Original Article

Systemic therapy for unresectable, mixed hepatocellular-cholangiocarcinoma: treatment of a rare malignancy

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Background: Combined hepatocellular-cholangiocarcinoma (HCC-CC) has a reported incidence of less than 5% of primary hepatic malignancies. The treatment approach to this malignancy is undefined. Our objective of this case series is to provide some insight into chemotherapy and/or targeted therapy in this setting.

Methods: Pathologic and radiographic review confirmed seven combined HCC-CC patients during a 5-year time frame [2009–2014]. Data points were demographics, chemotherapy and/or targeted therapy given in the first and second-line setting, localized treatment if given, first radiographic result, progression-free survival (PFS), and overall survival (OS).

Results: Seven patients were identified. Front-line treatment showed a median PFS of 3.4 months. Total median OS was 8.3 months. Regimens given included gemcitabine alone +/– bevacizumab, gemcitabine + platinum (GP) +/– bevacizumab, and sorafenib. Front-line treatment with these regimens showed progressive disease in 71% (5 patients) on first radiographic scan with all patients who received sorafenib front-line progressing at that restaging. Disease-control (complete response + partial response + stable disease) was seen in 29% of patients (2 patients) with 1 patient receiving GP and 1 patient receiving gemcitabine + bevacizumab. Of note, 2 patients that received GP +/– bevacizumab in the second-line setting had disease control on first radiographic scan.

Conclusions: Our retrospective review speaks to the rarity of this malignancy and challenges that are associated with its diagnosis and treatment. GP +/– bevacizumab showed disease control in first or second-line treatment in 3 patients. Treatment with this regimen in this rare malignancy subgroup warrants further investigation.

Keywords: Carcinoma; hepatocellular; cholangiocarcinoma (CC); antineoplastic agents

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Introduction

Combined hepatocellular-cholangiocarcinoma (HCC-CC) represents a small percentage (0.4–4.7%) of primary hepatic malignancies (1-3). Given the rarity of this disease, there are no clear treatment guidelines for advanced HCC-CC. The World Health Organization defines this malignancy as a tumor unequivocally admixed with both hepatocellular and CC (3). Surgical resection is the mainstay curative option;

Table 1 Pathology

Case	Diagnosis	Components	Positive IHC	Negative IHC
1 (biopsies)	Mixed hepatocellular cholangiocarcinoma	Both hepatocellular and cholangiocarcinoma component	HCC-HepPar-1, alpha-fetoprotein, CK7; cholangio-CK7	Melan A, TTF-1, CK20; cholangio-HepPar-1, alpha-fetoprotein
2 (biopsies)	Moderately differentiated adenocarcinoma	Both hepatocellular and cholangiocarcinoma component	Cholangio-CK7, MOC31	CK20, HepPar-1, polyclonal CEA, synaptophysin, chromogranin
3 (biopsy)	Mixed hepatocellular cholangiocarcinoma	Both hepatocellular and cholangiocarcinoma component	Pan CK, pCEA, Glpican-3, HepPar-1, VK7, CK20, MOC31, CDX-2	Pax-8, TTF-1, p63, inhibin, CD10
4 (biopsy)	Mixed hepatocellular cholangiocarcinoma	Both hepatocellular and cholangiocarcinoma component	HCC-pCEA, CD10; cholangio-CK7	HepPar-1, glypican-3, CK20, CDX-2, Pax-8, TTF-1, GATA-3, CDX-2, ER
5 (biopsy)	Poorly differentiated adenocarcinoma	Both hepatocellular and cholangiocarcinoma component	CK20, CK7, HepPar-1	CDX-2, TTF-1, HepPar-1
6 (biopsy)	Mixed hepatocellular cholangiocarcinoma	Both hepatocellular and cholangiocarcinoma component	HepPar-1	Glypican-3, mCEA
7 (biopsy)	Mixed hepatocellular cholangiocarcinoma	Both hepatocellular and cholangiocarcinoma component	CK7, CK19, Glypican-3, AFP, CK20	HepPar-1, synaptophysin, chromogranin, tTF-1, p63, CDX-2, TTF-1

IHC, immunohistochemistry; HepPar-1, hepatocyte paraffin 1 monoclonal antibody; pCEA, polyclonal carcinoembryonic antigen.

however, higher recurrence rates and shorter disease-free survival in HCC-CC have been reported compared to each separate malignancy (2,4-6). Liver transplantation appears to have poorer survival for combined HCC-CC in relation to HCC alone, although results are conflicting (2,7,8). Systemic therapy experience is limited to small case reports with regimens including sorafenib, doxorubicin + cisplatin, gemcitabine + cisplatin, fluorouracil monotherapy, and fluorouracil + oxaliplatin (9,10). With our case series, we aim to add to the existing knowledge with our institutional experience.

Methods

Our hepatobiliary database was reviewed during a 5-year time frame [2009–2014] for patients treated as mixed HCC-CC based on patient presentation, radiologic review, and multidisciplinary discussion. Of the 27 patients initially identified, seven were found to be independently confirmed by radiographic review as mixed HCC-CC and pathologically confirmed independently as either having a mixed HCC-CC diagnosis or having adenocarcinoma with both HCC and CC features. Pathologic features of these seven cases are listed in detail in *Table 1*. Similar to other reports, immunohistochemical (IHC) features identified for HCC were hepatocyte paraffin 1 monoclonal antibody (HepPar-1), polyclonal carcinoembryonic antigen (pCEA), and CD10 with CC features of cytokeratin 7 (CK7), cytokeratin 19 (CK19), MOC31 (1,2).

Data collection points included baseline demographics (age, gender, race, birth geographic region), relevant medical history such as hepatitis B or C (HBV or HCV) or cirrhosis, diagnosis date, carbohydrate antigen 19-9 (CA19-9) at baseline; alpha-fetoprotein (AFP) at baseline; first-line therapy, localized therapy if utilized, second-line therapy, progression date, and death date or last follow-up. Outcomes reported were disease control rate first scan result on first-line or second-line treatment, progression-free survival (PFS), and overall survival (OS). Response was determined at first radiographic reimaging and was classified as disease-control (complete response + partial response + stable disease) or progression. Progression

Table 2 Demographics

Case	Age/gender	Race/birth geographic region	Hepatitis/cirrhosis	CA19-9 elevation baseline	AFP elevation baseline
1	64/male	Caucasian/USA	+ HCV/+ cirrhosis	NR	NR
2	52/female	Caucasian/USA	None	No	No
3	34/female	Asian/China	+ HBV	Yes	Yes
4	57/female	Caucasian/USA	None	NR	NR
5	56/male	Caucasian/USA	+ HCV/+ cirrhosis	Yes	Yes
6	49/male	Asian/Southeast Asia	+ HCV/+ cirrhosis	Yes	Yes
7	61/female	Caucasian/USA	None	NR	NR

CA19-9, carbohydrate antigen 19-9; AFP, alpha-fetoprotein; HCV, hepatitis C virus; HBV, hepatitis B virus; NR, not reported; USA, United States of America.

Table 3 First and second-line treatment

Case	1st line treatment	Localized therapy	1st radiographic scan result	1st line PFS	2nd line treatment	2nd line treatment radiographic scan	2nd line PFS	OS
1	Gemcitabine + bevacizumab	None	Progression	2.4 months	None	N/A	N/A	4.5 months
2	Gemcitabine + cisplatin	IMRT given after 1st line therapy	Disease control	17 months	FOLFIRI	Progression	3.5 months	32.8 months
3	Sorafenib	Stereotactic radiation given after 1st line therapy	Progression	2.7 months	None	N/A	N/A	3.3 months
4	Sorafenib	None	Progression	6.9 months	Gemcitabine + oxaliplatin + bevacizumab	Disease control	6.5 months	14.5 months
5	Gemcitabine	None	Progression	3.6 months	None	N/A	N/A	5.3 months
6	Gemcitabine + bevacizumab	None	Disease control	7.3 months	None	N/A	N/A	8.3 months
7	Trial with sorafenib	None	Progression	2.3 months	Gemcitabine + oxaliplatin	Disease control	8.5 months	17.5 months

PFS, progression-free survival; OS, overall survival; IMRT, intensity-modulated radiation therapy.

included patients who discontinued therapy due to toxicity. PFS was defined from the start of therapy to radiographic progression/toxicity withdraw or last follow-up, and OS was defined from the diagnosis date to date of death or last follow-up. Descriptive statistics were used with continuous variables described using median or mean, and range with categorical data summarized using frequencies and percentages.

Results

Individual patient details and outcomes are summarized in *Tables 2* and *3*, respectively. Mean age was 53-year-old (range, 34–64 years) with most (57%) patients being female. A total of 57% had HBV or HCV with 42% having cirrhosis. When reported, CA19-9 and AFP were elevated at baseline in most cases. Regimens used in first-line were sorafenib (3 patients), gemcitabine + bevacizumab (2 patients),

gemcitabine alone (1 patient), and gemcitabine plus cisplatin (1 patient). Seventy-one percent had progressive disease at first reimaging. Disease control was seen in two patients; one patient received gemcitabine plus platinum and one patient received gemcitabine + bevacizumab. All first-line sorafenib patients progressed at first radiographic evaluation. Front-line treatment only showed a median PFS of 3.4 months (range, 2.3–7 months).

Three patients went on to receive second-line therapy after progression and showed a median PFS of 6.5 months (range, 3.5–8.5 months). Regimens given second-line were gemcitabine + oxaliplatin (1 patient), gemcitabine + oxaliplatin + bevacizumab (1 patient), and fluorouracil + leucovorin + irinotecan (FOLFIRI) (1 patient). The two patients who receive gemcitabine + oxaliplatin with or without bevacizumab had disease control on first-scan. The patient that received FOLFIRI in the second-line had progression on first-scan. Of note, all patients who received a platinum (cisplatin or oxaliplatin) in combination with gemcitabine during their disease showed disease control with this regimen regardless of timing of therapy. These three patients had an impressive median OS of 17.5 months. The median OS of the entire cohort was 8.3 months (range, 3.3–32.8 months). Of note, our patient that had a prolonged survival (32.8 months) received localized intensity-modulated radiation therapy (IMRT) after first-line disease control with gemcitabine + cisplatin.

Discussion

Our case review confirms the rarity of combined HCC-CC and the issues that surround its diagnosis with only 7 out of 27 patients having both radiographic and pathologically confirmation after initial multidisciplinary review. Baseline clinical characteristics for combined HCC-CC have been conflicting and appear dependent on the geographic location (1,2). Our case series showed overlapping characteristics for both individual malignancies: elevation in CA19-9, AFP, cirrhosis, and hepatitis history; however our limited size and diverse patient geographic distribution makes it difficult to determine which are more prominent for this mixed tumor type.

Similar to the poor outcomes seen in HCC-CC with surgical resection and transplantation, systemic therapy appears to only minimally impact survival (1,2,5-8). Our case series demonstrates a median PFS of 3.4 months with front-line therapy and a median OS of 8.3 months. Sorafenib, FDA approved for front-line treatment of advanced HCC, has a median PFS and OS of 5.5 and 10.7 months, respectively (11). Additionally, in CC, gemcitabine plus cisplatin in the front-line setting has a median PFS of 8 months and median OS of 11.7 months based on the phase III ABC-02 study (12). Our case series indicated poorer outcomes when HCC-CC was treated similarly to these two separate malignancies.

Rare malignancies such as HCC-CC often rely on case reports, anecdotal experience, and extrapolating from more common malignancies in order to provide a guide for rational treatment decision-making. Although our case series carries limitations, gemcitabine + platinum (GP) with or without bevacizumab showed disease control in all patients (3 patients) that received this treatment in the first or second-line setting. Patients with advanced combined HCC-CC disease that are deemed unresectable need viable treatment options. Our small case series suggests a regimen that may have efficacy in this difficult disease and warrants further investigation.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by Institutional Review Board of U.T. M.D. Anderson Cancer Center (PA11-1209) and a waiver of consent was granted due to patients lost to follow-up, no longer at the institution, or expired.

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