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Contents

Monthly Volume 16 Number 5 May 27, 2024

EDITORIAL

REVIEW

MINIREVIEWS

World Journal of Hepatology

Monthly Volume 16 Number 5 May 27, 2024

Contents

World Journal of Hepatology

Monthly Volume 16 Number 5 May 27, 2024

Contents

ABOUT COVER

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MINIREVIEWS

Combined hepatocellular cholangiocarcinoma: A clinicopathological update

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Abstract

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare primary liver cancer associated with an appalling prognosis. The diagnosis and management of this entity have been challenging to physicians, radiologists, surgeons, pathologists, and oncologists alike. The diagnostic and prognostic value of biomarkers such as the immunohistochemical expression of nestin, a progenitor cell marker, have been explored recently. With a better understanding of biology and the clinical course of cHCC-CCA, newer treatment modalities like immune checkpoint inhibitors are being tried to improve the survival of patients with this rare disease. In this review, we give an account of the recent developments in the pathology, diagnostic approach, and management of cHCC-CCA.

Key Words: Combined hepatocellular-cholangiocarcinoma; Immunotherapy; Nestin; Hepatocellular carcinoma; Cholangiocarcinoma; Liver cancer; Biomarker; Immune checkpoint inhibitors; Pathology; Genomic landscape

Core Tip: Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) represents a poorly understood rare primary liver tumor with a gruesome prognosis. Molecular and genetic characterization of this disease is vital for exploring newer treatment modalities to improve the survival of patients afflicted with this rare entity. In this review, we give an account of the recent developments in the pathology, diagnostic approach, and management of cHCC-CCA.

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INTRODUCTION

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare primary liver cancer with morphological features of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA). This unique cancer is drawing increasing clinical and pathological consideration due to its heterogenous morphological features, molecular characteristics, aggressive clinical nature, and diagnostic difficulties. The incidence of cHCC-CCA has been rising, probably because of its increased recognition in surgical specimens[1]. The natural history of this rare entity is still not fully understood. The ambiguous and complex nature of this cancer makes early diagnosis difficult for primary physicians and radiologists. Recently, the World Health Organization (WHO) updated its histological classification system for cHCC-CCA. Over the last decade there has been increasing interest and enthusiasm to explore the diagnostic and prognostic value of the immunohistochemical expression of a protein called 'nestin' in patients with cHCC-CCA[2,3]. This minireview focuses on the recent developments in the histological and genetic features of cHCC-CCA.

EPIDEMIOLOGY AND CLINICAL FEATURES

cHCC-CCA accounts for 0.4%-14.2% of all primary liver cancers depending on geographical location, risk factors, and criteria used for inclusion[4-9]. In the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute database, cHCC-CCA accounted for 0.77% of the cases[5]. The true incidence of cHCC-CCA is, however, likely to be underestimated, as most patients do not undergo liver resection or transplantation and may have thus been wrongly diagnosed with either hepatocellular or biliary cancer clinically. cHCC-CCA carries a poorer prognosis overall than HCC and iCCA alone[10]. Risk factors for cHCC-CCA include hepatitis B virus infection, hepatitis C virus infection, alcohol consumption, and primary sclerosing cholangitis[11]. Reports of cHCC-CCA are available in both cirrhotic and noncirrhotic livers, in contrast to HCC which is more common in cirrhosis, and iCCA, which is more common in patients with noncirrhotic liver[12]. Asian studies have shown male predominance. However, studies from Western countries have shown no gender predilection[13]. The median age at diagnosis of cHCC-CCA is sixth to seventh decade. Clinical signs and symptoms of cHCC-CCA are most often associated with the advanced stage of the cancer and may include weakness, jaundice, loss of weight, or abdominal discomfort. Few patients may present with increased levels of both alpha-fetoprotein (AFP) and CA 19-9 serum levels, suggesting the ambiguous nature of cHCC-CCA[14].

CELL OF ORIGIN

Although the cell of origin of cHCC-CCA remains elusive, various hypotheses have been proposed, such as: (1) Incidental coexistence of HCC and iCCA within the same cancer; (2) malignant transformation of a hepatic stem cell; and (3) dedifferentiation of an HCC or an iCCA.

EVOLUTION OF CHCC-CCA CLASSIFICATION

The definition of cHCC-CCA has evolved over time. Wells *et al* described the first case of cHCC-CCA more than 100 years ago and suggested the common embryological development of both hepatocytes and cholangiocytes as the origin of cHCC-CCA[14]**.** Fifty years later, ALLEN and LISA[15] reported 5 cases of mixed liver cancers and classified them into three types: (1) Separate nodules of hepatocellular and cholangiocarcinoma (CCA) (double); (2) contiguity with intermingling (combined); and (3) intimately associated due to origin from the same focus (mixed). Calderaro *et al*[2] in 1954 reported that 4% of primary liver cancer show both hepatocellular and biliary differentiation. In 1985, Goodman *et al* [16] reviewed 24 cases of cHCC-CCAs and modified cHCC-CCA classification into Type I or "collision tumors," displaying the occurrence of both HCC and CCA separately, Type II or "transitional tumors," in which there were areas of intermediate differentiation and an identifiable transition between HCC and iCCA and Type III or "fibrolamellar tumors" containing mucin-producing pseudoacini[16]. Currently, only the subtype with an intimate intermixing of HCC and CCA elements, labeled as type 3 tumor by ALLEN and LISA[15] and type II (transitional) tumor by Goodman *et al* [16] are considered as cHCC-CCA.

The WHO 2000 classification defined cHCC-CCA as a tumor containing both hepatocellular and distinct or separate CCA[17,18]. The tumor should show the presence of both bile and mucin. Immunohistochemical expression of polyclonal CEA and Hep Par was suggested for the hepatocellular component and demonstration of neutral mucin by the PAS-diastase reaction for the biliary component. The WHO 2010 Classification redefined this cancer, which ran into

controversy for various reasons. They proposed a classical type of cHCC-CCA (tumor containing unequivocal, intimately mixed elements of both HCC and iCCA), and cHCC-CCA with stem/progenitor cell features having 3 subtypes: Typical, intermediate cell, and cholangiocellular[19]. The consensus classification published in 2019 by WHO put forwarded the definition of cHCC-CCA as a primary hepatic cancer with unequivocal existence of both hepatocytic and cholangiocytic differentiation within a single tumor and recommended that the diagnosis should be based on morphology only[17]. Pathologists can perform immunostaining to confirm both histologic components, but the diagnosis should not be designated on immunostaining alone. There was no further subcategorization as progenitor cells can be seen in all forms of cHCC-CCA and there is no clinical relevance of subclassification. This was also suggested in a recently published consensus paper[20]. If stem/progenitor cells are identified in a tumor, the pathologist can mention it in the comments section of the pathology report. A separate category of intermediate carcinoma is added in the 2019 WHO classification. Cholangiocellular carcinoma is a biliary-derived tumor and is now classified as iCCA[21].

PATHOLOGICAL AND IMMUNOHISTOCHEMICAL FEATURES

Careful grossing of cHCC-CCA is recommended and all areas with any area showing change in tumor color, texture, and firmness should be adequately sampled[20]. The hepatocellular component in cHCC-CCA shows all growth patterns described for HCC including variable-sized trabeculae, pseudoglands, and arrangement in sheets (Figure 1). Similarly, all forms of cytological features and cellular differentiation are also reported. The cholangiocytic component shows malignant acini embedded in desmoplastic stroma and can be well or poorly differentiated. There is no minimum amount of hepatocytic and cholangiocytic components that certifies cHCC-CCA diagnosis. One can identify reactive ductular reaction at the edge of HCC and this should not be considered as a malignant cholangiocytic component. Both malignant components may be intermingled, or lie in separate areas of a tumor, though focal areas of merging can often be discerned[17]. The two components may show abrupt or gradual transition. It is important to keep in mind that clear histological distinction of both components may be difficult in areas of merging on HE stains as neoplastic cells of either hepatic or cholangiocytic morphologic type may contain intracytoplasmic inclusions such as hyaline material and/or steatosis and are often negative for mucin stains[20]. Rarely other histological components, such as squamous, endocrine or sarcomatous have been described in cHCC-CCA.

Stem/progenitor cell features consist of small cells with a high nucleo-cytoplasmic ratio, hyperchromatic nuclei, and scant cytoplasm, and are usually identified at the stromal epithelial interface[22]. One does not see mitosis in these stem cells. Intermediate carcinoma is characterized by trabeculae or strands of small, monotonous neoplastic cells with hyperchromatic round to oval nuclei and scant cytoplasm embedded in the desmoplastic stroma and shows simultaneous immunostaining by both hepatocytic and biliary markers, suggesting stem cell origin[23]. Pathological diagnosis of cHCC-CCA, stem/progenitor cell features, and intermediate carcinoma are also based on assessment on HE stains; immunostaining is supplementary to the morphological diagnosis. For hepatocellular differentiation, one can utilize Arginase-1, Hep-par1 (Figure 2A), Glypican 3, pCEA (canalicular expression), and CD10 (canalicular expression), and for CCA EMA (Figure 2B), CK7, CK19, EpCAM can be utilized. Awareness of positive expression of CK and CK19 in the hepatocellular component is important and this should not be mislabeled as cholangiocytic differentiation. Stem cells show overlap with immunohistochemical markers of cholangiocytic differentiation including CK19, CD56 and EpCAM; so, interpretation as cholangiocytes or stem cells should depend on morphological features. Positive immunostaining of nestin has been suggested to identify the subset of cHCC-CCA associated with the worst clinical outcome[2]. A few markers like CD117, CD133, Sox-9 can be considered stem cell markers. Recent studies have shown that intermediate cells stain with nestin[23] (Figure 2C). However, our team have shown that nestin can be negative in intermediate cell carcinoma[24].

GENOMIC LANDSCAPE OF CHCC-CCA

Considering the rarity, molecular studies of cHCC-CCA are limited, and like pathological features, reports describing the genomic character of these tumors have shown marked heterogeneity (Table 1)[8,10,11,21,25-33]. This also demonstrates that correct pathological diagnosis of cHCC-CCA is challenging, and these molecular studies might have included HCC or iCCA tumors for analysis[34]. Previously published studies demonstrated that these tumors have a distinct mutational profile with chromosomal instability, which is closer to iCCA[8]. Few molecular studies supported the concept of a stem/progenitor cell origin with enrichment in stem/progenitor-like signatures[11,26]. Some studies have showed that that the genetics of classical cHCC-CCA are recognizably different from iCCA but almost identical to typical HCC[27]. The most frequent somatic genetic alterations reported in HCC are TERT promoter, CTNNB1, AXIN1 and TP53 mutations. Studies on genomic landscape of CCA have reported mutations in IDH, FGFR2, BAP1, ARID1A, TP53, KRAS, and PBRM1.

Xue *et al*[25] performed genomic and transcriptomic landscaping of 133 cHCC-CCA cases which included separate, combined, and mixed subtypes and were classified according to Alan and Lisa classification. An integrative comparison of cHCC-CCA with HCC and intrahepatic CCA revealed that combined and mixed types of cHCC-CCAs are distinct subtypes with different clinical and molecular features. Combined type cHCC-CCA showed strong ICC-like features, such as higher expression of EPCAM, KRT19, and PRDM5, as well as enrichment of KRAS mutations and higher expression of KRAS. In contrast, mixed type cHCC-CCA showed Hoshida-S2-like HCC features, such as higher expression levels of AFP, GPC3, APOE, and SALL4, as well as a higher level of serum AFP. The most frequently mutated driver genes in their study were *TP53*, *TERT* promoter, *AXIN1*, and *KMT2D* mutations that may be associated with either

Table 1 Summary of the findings of studies having examined the molecular landscape of combined hepatocellular-cholangiocarcinoma

Ref.	Technology	Molecular features/conclusion
Fujii *et al*[30]	Loss of heterozygosity, polymerase chain reaction	4q, 17p, 8p, 16q; common clonal evolution
Cazals-Hatem *et al*[8]	Loss of heterozygosity, Genome wide allelotyping	TP53, chromosome instability
Coulouarn *et al*[26]	Genome-wide transcriptional analysis	TGFβ and Wnt/β-catenin; Stem/progenitor features
Fujimoto *et al* [31]	Whole genome sequencing	TERT/IDH1/2, KRAS; Closer to HCC if hepatitis background and to; CCA in absence of hepatitis
Moeini *et al* [21]	Whole exome sequencing	TP53, TERT, IDH1/2, Chromosomal instability, MYC, IGF2, mTOR, Stem/progenitor features
Chen *et al*[54]	Whole genome sequencing	IDH1/2; Stem/progenitor features
Sasaki *et al*[29]	Whole genome sequencing	KRAS, IDH1/2, ARID1A, TERT; Variable association of HCC and/or CCA mutations
Jeon *et al*[32]	Multiplexed polymerase chain reaction-based sequencing	TP53, PTEN, MET, c-MYC, CDK6, CTNNB1, CCND1; Clonal heterogeneity
Wang *et al*[11]	Whole exome sequencing	VCAN, ACVR21, FCGBP; Stemness nature, monoclonal origin, intratumoral heterogeneity
Liu *et al*[10]	Whole exome sequencing, RNAseq	TP53, CTNNB1
Joseph *et al* [27]	Capture-based next generation sequencing	TERT, TP53, cell cycle genes (CCND1, CCNE1, CDKN2A), receptor tyrosine kinase/Ras/PI3-kinase pathway genes (MET, ERBB2, KRAS, PTEN), chromatin regulators (ARID1A, ARID2) and Wnt pathway genes (CTNNB1, AXIN, APC)
Sasaki *et al*[33]	Direct sequence	TERT, ARID1A, PBRM1, ARID2, BAP1, p53, KRAS, IDH1/2; Cholangiocellular carcinoma is different from cHCC-CCA
Xue *et al*[25]	Whole genome sequencing	TP53, TERT, AXIN1, KMT2D; Monoclonal origin in combined and mixed type; Both mono- and multiclonal origins in the separate type

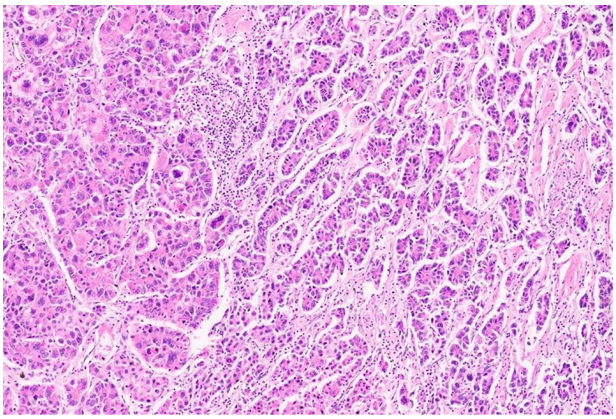

Figure 1 Combined hepatocellular-cholangiocarcinoma (HE, × 15).

HCC or iCCA. They also revealed both monoclonal and multiclonal origins in the separate type cHCC-CCAs, whereas combined and mixed type cHCC-CCA were all monoclonal origin. Notably, cHCC-CCAs showed significantly higher expression of nestin, suggesting nestin may serve as a biomarker for diagnosing cHCC-CCA.

Moeini *et al*[21] described the different genomic status of cHCC-CCA in 18 patients with mixed HCC-CCA encompassing all subclasses described in WHO 2010 classification. Progenitor/stem-cell cancers were characterized by enrichment of progenitor-like signatures, and specific activation of MYC, IGF, Notch, and mTOR oncogenic pathways and chromosomal instability. Classical cHCC-CCA showed a significant correlation in the copy number aberrations of the iCCA and HCC components, suggesting a clonal origin. Pure cholangiocellular carcinoma cases in their series showed significant upregulation of transforming growth factor beta signaling and enrichment for inflammation-related and immune response signatures, suggesting that they represent a form of iCCA and should not be included under cHCC-CCA. The reported molecular features of cHCC-CCA parallel its biphenotypic morphological appearance. However, the number of investigated cases remains low, and further validation in larger studies is needed to establish a robust pathomolecular classification of cHCC-CCA[34].

Table 2 Common mutational signatures in hepatocellular carcinoma, combined hepatocellular-cholangiocarcinoma and cholangiocarcinoma

Cholangiocarcinoma	Hepatocellular carcinoma	Combined hepatocellular-cholangiocarcinoma
TP53	*TERT promoter*	*TERT promoter*
KRAS	*TP53*	*TP53*
IDH1	*CTNNB1*	*MET*
PTEN		*ERBB2*
ARID1A		*KRAS*
EPPK1		*PTEN*
ECE2		
FYN		

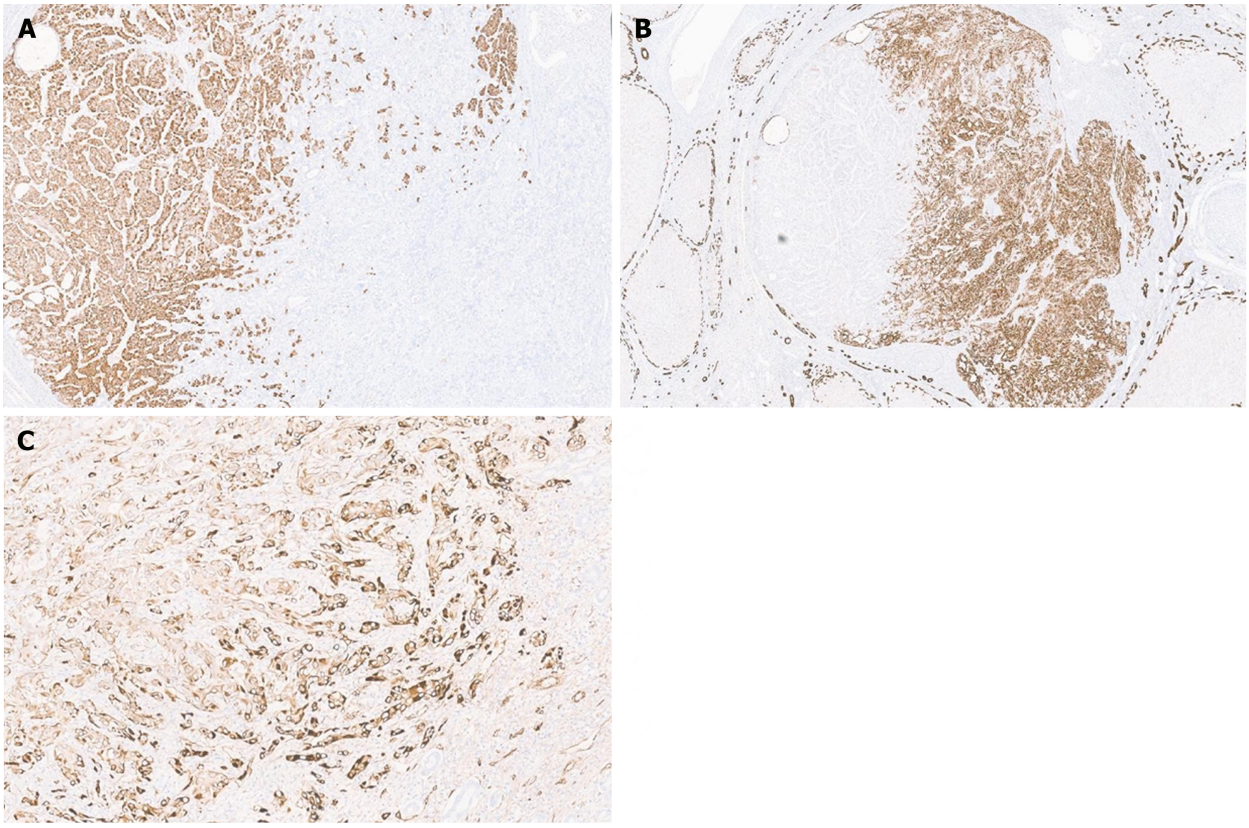

Figure 2 Demonstrates immunohistochemical features of combined hepatocellular-cholangiocarcinoma. A: Hep-par1 immunostaining in hepatocellular component (× 5); B: Strong EMA immunostaining in cholangiocarcinoma component (× 3); C: Nestin immunostaining in a combined hepatocellular-cholangiocarcinoma (× 7.5).

RNA-sequencing revealed enrichment of the interleukin 6 (IL-6) signaling pathway in cHCC-CCA tumors compared to HCC tumors. Single-cell RNA-sequencing analysis revealed that IL-6 is expressed by immune and parenchymal cells during senescence, and that IL-6 is part of the senescence-associated secretory phenotype. These results could be used for the development of novel treatments for these aggressive tumors. Recently may studies have reported several significantly mutated genes with different prevalence in HCC, iCCA and cHCC-CCA[35-37] (Table 2). Artificial intelligence (AI) is widely used for the analysis of images in pathology. Calderaro *et al*[38] demonstrated that AI-based recategorization of cHCC-CCA into one of the "pure" HCC or iCCA groups is feasible, and perhaps refine the prognostication, which is crucial given the therapeutic implications, and also enable us to find or whether a given cHCC-CCA tumor is genetically more identical to HCC or iCCA.

IMAGING FEATURES

Most cases of cHCC-CCA are detected on surveillance ultrasound in the cirrhotic population. Sonography often reveals a hypoechoic mass with a hyperechoic central area or a heterogenous hypoechoic mass reflecting the histological diversity of the tumor. The lesion often demonstrates a combination of typical enhancement patterns of both HCC and iCCA on contrast-enhanced computed tomography and is frequently categorized as 'LI-RADS metastasis (LR-M)'[39]. On magnetic resonance imaging (MRI), the cHCC-CC can be hypointense on T1W images and demonstrates intermediate to high signal intensity with or without the presence of a central hypointense focus on T2W images that corresponds to a fibrotic component or central CCA. A study by Hwang *et al*[40] evaluating features to differentiate cHCC-CCA from iCCA on gadoxetic acid-enhanced MRI demonstrated that a lobular shape with a complete target appearance and weak rim enhancement supported the diagnosis of CC, while strong peripheral enhancement with an irregular shape and the lack of the target sign was in favor of cHCC-CC, particularly the HCC predominant type.

TUMOR BIOPSY IN CHCC-CCA

The role of tru-cut biopsies for the diagnosis of cHCC-CCA is controversial, considering the histological heterogeneity in these cancers. Also, how many biopsies are to be done shows both components are represented for an accurate pathological diagnosis. It has also been suggested that owing to the lack of biopsies for primary liver cancers, as most management decisions are taken just on radiological findings, multiple cases of cHCC-CCA are currently misdiagnosed as HCC[34]. In a series of 21 cHCC-CCA, one recent study evaluated a two-step strategy, combining imaging using computed tomography and/or MRI as the first step and then biopsy as the second step. This improved the diagnostic performance of cHCC-CCA with a sensitivity of 60% and a specificity of 82%, as compared to the performance of radiology or pathology alone[41]. Tumor biopsy can also be evaluated for molecular features and specific oncogenic pathways involved in tumor biology which might help in patient management[34].

TREATMENT

Like HCC and CC, surgery remains the cornerstone of the management of cHCC-CC. In the case of localized disease with good liver reserve, the surgery is the best available treatment option for cHCC-iCCA at present and can provide the maximum overall survival (OS) (median OS of 25.7 months). Nevertheless, the majority of patients affected with this ailment are often not fit for a resection[42]. Liver transplantation (LT) is a reasonable treatment option in selected cHCC-CC patients with cirrhosis. A systematic review of retrospective studies has reported a median disease-free survival of 14.2 months and a median OS of 37.1 months with LT[43]. Recently, a group of Chinese researchers has come forward with a scoring system known as prognostic estimation of cholangiocellular-HCC after resection (PECAR) score to assess the recurrence risk after resection of cHCC-CC. Increased gamma-glutamyl transferase, macrovascular invasion, male sex, and hilar lymphoid metastasis are found to be independent predictors of recurrence[44]. The PECAR scoring system needs to be externally validated before it can be universally accepted.

cHCC-CC tumors are less vascularized compared to HCC, and the response to locoregional therapies like trans arterial chemoembolisation is suboptimal. However, they can be considered in selected inoperable cases and for downstaging larger lesions to potentially resectable ones. There is no optimal systemic therapy regimen for cHCC-CC patients yet. Though many researchers have tried a combination of gemcitabine, and platinum drugs with or without a tyrosine kinase inhibitor (sorafenib) or a vascular endothelial growth factor antibody (Bevacizumab), but all these studies were retrospective and heterogenous in nature[45-47].

In recent years, immunotherapy has made significant progress, opening up a new treatment alternative for HCC and CC[48-50]. A multicenter study from France comprising 96 patients with cHCC-CCA identified a subgroup of cHCC-CCA that exhibits features of an ongoing intratumor immune response, along with an activation of gene signatures predictive of response to immunotherapy in HCC[51]. This subclass may benefit from immunotherapy, with improved survival. Satake *et al*[52] reported promising results with atezolizumab plus bevacizumab in patients with advanced cHCC-CC. Recently, a retrospective, multicenter cohort study reported an overall response rate of 29% with immune checkpoint inhibitors in patients with cHCC-CC[53]. Recently published studies on the role of immunotherapy have been discussed in Table 3[52-60].

CONCLUSION

cHCC-CC represents a distinctive primary hepatic malignancy with ambiguous morphological and genomic characteristics mimicking both hepatocytic and cholangiocytic differentiation. Owing to the rarity of cHCC-CC, the pathological and molecular characteristics of this neoplasm remain poorly characterized. There is a lack of standardization in the treatment of cHCC-CC, especially for those patients with unresectable tumors. Further studies with international collaborations are essential to better understand the disease biology and improve the management of patients with this rare neoplasm.

Table 3 Reported cohorts of combined hepatocellular-cholangiocarcinoma patients treated with immunotherapy

Ref.	Study type	Drug	Number of patients	Outcome
Tahover *et al*[55]	Case report	Ipilimumab and nivolumab, followed by nivolumab	1	ECOG performance status improved from 3 to 0. Repeated PET-CT showed near complete response, ca125 decreased by 90% and liver function tests normalized
Rizell *et al*[56]	Case report	Pembrolizumab	1 (Post resection, pulmonary metastasis)	Complete remission of the pulmonary metastases. There was no sign of cancer recurrence neither in the liver nor in the lungs at 33 months after the start of the checkpoint inhibition treatment
Diab *et al* [57]	Retrospective case series	Of the six patients 4 (66%) received PD-1 inhibitor alone and 2 (34%) received combination therapy with CTLA-4 inhibitor	6	Objective response rate was 83.3%. One patient achieved complete response and had a treatment holiday after receiving treatment for 2 yr, and restarted immunotherapy upon relapse. Four patients had a partial response, of which two passed away after disease progression. One patient had stable disease on 2 different lines of immuno-therapy then progressed
Saito *et al* [58]	Case report	Atezolizumab plus bevacizumab	1 (3 months after resection, multiple lymph node metastases)	7.5-month progression-free survival
Satake *et al*[52]	Case series	Atezolizumab plus bevacizumab	6	Three partial responses and one stable disease as the best responses
Saint *et al*[59]	Case report	Pembrolizumab	1	Complete response which was maintained over time along with toxicity-free tumor control after 18 months treatment
Pomej *et al*[53]	Retrospective, multicenter cohort	Three (43%) patients received atezol-izumab plus bevacizumab, two (29%) patients were treated with nivolumab alone, and one (14%) patient each received pembrolizumab alone and nivolumab in combination with TACE, respectively	7	Overall response rate was 29% with a disease control rate of 43%
Zhou *et al*[60]	Case report	Sintilimab, lenvatinib, and nab-paclitaxel	1	

ECOG: Eastern cooperative oncology group; CT: Computed tomography; TACE: Trans arterial chemoembolization.

FOOTNOTES

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