Introduction

Cholangiocarcinoma (CCA) is rare malignancy that can occur anywhere along the intrahepatic or the extrahepatic biliary tree. Cholangiocarcinoma can be classified as intrahepatic, perihilar, or distal. Hilar CCAs and perihilar CCAs are associated with poor prognosis. Of the 3000 cases seen annually in the United States, less than one-half of the tumors are resectable. Patients typically present with abdominal pain, pruritus, weight loss, and jaundice. Computed tomography (CT), magnetic resonance imaging, and ultrasound are used to diagnose cancer and to characterize biliary lesions. Treatment consists of surgery, radiation therapy, chemotherapy and photodynamic therapy. Standard therapy consists of surgical margin-negative resection with extrahepatic bile duct resection.
duct resection, hepatectomy, and en-bloc lymphadenectomy. Complete resection of a hilar cholangiocarcinoma is the most effective and only potentially curative therapy, and it is now clear that concomitant hepatic resection is required in most cases. However, complete resection is sometimes difficult because of local extensions, which occur perineurally via lymphatic channels, subepithelial spread in the duct wall, and direct invasion of adjacent hepatic arteries or portal veins. Nonresected extrahepatic bile duct carcinoma has a dismal prognosis, with a life expectancy of about 6 months to 1 year.

In oncology, the term hyperthermia refers to the treatment of malignant diseases by administering heat and generating electromagnetic induction. Hyperthermia is usually applied as an adjunct to an already established treatment modality (radiotherapy and chemotherapy), and the goal is to kill tumor cells and influence the increase in tumor immunogenicity. The present study reports the case of a patient with unresectable hilar cholangiocarcinoma who received concurrent hyperthermia and chemotherapy.

Case Report

This case study was approved by the institutional review board of Cheonan Korean Medicine Hospital of Daejeon University (authorization number: DJUMC-P-2017-02).

A 54-year-old man was diagnosed with hilar cholangiocarcinoma (Klatskin tumor) and underwent percutaneous transhepatic biliary drainage at Seoul National University Hospital in June 2016. He was administered neoadjuvant and preoperative 28 days of radiation with 2 cycles of chemotherapy from July to August to be able to perform surgery. The patient was administered cisplatin 25 mg plus gemcitabine 1000 mg on the first and eighth days of a 21-day cycle for 6 weeks. Unfortunately, the tumor did not respond to radiation with chemotherapy and the patient was diagnosed as being unresectable. In July 2016, the patient, presenting with fatigue, dyspepsia, epigastralgia, and jaundice, visited Cheonan Korean Medicine Hospital of Daejeon University (Cheonan, Republic of Korea) to seek a second treatment option. At the time of the patient’s visit, his Eastern Cooperative Oncology Group (ECOG) grade scored 3 points. As a second line therapy, hyperthermia combined with chemotherapy (gemcitabine/cisplatin) was administered a total of 32 times from September to December 2016.

Radiofrequency (RF) hyperthermia was carried out using the REMISSION 1°C device (AdipoLABs Company, Seoul, Korea). Two 12-cm-diameter electrodes were applied in opposition to each other, and 0.46-MHz RF wave was applied. We administered heat to the patient for 70 minutes and measured the surface temperature (39°C to 41°C) continuously. The applied power was gradually increased from 50 to 100 W, depending on the tolerance of the patient.

RF hyperthermia was administered 32 times without the patient exhibiting any critical complications. The carbohydrate antigen 19-9 (CA 19-9) and the total bilirubin levels decreased during treatment (Figures 1 and 2). The patient’s ECOG grade had improved from 3 to 2 points. The several symptoms of fatigue, dyspepsia, epigastralgia, and jaundice were reduced. Judging from National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0, fatigue was improved from grade 3 to 1 and dyspepsia was improved from grade 2 to 1. The size of tumor during concurrent hyperthermia and chemotherapy was measured by using CT scans; no progression was noted (Figure 3). Thus, we verified stable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Discussion

CCA may arise anywhere within the biliary tree, but tumors involving the biliary confluence (hilar CCAs) are the most common. CCA accounts for 3% of all gastrointestinal tumors. Over the past 3 decades, the overall incidence of CCAs appears to have increased. The percentage of patients who survive 5 years after diagnosis has not increased during this time period, remaining at 10%. In several studies published over the past three decades, the proportion of patients with hilar tumors has remained fairly constant at 40% to 60%, with the remaining tumors arising from intrahepatic biliary radicles or the distal bile duct. Even though resection is well established as the conventional treatment, early transitions can occur, and at the time of discovery, surgery to remove the tumor is performed in one-third, or fewer, of the cases. The majority of patients with unresectable bile duct cancer die within 12 months of diagnosis, often from hepatic failure or infectious complications secondary to biliary obstruction. The prognosis has been considered to
be worse for lesions involving the biliary confluence than for distal lesions.\textsuperscript{11}

Hyperthermia is the process of raising the body temperature, either locally or globally, for medicinal purposes. Hyperthermia can kill or weaken tumor cells without affecting normal cells. Tumor cells, with disorganized and compact vascular structures, have difficulty dissipating heat. Hyperthermia may, therefore, let cancerous cells undergo apoptosis in direct response to applied heat while healthy tissues can more easily maintain normal temperature. Even if the cancerous cells do not die outright, they may become more susceptible to ionizing radiation therapy or to certain chemotherapy drugs, which may allow such therapy to be given in smaller doses.\textsuperscript{6} Hyperthermia generates electromagnetic induction, selectively deposits energy on the cell membrane, and induces apoptosis more efficiently.\textsuperscript{14,15} Also, hyperthermia can cause the generation of circumstantial antitumor immunity, influence the increase in tumor immunogenicity due to hydrostatic pressure and lead to immunogenic cell death.\textsuperscript{7}

Hyperthermia is rarely used as a single cancer treatment modality and is usually added to radiation therapy, chemotherapy, or radiochemotherapy, and recently to gene and immunotherapy. Many studies on hyperthermia are being conducted continuously in the field of oncology.\textsuperscript{16-18} As to CCA, a case series of 8 patients on regional hyperthermia with 8 MHz frequency in combination with chemoradiation therapy was reported to be a promising treatment, increasing both local control and long-term survival.\textsuperscript{19} The higher the frequency, the greater the attenuation and the lower is the penetration.\textsuperscript{20} The REMISSION 1°C device has a frequency of 0.46 MHz, the lowest frequency ever reported. A case study reported good result on a patient suffering from recurred hepatocellular carcinoma, in which the REMISSION 1°C device was combined with sorafenib.\textsuperscript{21} In this case study, the hyperthermia treatment was done using the REMISSION 1°C device and was combined with chemotherapy (gemcitabine/cisplatin).

The present case report shows the efficacy of combined RF hyperthermia and chemotherapy for the treatment of
patient with unresectable extrahepatic bile duct carcinoma. After the treatment, the CA 19-9 and the total bilirubin levels have been lowered. The patient’s symptoms, fatigue, dyspepsia, epigastralgia, and jaundice, were alleviated because of the combined treatment. Judging from NCI-CTCAE version 4.0, severe toxicity was not observed. The patient experienced no critical complications during treatment, and he remained in fine condition. The general toxicity observed in gemcitabin/cisplatin combination is febrile neutropenia, bleeding, anorexia, nausea, fatigue, and reduced white blood cell count, and so forth. Judging from NCI-CTCAE version 4.0, severe toxicity was not observed. The patient did not suffer from febrile neutropenia or bleeding. White blood cell count maintained a normal range. Anorexia, nausea, and fatigue were improved. And the patient’s ECOG grade had improved from 3 to 2 points. Although the results of the CT scans of the patient showed no improvement, neither did they indicate any progression of the disease, according to RECIST version 1.1.

To assure the quality for clinical studies in regional deep hyperthermia, the temperature in the target volume and in the area surrounding the target volume must be recorded. The REMISSION 1°C device used in this study did not allow that to be done, which is a limitation of this case study.

Based on these results, hyperthermia is thought to have contributed, at least in part, to the patient’s remaining in fine condition and to the reduced toxic effect of chemotherapy. The present case report suggests that RF hyperthermia combined with chemotherapy may be a treatment option for patient with unresectable cholangiocarcinoma.

Declaration of Conflicting Interests
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