

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Advances in Diagnosis and Treatment of Cholangiocarcinomas

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G&H What role do gastroenterologists play in the management of patients with cholangiocarcinomas?

ID/CL Gastroenterologists are involved in the care of these patients both because of the nature of the conditions predisposing them to cholangiocarcinoma and because these patients can develop biliary obstructions, in which case we must manage symptoms such as jaundice and pruritis. Unfortunately, these cancers can remain asymptomatic for a long period, especially in the case of intrahepatic cholangiocarcinomas, so patients often present very late in their disease course. Thus, a primary goal for gastroenterologists should be to secure the diagnosis in a timely fashion. Achieving this goal can be extremely difficult in some cases, particularly in patients with primary sclerosing cholangitis (PSC); these patients often have dominant strictures, and differentiating benign from malignant strictures can be challenging.

G&H In which patients are bile duct carcinomas most common?

ID/CL PSC is responsible for nearly 30% of all cholangiocarcinomas. Other risk factors include congenital biliary diseases such as Caroli disease and choledochal cysts, intrahepatic lithiasis, parasite infections (including *Clonorchis* and *Opisthorchis*), biliary papillomatosis, and male gender. Emerging risk factors that require further validation include chronic hepatitis C and B, alcohol abuse, diabetes, and obesity.

G&H What is the standard treatment for bile duct carcinomas?

ID/CL The treatment approach differs depending on the presence or absence of PSC and whether the cholangiocarcinoma is extrahepatic or intrahepatic. Surgical resection is the only curative treatment, but most patients are not surgical candidates at the time of diagnosis. As a result, prognosis is generally poor, with an overall median survival of only 27 months. Recently, there has been some investigation of liver transplantation for cholangiocarcinoma, but this treatment remains experimental and is reserved for early-stage hilar cholangiocarcinoma. For patients who are not surgical candidates, alternative treatments include radiation, chemotherapy, stenting, and photodynamic therapy.

G&H How does treatment differ when cholangiocarcinoma is associated with PSC?

ID/CL Because of the chronic inflammation associated with PSC, these patients are more prone to multifocal disease, and, frequently, these tumors cannot be resected. They are also diagnosed at a later stage, which increases the risk for involved margins after resection. Furthermore, these patients' liver disease increases their operative risk and imposes a high risk for hepatic decompensation.

Over the past few years, surgeons at Mayo Clinic have developed a protocol using surgical staging and neoadjuvant chemoradiation therapy followed by liver transplantation to treat early-stage hilar cholangiocarcinoma in patients with PSC or those whose tumor is deemed unresectable. Using this protocol, surgeons have achieved an overall 5-year survival rate of 54% for all patients who begin neoadjuvant therapy, 61% for PSC patients, and 42% for those with de novo cholangiocarcinoma. Five-year survival after transplantation is 73% for all patients, 79% for patients with PSC, and 63% for patients with

de novo cholangiocarcinoma. A recurrence rate of 18% was reported. It is important to note that these results have not yet been reproduced by other groups.

G&H When is surgical resection a viable treatment option?

ID/CL In order for patients to undergo surgery, they must not have any evidence of distant involvement (ie, no lymph node or distant metastases), and they cannot have any involvement of vessels, especially the portal vein or the hepatic artery. Also, there should not be any extrahepatic adjacent organ involvement. Other patients in whom surgical resection is contraindicated include those with atrophy of 1 lobe with contralateral biliary radical involvement, atrophy of 1 lobe with encasement of the contralateral portal vein branch, or encasement of the portal vein proximal to the bifurcation.

G&H How often is surgical resection performed? What is the survival rate in patients who undergo surgery?

ID/CL Approximately 30% of patients will be candidates for surgery, depending on the location of the tumor. Because patients with extrahepatic cholangiocarcinoma are typically more symptomatic, they come to our attention earlier in their disease course, and there is a greater chance that the tumor can be addressed before it spreads. Overall, only 20–30% of patients are surgical candidates; of those who undergo surgery, 5-year survival is approximately 30%.

G&H Why are bile duct carcinomas particularly challenging to treat?

ID/CL This tumor is frequently desmoplastic, so the yield of brush cytology and biopsies obtained during endoscopic retrograde cholangiopancreatography (ERCP) is quite low. The yield with cytology is 20–30%, and the yield with biopsy is 30–40%. With fluorescence in-situ hybridization (FISH) techniques, we can improve our yield to 50–60%, but there are still a large number of cases that remain undiagnosed for a long period. Thus, these tumors are often silent and diagnosed very late.

G&H Are there new techniques that can be used to improve diagnosis?

ID/CL In addition to using magnetic resonance imaging (MRI) and computed tomography scans to visualize intrahepatic cholangiocarcinomas, we can also use endoscopic ultrasound and ERCP to help diagnose extrahe-

patic and hilar cholangiocarcinomas. With endoscopic ultrasound, we can perform fine-needle aspiration to obtain tissue; during ERCP, brushings are obtained for cytology and FISH testing, and biopsies are obtained for histopathology. Other new endoscopic and imaging technologies include transpapillary intraluminal cholangioscopy, endoscopic intraductal ultrasound, and optical coherence tomography. In addition, immunologic studies have suggested targets for new diagnostic tests, including p53 and K-ras mutations in ERCP brushings and insulin growth factor 1 and matrix metalloproteinase 7 in bile.

While these new technologies may prove helpful, efforts to improve diagnosis should focus on screening patients who are at higher risk for cholangiocarcinomas, especially patients with PSC. Noncirrhotic patients with PSC should undergo an ultrasound and measurement of CA 19-9 every year. CA 19-9 is a serum tumor marker used to support the diagnosis of cholangiocarcinoma; it has a sensitivity near 80% and specificity near 100% for values over 129 U/L. If patients are cirrhotic, then ultrasound and CA 19-9 testing should be performed every 6 months. When patients show clinical and/or laboratory deterioration, they should undergo an MRI for better morphologic evaluation of the liver and ERCP with brushings and biopsies, especially if new dominant strictures are identified.

G&H What are some alternatives to surgery? Have there been any new treatments that show significant promise?

ID/CL For patients with unresectable cancers, alternatives to surgery include endoscopic or percutaneous stenting and photodynamic therapy. Typically, stenting is used in patients with bilirubin levels higher than 10 mg/dL, and most surgeons advocate using covered metal stents to prevent ingrowth stenosis. In addition, photodynamic therapy has recently been shown to improve quality of life and prolong survival in patients with advanced cholangiocarcinoma. Where available, photodynamic therapy is currently used in conjunction with stenting.

There are also new developments in terms of chemotherapy. While still investigational, gemcitabine appears to be the most active agent for treating cholangiocarcinomas; it is usually combined with cisplatin. In phase III studies, regimens using gemcitabine have achieved a median survival close to 1 year, with a 30% decrease in the death hazard ratio.

Radiation therapy also appears to improve survival by eradicating microscopic residue after surgery. New techniques currently being explored include conformal irradiation, specialized techniques using external beam

radiation therapy, brachytherapy via a tranhepatic catheter or endoscopic stent, and intraoperative radiation.

G&H What further research is needed to improve the treatment of bile duct carcinomas?

ID/CL We need to improve diagnosis, so identifying tests that improve the yield of biopsy is very important. There is currently much work being performed with gene profiling in bile and identifying serum markers such as interleukin 6, trypsinogen, mucin-5AC, soluble fragment for cytokeratin 19, and platelet-lymphocyte ratio. In terms of new treatments, researchers are looking at targeted therapy with multikinase inhibitors (including sorafenib, which has been used for hepatocellular carcinoma), endothelial growth factor inhibitors, COX-2 inhibitors, small molecules, and monoclonal antibodies.

Suggested Reading

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