Cholangiocarcinoma: New Insights into Disease Pathogenesis and Biology

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OVERVIEW

Recent studies have shown an increased global incidence of cholangiocarcinomas, rare malignant tumors with morphologic features of biliary tract epithelia. This aggressive and poorly understood malignancy remains largely incurable. Biliary tract inflammation resulting from liver fluke infection or other causes is a well-defined risk factor for cholangiocarcinoma. Recent studies have explored the relationship between inflammatory mediators and biliary tract carcinogenesis and provided an insight into the molecular and genetic perturbations involved in the pathogenesis of cholangiocarcinoma.

CLASSIFICATION

Cholangiocarcinomas are classified into 2 major categories based on their anatomic location. Intrahepatic cholangiocarcinomas (ICCs) arise within the hepatic parenchyma and most often present as a mass lesion without major bile duct obstruction or jaundice. Ductal cholangiocarcinoma arises within the large bile ducts, namely common bile duct, common hepatic duct, and right or left hepatic duct up to the secondary bifurcation. Perihilar cholangiocarcinomas, or Klatskin tumors, are often considered separately but should be classified as ductal cholangiocarcinomas based on their location and presentation. These lesions can extend into the hepatic parenchyma and have also been classified as intrahepatic or extrahepatic. The lack of a consistent convention has led to inaccurate reporting of the epidemiology, natural history, and prognosis. Among the hilar lesions, the Bismuth classification has been widely used as a guide to surgical intervention. Intrahepatic and ductal cholangiocarcinomas can be further classified on the basis of the pathology. The staging system

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used by the Liver Cancer Study Group of Japan classifies ICCs as mass forming, peri-
ductal infiltrating, intraductal, or mixed. Similarly, extrahepatic ductal cholangiocarci-
noma can be further described as sclerosing, nodular, or papillary. However, these
clinical and pathologic classifications require modifications to incorporate hilar
lesions. The TNM classification for biliary tract cancers has not been useful in clinical
practice because the T category does not differentiate prognosis, for example, in T2
and T3 tumors. In a recent study, the number of lesions and presence of vascular
invasion were important prognostic factors, whereas tumor size was not.

EPIDEMIOLOGY

The incidence of these cancers shows a marked variation worldwide. In regions where
liver flukes are endemic, the rates of ICC are extremely high; for example, in the Khon
Kaen region in Thailand, cholangiocarcinoma accounts for more than 85% of all
cancers. In the United States, the incidence ranges from 3 to 8 per 100,000. In
most other parts of the world, the incidence of ICC has increased during the last
few decades, with an annual percentage change of about 9%. However, observa-
tions during the past decade have indicated that the rate of increase may be leveling
off. The grouping together of ICC and hepatocellular cancer in epidemiologic reports
has confounded an analysis of the true incidence of these cancers in the United
States. The incidence of ductal cholangiocarcinoma is less variable. The reported inci-
dence of extrahepatic cholangiocarcinoma, for example, is twice as high in Manitoba,
Canada, compared with that in the United Kingdom.

There are racial and gender differences in the incidence of these cancers. The inci-
dence of ICC is higher in men than in women, whereas the incidence of extrahepatic
cholangiocarcinoma is comparable between the 2 sexes. The incidence is increased in
African Americans (1.5-fold), American Indians and Hispanics (1.8-fold), and Asian
Americans and Pacific Islanders (2.5-fold) compared with whites in the United States.
Overall, the prevalence is greater in men, except in Hispanics, in whom the prevalence
is greater in women. The overall age-adjusted mortality rates for ICC in the United
States are highest for the American Indian/Alaska Native and Asian/Pacific groups. However,
the increase in mortality rates is similar for all racial groups, with an annual percentage
change of greater than 3.5%, except for Asian/Pacific Islander women, for whom
mortality rates have been slightly decreasing. According to the American Cancer
Society, in the United States, the estimated number of deaths caused by extrahepatic
cholangiocarcinoma in 2008 were 3340 per year, with 62% of these occurring in men.

RISK FACTORS

Several risk factors have been identified for cholangiocarcinoma. Although the
risk factors vary geographically, there is a strong association of cholangiocarcinoma
with chronic biliary tract infection and inflammation. Well-characterized risk factors
include liver fluke infestations, chronic viral hepatitis, hepatolithiasis, choledochal
cysts, and primary sclerosing cholangitis (PSC).

Liver Fluke Infestation

Infestation with either Clonorchis sinensis or Opisthorchis viverrini leads to an
increased risk of cholangiocarcinoma. Both these liver flukes are now considered as
grade 1 carcinogens by the World Health Organization and International Agency for
Research on Cancer.

C sinensis infection is endemic in south China, Japan, Korea, and Taiwan because of
a long tradition of consuming raw fish or shellfish. Chronic infection with heavy parasite
loads has been associated with various hepatobiliary diseases. *Clonorchis* dwells in the bile ducts and induces an inflammatory reaction that causes a malignant transformation of cholangiocytes. Patients affected by clonorchiasis have a higher risk for developing cholangiocarcinoma. In a recent analysis of more than 3000 Korean patients, the incidence of cholangiocarcinoma was 8.6%. Since the introduction of praziquantel, the incidence of clonorchiasis has been reduced in the endemic areas. However, this condition has not been eradicated, and chronic infestation remains the main cause of cholangiocarcinoma in these areas. The detection of *C. sinensis* is problematic because fecal examination for eggs has low sensitivity and, in the intradermal test, diluted antigens of *Clonorchis* can cross-react with other parasites such as *Paragonimus westermani*. Thus, the diagnosis can be missed. Adult worms can remain in the peripheral intrahepatic bile ducts for 20 to 30 years, causing chronic persistent infection and subsequently resulting in cholangiocarcinoma.

*O. viverrini* is highly prevalent in Thailand and Laos. As with *C. sinensis*, humans are infected by ingesting undercooked fish containing infective metacercariae. This infection is associated with several benign hepatobiliary diseases, including cholangitis, obstructive jaundice, hepatomegaly, and cholecystitis. The risk of cholangiocarcinoma depends on the intensity of the infection, previous or current exposure to infection, and host genetic polymorphisms. Less than 10% of people infected with *O. viverrini* may develop cholangiocarcinoma. However, other than for Thailand, cancer registration and statistics are not available for many other countries in the region. Thus, an accurate estimation of the risk of developing cholangiocarcinoma is difficult. Conversely, in Thailand, more than 80% of cholangiocarcinomas test positive for the presence of *O. viverrini* by real-time polymerase chain reaction (PCR). Repeated infection with *O. viverrini* induces oxidative DNA lesions, such as 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), in the bile duct epithelium, which are carcinogenic. The urinary level of 8-oxodG was found to be significantly higher in patients with cholangiocarcinoma than in *O. viverrini*-infected patients and healthy subjects. Praziquantel is effective against *O. viverrini* and can significantly decrease the urinary level of 8-oxodG. Thus, urinary 8-oxodG may be a useful biomarker to monitor infection and the efficacy of treatment, as well as for surveillance for tumors. Repeated infections with *O. viverrini* may accelerate DNA damage. Thus, a preventive strategy to reduce infection, such as by decreasing the consumption of infected fish,
may be more rational to reduce the incidence of cholangiocarcinoma than a strategy that is focused on treating established infections.

**Primary Sclerosing Cholangitis**

In the Western world, the incidence of liver fluke infestation is quite low, and PSC is the main risk factor for cholangiocarcinoma. PSC is a chronic idiopathic inflammatory disorder characterized by fibrosis and bile duct strictures. The risk of cholangiocarcinoma varies from 7% to 40%.18,19 The duration of PSC does not correlate with the development of cholangiocarcinoma, and the estimated risk of cholangiocarcinoma at 10 years is similar to that at 20 years.19 In a recent study, the median interval between the diagnosis of PSC and cholangiocarcinoma was 2.5 years, with all cases developing within 3 years. Thus, it is unclear whether or not cholangiocarcinoma occurs as a synchronous condition or as a consequence of PSC in these patients.20

**Congenital Abnormalities of the Biliary Tract**

Patients with choledochal cysts, congenital cystic dilations of the biliary tract, are at risk of malignancy. Similarly, patients with Caroli disease or congenital hepatic fibrosis, which are developmental abnormalities resulting in multiple intrahepatic cysts, are also at risk of developing cholangiocarcinoma.

**Chronic Viral Hepatitis**

Hepatitis C virus (HCV) infection has been recently described as a risk factor for cholangiocarcinoma. In a retrospective US cohort study, HCV infection was significantly associated with an increased risk of cholangiocarcinoma. Although the rate of infection remained low (4 per 100,000 person-years), the risk was more than doubled in the HCV-infected cohort than in the uninfected cohort. The risk for extrahepatic cholangiocarcinoma was not increased.21 A prospective cohort study from Japan showed that 2.3% of 600 patients with HCV-related cirrhosis developed ICC during a mean follow-up of 7 years and had a significantly higher risk of developing cholangiocarcinoma than the general population.22 Although growing evidence is supporting the carcinogenic effects of HCV proteins in hepatocellular carcinoma, the involvement of HCV in cholangiocarcinogenesis is less clear. The HCV core protein can alter cellular proliferation and apoptosis in hilar cholangiocarcinoma cells.23 Because ICC and hepatocellular carcinoma may arise from the same progenitor cells, common mechanisms may account for the malignant transformation.24

Hepatitis B virus (HBV) infection is also a recognized risk factor. In China, where HBV infection is endemic, the main risk factors are HBV infection and hepatolithiasis. The prevalence of hepatitis B surface antigen (HBsAg) seropositivity and hepatolithiasis was increased from 9% to 48% and from 1% to 5%, respectively, in patients with ICC compared with controls.25 In studies conducted in other regions such as Korea, Italy, and the United States, HBsAg seropositivity in patients with ICC ranged from 0.2% to 13%.26–29 It is hoped that screening and vaccination strategies for HBV in regions of high endemicity may lead to a reduction of cholangiocarcinoma, similar to the dramatic effects of these strategies in reducing hepatocellular cancer.

**Hepatolithiasis**

The relationship between hepatolithiasis and cholangiocarcinoma has been long recognized.30 In cholangiocarcinoma associated with hepatolithiasis, the stones are closely situated within or adjacent to the tumor foci. Carcinomatous cells spread along the luminal surface of the stone-containing bile ducts and invade the ductal walls. Features of chronic proliferative cholangitis are usually found within these bile ducts.31
A wide range of molecular alterations has been described in this setting, such as inactivation of p16, increased expression of cyclooxygenase (COX)-2 and prostaglandin E2, overexpression of the proto-oncogene c-met, and lack of the tumor suppressor, caudal-related homeobox gene 2. These alterations have been noted in precursor lesions and in established cholangiocarcinoma. Most primary hepatolithiasis involves calcium bilirubinate; cases of cholesterol hepatolithiasis have also been described, although rare.

**Alcohol and Toxins**

Certain exposures may lead to increased risk of cholangiocarcinoma. Multiple case-control analyses have reported an association between cholangiocarcinoma and alcohol use. Several cases of cholangiocarcinoma have been described after the iatrogenic exposure to thorium dioxide (Thorotrast), a radiocontrast agent used in the past. Exposure to toxins may be linked to outbreaks of cholangiocarcinoma, which have been noted in Italy, West Virginia, and British Columbia, although convincing evidence for any likely culprits is lacking.

**Cirrhosis and Other Causes**

Cirrhosis has been previously associated with a higher incidence of cholangiocarcinoma in a large cohort study in Denmark. The risk of cholangiocarcinoma might be mediated by HCV-induced liver cirrhosis. Analysis of the Surveillance, Epidemiology and End Results–Medicare database established the relationship between several risk factors in the US population. Cirrhosis and primary biliary cirrhosis were significantly more common among extrahepatic cholangiocarcinoma and ICC cases than in controls. Alcoholic liver disease, type 2 diabetes, obesity, and human immunodeficiency virus infection are also significantly associated with cholangiocarcinoma.

**SCREENING FOR CHOLANGIOCARCINOMA**

The lifetime risk for cholangiocarcinoma varies according to the specific risk factors involved. These tumors are usually silent or associated with nonspecific symptoms, and diagnosis is frequently late (**Fig. 1**). Although early detection is needed to improve survival rates, there are no proven effective screening tests to date. Serum or stool tests for liver flukes and estimation of urinary levels of 8-oxodG might be promising.

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**Fig. 1.** Magnetic resonance image of the liver showing a multifocal, poorly differentiated ICC with vascular invasion.
strategies in endemic areas. Several tumor markers may support a diagnosis of cholangiocarcinoma, but none are sensitive enough to be used for screening purposes. The most commonly used markers are carbohydrate antigen 19-9 and carcinoembryonic antigen. However, the levels of these markers can be elevated in the presence of other malignancies as well as in benign conditions such as cholangitis and hepatolithiasis. Moreover, the value of screening for cholangiocarcinoma is debatable given the poor response to treatment.

PATHOGENESIS

Study of the pathogenesis of cholangiocarcinoma provides a paradigm for the study of the role of infection and chronic epithelial inflammation in malignancy. The pathogenic mechanisms involved in biliary fluke-associated cholangiocarcinoma are likely to be multifactorial. Biliary tract injury arises as a consequence of mechanical injury caused by the migration of the flukes, metabolic toxins, and immunopathologic processes.\(^3^9\)

Metabolic products released by liver flukes may be directly toxic or may promote an immunologic response that results in proliferation of fibroblasts and overexpression of transforming growth factors (TGFs)\(^4^0\) and metalloproteinases.\(^4^1\) Evidence for fluke-induced host inflammatory response in mediating biliary damage is further provided by the expression of opisthorchis antigens in peripheral macrophages and epithelioid cells.\(^4^2\) Subsequent cytokine-dependent activation of effector cells results in oxidative stress, which causes cytotoxicity and enhances mutagenesis. This oxidative stress results in DNA damage with malfunctioning of mismatch repair systems and aberrant regulation of cellular apoptosis. \(N\)-nitroso compounds are primary carcinogens leading to cholangiocarcinoma. Humans infected with \textit{Opisthorchis} seem to have a higher endogenous nitrosation potential than uninfected people, as a result of the production of nitric oxide (NO) and the stimulation of NO synthase (NOS). Population-based variations in the expression of genes involved in the detoxification of carcinogens may also contribute to the higher incidence in endemic areas, such as Thailand, than in nonendemic areas.\(^4^3\)

\textbf{Biliary Constituents}

Carcinogenesis of biliary epithelia is a multistep process that involves the transformation from hyperplasia to dysplasia and eventually to carcinoma. Chronic inflammation and cellular injury together with partial obstruction of bile flow result in bile stasis and chronic exposure of biliary cells to the carcinogenic action of bile components. The bile from patients with inflammatory biliary injuries contains increased levels of oxysterols, oxygenated derivatives of cholesterol. Oxysterols and bile acids, such as deoxycholic acid, may promote carcinogenesis by inducing the expression of COX-2, transactivating the epidermal growth factor receptor (EGFR), repressing E-cadherin, and blocking the degradation of the antiapoptotic myeloid cell leukemia protein 1 (Mcl-1).\(^4^4,4^5\) In experimentally induced cholestasis, levels of reduced glutathione (GSH) and the enzymes indispensable for GSH synthesis are decreased in the bile. GSH participates in the detoxification of many molecules and in the defense against oxidative stress. Therefore, the alteration in GSH content may lead to DNA damage and deregulation of apoptosis in cells of patients with chronic biliary disorders.\(^4^6\)

\textbf{Genetic and Epigenetic Abnormalities}

Neoplastic transformation of biliary epithelia is accompanied by several molecular and genetic alterations. Activation of autonomous growth signaling molecules, such as hepatocyte growth factor (HGF)/met, interleukin (IL)-6, c-erbB2, K-ras (20%–50%), BRAF,
and COX-2, are responsible for abnormal cell proliferation and survival. Abnormalities of DNA mismatch repair, such as microsatellite instability, increase the risk of genetic damages. Immortalization of biliary cells is mediated by the modulation of telomerase activity. Several tumor suppressor genes are inactivated in cholangiocarcinoma. For example, p53 is usually lost in cholangiocarcinoma cells (20%–70%) because of the loss of heterozygosity or inactivating mutations, and p16Ink4A is frequently silenced by promoter hypermethylation. Inactivation of p16, together with the lack of p21WAF1/CIP1, p27Kip1, and p57Kip2 and increased levels of cyclin D1, is responsible for cell cycle dysregulation. Regulation of apoptosis is aberrant in cholangiocarcinoma cells because of the overexpression of antiapoptotic proteins, such as Bcl2, Bclxl, and Mcl-1. Specific mucin antigen expression profiles have been associated with predictive value. Invasion and metastasis are favored by the loss of E-cadherin and catenins. Cholangiocarcinoma growth may be facilitated by increased angiogenesis mediated by overexpression of vascular endothelial growth factor, COX-2, and TGF-β.

**Cytokine-Mediated Signaling Pathways**

Several cytokines or growth factors, such as IL-6, HGF, TGF-α, endothelial growth factor, c-erbB2, heterogeneous IgA, and leukocyte inhibitory factor, are known to have mitogenic or proliferative effects on biliary cells via an autocrine or a paracrine effect. Neoplastic transformation of biliary cells is associated with a constitutive production of IL-6, as demonstrated by positive cytoplasmic immunohisotchemical staining and overexpression of IL-6 messenger RNA and protein in cholangiocarcinoma cells. This production is significantly enhanced by other inflammatory cytokines, such as tumor necrosis factor α and IL-1, as a result of the complex paracrine-autocrine stimulation that takes place in inflammatory-mediated carcinogenesis. In addition, expression of IL-6 receptor on tumor cells makes the cells hypersensitive to the exogenous IL-6 from environmental sources, such as stromal and immune cells. The response to IL-6 stimulation differs between normal and malignant cholangiocytes, with aberrant expression of p38 mitogen-activated protein kinase (MAPK) in the latter. IL-6 signaling modulates gene expression and sustains mitogenic signals that promote cholangiocarcinoma cell growth and survival through different mechanisms. Some of these effects are exerted through the modulation of microRNAs, small noncoding RNAs that regulate gene expression. In in vitro and animal models, IL-6 overexpression was shown to reduce the expression of miR-370, resulting in the enhancement of p38 MAPK activation. In other disease models, IL-6 expression is regulated by microRNAs, suggesting that a circulatory loop might be responsible for the sustained expression of IL-6 in cholangiocarcinoma. IL-6 may also alter the methylation status of cholangiocarcinoma cells by increasing the expression of DNA methyltransferase 1, which results in methylation-mediated silencing of oncosuppressor genes and promotion of cellular proliferation and survival. Furthermore, IL-6 mediates chemoresistance of cholangiocarcinoma cells by the p38- and STAT 3–dependent modulation of the antiapoptotic protein Mcl-1. Together, these data suggest that IL-6 signaling plays a central role in colangiocarcinogenesis and provide the rationale for the evaluation of IL-6 targeting agents as sensitizers or cytotoxic agents useful in cholangiocarcinoma treatment.

**Oxidative Injury and DNA Damage**

Biliary injury of diverse causes results in the recruitment of inflammatory cells and release of proinflammatory cytokines, which increase the generation of NO by inducing NOS. NO may favor the possibility of oncogenic mutations, may inhibit
apoptosis through the nitrosylation of caspase 9, and may cause bile ductular cholestasis by inhibiting ion transporters of the biliary cells.\textsuperscript{58}

All this evidence confirms that the pathogenesis of cholangiocarcinoma is enhanced by inflammatory mediators that mediate oncogenic signaling. The relevance of inflammation in cholangiocarcinoma is also supported by recent findings that show that patients with a neutrophil to lymphocyte ratio greater than 5 have larger tumors with intrahepatic satellite lesions, microvascular invasion, and lymph node involvement; the ratio also predicts poorer overall and disease-free survival in patients undergoing radical surgery. This index may reflect a weaker lymphocyte-mediated immune response to the tumor and the enrichment of cytokines produced by circulating and intratumoral neutrophils that can enhance tumor cell growth.\textsuperscript{59}

**DIAGNOSIS**

**Clinical Presentation**

A suspicion of cholangiocarcinoma may be raised in several different clinical scenarios (Box 2). ICCs usually present as a mass lesion within the liver and may be asymptomatic until they are quite advanced. Ductal cancers are more likely to be symptomatic because of biliary obstruction and often present with jaundice. Because of the tendency of these cancers to spread along the biliary tract, they may also be more extensive at the time of diagnosis.

**Risk Factor Analysis**

In regions where liver flukes are endemic, an assessment of liver fluke infection can be performed using stool studies to look for eggs. PCR-based techniques capable of amplifying DNA taken directly from eggs of species of flukes have a better sensitivity and specificity than the standard microscopic examination of stool samples.\textsuperscript{60} Use of these or other similar noninvasive assays may be helpful for diagnosis as well as for epidemiologic surveys of the distribution of liver flukes and may enable individual or population-based targeted approaches. In patients with known ulcerative colitis, evaluation for serum markers of cholestasis, abdominal imaging, ultrasonography, or cholangiography may be useful to diagnose PSC.

**Diagnostic Studies**

A combination of tumor markers, imaging, and cytologic studies may be used to diagnose cholangiocarcinoma (Table 1). The diagnosis is difficult to make, especially in patients with underlying PSC who may have biliary strictures. For patients with ICC, biopsy may reveal adenocarcinoma, which may prompt evaluation and exclusion of potential other primary sites.

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**Box 2**

**Clinical scenarios in which a suspicion of cholangiocarcinoma should be raised**

- Jaundice, systemic illness, and weight loss in patients with known risk factors, such as liver fluke infection, PSC, and hepatolithiasis
- Jaundice or systemic illness in patients from areas with liver fluke endemicity
- Bile duct stricture causing jaundice
- Intrahepatic liver mass
TREATMENT

Surgery

Survival from cholangiocarcinoma is extremely poor, with an average 5-year survival rate of approximately 5%. Surgical resection or transplantation could be curative in selected patients who have no evidence of distant spread, vascular invasion, or extra-hepatic spread with limited resectable disease. For patients with ductal carcinomas, exploration to assess resectability may be appropriate. For ICC, hepatic resection may be appropriate. Reported outcomes show a wide variation with 5 year survival ranging from 10–40%. Although recent series suggest that outcomes have improved in recent years, variable classifications and differing patient populations make interpretation difficult. Liver transplantation is appropriate for very few individuals with localized, early-stage disease and is offered only at a handful of centers worldwide. Neither transplantation nor resection is appropriate for individuals with evidence of portal vein or hepatic artery invasion on preoperative imaging or endoscopic ultrasonography. There are no data on the benefit of using adjuvant therapy after a margin-negative resection.

Photodynamic Therapy

Photodynamic therapy involves the intravenous administration of a photosensitizer followed by endoscopic delivery of light at a specific wavelength, which causes tumor cell death because of oxidative injury. Use of this approach with stenting can improve survival compared with stenting alone. Photodynamic therapy should be considered for patients with locally advanced disease, but it is not widely available.

Medical

Cholangiocarcinoma is highly resistant to chemotherapy. However, systemic chemotherapy may be considered in patients with advanced cholangiocarcinoma, as there may be some benefit compared with best supportive care.61 The literature is limited and consists of several small series involving multiple tumor types. Various chemotherapeutic agents, dosing regimens, and combinations have been tested with overall poor results.

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Sensitivity (%)</th>
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<td>Tumor markers</td>
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<td>CA 19-9</td>
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<tr>
<td>CEA</td>
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<td>Fluorescence in situ hybridization</td>
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Abbreviations: CA, carbohydrate antigen; CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen.
survival improvement. 5-Fluorouracil, gemcitabine, oxaliplatin, and docetaxel have shown the most activity as single agents. A recent phase 3 trial evaluated the combination of gemcitabine and cisplatin and showed this combination to be superior to single-agent chemotherapy, with a higher response rate and a prolonged overall survival that reached 11.7 months in the combination arm. According to these data, gemcitabine and cisplatin should be considered as the standard therapy for locally advanced and metastatic cholangiocarcinomas. Several new molecular targeted agents and biologic agents are being explored for the treatment of cholangiocarcinoma.

**Palliative Therapy**

In patients with biliary tract obstruction, decompression may be helpful. Cholestatic liver dysfunction and biliary cirrhosis may rapidly occur in patients with unrelieved obstruction. However, placement of stents in patients who are candidates for surgery may interfere with preoperative evaluation for resectability and intraoperative determination of tumor extent.

**PREVENTION**

In regions of high liver fluke endemicity, the optimal approach to chemoprevention involves appropriate public health measures and education to reduce the effect and incidence of liver fluke infestation. However, an estimated 40 million to 50 million people in Southeast Asia may have fluke infection and may be candidates for eradication efforts. Although reducing the consumption of uncooked fish may be an effective strategy, these cultural and traditional practices are deeply entrenched and difficult to change. Active surveillance for fluke infection and potential interventions for eradication using chemotherapy may reduce the development of cholangiocarcinoma, but such approaches have not been evaluated for their chemopreventive efficacy in reducing the incidence of cholangiocarcinoma.

In the West, chemopreventive strategies may be considered for patients with PSC, who have a higher frequency of cholangiocarcinoma and may be associated with inflammatory bowel disease or colorectal cancer. Ursodeoxycholic acid (UDCA) is a hydrophilic bile salt that may protect the biliary tree by stabilizing bile duct epithelium and hepatocyte cell membranes and increasing bile flow from the liver, thereby reducing intrahepatic bile stasis and exposure time to toxic bile salts. UDCA also seems to exert a protective effect on colic mucosa by reducing fecal concentrations of deoxycholic acid. UDCA has been evaluated as a potential chemopreventive measure for PSC, but there is no clear benefit of efficacy in reducing the rate of tumor formation. Further evaluation in randomized trials is necessary.

Novel approaches to chemoprevention may be based on new insights from molecular pathogenesis. The EGFR gene, for example, is located on the short arm of chromosome 7. Patients with PSC who show trisomy 7 and/or EGFR expression in biliary tract epithelia may be appropriate to consider for chemoprevention with EGFR blockers, if they have a higher risk of cholangiocarcinoma. Overexpression of COX-2 has been reported in extrahepatic cholangiocarcinoma, and COX-2 inhibitors could be potentially useful chemopreventive agents in such patients.

**CHALLENGES IN CHOLANGIOCARCINOMA**

Cholangiocarcinoma has a dismal prognosis and is almost always incurable because it is refractory to most currently used surgical or medical interventions. A major limitation in the management of cholangiocarcinoma has been that the disease and its nosology are poorly defined, which has limited the information that can be obtained
from epidemiologic studies and has made it difficult to compare outcomes of different management strategies. Oncologic trials for biliary cancers, for example, have often included intrahepatic and extrahepatic malignancies. A clinically useful classification system that separates these 2 different diseases with different risk factors, pathogenetic mechanisms, and clinical behavior is needed. Risk factors for cholangiocarcinoma vary considerably, being primarily infectious in the East and noninfectious in the West. Thus, the clinical behavior and management of this tumor show regional variations despite shared pathogenetic mechanisms. Investigation on the role of inflammatory mediators and processes on cholangiocarcinoma pathogenesis is likely to be beneficial, given the common involvement of chronic biliary tract inflammation in cholangiocarcinoma. The epidemiologic trends are concerning, in that they show a global increase in incidence and mortality, but the disease has received little interest among research funding bodies and public health administrators, and it continues to be regarded as a rare disease of little importance in the West. There are many challenges in the current management and approach to cholangiocarcinoma, both from the perspective of the individual as well as from a public health perspective.

REFERENCES


