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Review Article

Cholangiocarcinoma: A Literature Review

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Abstract

Cholangiocarcinoma is a malignant neoplasm that affects the epithelium of the bile duct. It has low incidence and prevalence, usually appearing after the sixth decade of life, with a slight predominance in the male population. It mostly affects the confluence of the hepatic ducts, where it is called "hilar cholangiocarcinoma" or "Klatskin tumor". Its etiology is still partially unknown, but it has well-defined predisposing conditions and risk factors such as primary sclerosing cholangitis, parasitic infections, and exogenous toxins. The initial clinical presentation is nonspecific and can later include jaundice, weight loss, and right upper abdominal pain. Diagnosis is confirmed through clinical alterations, laboratory tests, imaging, and histopathology. Two clinical staging classifications are used: Bismuth-Corlette and TNM. The gold standard treatment is surgical excision with negative histological margins. However, the resectability rate is still low due to late diagnosis. Patients with unresectable tumors may benefit from palliative treatment, such as endoscopic stent placement or percutaneous drainage. New chemotherapy/phototherapy treatments are being studied to improve the quality of life of patients.

Keywords: Practice Guideline; Cholangiocarcinoma; Biliary markers; Treatment

Introduction

Cholangiocarcinoma (CC) is a rare and heterogeneous group of neoplasms of the biliary tract, originating from the epithelium of the intrahepatic, peri-hilar, and extrahepatic bile ducts [1]. It was first described in 1840 by Durand-Fardel [1]. CCs are epithelial tumors with characteristics of cholangiocyte differentiation. Despite CC still having a high mortality rate, mainly due to its aggressiveness and late diagnosis, molecular characterization and immunological evaluation have been crucial for the study of new therapeutic modalities, such as immunotherapy, increasing the overall survival of these patients.

Methodology

This is a descriptive literature review that aimed to highlight, through current analyses, the updates and advancements in the diagnosis and treatment of cholangiocarcinoma. The research was conducted through online access to the National Library of Medicine (PubMed MEDLINE) and Scientific Electronic Library Online (Scielo) databases in April 2023. The following keywords from the Health Science Descriptors (DeCS) in English, "Practice Guideline," "cholangiocarcinoma," and "treatment," were used to search for relevant articles. As inclusion criteria, articles that addressed the researched topic and allowed full access to the study's content, published from 1992 to 2023, in English, Spanish, and Portuguese, were considered. The exclusion criterion was applied to works that did not address the inclusion criteria, as well as articles that did not undergo peer review. The article selection strategy followed the steps of searching the selected databases, reading the titles of all found articles, excluding those that did not address the subject, critically reading the abstracts of the articles, and reading the selected articles in full from the previous steps. Therefore, a total of 38 materials were reviewed.

Classification

CCs are classified according to anatomical location as intrahepatic, peri-hilar, or distal. Intrahepatic CCs are located within the hepatic parenchyma. The landmark that determines the boundary between intrahepatic and extrahepatic tumors is the confluence of the secondary bile ducts. The junction of the cystic

duct with the common hepatic duct divides extrahepatic tumors from peri-hilar and distal tumors [2].

Epidemiology

Intrahepatic CC is the second most common primary liver cancer, with hepatocellular carcinoma being the first. It accounts for approximately 10-15% of all hepatobiliary malignancies [3-4]. Its incidence has significantly increased in the last three decades, particularly in Israel and Japan [3].CC mortality has also increased, with data from 2020 showing 1-6 per 100,000 population per year [5-35]. In recent decades, its overall incidence has increased by 109% from 0.67 per 100,000 in 2007 to 1.40 per 100,000 in 2016 [35]. Despite the increase in incidence, it is still rare, representing less than 2% of all malignant tumors. Like many cancers, it is most commonly found in individuals after the sixth decade of life and slightly more frequent in men, with a ratio of 1.3/1, possibly related to a higher prevalence of primary sclerosing cholangitis in this group [2].

Etiology

Only 30% of CCs are related to risk factors that have in common chronic inflammation of the biliary tract and biliary stasis [2] and some diseases have been well-established, including primary hepatobiliary disease, infections, genetic diseases, helminthic infestations, and toxic exposures [5]. Hepatobiliary diseases include primary sclerosing cholangitis (PSC), polycystic liver disease, cholelithiasis, cholecystitis, choledochal cysts, and chronic liver disease. It is worth noting that PSC has a strong association with CC, present in 30% of patients with this neoplasia [4]. Some studies report a 400-fold increased risk of CC in patients with PSC compared to the general population. Despite this, there is still no consensus on the best prevention strategy for these patients [35].

Recently, viral hepatitis B and C have been recognized as risk factors for CC. Pathogenetically, the release of inflammatory cytokines, cell death associated with increased cell proliferation, and liver fibrosis promote oncogenesis [34].

A case-control study conducted in 2013 showed an association between asbestos exposure and hidden risk factor for CC [5]. Other substances with toxicity and association with the disease include digoxin and nitrosamines [1]. Chronic infestation of the biliary tract by endemic parasites from Southeast Asia, such as Clonorchis sinensis and Opisthorchis viverrini, and chronic infection with Salmonella typhosa have been shown to be predisposing factors [1].

Genetic alterations have also been studied as risk factors for CC. However, information is still scarce. The main data available is from the Genome-wide Association Study (GWAS). CC has a high mutation rate, and some studies have shown associations, such as with oncogene mutations (KRAS, c-myc, c.erbB-2) [7]. and inactivation of tumor suppressor genes (p53, pl6, bel-2) [6]. Studying the pathogenesis of CC has led to the discovery of new molecular biomarkers. The most identified mutations are in the isocitrate dehydrogenase (IDH1) isoenzyme and KRAS. IDH1 mutations are present in approximately 15-25% of intrahepatic CCs, leading to epigenetic and genetic alterations that promote oncogenesis due to the production of oncometabolite 2-hydroxyglutarate (2-HG). 30 Fibroblast growth factor receptor 2 (FGFR2) fusion is also associated and occurs in 13 to 17% of CCs [30].

There is also believed to be a causal relationship with the increasing prevalence of obesity and metabolic dysfunction-associated fatty liver disease (MASLD). Recent studies have shown a potential protective role of metformin in the development of CC; however, further studies are needed to clarify the strength of this association and the responsible mechanisms [5, 35].

Pathophysiology

Similarly to many neoplasms, CC can arise from precursor lesions such as biliary intraepithelial neoplasia, intraductal papillary neoplasm of the bile ducts, and papillary mucinous neoplasm or cystadenoma [4].

The first premalignant lesion is biliary intraepithelial neoplasia, which progresses to tubular adenocarcinoma and is microscopic in nature, making it difficult to diagnose early through imaging exams [2, 4].

Biliary intraductal papillary neoplasm includes adenomas and borderline tumors that early progress to CC (tubular or mucinous adenocarcinoma), with a better prognosis compared to advanced carcinomas. They are characterized by abundant mucin production, diffuse dilation of the bile ducts, and intraluminal macroscopic growth that extends superficially without invading the wall or other structures, resulting in higher rates of diagnosis through imaging [2,4].

The third lesion is papillary mucinous neoplasm or cystadenoma, which is associated with a cyst that causes closure of the duct and must be differentiated from the mucinous variant of biliary intraductal papillary neoplasm. Confirmation is made pathologically by ovarian stroma [8, 4].

Histopathology

CC is a histologically diverse hepato-biliary neoplasm that develops from biliary epithelial cells or hepatic progenitor cells [4]. Approximately 90-95% of CCs are adenocarcinomas, while the remaining are primarily squamous/epidermoid carcinomas.

They can be classified into subtypes depending on morphology: sclerosing, nodular, and papillary. The papillary type

is the rarest, while the nodular type is more invasive with a lower cure rate, and the sclerosing type presents with extensive fibrosis, making histological diagnosis difficult [8].

CCs can range from undifferentiated to well-differentiated. They are often surrounded by a rapid response of fibrotic or desmoplastic tissue; in the presence of extensive fibrosis, it can be difficult to distinguish well-differentiated CC from normal reactive epithelium. There is no entirely specific immunohistochemical staining that can distinguish biliary duct tissue [8].

Clinical Presentation

CC is generally asymptomatic in the early stages. The clinical picture can be nonspecific depending on the tumor location [5]. Extrahepatic tumors present symptoms earlier due to biliary obstruction, with jaundice, itching, pale stools, and dark urine. On the other hand, intrahepatic CCs are generally asymptomatic or oligosymptomatic, leading to a later diagnosis after tumor growth with mass effect and invasion of the hepatic parenchyma [4].

The most prevalent sign is progressive jaundice, present in approximately 90% of cases and often appearing after the onset of itching [1]. General symptoms may include abdominal pain, primarily in the right hypochondrium, weight loss, fever, and asthenia. In advanced cases, palpable abdominal mass [9].

Around 20% of cases present with cholangitis, with abdominal pain in the right hypochondrium, jaundice, and fever, which can progress to more severe conditions with shock (low blood pressure, rapid heart rate) and altered mental status, forming the Reynolds' Pentad [12].

The presence of the Courvoisier's sign, defined as painless palpation of the gallbladder in a patient with jaundice, can also be present in distal extrahepatic tumors [10].

Diagnosis

The diagnosis is made through the combination of clinical presentation, laboratory tests, imaging, endoscopy, and histopathological examination [1].

Laboratory

Laboratory tests include hepatic biochemical tests, including aminotransferases, canalicular enzymes, total bilirubin, direct bilirubin, and indirect bilirubin. Extrahepatic tumors show more pronounced elevation in alkaline phosphatase, gamma-glutamyl transferase, and bilirubin. Intrahepatic tumors present more subtle laboratory changes, with increased levels of alkaline phosphatase and late elevation of bilirubin [4] In advanced cases, coagulopathies may also be observed due to cholestasis and vitamin K deficiency.

The tumor markers that should be evaluated are CA 19-9, CA-125, and CEA, which are elevated in 85%, 45%, and 30% of CC cases, respectively. A Chinese study conducted in 2004 compared CA 19-9 and CEA and showed that CA 19-9 is a more reliable serum marker for the diagnosis of CC, although a negative result cannot exclude the pathology [1].

The tumor biomarker CA 19-9 has a sensitivity of 62% and specificity of 63%, but it can also be elevated in various other pathologies, including other malignancies, bacterial cholangitis, and advanced liver disease [38]. CA 19-9 not only aids in the diagnosis but also in evaluating recurrence after treatment. High levels of CA 19-9 (> 1,000 U/mL) are associated with metastatic CC [38].

Imaging

Imaging studies start with abdominal ultrasound, a readily available exam that is essential for assessing biliary tract dilation, identifying the site of obstruction, and ruling out other factors such as gallstones. However, it has technical limitations for characterizing and determining tumor extension. The use of Doppler allows visualization of vascular involvement [14].

Although the ultrasound study assists in the initial investigation, it is necessary to complement it with other imaging exams, such as multiphasic contrast-enhanced multidetector computed tomography (MDCT) and magnetic resonance imaging with cholangiopancreatography (MRCP). MDCT is an excellent modality for detection and staging, and it can accurately calculate liver volume, which is crucial for treatment planning. The use of hepatobiliary contrast agents (gadoxetate disodium or gadobenate dimeglumine) allows better visualization with border delineation and detection of multiple lesions. Among radiological exams, MRCP is the preferred imaging modality as it can assess resectability and tumor extension with up to 95% accuracy [38].

Positron emission tomography-computed tomography (PET-CT) may have utility in visualizing metastases but has not been validated for CC staging [15].

Endoscopy

Endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (CPRE) are useful for distal extrahepatic tumors as they enable lesion visualization, collection of biopsies through fine-needle aspiration or brush cytology, and placement of biliary stents for managing obstruction and relieving symptoms. CPRE remains the modality of choice for initial characterization of biliary strictures. However, the sensitivity of CPRE with brush cytology alone for diagnosing malignant biliary strictures varies from 33% to 58% [38].

The Spyglass Spyscope was first described in 2006 and consists of single-operator cholangioscopy. It is a new endoscopic modality that has been shown to be highly accurate and safe in

diagnosing extrahepatic CC by enabling biopsy of lesions [38]. Despite being described in 2006, it is still not widely available due to high cost and the need for an experienced professional.

Interventional Radiology

Percutaneous transhepatic cholangiography can be useful when the endoscopic route is not possible to access, allowing for the collection of biopsy through fine needle aspiration and external biliary drainage with placement of a Kehr drain [14]. Sample collection is essential for the diagnosis of CC when surgical resection is not indicated, thus requiring guided puncture using imaging or invasive techniques, such as laparoscopy or brush cytology [14].

In cases of inoperable malignant biliary obstruction with typical findings and exclusive palliative care, anatomopathological evaluation is not necessary [17].

Radiological Findings

Intrahepatic CC: accounts for 20% of CC cases and the most frequent type of growth is expansive, which can spread to venous and lymphatic vessels. It presents with large dimensions, irregular and lobulated contours. Prognosis is related to the number of lesions, vascular invasion, lymph node involvement, or distant metastasis. It is characterized by masses of variable echogenicity without a hypoechoic halo on abdominal ultrasonography. Generally, it is hypodense on MDCT and shows hyperintense signal on T2 and hypointense on T1 at the periphery, with minimal irregular and incomplete peripheral enhancement, progressing centripetally in the late phases on MRI.

Perihilar CC (Klatskin): accounts for 50-60% of CC cases, and the growth type is mixed (periductal infiltrating with expansive mass), spreading through perineural and lymph node pathways. It expands along the bile duct, leading to thickening of the wall and progressing to the hepatic parenchyma in up to 80% of cases. On ultrasound, dilation of the intrahepatic bile duct is observed, and the lesion is often as echogenic as the liver, making it difficult to visualize. On MDCT, focal ductal wall thickening with luminal narrowing and proximal dilation is seen, and it may present as a mass with greater enhancement than the hepatic parenchyma.

Distal CC: represents approximately 20% of CC cases, and the predominant growth type is periductal infiltrating. It has the characteristic of infiltrating structures such as vessels and the pancreas and involving lymph nodes, thereby determining a worse prognosis. The image is compatible with a mass with late enhancement at the site of stenosis or concentric and asymmetrical thickening of the bile duct. Periampullary tumors originate in the periampullary region (area that extends radially 2 cm from the major papilla).

Staging

Staging becomes important for therapeutic programming. It is estimated that up to 50% of patients have affected lymph nodes at the time of diagnosis, and up to 20% of patients have peritoneal involvement (peritoneal thickening or nodules) at the time of diagnosis [18].

For peri-hilar tumors, the Bismuto-Colette classification is used, which is the main staging system. It is able to stratify the longitudinal tumor extension in the bile ducts, an important factor for evaluating surgical resection. This classification includes four types and does not take into account vascular involvement or the presence of metastasis [18].

Bismuto Corlette Classification for peri-hilar tumors:

- Type I: limited to the common hepatic duct, below the level of the confluence of the right and left hepatic ducts.
- Type II: involves the confluence of the right and left hepatic ducts.
- Type IIIa: Type II and extends to involve the origin of the right hepatic duct.
- Type IIIb: Type II and extends to involve the origin of the left hepatic duct.
- Type IV: extending and involving the origins of the right and left hepatic ducts (i.e. a combination of types IIIa and IIIb) or multifocal involvement.

For other presentations (intrahepatic and extrahepatic), the TNM classification is used, which takes into account local tumor involvement (T), lymph node involvement (N), and presence of distant metastasis (M).

The latest edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Combined Cancer Staging Manual provides staging systems for distal and intrahepatic bile duct neoplasms, which differ in their definitions of tumor stage and their prognostic stage groupings [19].

The TNM classification for distal bile duct carcinoma includes the following stages:

- T: localized carcinoma
- T1a: tumor invades the lamina propria
- T1b: tumor invades the muscular layer
- T2: tumor invades the perimuscular connective tissue without extension beyond the serosa layer (visceral peritoneum) (T2a) or invades the liver (T2b)

- T3: tumor perforates the serosa or directly invades the liver or adjacent organs or structures, involving the hepatic or portal veins
- T4: tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures
- N1: metastasis to 1-3 regional lymph nodes
- N2: metastasis to 4 or more regional lymph nodes
- M1: distant metastasis

For intrahepatic cholangiocarcinoma:

- T1a: solitary tumor less than or equal to 5 cm without vascular invasion
- T1b: solitary tumor larger than 5 cm without vascular invasion
- T2: solitary tumor with intrahepatic vascular invasion or multiple tumors 5 cm or smaller with or without vascular invasion
- T3: tumor perforates the visceral peritoneum
- T4: tumor invades adjacent organ (except gallbladder)
- N1: regional lymph node metastasis
- M1: distant metastasis

Note that vascular involvement is characterized by vessel occlusion, ipsilateral hepatic atrophy, vascular contour deformity, or tumor-vessel contact greater than or equal to 180 degrees [16].

Differential Diagnosis

The differential diagnosis includes benign strictures (such as Primary Sclerosing Cholangitis, Primary Biliary Cholangitis, iatrogenic strictures, IgG4-related cholangiopathy, and AIDS-related cholangiopathy), pathologies that present with jaundice and abdominal pain (choledocholithiasis, cholelithiasis, cholangitis), and other malignant neoplasms (pancreatic cancer and hepatocellular carcinoma) [20].

Treatment

Surgical Treatment

Surgical resection with negative histological margins, with or without adjuvant therapy, is the only potentially curative therapy for patients with resectable disease, but only one-third of potentially operable CC patients undergo surgical resection [21].

Five-year survival rates after resection are still low, around 22-44% for intrahepatic CC, 11-41% for peri-hilar CC, and 27-37% for distal CC [22]. Resectability depends on variables such as the lesion's location, taking into consideration its relationship with vascular structures, and the amount and quality of the remaining liver parenchyma after resection. The remaining liver can be assessed using the indocyanine green test in association with hepatobiliary scintigraphy or hepatic volume quantification by computed tomography or magnetic resonance imaging [35].

In large resections, some centers perform portal vein embolization three weeks prior to surgery in order to cause hypertrophy of the remaining liver, leading to a reduction in postoperative hepatic failure mortality [24]. Resection of part of the portal vein has been studied in Japan when there is portal tumor infiltration, with no increase in morbidity and mortality, however, more studies are needed [25]. It is estimated that 50% of patients experience tumor recurrence after the second year of resection. The main risk factors associated with increased recurrence are non-radical resection, lymph node involvement, and vascular and perineural invasion [22]. Studies indicate that after the identification of tumor recurrence, a selected group of patients can be evaluated for a second radical surgical treatment, resulting in an increased survival rate [5].

Due to advances in hepatobiliary surgery in recent years, it is possible to perform increasingly extensive tumor resections with the goal of achieving clear margins, resulting in improved survival. It should be noted that the surgical modality will be based on anatomical subtype and tumor location. In tumor resections, it is important to evaluate albumin levels and total bilirubin, as they can be used to predict the risk of postoperative hepatic failure. Studies have shown that preoperative serum albumin levels below 3 g/dl are associated with worse prognosis. Strategies for preoperative biliary drainage, aiming to reduce obstruction and consequently, bilirubin levels, should be considered [30].

The surgical treatment of choice for intrahepatic CC is liver resection. Spanish studies have shown approximately 80% 5-year survival in the absence of lymph node involvement and with a tumor-free margin of 1 cm [23]. For peripheral intrahepatic tumors, resection of the affected hepatic segment or lobe is recommended. In intraductal intrahepatic tumors, hepatic lobectomy or segmentectomy is performed with removal of the involved hepatic duct. The surgical modality of choice for peri-hilar CC is bile duct resection, associated with hepatectomy, lymphadenectomy, and biliodigestive anastomosis. Currently, the extent of resection is recommended based on the Bismuth-Corlette classification. For Types I and II: removal of the entire extrahepatic bile duct, associated with cholecystectomy, regional lymphadenectomy, and hepatic-jejunal Roux-en-Y anastomosis. Type III: in addition to the above, hepatic lobectomy. Type IV: addition of resection of multiple hepatic segments, with hilar block resection of the portal vein. For extrahepatic CC, pancreatoduodenectomy or Whipple surgery with preservation of the pylorus is recommended [26].

Liver Transplantation

In the late 1980s, liver transplantation was proposed for patients with hilar CC due to the presence of clear margins in tumors considered unrespectable. Initial studies were discouraging, showing high recurrence rates (around 50%). More recent studies have shown the potential benefit of liver transplantation for hilar and peripheral CC after careful evaluation [27].

In 1993, surgeons at the Mayo Clinic conducted a comparative protocol between CC patients undergoing tumor resection with lymphadenectomy versus patients undergoing liver transplantation with adjuvant therapy (external radiotherapy combined with 5-fluorouracil injection, iridium-192 brachytherapy, and capecitabine). It was observed that the 3- and 5-year survival rates were 82% and 82%, respectively, in the liver transplant group with adjuvant therapy. In the hepatic resection group, the survival rates were 48% and 21%, respectively. This study demonstrated that liver transplantation with adjuvant therapy seems to be more effective than resection for selected patients with hilar CC [27].

There are no well-defined criteria for selecting candidates for liver transplantation; however, this therapy should be considered only at referral centers, for patients with early CC (single tumor size ≤ 2 cm) and no evidence of metastatic disease [27].

Adjuvant Therapy

Due to the high incidence of local failure after surgical resection, retrospective studies suggest a survival benefit with the addition of adjuvant chemo radiotherapy based on fluorouracil [4].

A multicenter randomized phase III study (BILCAP) conducted in 2019 demonstrated that capecitabine can improve overall survival in resected intrahepatic CC when used as adjuvant chemotherapy after surgery. Based on these data, capecitabine has become the standard adjuvant treatment after tumor resection with curative intent according to the guidelines of the American Society of Clinical Oncology (ASCO) [30].

Therapy for Metastatic Disease

The high recurrence rates provide the basis for the exploration of systemic therapies, which have become the preferred approach for advanced or metastatic neoplasms. Until 2010, there was no specific first-line treatment for advanced or metastatic CC. Several factors influence the effect of chemotherapy, such as control of cholangitis, performance status, liver function, and tumor-related factors.

The currently available drugs are gemcitabine, fluoropyrimidines, and platinum-based therapy. Gemcitabine has been increasingly used for hepatobiliary cancer treatment. Cisplatin has a synergistic effect when combined with gemcitabine. This effect is due to interactions within the stroma and the effects on tumor-associated macrophages and fibroblasts, leading to increased uptake of chemotherapy drugs by tumor cells, resulting in apoptosis and depletion of cancerous collagen deposition [30]. A phase III study (ABC-02) demonstrated that the combination of cisplatin and gemcitabine improved disease-free survival, becoming the first-line treatment.

Despite this, the prognosis is still poor, with a median overall survival of approximately 1 year. In patients with contraindications to cisplatin use, such as renal insufficiency, it is recommended to replace it with oxaliplatin [5]. Until 2021, there was no robust evidence for second-line chemotherapy. However, the ABC-06 clinical trial, a randomized phase 3 study, demonstrated improved median overall survival at 6 and 12 months in advanced CC with the addition of 5-fluorouracil/leucovorin/oxaliplatin (mFOLFOX). Since then, FOLFOX has been considered the standard chemotherapy treatment after progression on cisplatin and gemcitabine [31].

Despite the emergence of new therapeutic modalities, additional strategies are needed due to high morbidity and mortality.

Immunotherapy

On October 17, 2022, the use of durvalumab, an immune checkpoint inhibitor, was approved by ANVISA (National Health Surveillance Agency), which is a humanized monoclonal antibody with high affinity that blocks and inhibits PD-L1 - Death-ligand 1, increasing the anti-tumor immune response, in combination with gemcitabine and cisplatin for the first-line treatment of patients with locally advanced or metastatic CC. The phase III study (TOPAZ-1) randomized 685 patients with advanced or metastatic CC without systemic treatment to receive either durvalumab or placebo combined with gemcitabine and cisplatin. The inclusion of patients with recurrent disease after adjuvant surgical treatment (with a minimum interval between the end of adjuvant therapy and recurrence of 6 months) was allowed.

The results showed that the combination of durvalumab with the standard chemotherapy regimen reduced the risk of death by 24% and the 24-month survival rate was 23.5% versus 11.5% (standard therapy with placebo). The percentage of discontinuation due to severe adverse events was 6%. The most frequent events were: nausea, anemia, constipation, skin rash, cholangitis, fever, and sepsis [28]. Due to these results, the combination of cisplatin, gemcitabine, and durvalumab becomes the standard therapy for advanced CC in the first-line setting [35].

The KEYNOTE-016 and KEYNOTE-158 phase 2 studies demonstrated antitumor activity in 6% to 13% regardless of PD-L1 expression and the safety of Pembrolizumab, with manageable toxicity. Pembrolizumab is a monoclonal antibody that binds to the programmed death 1 (PD-1) receptor in patients with advanced CC

and blocks the interaction with ligands. In retrospective studies, PD-L1 expression has been observed in CC, suggesting a potential role for immunotherapy targeting the PD-1 pathway. Preliminary results have shown promising responses [32].

Loco-Regional Therapies

CC has a predilection for liver metastasis, so loco-regional therapies, including transarterial chemoembolization (TACE), transarterial radioembolization, and ablative therapies, play a role in the intra-hepatic variants of the disease for palliation. Intra-arterial hepatic therapy refers to treatments administered through the hepatic arteries to improve access to the tumor due to the preferential arterial blood supply to hepatic tumors. Some studies have suggested a possible benefit of such therapies in terms of tumor progression and survival [37].

Three main approaches have been tested in CC:

Hepatic Artery Infusion

Hepatic artery infusion (HAI) consists of injecting chemotherapeutic agents directly into the hepatic artery, usually in repeated cycles similar to systemic chemotherapy.

Transarterial Chemoembolization (Tace)

TACE is considered a safe treatment option, with a median overall survival of 12 to 15 months. It involves the injection of chemotherapeutic agents mixed with lipiodol contrast followed by embolic agents (gelatin sponge or calibrated/pharmacological particles). TACE with pharmacological particles may have similar efficacy to systemic chemotherapy and performs better than conventional TACE [34].

Selective Internal Radiation Therapy

Selective internal radiation therapy, known as radioembolization, involves the injection of a radioisotope (yttrium-90) loaded into glass or resin microspheres and is a treatment option for unresectable CC, with reasonable efficacy. Recently, the use of selective intra-arterial radiotherapy with radioactive Yttrium in an adjuvant setting has been reported. The group reported a median overall survival of 22 months with minimal toxicity [34].

Palliation

In patients with advanced disease, the goal of treatment is well-managed palliation. Biliary drainage with endoscopic or percutaneous stent placement plays an important role in patients with cholestasis, as it improves quality of life by providing control of itching and jaundice. However, biliary drainage is limited by tumor growth, which has necessitated new studies and therapeutics. Radiofrequency ablation (RFA) guided by ERCP plays an important role in palliative management, as it improves stent patency and contributes to improvements in quality of life. RFA allows for tissue necrosis through thermal energy, leading to necrosis of tumor cells and good control of tumor growth. A study conducted in 2017 demonstrated increased survival in patients with advanced CC undergoing biliary drainage with stent placement associated with RFA [33].

In cases of stent failure, biliary bypass surgery should be considered depending on the patient's performance status.

Ongoing Studies

In recent years, many studies have identified potentially useful molecular targets as targeted therapies, such as fibroblast growth factor receptor (FGFR), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), metabolic regulators such as isocitrate dehydrogenase 1 and 2 (IDH1/2), BRAF, tyrosine kinase receptor inhibitors, and transcription factor FOSL1. Molecular profiling of tumors to identify specific mutations can enable the offering of targeted therapies in personalized treatments [38].

Fgfr Antagonists

Fibroblast growth factor (FGF) signaling plays a role in cellular development and angiogenesis and is expressed in various cell types. FGF receptor 2 fusions occur in 13 to 17% of CC cases. In 2018, a phase II study evaluated infigratinib, an oral selective ATP-competitive tyrosine kinase inhibitor of FGFR1-3, in patients with advanced CC refractory to chemotherapy with positive FGFR2 fusions. The results suggest significant activity after chemotherapy and that these agents may be useful in the neoadjuvant setting [30].

Pemigatinib (Pemazyre) is an oral selective inhibitor of FGFR1-3, and in April 2020, it was approved by the US FDA as the first targeted therapy for patients with refractory advanced CC with FGFR2 fusion or rearrangement [30].

Idh1/2 Mutant Inhibitors

Mutant IDH converts α-ketoglutarate to 2-hydroxyglutarate, an oncometabolite. The accumulation of 2-hydroxyglutarate leads to epigenetic changes, impaired DNA repair, and aberrant cellular metabolism, resulting in oncogenesis. IDH1 mutations are present in approximately 15-25% of CC cases [30].

Several mutant IDH1 protein inhibitors have been developed and studied in clinical trials. Most notably, Ivosidenib (AG-120), an IDH1 inhibitor, was evaluated in patients with CC in a phase I study, and 56% of patients treated with this drug had stable disease, and 5% had a partial response. Other IDH inhibitors and IDH pathway-targeted therapies are under evaluation [30].

Mapk Pathway Inhibitors (Mitogen-Activated Protein Kinase)

BRAF is a serine/threonine kinase that activates the MAP

kinase/ERK signaling pathway, leading to cell proliferation and differentiation. Mutated BRAF activation leads to hyper activation, promoting cell proliferation, differentiation, and survival. BRAF mutations are described in CC, with a prevalence of 1-3% [30].

BRAF inhibitors appear to have limited activity in CC, which may be due to EGFR activation through feedback, as in colorectal cancer. Dual BRAF and MEK inhibition is a potentially effective strategy for targeting the RAS-ERK pathway. The combination of Dabrafenib and Trametinib has shown durable clinical responses [30].

Tyrosine Kinase Receptor Inhibitors

There are three tyrosine kinase receptors TRK, TRKA, TRKB, and TRKC, encoded by the genes NTRK1, NTRK2, and NTRK3, respectively. NTRK inhibitors larotrectinib and entrectinib have shown high response rates with durable responses in early-phase trials. Larotrectinib and entrectinib were approved by the US FDA for patients with NTRK fusion-positive solid tumors who have no alternative treatment or have progressed after treatment. The National Comprehensive Cancer Network (NCCN) guidelines also recommend NTRK inhibitor as first-line or subsequent therapy in NTRK fusion-positive CC [30].

Conclusion

CC, although rare, has become an oncological emergency due to its increasing incidence rates and changing epidemiology. Its diagnosis relies on various imaging modalities and invasive biopsy techniques. Thankfully, advances in diagnosis and therapeutics have led to lower morbidity and mortality rates. The advent of genetic sequencing and mutation detection has allowed the identification of potential therapeutic targets. Currently, a large percentage of patients are still diagnosed in advanced stages, necessitating the improvement of detection methods, with better screening modalities and diagnostic tests.

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