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Current Therapy and Future Directions in Biliary Tract Malignancies

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OPINION STATEMENT

Cancers of the biliary tree represent a rare group of diseases with a devastating impact on patients. Gallbladder cancer is often associated with cholelithiasis. Cholangiocarcioma may arise in the setting of biliary inflammation such as primary sclerosing cholangitis but most commonly occurs in patients without a particular risk factor. Surgical removal of biliary cancer is essential for cure, but it is associated with a very high rate of recurrence and for many patients is not possible at the time of diagnosis. Although risk factors differ for each anatomic site, systemic treatment is generally similar. Various adjunctive therapies such as radiation and embolization have been investigated for biliary tract cancers with modest success and efforts are ongoing to understand how to optimize these tools. Retrospective series and pooled analysis suggest a benefit for adjuvant treatment following resection, but prospective data is limited. Ongoing and planned phase 3 trials should help clarify the role of adjuvant chemotherapy and radiation. For advanced disease, chemotherapy improves quality of life and survival, and gemcitabine with cisplatin represents the standard of care. However, all patients ultimately progress on this therapy, so clinical trials of new and better agents are essential to expand the existing treatment options for patients.

Keywords

biliary tract cancer; cholangiocarcinoma; gallbladder carcinoma; chemotherapy

INTRODUCTION

Biliary tract cancers (BTCs) encompass a diverse group of malignancies including gallbladder cancers, intrahepatic and extrahepatic cholangiocarcinomas, Klatskin tumors (hilar cholangiocarcinomas), and at times, ampullary carcinomas. Annual incidence of BTCs in the United States is approximately 14,000. Given the diverse anatomy and rarity of these tumors, underlying molecular mechanisms have yet to be fully defined. While surgery remains the mainstay of therapy for patients with resectable BTCs, cytotoxic chemotherapy is often needed for the treatment of advanced or recurrent disease. Targeted therapies in BTC are also being explored.

Epidemiology

The exact incidence of biliary cancers is difficult to quantify due to long-standing overlap in reporting with hepatocellular carcinoma. In 2013, it is estimated that there will be 30,640 new cases of liver and intrahepatic bile duct tumors and 10,310 new cases of gallbladder and

extrahepatic bile duct tumors [1]. It has been estimated that intrahepatic cholangiocarcinomas comprise approximately 10-15% of the former group [2], leading to an overall projection of approximately 14,000 new cases of BTC in the United States in 2013. BTCs are highly lethal malignancies, largely due to the advanced stages at which they are diagnosed.

Conditions leading to prolonged biliary inflammation predispose patients to developing cholangiocarcinoma, notably primary sclerosing cholangitis (PSC), liver fluke infestation, congenital abnormalities such as choledochal cysts, and hepatitis B and C [3]. Cholangiocarcinoma is slightly more common in men, and the risk increases progressively with age. For unclear reasons, though potentially attributable to increases in such risk factors as cirrhosis, alcoholic liver disease and hepatitis C infection, the incidence of intrahepatic cholangiocarcinoma has been increasing in the U.S., Europe, Asia and Australia, while rates of extrahepatic cholangiocarcinoma have been decreasing [4].

Gallbladder cancer rates are increasing worldwide, likely related to obesity [5]. Chronic gallbladder irritation from gallstones increases the risk by thirty-four times that of the average person [6]. Additionally, infections with Salmonella typhi and possibly Helicobacter also increase the risk of gallbladder cancer. Gallbladder cancer becomes more common as people age and unlike cholangiocarcinoma, women are up to five times more likely to be affected than men [7]. South America and specifically Chile have very high rates of gallbladder cancer, perhaps reflective of disproportionate gallstone prevalence in these areas [7]. Furthermore, gallbladder cancer is the most common GI malignancy among Mexican Americans and Southwestern Native Americans. In several countries, the mortality of gallbladder cancer is decreasing, perhaps reflective of adoption of new diagnostic techniques and changing patterns of elective cholecystectomy [8].

Presentation

The presentation of these cancers depends upon where along the biliary tree they arise. Painless jaundice is a frequent presenting symptom, but patients with intrahepatic cholangiocarcinoma may have little or no alteration in bilirubin. Right upper quadrant pain, either biliary colic or more steady hepatic pain, weight loss, pruritus and fever can also occur. Courvoisier's sign, or the presence of a palpable gallbladder caused by tumor and not obstruction by a common duct stone leading to scarring and lack of distension, is uncommon but can occur.

Besides elevations in total and direct bilirubin, laboratory abnormalities such as increased alkaline phosphatase and gamma-glutamyltransferase (GGT) are often seen with biliary tract cancers. Elevations in liver transaminases (aspartate aminotransferase, or AST, and alanine aminotransferase, or ALT) are commonly seen as the disease progresses and causes liver dysfunction.

Diagnosis

As mentioned above, routine laboratory values of patients with undiagnosed BTC may demonstrate biliary obstruction, but other laboratory abnormalities present may be more nonspecific. The tumor markers CA 19-9, CA-125 and CEA may be helpful to follow once a diagnosis is established but neither is specific or sensitive enough for diagnosis. In addition to other benign causes of tumor marker elevation, levels can be falsely elevated due to unrelieved biliary obstruction or the presence of primary sclerosing cholangitis [9]. Obtaining sufficient tissue for diagnosis of these tumors can also be difficult, particularly in proximal bile duct cancers and Klatskin tumors.

Imaging studies such as computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) are important noninvasive tools for staging and planning resection, although both have limitations in fully assessing the extent of disease preoperatively [10].

The role of positron emission tomography (PET) is still undefined for biliary tree cancers. Reported sensitivities and specificities for the use of PET scans vary widely, and there are many reports which find the added value minimal, particularly for infiltrating tumors [11,12]. Most concerning are false positive rates for nodal involvement in the setting of biliary obstruction or PSC.

Endoscopic ultrasound (EUS) is helpful for both diagnosis via directed biopsy and to stage tumors based on lymph node and vascular involvement. Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiogram (PTC) may be required for both relief of biliary obstruction and obtaining diagnostic cytologic brushings.

TREATMENT OPTIONS

- Depending on the extent of disease, management of biliary tract malignancies often requires at least one of several therapy modalities, including surgical resection, chemotherapy, radiation and/or palliative localized procedures. As a result, multidisciplinary evaluation is a critical component of optimal care in biliary tract cancers. Given unanswered questions regarding best therapies in the adjuvant and metastatic settings, clinical trial enrollment is preferred if possible.

SURGICAL MANAGEMENT

Surgery for localized disease

- Surgery is the mainstay for resectable, localized cancers of the biliary tract and represents the only curative treatment modality. Five-year survival rates for cholangiocarcinoma range from 15-50% following resection. Solitary tumors, lack of vascular invasion, R0 resection and no involvement of lymph nodes are all associated with a better prognosis [13]. In one retrospective case series of extrahepatic cholangiocarcionma, 5-year survival rates for patients with node-negative disease was 38%, but less than 10% for those with node-positive disease [14] Cholangiocarcinoma most frequently recurs locally while gallbladder cancer recurs with distant metastases the majority of the time [15].
- Transplantation is considered in select cases of perihilar and intrahepatic cholangiocarcinoma. Although historically, cure rates achieved with transplantation were only 10-20%, more recently patients with PSC treated with neoadjuvant chemoradiation followed by transplantation have had an impressive five-year overall survival rate exceeding 80% [16].

Re-resection after simple cholecystectomy

- Not infrequently, gallbladder cancer may go unrecognized until pathology review following simple cholecystectomy. Patients with T1a tumors who undergo simple cystectomy do not have inferior survival to those who undergo radical re-resection; therefore they do not require any further therapy beyond the original surgery [17]. However, patients with T1b or T2 cancers should be considered for radical re-resection to include the hepatic bed and regional lymph nodes. There is a 15.6% chance or finding positive lymph nodes in patients with T1b cancers [18]. In one

representative series, 5-year survival rates of patients with T2 cancers who underwent extended re-resection improved from 35% to 55% [19].

ADJUNCTIVE THERAPIES

Palliative procedures

- For patients with unresectable biliary tract cancers, palliative procedures such as endoscopic or percutaneous biliary drainage, endoscopic stenting, and biliary or intestinal bypass can be useful for relief of biliary obstruction, while minimizing post-procedural morbidity and mortality [20].

Locoregional therapy for unresectable disease

- For patients with unresectable intrahepatic disease, locoregional therapies such as stereotactic body radiotherapy (SBRT) or transarterial chemoembolization (TACE) with or without drug-eluting beads (DEB) can be useful.
- In one prospective, multicenter study of intrahepatic cholangiocarcinoma patients who received hepatic arterial DEB therapy with irinotecan or doxorubicin, the median OS was significantly greater than historical controls of chemotherapy-treated patients (17.5 vs. 7.4 months, $p = 0.02$) [21].
- Results of another study of 26 patients treated with transarterial chemoembolization with irinotecan-eluting beads (iDEB-TACE) were retrospectively compared with the results of 10 patients treated with conventional transarterial chemoembolization with mitomycin-C (cTACE) or 31 patients treated with systemic chemotherapy with oxaliplatin and gemcitabine [22]. In this study, local tumor control, PFS and OS were similar in the iDEB-TACE and systemic chemotherapy groups but prolonged in the iDEB-TACE group when compared to patients receiving cTACE, though these results could not be formally statistically compared given the small sample size and nonrandomized, retrospective nature of the data.
- Several small studies of cholangiocarcinoma patients treated with SBRT have generated interest in this therapy for unresectable disease [23,24,25]. Various doses of 30-60 Gy given in 1-6 fractions have been explored. Provocative one year survival rates ranging from 58-73% have been reported in these uncontrolled series, but these were highly selected patients.

PHARMACOLOGIC MANAGEMENT

Neoadjuvant therapy

- Limited data exist to recommend neoadjuvant therapy routinely prior to surgical resection or orthotopic liver transplantation for BTC. In small, nonrandomized studies, pathologic complete responses to neoadjuvant chemoradiation have been seen, as well as a higher number of R0 resections in patients with extrahepatic cholangiocarcinoma [26,27]. Patients with BTC are often not candidates for neoadjuvant therapy due to poor performance status or disease-associated symptoms, but prospective data of eligible patients should be collected to answer whether neoadjuvant therapy might have a role in this disease.

Adjuvant therapy

- Due to the high incidence of relapse after surgery, various adjuvant therapies have been explored, including radiation, chemoradiation, and chemotherapy alone.
- Prospective, randomized data is limited due to the rarity of these cancers.

- A large pooled analysis was performed of twenty studies performed between 1960 and 2010 to examine the effect of adjuvant therapy on patient survival [••28]. There was a non-significant trend toward improvement with any adjuvant therapy compared with surgery alone. If the analysis were limited to institutional series, this association became significant. Patients with involved lymph nodes or margin positivity derived the greatest benefit in this study and chemotherapy or chemoradiation was better than radiation alone. However, because of the wide variety of regimens used in the primary studies, it is difficult to recommend adjuvant therapy as a standard at the current time.
- Adjuvant chemoradiotherapy may play a particular role in biliary tract cancers resected with a microscopically positive margin. Historically, R1 resections have a 0% 5-year survival. In one series, patients who underwent adjuvant chemoradiation with 5-fluorouracil (5FU) improved this to 35% 5-year survival [29].
- The European Study Group for Pancreatic Cancer (ESPAC)-3 trial specifically studied the effectiveness of adjuvant chemotherapy (fluorouracil or gemcitabine) versus observation in patients with resected periampullary adenocarcinomas [•30]. Although a survival benefit for ampullary carcinomas did not meet statistical significance, when other periampullary carcinomas (intrapancreatic bile duct and duodenal tumors) were included and after adjusting for independent prognostic variables, the hazard ratio for chemotherapy compared with observation was 0.75 (95% CI, 0.57-0.98, $p = 0.03$).
- Two large phase 3 studies are ongoing in Europe which will hopefully provide more definitive information regarding the magnitude of benefit from adjuvant chemotherapy for cholangiocarcinomas and gallbladder cancers as well as direction regarding the optimal regimen. In the United Kingdom, the BILCAP study randomizes patients who have undergone macroscopically complete surgical resection to either capecitabine or observation [31]. The French group is investigating gemcitabine and oxaliplatin (GEMOX) compared to observation [32].

Chemotherapy for advanced disease

- Chemotherapy has demonstrated improved quality of life (QOL) scores and improved survival when compared with best supportive care. In one study from 1991 to 1995, 90 patients with pancreatic or biliary cancer were randomized to chemotherapy (5FU/leucovorin +/- etoposide) plus best supportive care (BSC) or BSC alone [33]. Mean QOL scores improved more often and deteriorated less frequently in the chemotherapy group, with more patients in this group experiencing an improved or prolonged high QOL for a minimum period of months than those in the BSC group (36% vs. 10%, $p < 0.01$). Both OS (median 6 months vs. 2.5 months, $p < 0.01$) and quality-adjusted survival time (4 months vs. 1 month, $p < 0.01$) were longer for patients treated with chemotherapy.
- Historically, response rates with chemotherapy were highest with gemcitabine and 5FU-based regimens, and rates of 30-40% were noted with combination chemotherapy.
- A retrospective analysis of advanced biliary tract carcinoma chemotherapy trials published in English from 1985 to July 2006 and ASCO abstracts from 1999 to 2006 was performed [34]. Subgroup analyses of 104 trials including 2810 patients found superior response rates (RR) but shorter overall survival (OS) for gallbladder carcinoma when compared with cholangiocarcinoma. Superior RR and tumor control rates (TCR) were found with combination gemcitabine and platinum-containing regimens.

- Several trials have investigated the safety and efficacy of irinotecan in combination with 5FU and/or oxaliplatin in the treatment of advanced biliary tract cancers. Two of 11 responses among 34 patients were seen in biliary cancers with the three drugs combined in a phase I study [35], but subsequent phase II trials of either irinotecan plus oxaliplatin [36] or irinotecan plus 5FU [37] were disappointing in the first-line setting.
- A prospective phase II trial of gemcitabine in combination with irinotecan in the first-line setting for patients with advanced biliary tract cancer demonstrated a 20.5% objective RR, with disease control rate of 66.7% in an intention-to-treat analysis [38].
- The ABC-02 trial prospectively investigated the role of doublet chemotherapy in biliary cancers [••39]. Patients with intra- and extrahepatic cholangiocarcinoma, gallbladder cancer or ampullary carcinoma were randomized to receive either gemcitabine 1000 mg/m^2 given on days 1, 8, and 15 every 28 days or gemcitabine 1000 mg/m^2 given with cisplatin 25 mg/m^2 on days 1 and 8 every 21 days. Survival was improved in the gemcitabine and cisplatin arm with a hazard ratio of 0.64; median overall survival was 11.7 months in the cisplatin-gemcitabine group versus 8.1 months in the gemcitabine alone group ($p < 0.001$). Notably, this improvement in survival did not come with increased grade 3 or 4 toxicities compared to gemcitabine alone. Because of this study, gemcitabine with cisplatin was established as a standard regimen in the first-line treatment of advanced biliary cancer.
- Recently, a large retrospective study was published analyzing the efficacy of second-line chemotherapy in advanced biliary tract cancer [•40]. Objective response rate was only 9% but 34% of patients had stable disease. Progression free survival was better for patients who received doublet chemotherapy rather than monotherapy, although this did not appear to impact overall survival.

NOVEL TARGETS AND THERAPIES

- While cytotoxic chemotherapeutics have improved overall survival of patients with recurrent and/or metastatic BTC, further treatment advances are needed. As a result, investigation into the molecular underpinnings of BTC is underway and may lead to effective treatments with more targeted therapies. Molecular heterogeneity is a prominent feature of BTCs; therefore, a variety of molecular targets are being studied.

Promising targets

VEGF/BRAF

- Vascular endothelial growth factor (VEGF) expression is increased in many biliary tract cancers, and its expression is associated with metastasis and poor survival. In one retrospective study of 239 cholangiocarcinomas, VEGF was overexpressed in 53.8% and 59.2% of intrahepatic and extrahepatic cholangiocarcinomas, respectively [41]. Furthermore, *BRAF* gene mutations were detected in 15 out of 69 (22%) biliary cancer specimens in another study [42], with Raf-1 inhibitors causing a cholangiocarcinoma cell line to be more susceptible to apoptosis [43].
- On this basis, the multitargeted kinase inhibitor of VEGF receptors (VEGFR) 2 and 3, platelet derived growth factor (PDGF) and Raf kinase sorafenib was studied in patients with metastatic or unresectable gallbladder carcinoma and cholangiocarcinoma. Unfortunately, sorafenib had a 0% confirmed response rate in this setting, although 39% of patients had stable disease [44]. A phase II study of

sorafenib in a more pre-treated population gave similar results, with a 2% response rate and median overall survival of only 4.4 months [45].

- Studies of combined sorafenib and gemcitabine, sorafenib, oxaliplatin and capecitabine, or the related antiangiogenic drug sunitinib, also had minimal objective response rates but higher rates of stable disease [46,47,48].
- Addition of the antiangiogenic agent bevacizumab to either cytotoxic chemotherapy such as gemcitabine and oxaliplatin or other targeted agents such as erlotinib have been investigated, with the former demonstrating a RR of 40% and OS of 12.7 months, and the latter an 18.4% RR and OS of 9.9 months [49,50].

EGFR

- In one study, epidermal growth factor receptor (EGFR) was expressed in 27.4% of intrahepatic cholangiocarcinomas and 19.2% of extrahepatic cholangiocarcinomas [41], though these rates can vary both by anatomic site and patient population. EGFR overexpression and mutations are less common, though gene amplification is nearly ubiquitous in EGFR-overexpressed biliary tract cancers [51,52].
- The EGFR tyrosine kinase inhibitor (TKI) erlotinib was investigated as a single agent in a phase II trial [53]. While 81% of the biliary tract cancer patients had expression of EGFR by immunohistochemistry, there was only an 8% overall RR; 17% of patients were progression free at 6 months.
- Combination therapies with EGFR TKIs and cytotoxic chemotherapy have been more promising. One randomized phase III trial of gemcitabine, oxaliplatin and continuous-dose erlotinib showed an overall RR of 30% compared with 16% in the non-erlotinib arm; however, PFS and OS did not differ between arms [54].
- Due to potential cell cycle sequence-specific synergy of erlotinib with gemcitabine, however, a phase Ib study is investigating the combination of gemcitabine, oxaliplatin and intermittent pulsatile erlotinib [55]. Preliminary results of this study have demonstrated a 24% ORR and 6-month PFS rate of 75%.
- Several clinical trials have also investigated the combination of cytotoxic chemotherapy with one of the anti-EGFR antibodies, either cetuximab or panitumumab. One phase II trial reported an ORR of 63% to gemcitabine, oxaliplatin and cetuximab, of which 9/19 responders ultimately underwent potentially curative secondary resection [56], but a randomized phase II study with this regimen failed to show a survival benefit with the addition of cetuximab [57].
- Appropriate selection criteria such as wild-type KRAS or EGFR mutations have not been defined for biliary cancers.

HER2

- Combined human epidermal growth factor receptor 2 (HER2) and EGFR blockade has been investigated for the treatment of biliary tract cancers in the context of lapatinib therapy, as preclinical models demonstrated growth inhibition of intrahepatic cholangiocarcinomas [58]. Clinical trial results have been disappointing, however. A phase II study of lapatinib in a planned 25 biliary cancer patients was terminated early for futility, with no objective responses and median OS of 5.1 months (95% CI 2.0-16.5) [59]. Of note, no EGFR or HER2/neu mutations, and no evidence of HER2 overexpression, were found in these tumor samples. Another phase II study of lapatinib in biliary tract and hepatocellular carcinoma demonstrated a 0% RR and OS of 5.2 months in biliary cancers [60]. It

is unclear whether other HER2-directed therapies might be more effective in these cancers, however.

MEK

- One of the more promising new targeted therapies for biliary tract cancer involves inhibition of the mitogen-activated extracellular signal-regulated kinases (MEKs). A multi-institutional phase II study of the MEK1/2 inhibitor selumetinib was performed in 28 patients with advanced biliary tract cancer [•61]. Only 12% of patients had an ORR, but an additional 68% had stable disease, of which many patients had stable disease for greater than 16 weeks; the majority of patients experienced target lesion decrease. Median OS was 9.8 months.
- The planned ABC-04 study proposes to examine selumetinib a MEK inhibitor, in combination with gemcitabine and cisplatin [62].
- With regard to combination regimens including MEK inhibitors, preclinical evidence demonstrates significant schedule dependence in biliary cancer models. When primary xenografts established from patient biliary tract cancers were treated with gemcitabine and selumetinib, DNA synthesis was suppressed during treatment with the MEK inhibitor, and reentry into S-phase was delayed by approximately 48 hours after treatment [63]. This suggests that maximal efficacy of treatment with selumetinib and cytotoxic chemotherapy may require non-continuous dosing of the MEK inhibitor, challenging current thought of optimal trial design of these and other targeted therapies.

Immunotherapy

- Development of cancer vaccines and investigation of their efficacy are ongoing in many tumor types, including biliary tract cancers.
- One phase I study reported adequate safety data of a Wilms tumor 1 (WT1) peptide vaccine in combination with gemcitabine for patients with advanced pancreatic or biliary tract cancer [64]. A randomized phase II study of the WT1 vaccine in combination with gemcitabine and cisplatin is ongoing [65].

Others

- Further investigation into the underlying molecular and genetic mechanisms of biliary tract cancers is continuing. Thus far, mutations in genes such as PIK3CA, KRAS, NRAS, IDH1, and IDH2, among others, have also been found in biliary cancers [66, 67, 68]. Furthermore, c-MET is expressed in a significant number of biliary tract cancers. In addition, ROS fusions are seen in a subset of cholangiocarcinomas [69], raising the question of whether crizotinib, the multi-targeted ALK-MET kinase inhibitor which also inhibits ROS kinase activity, might be efficacious in these patients. Given the significance of these targets and the recent push in the field of oncology to develop effective drugs against them, it is expected that many new therapies will be investigated against this lethal disease in the near future.

DIET AND LIFESTYLE

- There is no evidence to support any role for diet and lifestyle changes in the treatment of biliary tract cancers.

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