Published in final edited form as:
Clin Adv Hematol Oncol. 2013 January ; 11(1): 28–34.

Advances in the Management of Biliary Tract Cancers

Kristen Keon Ciombor, MD and **Laura Williams Goff, MD, MSCI**

Abstract

Biliary tract cancers (BTC), though uncommon, are highly fatal malignancies, and current treatments fail to cure or control the majority of tumors. Given the complexity of the anatomy and often aggressive nature of the disease, multidisciplinary treatment, including palliation, is often required. However, systemic therapy with cytotoxics and/or targeted agents are 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 (BTC) 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 biliary tract cancers only approaches 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 both for recurrent disease or for tumors 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 or liver transplantation remain the only potential mechanisms of cure. Patients who have undergone R0 (microscopically margin-negative) resections have five-year survival rates of 10–62% overall,[2] while 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 approach 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 on 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 non-transplant resection outcomes, but the potential benefit remains intriguing nonetheless.

Neoadjuvant Therapy

There is limited, nonrandomized data suggesting possible benefit, both in quality of resection as well as survival, of neoadjuvant chemoradiation in patients with BTC. In one small study, 9 patients with perihilar or distal extrahepatic cholangiocarcinoma underwent preoperative continuous infusion 5-fluorouracil with concurrent external beam radiotherapy, and one-third of these patients had a pathologic complete response at resection, with the others treated neoadjuvantly demonstrating varying degrees of histologic response.[8] 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 53% vs. 23%, p=0.07), 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 is 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 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 +/− 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 biliary tract cancers largely relied 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 vs. 2.5 months with 5-fluorouracil/leucovorin +/− etoposide treatment, p<0.01).[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 vs. 1 months, $p > 0.01$).

While leucovorin-modulated 5-FU is often well tolerated in biliary tract cancers, its efficacy as a single agent has been disappointing. Therefore, 5-FU/LV has been combined with additional cytotoxic agents, but none with impressive results, and often with significantly increased toxicity. Despite objective response rates of 40% and median duration of response of 10 months in patients treated with the ECF (epirubicin, cisplatin, 5-FU) regimen in an early phase clinical trial,[13] 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/LV/etoposide arm, and ECF failed to improve median overall survival when compared to 5-FU/LV/etoposide (9.02 months vs. 12.03 months, $p = 0.2059$). Similarly, the PIAF regimen (cisplatin, interferon alpha-2b, doxorubicin and 5-FU) only had a 21.1% overall response rate in biliary tract cancer 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, like 5-FU, is an active agent in biliary tract cancers, though 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, though survival was similar (9.9 months vs. 8.1 months).[18] Studies combining capecitabine with either gemcitabine[19,20] or oxaliplatin[21] show overall response rates ranging from 25–31% and overall survival of 12.7–13.2 months, though the CAPOX regimen had significantly more efficacy in gallbladder carcinoma and extrahepatic cholangiocarinoma than intrahepatic cholangiocarcinomas.

Gemcitabine-based chemotherapy is of proven value in this disease, though with limited efficacy as a single agent. A small, non-randomized phase II study investigating the efficacy and safety of gemcitabine alone for unresectable biliary tract cancers 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 biliary tract cancers, 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 biliary tract cancer and remains the most favorable cytotoxic chemotherapy regimen in this tumor thus far. ABC-01 was a randomized phase II study evaluating gemcitabine and

cisplatin versus gemcitabine alone;[30] with promising toxicity, progression-free survival and time to progression data in the gemcitabine and cisplatin arm, a phase III study was conducted. ABC-02 randomized 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer of ampullary cancer to receive cisplatin 25 mg/m^2 followed by gemcitabine (1000 mg/m^2) on days 1 and 8 every 21 days or gemcitabine (1000 mg/m^2) 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% CI, 0.52–0.80, $p < 0.001$), with no increase in adverse events for the combination arm when compared with single-agent gemcitabine. On the basis of this data, the combination of gemcitabine and cisplatin has become a standard of care in advanced biliary tract cancers.

Targeted Therapies

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

EGFR

Epidermal growth factor receptor (EGFR) is variably expressed in biliary tract cancers, with expression occurring nearly 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 biliary tract cancers, but their frequency is unclear.[36]

Due to these findings, the EGFR inhibitor erlotinib 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 +/− continuous dosing of erlotinib.[38] While overall response rate was significantly higher in the chemotherapy + erlotinib group (30% vs. 16%, p=0.005), progression-free 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 1b 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 progression-free survival 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 biliary tract cancers, particularly in combination with traditional cytotoxic drugs. Two phase II trials have evaluated the efficacy of cetuximab with gemcitabine and oxaliplatin. Gruenberger *et al.* 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 trial was recently presented in which the primary endpoint of 4-month PFS ≥ 60% was exceeded in the gemcitabine/oxaliplatin + cetuximab arm, but median PFS and OS were similar in both arms.[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, perhaps 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 enrolled patients with KRAS wild-type cholangiocarcinoma only, with a 71.6% 6-month PFS, response rate of 33% and overall survival of 9.8 months.[42] Several other trials examining the efficacy of panitumumab in combination with various chemotherapy regimens are underway.

VEGF

Much like EGFR, vascular endothelial growth factor (VEGF) is often highly expressed in biliary tract cancers, 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 *et al.* reported results of a phase II study of gemcitabine, oxaliplatin and bevacizumab in BTC, with response rates of 40%, median PFS of 7 months and OS 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 (TTP) of 4.4 months, and OS of 9.9 months, with potential predictive signal seen from EGFR and KRAS status.[44] Two other phase II trials for BTCs with bevacizumab, in combination with mFOLFOX6 or gemcitabine and capecitabine, are currently underway. Other anti-angiogenic agents such as sorafenib and sunitinib have failed to show efficacy in this disease either as single agents or in combination with gemcitabine, with response rates less than 10% and survival times less than seen with other regimens.[45–48] A phase I/II study of gemcitabine/oxaliplatin with sorafenib is underway to see if efficacy can be improved with this regimen, and other studies utilizing more novel anti-angiogenic agents such as cediranib and vandetanib are planned.

HER2

Human epidermal growth factor receptor 2 (HER2) is overexpressed in only a minority of biliary tract cancers,[34] but preclinical experiments have shown that simultaneous blockade of EGFR and HER2 by lapatinib 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] but notably, HER2 expression was not tested. Though no other trials studying HER2 inhibitors in BTC are currently planned, it seems reasonable to pursue this target in a more judicious way, given the present availability of excellent HER2 inhibitors.

MEK

Mitogen-activated ERK (extracellular signal regulated kinase) kinase, or MEK, inhibition is a very promising therapy currently under investigation for multiple solid tumor types, including biliary tract cancers. A multi-institutional phase II trial of single-agent selumetinib, a MEK1/2 inhibitor, for patients with advanced BTC was performed with an overall response rate (ORR) of 12% and median overall survival of 9.8 months.[51] Despite a low ORR, 68% of patients had stable disease, including 44% with duration of stable disease at least 16 weeks and 12% with stable disease for more than one year. The majority of patients (52%) had 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 (pERK) and AKT (pAKT) testing by immunohistochemistry.

Correlative analysis demonstrated that patients with short-lived stable disease had KRAS mutations, and absence of pERK 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 biliary tract cancers 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 have been seen in 8.7% of cholangiocarcinoma patients in one study,[55] which has sparked interest in the potential use of crizotinib, 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

While biliary tract cancers 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 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.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA: a cancer journal for clinicians. 2012 Jan-Feb;62(1):10–29. [PubMed: 22237781]
2. Aljiffry M, Abdulelah A, Walsh M, Peltekian K, Alwayn I, Molinari M. Evidence-based approach to cholangiocarcinoma: a systematic review of the current literature. Journal of the American College of Surgeons. 2009 Jan; 208(1):134–147. [PubMed: 19228515]
3. Witzigmann H, Berr F, Ringel U, et al. Surgical and palliative management and outcome in 184 patients with hilar cholangiocarcinoma: palliative photodynamic therapy plus stenting is comparable to r1/r2 resection. Annals of surgery. 2006 Aug; 244(2):230–239. [PubMed: 16858185]
4. Skipworth JR, Olde Damink SW, Imber C, Bridgewater J, Pereira SP, Malago M. Review article: surgical, neo-adjuvant and adjuvant management strategies in biliary tract cancer. Alimentary pharmacology & therapeutics. 2011 Nov; 34(9):1063–1078. [PubMed: 21933219]
5. Rea DJ, Heimbach JK, Rosen CB, et al. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. Annals of surgery. 2005 Sep; 242(3): 451–458. discussion 458-461. [PubMed: 16135931]

6. Heimbach JK, Gores GJ, Haddock MG, et al. Liver transplantation for unresectable perihilar cholangiocarcinoma. Seminars in liver disease. 2004 May; 24(2):201–207. [PubMed: 15192792]
7. Darwish Murad S, Kim WR, Harnois DM, et al. Efficacy of Neoadjuvant Chemoradiation, Followed by Liver Transplantation, for Perihilar Cholangiocarcinoma at 12 US Centers. Gastroenterology. 2012 Jul; 143(1):88–98. e83. [PubMed: 22504095]
8. McMasters KM, Tuttle TM, Leach SD, et al. Neoadjuvant chemoradiation for extrahepatic cholangiocarcinoma. American journal of surgery. 1997 Dec; 174(6):605–608. discussion 608-609. [PubMed: 9409582]
9. Nelson JW, Ghafoori AP, Willett CG, et al. Concurrent chemoradiotherapy in resected extrahepatic cholangiocarcinoma. International journal of radiation oncology, biology, physics. 2009 Jan 1; 73(1):148–153.
10. Jarnagin WR, Ruo L, Little SA, et al. Patterns of initial disease recurrence after resection of gallbladder carcinoma and hilar cholangiocarcinoma: implications for adjuvant therapeutic strategies. Cancer. 2003 Oct 15; 98(8):1689–1700. [PubMed: 14534886]
11. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012 Jun 1; 30(16):1934–1940. [PubMed: 22529261]
12. Glimelius B, Hoffman K, Sjoden PO, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 1996 Aug; 7(6):593–600. [PubMed: 8879373]
13. Ellis PA, Norman A, Hill A, et al. Epirubicin, cisplatin and infusional 5-fluorouracil (5-FU) (ECF) in hepatobiliary tumours. Eur J Cancer. 1995 Sep; 31A(10):1594–1598. [PubMed: 7488407]
14. Rao S, Cunningham D, Hawkins RE, et al. Phase III study of 5FU, etoposide and leucovorin (FELV) compared to epirubicin, cisplatin and 5FU (ECF) in previously untreated patients with advanced biliary cancer. British journal of cancer. 2005 May 9; 92(9):1650–1654. [PubMed: 15856037]
15. Patt YZ, Hassan MM, Lozano RD, et al. Phase II trial of cisplatin, interferon alpha-2b, doxorubicin, and 5-fluorouracil for biliary tract cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2001 Nov; 7(11):3375–3380. [PubMed: 11705850]
16. Ducreux M, Rougier P, Fandi A, et al. Effective treatment of advanced biliary tract carcinoma using 5-fluorouracil continuous infusion with cisplatin. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 1998 Jun; 9(6):653–656. [PubMed: 9681080]
17. Taieb J, Mitry E, Boige V, et al. Optimization of 5-fluorouracil (5-FU)/cisplatin combination chemotherapy with a new schedule of leucovorin, 5-FU and cisplatin (LV5FU2-P regimen) in patients with biliary tract carcinoma. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2002 Aug; 13(8):1192–1196. [PubMed: 12181241]
18. Patt YZ, Hassan MM, Aguayo A, et al. Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer. 2004 Aug 1; 101(3):578–586. [PubMed: 15274071]
19. Knox JJ, Hedley D, Oza A, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005 Apr 1; 23(10):2332–2338. [PubMed: 15800324]
20. Koeberle D, Saletti P, Borner M, et al. Patient-reported outcomes of patients with advanced biliary tract cancers receiving gemcitabine plus capecitabine: a multicenter, phase II trial of the Swiss Group for Clinical Cancer Research. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008 Aug 1; 26(22):3702–3708. [PubMed: 18669455]
21. Nehls O, Oettle H, Hartmann JT, et al. Capecitabine plus oxaliplatin as first-line treatment in patients with advanced biliary system adenocarcinoma: a prospective multicentre phase II trial. British journal of cancer. 2008 Jan 29; 98(2):309–315. [PubMed: 18182984]
22. Park JS, Oh SY, Kim SH, et al. Single-agent gemcitabine in the treatment of advanced biliary tract cancers: a phase II study. Japanese journal of clinical oncology. 2005 Feb; 35(2):68–73. [PubMed: 15709089]

23. Penz M, Kornek GV, Raderer M, et al. Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2001 Feb; 12(2):183–186. [PubMed: 11300321]
24. Raderer M, Hejna MH, Valencak JB, et al. Two consecutive phase II studies of 5-fluorouracil/leucovorin/mitomycin C and of gemcitabine in patients with advanced biliary cancer. Oncology. 1999 Apr; 56(3):177–180. [PubMed: 10202270]
25. Kubicka S, Rudolph KL, Tietze MK, Lorenz M, Manns M. Phase II study of systemic gemcitabine chemotherapy for advanced unresectable hepatobiliary carcinomas. Hepato-gastroenterology. 2001 May-Jun;48(39):783–789. [PubMed: 11462924]
26. Gebbia V, Giuliani F, Maiello E, et al. Treatment of inoperable and/or metastatic biliary tree carcinomas with single-agent gemcitabine or in combination with levofolinic acid and infusional fluorouracil: results of a multicenter phase II study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2001 Oct 15; 19(20):4089–4091. [PubMed: 11600613]
27. Jacobson SDAS, Mahoney MR, Green EM, Al-Khatib K, Burgart L, Cera PJ, Flynn BJ, Fitech TR, Goldberg RM. Phase II trial of gemcitabine, 5-fluorouracil, and leucovorin in patients with unresectable or metastatic biliary and gallbladder carcinoma: a North Central Cancer Treatment Group (NCCTG)study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003; 22 (suppl; abstr 1102).
28. Alberts SR, Al-Khatib H, Mahoney MR, et al. Gemcitabine, 5-fluorouracil, and leucovorin in advanced biliary tract and gallbladder carcinoma: a North Central Cancer Treatment Group phase II trial. Cancer. 2005 Jan 1; 103(1):111–118. [PubMed: 15558814]
29. Iqbal S, Rankin C, Lenz HJ, et al. A phase II trial of gemcitabine and capecitabine in patients with unresectable or metastatic gallbladder cancer or cholangiocarcinoma: Southwest Oncology Group study S0202. Cancer chemotherapy and pharmacology. 2011 Dec; 68(6):1595–1602. [PubMed: 21556747]
30. Valle JW, Wasan H, Johnson P, et al. Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study - The UK ABC-01 Study. British journal of cancer. 2009 Aug 18; 101(4):621–627. [PubMed: 19672264]
31. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. The New England journal of medicine. 2010 Apr 8; 362(14):1273–1281. [PubMed: 20375404]
32. Pignochino Y, Sarotto I, Peraldo-Neia C, et al. Targeting EGFR/HER2 pathways enhances the antiproliferative effect of gemcitabine in biliary tract and gallbladder carcinomas. BMC cancer. 2010; 10:631. [PubMed: 21087480]
33. Yoshikawa D, Ojima H, Iwasaki M, et al. Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. British journal of cancer. 2008 Jan 29; 98(2):418–425. [PubMed: 18087285]
34. Nakazawa K, Dobashi Y, Suzuki S, Fujii H, Takeda Y, Ooi A. Amplification and overexpression of c-erbB-2, epidermal growth factor receptor, and c-met in biliary tract cancers. The Journal of pathology. 2005 Jul; 206(3):356–365. [PubMed: 15892172]
35. Leone F, Cavalloni G, Pignochino Y, et al. Somatic mutations of epidermal growth factor receptor in bile duct and gallbladder carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2006 Mar 15; 12(6):1680–1685. [PubMed: 16551849]
36. Faris JE, Zhu AX. Targeted therapy for biliary tract cancers. Journal of hepato-biliary-pancreatic sciences. 2012 Feb 9.
37. Philip PA, Mahoney MR, Allmer C, et al. Phase II study of erlotinib in patients with advanced biliary cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006 Jul 1; 24(19):3069–3074. [PubMed: 16809731]
38. Lee J, Park SH, Chang HM, et al. Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. The lancet oncology. 2012 Feb; 13(2):181–188. [PubMed: 22192731]

39. Ciombor KKCD, Chan E, McClanahan P, Fan KH, Flynn J, Young RT, DeMers A, Smith SJ, Berlin J, Goff LW. Phase Ib study of gemcitabine and oxaliplatin with erlotinib in patients with advanced biliary tract cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012; 30 (suppl; abstr 14503).
40. Gruenberger B, Schueller J, Heubrandtner U, et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. The lancet oncology. 2010 Dec; 11(12):1142–1148. [PubMed: 21071270]
41. Malka DFL, Rousseau V, Trarbach T, Boucher E, De La Fouchardiere C, Faivre SJ, Viret F, Blanc JF, Assenat E, Hammel P, Louvet C, von Wichert G, Ducreux M, Rosmorduc O, Pignon JP, Greten TF. Gemcitabine and oxaliplatin alone or in combination with cetuximab as first-line treatment for advanced biliary cancer: Final analysis of a randomized phase II trial (BINGO). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012; 30 (suppl; abstr 4032).
42. Jensen LHLJ, Ploen J, Hansen T, Jakobsen AKM. Marker driven systemic treatment of inoperable cholangiocarcinomas: panitumumab and combination chemotherapy in KRAS wild-type tumors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011; 29 (suppl; abstr 4101).
43. Zhu AX, Meyerhardt JA, Blaszkowsky LS, et al. Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome: a phase 2 study. The lancet oncology. 2010 Jan; 11(1):48–54. [PubMed: 19932054]
44. Lubner SJ, Mahoney MR, Kolesar JL, et al. Report of a multicenter phase II trial testing a combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer: a phase II Consortium study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010 Jul 20; 28(21):3491–3497. [PubMed: 20530271]
45. Bengala C, Bertolini F, Malavasi N, et al. Sorafenib in patients with advanced biliary tract carcinoma: a phase II trial. British journal of cancer. 2010 Jan 5; 102(1):68–72. [PubMed: 19935794]
46. El-Khoueiry AB, Ramanathan RK, Yang DY, et al. A randomized phase II of gemcitabine and sorafenib versus sorafenib alone in patients with metastatic pancreatic cancer. Investigational new drugs. 2012 Jun; 30(3):1175–1183. [PubMed: 21424698]
47. Moehler MHSC, Kanzler S, Woerns S, Denzer U, Kolligs FT, et al. A randomized, double-blind, multicenter phase II AIO trial with gemcitabine plus sorafenib versus gemcitabine plus placebo in patients with chemotherapy-naive advanced or metastatic biliary tract cancer: first safety and efficacy data. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011; 29 (suppl; abstr 4077).
48. Yi JTS, Doval D, Lee J, Cho MN, Park SH, et al. Phase II study of sunitinib as second-line treatment in advanced biliary tract carcinoma: multicenter, multinational study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011; 29 (suppl; abstr 14653).
49. Zhang Z, Oyesanya RA, Campbell DJ, Almenara JA, Dewitt JL, Sirica AE. Preclinical assessment of simultaneous targeting of epidermal growth factor receptor (ErbB1) and ErbB2 as a strategy for cholangiocarcinoma therapy. Hepatology. 2010 Sep; 52(3):975–986. [PubMed: 20607690]
50. Ramanathan RK, Belani CP, Singh DA, et al. A phase II study of lapatinib in patients with advanced biliary tree and hepatocellular cancer. Cancer chemotherapy and pharmacology. 2009 Sep; 64(4):777–783. [PubMed: 19169683]
51. Bekaii-Saab T, Phelps MA, Li X, et al. Multi-institutional phase II study of selumetinib in patients with metastatic biliary cancers. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011 Jun 10; 29(17):2357–2363. [PubMed: 21519026]
52. Deshpande V, Nduaguba A, Zimmerman SM, et al. Mutational profiling reveals PIK3CA mutations in gallbladder carcinoma. BMC cancer. 2011; 11:60. [PubMed: 21303542]
53. Tannapfel A, Sommerer F, Benicke M, et al. Mutations of the BRAF gene in cholangiocarcinoma but not in hepatocellular carcinoma. Gut. 2003 May; 52(5):706–712. [PubMed: 12692057]

54. Borger DR, Tanabe KK, Fan KC, et al. Frequent mutation of isocitrate dehydrogenase (IDH)1 and IDH2 in cholangiocarcinoma identified through broad-based tumor genotyping. The oncologist. 2012; 17(1):72–79. [PubMed: 22180306]

55. Gu TL, Deng X, Huang F, et al. Survey of tyrosine kinase signaling reveals ROS kinase fusions in human cholangiocarcinoma. PloS one. 2011; 6(1):e15640. [PubMed: 21253578]

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

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

Clin Adv Hematol Oncol. Author manuscript; available in PMC 2013 July 17.