Improving Outcomes in Cholangiocarcinomas

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Biliary-tract cancers are associated with a poor prognosis and are frequently diagnosed in advanced stages. Until recently, no gold-standard treatment had been established for biliary-tract cancers for patients ineligible for surgical resection. The ABC-02 trial randomized 410 patients with advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer who received either cisplatin and gemcitabine or gemcitabine alone.[1,2] In those who received the combination therapy, the primary end point of overall survival was significantly extended (11.7 months vs. 8.1 months, hazard ratio 0.64, $p < .001$). Adverse events in both groups were similar, with the exception of greater neutropenia in the combination group. These data, building upon a number of earlier phase II studies, strongly suggested that the cisplatin-gemcitabine combination should be the standard of care for patients with advanced biliary tract cancers.

This evidence-based approach must be tempered by two other issues. First, the context of the "real-life" setting requires consideration. Initial data from phase III studies invariably performed in specialized centers recruiting only those patients with a good performance status have often not been broadly applicable. In gastrointestinal cancers, this is probably best exemplified by the experience with IFL (irinotecan/leucovorin/5-fluorouracil [5-FU]), which is no longer used due to its toxicity,[3] despite encouraging initial efficacy data.[4] It is notable and appropriate that recent randomized data regarding FOLFIRINOX (folinic acid/irinotecan/5-FU/oxaliplatin) in pancreatic cancer makes toxicity a central point.[5] Second, patients with biliary tract cancers should ideally be stratified according to the location of their tumor and probably on the basis of their histology; for example, whether they are squamous cell or nonsquamous cell.

As the authors point out, one limitation of many studies is they have typically included diverse patient populations in an era when cancer heterogeneity is becoming central to advances in therapeutic strategies. Regarding these issues, the M. D. Anderson experience reported by Eckmann et al is a very welcome addition to the literature, focusing exclusively on intrahepatic or hilar cholangiocarcinoma.

In keeping with other recent data, gemcitabine doublets offered the optimal disease control rate, with one regimen not looking particularly different from others. While these "real-world" data are supportive of the randomized trials, the authors are correct in stating that regimen selection should be based on the toxicity profile. This reflects oncology practice as we see it; we have found considerably more neutropenia, fatigue, and neuropathy with use of gemcitabine and platinum compared with gemcitabine alone,[6] so it is also encouraging that other doublets appear effective. As they point out, it is intriguing that some individuals have very durable responses (> 4 years), and these patients merit further investigation.

The totality of data also suggest that to build upon these results, new therapies including biologics will need to be studied, as opposed to differing combinations of older chemotherapeutics, however novel they may seem. (It is notable that in Eckmann's cohort, two patients received erlotinib and one received bevacizumab.) To take this further, the genetic stratification of cholangiocarcinomas will be relevant. A recent study identified DNA copy number gains in the region of 11 useful molecular targets, including regions covering mTOR, vascular endothelial growth factor isoforms, and endothelial growth factor receptor genes.[7]

In addition, improvements in surgical resection should not be neglected, especially in the context of neoadjuvant chemotherapy. The necessity for aggressive procedures, to provide potentially curative outcomes, must be balanced by the fact that postoperative morbidity and mortality, including the risk of hepatic failure, increases with the size of resection.[8,9] More recently, however, data suggest that all-cause mortality between patients undergoing extended resection (including portal vein resection) and those without may be similar,[10] despite the fact that patients undergoing portal vein resection are likely to have more advanced tumors.[11]

Neuhaus demonstrated that perioperative mortality was comparable between radical and standard resections (13% vs. 10%) with the main cause of death in extended resections being hepatic insufficiency secondary to reduced volume of functioning parenchyma.[9] Surgeons at Nagoya University similarly operated upon 53 patients undergoing concomitant hepatic artery resection and reconstruction, with and without portal vein resection, and demonstrated a postoperative mortality rate of only 2% (1/53).[12] Portal vein embolization has been central here in reducing rates of liver failure following extended hepatectomy from 20% to 6%.

Ongoing improvements in presurgical optimization and surgical technique mean that the number of potential resections continues to increase (from 17% [1985–1994] vs. 69% [1995–2006] in one study[13]), and there is evidence to suggest that recent alterations in surgical approach, such as concomitant radical, extended liver resection, have led to higher R0 resection rates,

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improved disease-free survival, and decreased incidence of initial recurrence within the liver in patients with resectable biliary tract cancers.[11,13] Neuhaus compared standard right and left hepatectomy with more radical resection (trisegmentectomy with or without portal vein resection) in 133 patients with biliary tract cancers and reported an improved 5-year survival rate (23% and 18% vs. 72% and 52%, respectively).[9]

Recently patients with unresectable perihilar or intrahepatic biliary tract cancers, in the absence of extrahepatic disease, have been successfully treated by orthotopic liver transplantation after en bloc excision of the liver, bile ducts, and hilar lymph nodes. The concomitant use of neoadjuvant radiotherapy and surgical staging has allowed many centers to develop working protocols for liver transplantation in this setting to achieve histologically negative margins in up to 93%, with 5-year survival rates of up to 80% in patients with unresectable disease.[14,15]

Studies to date have highlighted the importance of neoadjuvant therapy as a crucial determinant in achieving optimal outcomes and selection of the most potent regimens here requires further study. Although the number of potential procedures is likely to be limited by a lack of available donors, orthotopic liver transplantation remains an option for a selected minority of patients, particularly in the context of unresectable disease.

In aggregate, further studies of cancer heterogeneity including anatomic location, mutational spectra, chromosomal aberrations, miRNA profiles, epigenetics, and transcriptomics will reveal the existence of biologically distinct types of cholangiocarcinomas. Improvements in imaging, our characterization of molecular genetics, and genomics of these tumors in will, in turn, be increasingly valuable to guide patient care. At the same time, the role of improvements in standard chemotherapy and surgery should not be forgotten.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.