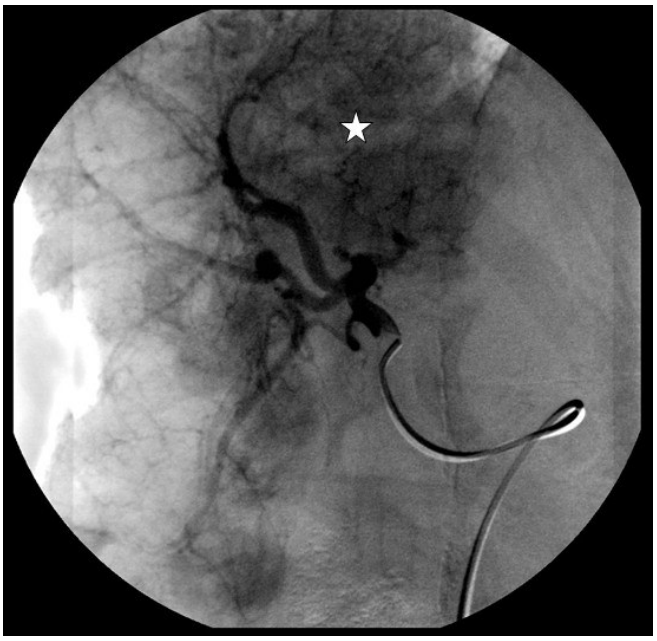

Figure 3: Selective proper hepatic angiogram demonstrates hypervascular intrahepatic masses (white star).

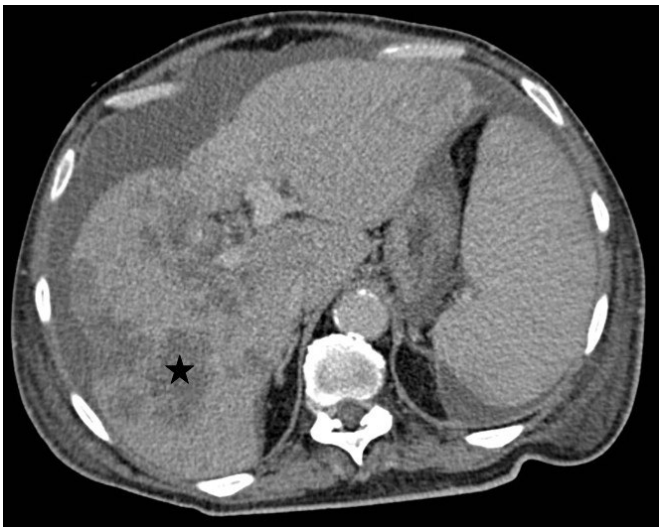

Figure 5: Follow up contrast enhanced CT scan one month after DEB injection reveals development of necrosis and significant decrease of the lesions' vascularization (black star).

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