Cancer Res Treat. 2010;42(4):235-238 DOI 10.4143/crt.2010.42.4.235

Case Report Open Access

A Case of Combined Hepatocellular-Cholangiocarcinoma with Favorable Response to Systemic Chemotherapy

Gun Min Kim, M.D.[1]
Hei-Cheul Jeung, M.D.[1]
Dokyung Kim, M.D.[2]
Joo Hoon Kim, M.D.[1]
Sang Hyun Yoon, M.D.[1]
Eun Suk Jung, M.D.[1]
Sang Joon Shin, M.D.[1]

[1]Division of Oncology, Department of Internal Medicine, [2]Department of Pathology, Yonsei University College of Medicine, Seoul, Korea

Correspondence: Sang Joon Shin, M.D.
Division of Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Sinchon-dong, Seodaemun-gu, Seoul 120-752, Korea
Tel: 82-2-2227-4152
Fax: 82-2-2228-8124
E-mail: SSJ338@yuhs.ac
Received May 4, 2010
Accepted May 23, 2010

Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare form of primary liver cancer composed of cells with histopathologic features of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). Because of its low incidence, the information on clinical outcomes of cHCC-CC is very limited and there are no published reports describing non-surgical treatment options for cHCC-CC. We report a case of cHCC-CC exhibiting a favorable response to systemic chemotherapy with doxorubicin and cisplatin. A 62-year-old man who recurred after a right lobectomy for cHCC-CC received sorafenib for palliative systemic therapy, but follow up imaging studies showed disease progression. He received 2nd line chemotherapy with doxorubicin at 60 mg/m^2 together with cisplatin at 70 mg/m^2. After 2 cycles of chemotherapy, a computed tomography scan of the chest showed markedly decreased size and number of the multiple lung metastases. After completing 8 cycles of 2nd line therapy, we changed the regimen to a fluorouracil (5-FU) mono therapy because of the toxicities associated with doxorubicin and cisplatin. To date, the patient has completed his 15th cycle of 5-FU mono therapy with the disease status remaining stable during 18 months of follow-up.

Key words
Cholangiocarcinoma, Hepatocellular carcinoma, Doxorubicin, Cisplatin

Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CC) is a rare form of primary liver cancer composed of cells with histopathologic features of both hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). It accounts for up to 14.3% of primary liver cancers, with incidence varying between multiple studies (1-4). cHCC-CC was first described in 1949 by Allen and Lisa (2), but the demographics and clinical features of these tumors remain ill-defined. In addition, the diagnostic features are not well established, which may have contributed to the variability in clinical outcomes (1,3-5). To our knowledge, surgery is the only treatment modality offering possibility for a cure (6), and there are at present no published reports describing non-surgical treatment options for cHCC-CC. For patients with disseminated disease, systemic chemotherapy may be an option, but no known treatment to date has demonstrated any chance of significantly improving survival. We report a case of cHCC-CC exhibiting a favorable response to systemic chemotherapy with doxorubicin and cisplatin.

Case Report

A 62-year old man was admitted to our hospital for recurrence of cHCC-CC. He was diagnosed as stage II HCC (T2N0M0) by tumor marker and imaging study in February 2004. The patient did not have any known risk factors for HCC and thus underwent a right lobectomy at that time. Surgical pathologic report revealed cHCC-CC (Fig. 1). Four years after the operation, a computed tomography

(CT) scan of the chest showed multiple lung metastasis, along with a whole body bone scan (WBBS) revealing multiple bone metastasis (T-spine, rib, scapula). At the time of recurrence, laboratory tests including a liver function test were normal and his overall performance status was categorized as good. He received 1st line palliative therapy with sorafenib from July 2008 to September 2008, but a follow up imaging study showed disease progression with further lung metastasis (Fig. 2) and a PIVKA-II elevated to more than 2,000 mAU/mL.

He then received 2 cycles of palliative therapy with doxorubicin and cisplatin (AC regimen, doxorubicin 60 mg/m^2 day 1, cisplatin 70 mg/m^2 day 1 of a 3-week cycle) as 2nd line treatment.

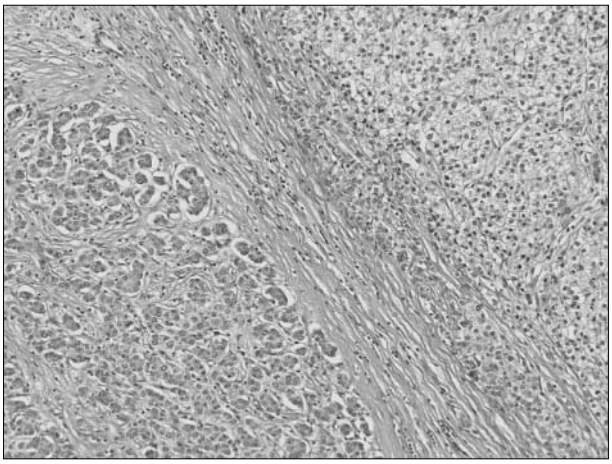

Fig. 1. Pathologic features of the combined hepatocellular-cholangiocarcinoma. There were two components - hepatocellular element showing bile production, an intercellular bile canaliculi, and a cholangiocellular component showing mucin production or definite gland formation. There was no transition from the hepatocellular carcinoma (right) to the cholangiocarcinoma (left) (H&E, ×100).

Surprisingly, a CT scan of the chest after the 2nd cycle of therapy showed markedly decreased size and number of his multiple hematogenous lung metastases (Fig. 3) and in addition his PIVKA-II returned to within normal range. After 6 more cycles of chemotherapy, the maintenance of response was confirmed by follow up imaging studies. Toxicities associated with the AC regimen (grade 2 neutropenia and grade 2 neuropathy) were manageable with supportive care.

After a total of 8 cycles of therapy with the AC regimen, he presented with a grade 3 neuropathy, but no symptomatic cardiac function abnormalities. However, considering the accumulation dose of doxorubicin and grade 3 neuropathy associated with cisplatin, we changed his regimen to intravenous fluorouracil (5-FU) mono therapy (1,000 mg/m^2 day 1 to 4 continuous infusion for a 3-week cycle). To date, he has completed his 15th cycle of 5-FU mono therapy with the disease status remaining stable during 18 months of follow-up.

Discussion

Almost all primary liver carcinomas are broadly classified as either HCC, derived from hepatocytes, or CC, arising from intrahepatic bile duct epithelium. Cases involving both hepatocellular and cholangiocellular components in the same tumor have been designated as cHCC-CC. According to the World Health Organization tumor classification system, cHCC-CC is defined as a tumor in which both HCC and CC components coexist in either the same tumor or the same liver (1,7). As HCC and CC differ in their clinical characteristics including etiology and epidemiology, cHCC-CC is thought to be a result of dual differentiation of hepatic precursor cells toward hepatocytes and biliary epithelia based on clinicopathologic studies (8).

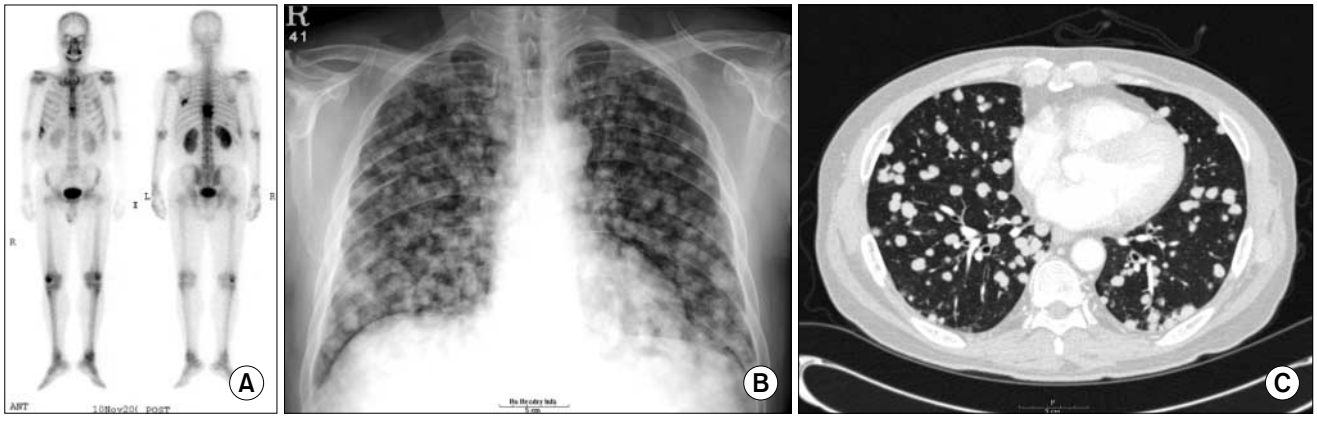

Fig. 2. The follow up imaging studies at disease progression after 2 cycles of sorafenib. (A) Whole body bone scan showed multiple uptakes in T-spine, left scapula, ribs. (B) Chest radiograph showed bilateral multiple various sized lung nodules. (C) CT scan of chest showed innumerable hematogenous lung metastasis.

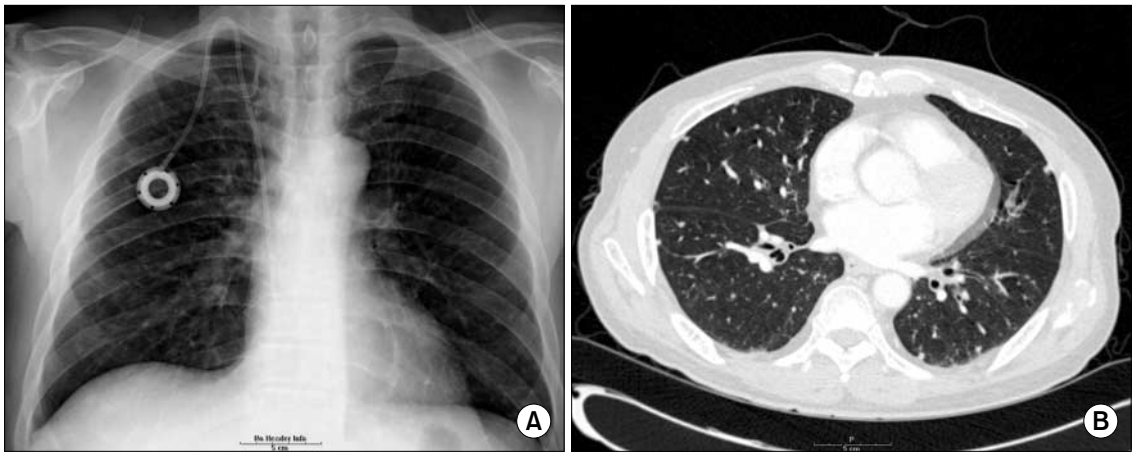

Fig. 3. The follow up imaging studies after 2 cycles of chemotherapy with doxorubicin and cisplatin. (A) Chest radiograph showed much improved hematogeneous lung metastasis. (B) CT scans of chest showed markedly decreased size and number of multiple hematogenous lung metastases.

Two histopathologic classification schemes for these tumors have been described. Allen and Lisa classified cHCC-CC into the three categories: 1) separate tumors, each composed of only one type of cell; 2) contiguous tumors, each of a different cell type that may mingle as they grow; and 3) individual lesions that have both types of cells and are interpreted to have arisen from the same site (2). Goodman et al. (1) also classified three types: 1) Type I or "collision tumors"; 2) Type II or "transitional tumors"; 3) Type III or "fibrolamellar tumors." In our case, there is no transition from the hepatocellular components to the cholangiocellular components and thus we may define this case as type I or collision tumors (Fig. 1).

The incidence of cHCC-CC varies between studies, as 1.0 to 6.3% in Asia (3,8-10) and 2.4 to 14.3% in Western countries (1-4). Because of its low incidence, information on the prognosis of patients with cHCC-CC is very limited and the reported clinical outcomes vary and may not accurately represent the actual prognosis of patients with cHCC-CC (3,5,6).

Surgery is the only treatment offering the possibility of a cure at the present time (6). However, commonly combined liver cirrhosis has the potential for serious complications, so strict selection of patients is required, taking into consideration any pre-existing cirrhosis, general physical condition, tumor extent as examples (6,11,12). Currently, aggressive treatments including liver transplantation have been attempted on cHCC-CC patient (13). However, further data regarding long term outcomes with liver transplantation in the treatment of cHCC-CC is required.

Transarterial chemoembolization (TACE) and percutaneous treatments such as percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are the most widely used management treatments for unresectable HCC and post resection recurrence. However, to our knowledge, cHCC-CCs are more fibrotic and less vascular than HCC (14). As a result, they are less responsive to local treatments like TACE or PEI (15). For disseminated disease, systemic chemotherapy may be an option, but there is little data supporting its role in the treatment against cHCC-CC.

In our case, the patient was diagnosed with cHCC-CC after a right lobectomy was performed for a liver mass. After a 4-year postoperative period, cHCC-CC recurred presenting as multiple lung metastasis with high levels of PIVKA-II. The patient first received sorafenib as a 1st line palliative therapy, but the disease was refractory to this chemotherapy. We then chose a combination of doxorubicin and cisplatin as a 2nd line chemotherapeutic regimen with favorable results as almost all multiple lung nodules disappeared. After completing 8 cycles of therapy with the AC regimen, he was then amended to receive 15 cycles of 5-FU mono therapy due to the toxicities associated with AC. This long period of disease control is a very encouraging result and requires further investigation in clinical trials.

References

1. Goodman ZD, Ishak KG, Langloss JM, Sesterhenn IA, Rabin L. Combined hepatocellular-cholangiocarcinoma. A histologic and immunohistochemical study. Cancer. 1985;55:124-35.
2. Allen RA, Lisa JR. Combined liver cell and bile duct carcinoma. Am J Pathol. 1949; 25:647-55.
3. Jarnagin WR, Weber S, Tickoo SK, Koea JB, Obiekwe S, Fong Y, et al. Combined hepatocellular and cholangiocarcinoma: demographic, clinical, and prognostic factors. Cancer. 2002;94:2040-6.
4. Koh KC, Lee H, Choi MS, Lee JH, Paik SW, Yoo BC, et al. Clinicopathologic features and prognosis of combined hepatocellular cholangiocarcinoma. Am J Surg. 2005;189:120-5.
5. Hayashi H, Beppu T, Ishiko T, Mizumoto T, Masuda T, Okabe K, et al. A 42-month disease free survival case of combined hepatocellular-cholangiocarcinoma with lymph node metastases treated with multimodal therapy. Gan To Kagaku Ryoho. 2006;33:1941-3.
6. Kassahun WT, Hauss J. Management of combined hepatocellular and cholangiocarcinoma. Int J Clin Pract. 2008;62:1271-8.

7. Tanaka S, Yamamoto T, Tanaka H, Kodai S, Ogawa M, Ichikawa T, et al. Potentiality of combined hepatocellular and intrahepatic cholangiocellular carcinoma originating from a hepatic precursor cell: Immunohistochemical evidence. Hepatol Res. 2005;32:52-7.
8. Yano Y, Yamamoto J, Kosuge T, Sakamoto Y, Yamasaki S, Shimada K, et al. Combined hepatocellular and cholangiocarcinoma: a clinicopathologic study of 26 resected cases. Jpn J Clin Oncol. 2003;33:283-7.
9. Taguchi J, Nakashima O, Tanaka M, Hisaka T, Takazawa T, Kojiro M. A clinicopathological study on combined hepatocellular and cholangiocarcinoma. J Gastroenterol Hepatol. 1996;11:758-64.
10. Maeda Y, Nishida M, Mori N, Tamesa T, Okada T, Tangoku A, et al. Combined hepatocellular carcinoma and cholangiocellular carcinoma. Nippon Rinsho. 2001;59(Suppl 6):401-5.
11. Shimoda M, Kubota K. Multi-disciplinary treatment for cholangiocellular carcinoma. World J Gastroenterol. 2007;13:1500-4.
12. Kim KH, Lee SG, Park EH, Hwang S, Ahn CS, Moon DB, et al. Surgical treatments and prognoses of patients with combined hepatocellular carcinoma and cholangiocarcinoma. Ann Surg Oncol. 2009;16:623-9.
13. Chan AC, Lo CM, Ng IO, Fan ST. Liver transplantation for combined hepatocellular cholangiocarcinoma. Asian J Surg. 2007;30:143-6.
14. Chantajitr S, Wilasrusmee C, Lertsitichai P, Phromsopha N. Combined hepatocellular and cholangiocarcinoma: clinical features and prognostic study in a Thai population. J Hepatobiliary Pancreat Surg. 2006;13:537-42.
15. Dick EA, Taylor-Robinson SD, Thomas HC, Gedroyc WM. Ablative therapy for liver tumours. Gut. 2002;50:733-9.