Advances in the Management of Biliary Tract Cancers

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Abstract: Biliary tract cancers, although uncommon, are highly fatal malignancies. Current treatments fail to cure or control the majority of tumors. Given the complexity of the anatomy and the often aggressive nature of the disease, multidisciplinary treatment, including palliation, is often required. However, systemic therapy with cytotoxics and/or targeted agents is routinely the mainstay of treatment for patients with advanced biliary tract cancers, and new targets and agents provide hope for this disease. This article focuses on recent advances in the management of biliary tract cancers, with a special focus on the molecular basis for current therapeutic investigation in this disease.

Introduction

Biliary tract cancers (BTCs) comprise a heterogeneous group of neoplasms, including gallbladder cancer, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and, variably, ampullary carcinoma. These tumors are relatively rare, with 9,810 new cases and 3,200 deaths from bile duct cancers and gallbladder cancers (excluding intrahepatic cholangiocarcinoma) expected in the United States in 2012.[1] Despite this relative rarity, these tumors present a significant therapeutic challenge in that they are often diagnosed at an advanced stage when surgical resection is not feasible and treatment options are limited. The 5-year overall survival for patients with BTCs approaches only 15%.[1] While surgical resection remains a mainstay of curative therapy when tumors are indeed resectable, and both chemotherapy and radiation can potentially be useful in the adjuvant setting, systemic therapies remain a necessary component of treatment for both recurrent disease and for tumors that are advanced at diagnosis. Traditional cytotoxic chemotherapies, whether as single agents or in combination, have not been as promising as hoped. However, recent insights into the molecular underpinnings of these heterogeneous tumors will hopefully lead to more effective systemic targeted therapies.

Role for Surgical Resection and Liver Transplantation

For the minority of patients whose tumors appear resectable on staging assessments, surgical resection with negative margins and liver transplantation remain the only potential mechanisms of

cure. Patients who have undergone R0 (microscopically margin-negative) resections have 5-year survival rates of 10–62% overall,[2] whereas R1 (microscopically margin-positive) and R2 (macroscopic residual disease) resections are associated with an overall 5-year survival rate of 0%.[3] Even with successful R0 resections, however, short-term postoperative complications, including bile leakage, intra-abdominal abscess, and liver failure, are significant risks, and many patients ultimately have disease recurrence as well. Fortunately, recent advances in preoperative optimization and surgical approaches have resulted in higher R0 resection rates and improved survival when compared to prior series, and hopefully this trend will continue.[4]

For a subset of patients with unresectable perihilar or intrahepatic cholangiocarcinoma, orthotopic liver transplantation is a potential avenue for cure as well. Studies of patients with unresectable disease or cholangiocarcinoma against a background of primary sclerosing cholangitis who have undergone liver transplantation after neoadjuvant therapy have demonstrated impressive 5-year overall survival rates exceeding 80%.[5,6] A recent analysis of outcomes for liver transplantation in patients with perihilar cholangiocarcinoma suggests that the benefit of this therapy may be more broadly applicable across transplant centers if strict selection criteria are used.[7] Selection biases inherent in these groups, including receipt of neoadjuvant therapy, younger age, and node-negative disease, preclude comparison of these survival outcomes with nontransplant resection outcomes, but the potential benefit remains intriguing nonetheless.

Neoadjuvant Therapy

There are limited, nonrandomized data suggesting possible benefit, in both quality of resection and survival, of neoadjuvant chemoradiation in patients with BTC. In one small study, among 9 patients with perihilar or distal extrahepatic cholangiocarcinoma who underwent preoperative continuous infusion with 5-fluorouracil (5-FU) with concurrent external beam radiotherapy, one-third had a pathologic complete response at resection.[8] Patients in the study who were treated neoadjuvantly demonstrated varying degrees of histologic response. Importantly, the rate of margin-negative resection was 100% in patients who had received neoadjuvant therapy, compared with 54% in patients who had not received such treatment. In another study, 12 patients with primarily borderline or unresectable extrahepatic cholangiocarcinoma underwent neoadjuvant radiotherapy with concurrent fluoropyrimidine-based chemotherapy.[9] Despite more advanced local disease, these patients showed a trend toward improved survival when compared with patients treated adjuvantly (5-year survival was 53% vs 23%; P=.07), and rates of surgical morbidity were similar.

However, despite these encouraging results, and those of patients treated neoadjuvantly prior to orthotopic liver transplantation, many patients are not candidates for a neoadjuvant approach, as they are often symptomatic from bile duct obstruction or have a poor performance status at initial presentation. In order to clarify the benefit of neoadjuvant therapy for patients who are candidates for this approach, prospective studies are needed.

Adjuvant Therapy

For the minority of biliary tract tumors that are able to be surgically resected, recurrence occurs frequently, with more local than distant relapse.[10] Use of adjuvant therapies, such as chemotherapy, radiation, or chemoradiation, remains controversial; given the rarity of resectable biliary tract tumors, prospective randomized data on adjuvant strategy are limited, but trials are planned or ongoing. A recent meta-analysis of published data evaluated the benefit of adjuvant therapy in patients who had undergone curative-intent surgery, either R0 (negative margins) or R1 (microscopic positive margins).[11] In the overall population, a nonsignificant improvement in survival with adjuvant therapy compared with surgery alone was seen. However, the effect of adjuvant therapy was dependent on the treatment modality, with patients receiving either chemotherapy or chemoradiation postoperatively showing an improvement in survival compared with those receiving radiation alone. In addition, patients with node-positive disease or R1 resection appeared to benefit from adjuvant therapy. From these data, it is reasonable to consider postoperative radiation for patients with positive surgical margins and chemotherapy with or without radiation for those with node-positive disease, although the best regimen has not been defined in this setting.

Cytotoxic Chemotherapy

Until recently, systemic therapy for BTCs relied largely on cytotoxic chemotherapy. 5-FU–based chemotherapy was initially shown to improve median survival times of patients with pancreatic and biliary cancers when compared to best supportive care alone (6.0 months vs 2.5 months with 5-FU/leucovorin with or without etoposide treatment; P<.01).[12] In addition, quality of life measures improved more often and deteriorated less frequently in the chemotherapy group than in the best supportive care group, with 36% of the patients on the chemotherapy arm enjoying an improved or prolonged high quality of life for a minimum of 4 months, compared with 10% of the best supportive care group. Quality-adjusted survival time was longer for patients receiving 5-FU–based chemotherapy as well (median 4 months vs 1 month; P<.01).

While leucovorin-modulated 5-FU is often well tolerated in BTCs, its efficacy as a single agent has been disappointing. Therefore, 5-FU/leucovorin has been combined with additional cytotoxic agents, but no combination has shown impressive results, and toxicity is often significantly increased. Despite objective response rates of 40% and a median duration of response of 10 months in patients treated with the epirubicin, cisplatin, and 5-FU (ECF) regimen in an early-phase clinical trial,[13] a subsequent phase III study of this regimen failed to confirm these findings.[14] In this larger randomized trial, response rate for the ECF arm was only 19.2%, which was similar to the study's 5-FU/leucovorin/etoposide arm, and ECF failed to improve median overall survival when compared to 5-FU/leucovorin/etoposide (9.02 months vs 12.03 months; P=.2059). Similarly, a regimen of cisplatin, interferon alpha-2b, doxorubicin, and 5-FU (PIAF) had only a 21.1% overall response rate in BTC but was associated with significantly increased grade 3 and 4 toxicity.[15] In contrast, more simplified regimens such as 5-FU/cisplatin showed overall response rates of 24–34% in phase II trials but with much more acceptable toxicity.[16,17]

Capecitabine (Xeloda, Genentech), like 5-FU, is an active agent in BTCs, although single-agent use leaves considerable room for improvement. Interestingly, one retrospective analysis demonstrated significantly increased response rates (50% vs 6%) with capecitabine in gallbladder carcinoma compared with cholangiocarcinoma, although survival was similar (9.9 months vs 8.1 months).[18] Studies combining capecitabine with gemcitabine (Gemzar, Lilly)[19,20] or oxaliplatin (Eloxatin, sanofi-aventis)[21] show overall response rates ranging from 25–31% and overall survival of 12.7–13.2 months, although the capecitabine/oxaliplatin regimen had significantly more efficacy in gallbladder carcinoma and extrahepatic cholangiocarcinoma than intrahepatic cholangiocarcinomas.

Gemcitabine-based chemotherapy is of proven value in this disease, although gemcitabine has limited efficacy as a single agent. A small, nonrandomized phase II study investigating the efficacy and safety of gemcitabine alone for unresectable BTCs demonstrated a 26.1% overall response rate, with a median time to disease progression of 8.1 months and median overall survival of 13.1 months.[22] There was wide variability in survival among these patients, however, perhaps indicating the heterogeneous nature of this disease and underscoring the need for controlled studies when evaluating treatment efficacy. Other small trials investigating the usefulness of single-agent gemcitabine have shown response rates ranging from 16–30%, with overall survival in the range of 6.5–11.5 months.[23-25]

Given the separate evidence for gemcitabine and 5-FU/leucovorin in the treatment of BTCs, several studies looked at the combination of these drugs in hopes of improving efficacy.[26-28] However, the combination of gemcitabine and 5-FU, while manageable in terms of toxicity profiles, did not improve survival as had been hoped. Additionally, the combination of gemcitabine and capecitabine is well-tolerated, but with an overall survival of only 7 months.[29] As a result, more trials were done with the combination of gemcitabine and platinums, including cisplatin.

The combination of gemcitabine and cisplatin has proven to improve overall survival the most in BTC and remains the most favorable cytotoxic chemotherapy regimen in this tumor thus far. The ABC-01 (Advanced Biliary Cancer) trial was a randomized phase II study evaluating gemcitabine and cisplatin versus gemcitabine alone.[30] It showed promising toxicity, progression-free survival (PFS), and time to progression data in the gemcitabine and cisplatin arm, and led to a phase III study. ABC-02 randomized 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to receive cisplatin 25 mg/m² followed by gemcitabine (1,000 mg/m²) on days 1 and 8 every 21 days or gemcitabine (1,000 mg/m²) on days 1, 8, and 15 every 28 days.[31] A significant benefit in both response rate and PFS was seen favoring the gemcitabine/cisplatin arm. Furthermore, median overall survival was 11.7 months in the gemcitabine/cisplatin group compared with 8.1 months in the gemcitabine-only group (hazard ratio 0.64; 95% confidence interval, 0.52–0.80; P<.001), with no increase in adverse events for the combination arm when compared with single-agent gemcitabine. On the basis of these data, the combination of gemcitabine and cisplatin has become a standard of care in advanced BTCs.

Targeted Therapies

While cytotoxic chemotherapeutic agents are useful in the treatment of BTCs, the magnitude of their beneficial effects is less than desired. Targeted therapies based on the understanding of the molecular basis of tumors are being investigated in BTCs with some promising results. Given the rarity of BTCs and the known pathologic and molecular heterogeneity among the tumors that compose this group, however, difficulties have arisen in the design of and accrual to the clinical trials needed to test these molecular targets. Nonetheless, a significant number of trials investigating the usefulness of various targeted agents have already been completed or are under way, providing initial insights into ways to effectively tailor therapies for patients with BTCs (Table 1).

EGFR
Epidermal growth factor receptor (EGFR) is variably expressed in BTCs, with expression occurring nearly

Table 1. Clinical Trials of Targeted Therapies in Biliary Tract Cancer

Agent	Pathway	Trial Phase	ORR	PFS	OS
Erlotinib[37]	EGFR (TKI)	II (single-arm)	8%	6-month PFS: 17%	7.5 months
Gemcitabine + oxaliplatin +/- continuous erlotinib[38]	EGFR (TKI)	III (randomized)	30% vs 16%	5.8 vs 4.2 months	9.5 vs 9.5 months
Gemcitabine + oxaliplatin + pulsed erlotinib[39]	EGFR (TKI)	Ib (single-arm)	24%	6-month PFS: 75%	NR
Gemcitabine + oxaliplatin + cetuximab[40]	EGFR (mAb)	II (single-arm)	63%	8.8 months	15.2 months
Gemcitabine + oxaliplatin +/- cetuximab[41]	EGFR (mAb)	II (randomized)	23% vs 29%	6.0 vs 5.3 months	11.0 vs 12.4 months
Gemcitabine + oxaliplatin + capecitabine + panitumumab[42]	EGFR (mAb)	II (single-arm)	33%	8.3 months	9.8 months
Gemcitabine + oxaliplatin + bevacizumab[43]	VEGF (mAb)	II (single-arm)	40%	7.0 months	12.7 months
Erlotinib + bevacizumab[44]	EGFR (TKI) + VEGF (mAb)	II (single-arm)	18.4%	TTP: 4.4 months	9.9 months
Sorafenib[45]	VEGF (TKI)	II (single-arm)	2%	2.3 months	4.4 months
Sorafenib +/- gemcitabine[46]	VEGF (TKI)	II (randomized)	2.7% vs 0%	2.9 vs 2.3 months	6.5 vs 4.3 months
Gemcitabine +/- sorafenib[47]	VEGF (TKI)	II (randomized)	7%	2.9 months	9.4 months
Sunitinib[48]	VEGF (TKI)	II (single-arm)	8.9%	TTP: 1.7 months	4.8 months
Lapatinib[50]	HER2 (TKI)	II (single-arm)	0%	1.8 months	5.2 months
Selumetinib[51]	MEK (TKI)	II (single-arm)	12%	3.7 months	9.8 months

EGFR=epidermal growth factor receptor; HER2=human epidermal growth factor receptor 2; mAb=monoclonal antibody; MEK=mitogen-activated protein kinase/extracellular-signal regulated kinase; NR=not reported; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; TKI=tyrosine kinase inhibitor; TTP=time to progression; VEGF=vascular endothelial growth factor.

ubiquitously in intrahepatic cholangiocarcinomas and to a slightly lesser extent in the other tumor types.[32] Interestingly, EGFR expression appears prognostic and portends a worse survival, at least in intrahepatic cholangiocarcinoma.[33] EGFR overexpression occurs less frequently but often is seen with EGFR gene amplification,[34] and EGFR mutations are found in a minority.[35] Related to EGFR, *KRAS* mutations are also seen in BTCs, but their frequency is unclear.[36]

Due to these findings, the EGFR inhibitor erlotinib (Tarceva, Roche) was studied as monotherapy in a single-arm phase II trial.[37] The overall response rate was only 8%, with 81% of the assessable tumors demonstrating EGFR expression. In this study, EGFR mutational status was not assessed. Subsequently, a randomized phase III trial evaluated the combination of gemcitabine and oxaliplatin with or without continuous dosing of erlotinib.[38] Although the overall response rate was significantly higher in the chemotherapy plus erlotinib group (30% vs 16%; *P*=.005), PFS and overall survival did not differ. Due to the mechanism of erlotinib and potential cell cycle sequence–specific synergy of erlotinib with gemcitabine, a phase Ib study has recently evaluated the combination of gemcitabine and oxaliplatin with intermittent pulsatile dosing of erlotinib.[39] Preliminary results demonstrated a

24% overall response rate and 6-month PFS rate of 75% and highlighted the potential importance of mechanistic-driven dosing of targeted therapies when combined with cytotoxic chemotherapies.

Monoclonal antibodies targeting EGFR have shown even more promising results in BTCs, particularly in combination with traditional cytotoxic drugs. Two phase II trials have evaluated the efficacy of cetuximab (Erbitux, Bristol-Myers Squibb/Lilly) with gemcitabine and oxaliplatin. Gruenberger and colleagues reported an objective response rate of 63% in a trial of 30 BTC patients, with 30% of the patients undergoing potentially curative resection after chemotherapy due to their response to therapy.[40] Final analysis of the randomized phase II BINGO (French Biliary Cancers: EGFR Inhibitor, Gemcitabine and Oxaliplatin) trial was recently presented; this trial examined whether the addition of cetuximab to a gemcitabine/oxaliplatin regimen conferred any benefit. The primary endpoint—the percentage of patients reaching a 4-month PFS of at least 60%—was higher in the gemcitabine/oxaliplatin plus cetuximab arm, but median PFS and overall survival were similar with and without cetuximab.[41] Enrollment was not limited according to *KRAS* status in either of these trials, and given the proven importance of this biomarker in colorectal cancer, per-

haps the efficacy of anti-EGFR antibodies in BTCs could be further improved by biomarker-driven patient selection. In contrast to the cetuximab trials, a phase II trial evaluating gemcitabine, oxaliplatin, capecitabine, and panitumumab (Vectibix, Amgen) enrolled patients with *KRAS* wild-type cholangiocarcinoma only and showed a 71.6% 6-month PFS, a response rate of 33%, and an overall survival of 9.8 months.[42] Several other trials examining the efficacy of panitumumab in combination with various chemotherapy regimens are under way.

VEGF

Much like EGFR, vascular endothelial growth factor (VEGF) is often highly expressed in BTCs, with exact percentages dependent on tumor type.[33] VEGF expression in BTC is associated with poor survival, metastasis, and disease recurrence; therefore, anti-VEGF therapies have been studied in this disease. Zhu and coworkers reported results of a phase II study of gemcitabine, oxaliplatin, and bevacizumab (Avastin, Genentech) in BTC, with response rates of 40%, median PFS of 7 months, and overall survival of 12.7 months.[43] A single-arm phase II trial of erlotinib and bevacizumab without traditional cytotoxic chemotherapy demonstrated an 18.4% response rate, time to progression of 4.4 months, and overall survival of 9.9 months, with a potential predictive signal seen from EGFR and *KRAS* status.[44] Two other phase II trials for BTCs with bevacizumab, in combination with modified FOLFOX6 or gemcitabine and capecitabine, are currently under way. Other antiangiogenic agents such as sorafenib (Nexavar, Bayer HealthCare/Onyx) and sunitinib (Sutent, Pfizer) have failed to show efficacy in this disease either as single agents or in combination with gemcitabine, with response rates of less than 10% and survival times less than those seen with other regimens.[45-48] A phase I/II study of gemcitabine/oxaliplatin with sorafenib is under way to see if efficacy can be improved with this regimen, and other studies utilizing more novel antiangiogenic agents, such as cediranib and vandetanib (Caprelsa, AstraZeneca), are planned.

HER2

Human epidermal growth factor receptor 2 (HER2) is overexpressed in only a minority of BTCs,[34] but preclinical experiments have shown that simultaneous blockade of EGFR and HER2 by lapatinib (Tykerb, GlaxoSmithKline) leads to growth inhibition of an orthotopic rat model of intrahepatic cholangiocarcinoma if administered early.[49] A single phase II study investigated lapatinib, a dual EGFR/HER2 inhibitor, for the treatment of BTC and hepatocellular cancer with disappointing results.[50] Notably, HER2 expression was not tested. Although no other trials studying HER2 inhibitors in BTC are cur-

rently planned, it seems reasonable to pursue this target in a more judicious way, given the present availability of excellent HER2 inhibitors.

MEK

Mitogen-activated extracellular signal–regulated kinase (MEK) inhibition is a very promising therapy currently under investigation for multiple solid tumor types, including BTCs. A multi-institutional phase II trial of single-agent selumetinib, a MEK1/2 inhibitor, for patients with advanced BTC showed an overall response rate of 12% and median overall survival of 9.8 months.[51] Despite this low overall response rate, 68% of patients had stable disease, including 44% with stable disease for at least 16 weeks and 12% with stable disease for more than 1 year. The majority of patients (52%) had a measured decrease in their target lesions, and the treatment was well-tolerated overall. Of note, all enrolled patients provided tissue for *KRAS/BRAF* genotyping and phosphorylated ERK and AKT testing by immunohistochemistry. Correlative analysis demonstrated that patients with short-lived stable disease had *KRAS* mutations, and absence of phosphorylated ERK staining was associated with lack of response, but predicting which patients will respond to MEK inhibitors will require analysis of larger studies with these drugs. Several other trials studying selumetinib or other MEK inhibitors (ARRY-438162, GSK1120212) in BTC with or without cytotoxic chemotherapy are ongoing.

Other Targets

Other signaling pathways of interest are being elucidated in BTCs and hold promise for the development of future targeted therapies. Molecular characterizations of BTCs have revealed mutations in target genes such as *KRAS, PIK3CA, BRAF, NRAS, IDH1,* and *IDH2.*[52-54] In addition, ROS kinase fusions were seen in 8.7% of cholangiocarcinoma patients in one study,[55] which has sparked interest in the potential use of crizotinib (Xalkori, Pfizer), a multi-targeted ALK/MET kinase inhibitor, for this disease. High expression of c-MET has also been seen in a subset of BTCs and correlates with EGFR overexpression.[34] As c-MET activation may be a mechanism of resistance to anti-EGFR therapies, the combination of a c-MET inhibitor and anti-EGFR therapy in BTC warrants further study.

Conclusions

Although BTCs often carry a fatal prognosis, advances in the management of these tumors are indeed being made. There is an inherent difficulty in investigation of new treatments for these tumors, given the changing definitions and stratifications of this class of tumors over time,

as well as their remarkable molecular heterogeneity. Earlier tumor detection and improvement in surgical techniques are still needed for this disease, but the opportunity for advancement in the systemic treatment of these cancers is particularly great and must be exploited. Improvements in survival have been attained through systematic investigation of cytotoxic chemotherapy regimens, with gemcitabine/cisplatin as the current standard of care for advanced tumors, but it appears that the limit has been reached in terms of maximal benefit with traditional agents. Targeted therapies, perhaps in combination with cytotoxic agents, hold the most promise for advancement in this tumor type. Future studies must be designed rationally and should be biomarker-driven, with optimization of resources to elucidate the molecular underpinnings of BTC. Patient enrollment on clinical trials is vital for evidence-based determination of optimal treatment strategies in BTC, whether surgical, adjuvant, neoadjuvant, or palliative in nature.

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