Perspective

# Molecular targeted therapy for biliary tract malignancy: defining the target

**Sarah B. Fisher[1], Kevin E. Fisher[2], Shishir K. Maithel[1]**

[1]Division of Surgical Oncology, Department of Surgery, [2]Department of Pathology and Laboratory Medicine, Winship Cancer Institute, Emory University, Atlanta, GA, USA

*Corresponding to:* Shishir K. Maithel, MD, FACS, Assistant Professor of Surgery. Division of Surgical Oncology, Dept of Surgery, Winship Cancer Institute, Emory University, 1365C Clifton Road, NE; Building C, 2nd Floor, Atlanta, GA 30322, USA. Email: smaithe@emory.edu.

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Malignancies of the biliary tract are rare, diagnosed in approximately 9,000 patients each year in the United States (1). Unfortunately, most patients present with advanced disease. Of the small subset who present with resectable (and thus potentially curable) disease, many experience recurrence (2), reinforcing the fact that a multidisciplinary approach to these cancers is critical. Traditionally, our success with medical therapy for patients with locally advanced or metastatic disease has been poor. Recently, however, the ABC-02 trial demonstrated a survival advantage with the combination of gemcitabine and cisplatin as compared to gemcitabine monotherapy (11.7 *vs.* 8.1 months, P<0.0001) and established the combination regimen as standard-of-care for advanced biliary tract cancers (3). Although this trial does provide a step in the right direction, we must maintain a healthy sense of humility and accept the fact that the molecular complexity of these tumors will not be overcome with one or two drugs. As our knowledge and understanding of the molecular basis of cancer slowly improves, interest in the development and clinical application of molecular targeted therapy (MTT) is increasing.

Most would agree that the current shining star that exemplifies the success of MTT for gastrointestinal (GI) malignancy is the application of imatinib for gastrointestinal stromal tumors (GISTs). Its benefits are not only realized in the advanced/metastatic setting, but also in the adjuvant setting after complete resection in well selected patients. GIST tumors are unique in that approximately 85% of tumors harbor the *KIT* mutation that makes them susceptible to imatinib therapy. However, the story is not so clear-cut in other GI malignancies.

The results of MTT in hepatocellular carcinoma (HCC) and pancreas cancer thus far are not as impressive. Although the major phase III randomized trials that have assessed an MTT have reported a statistically significant improvement in survival, the actual clinical benefit is debatable. For example, patients taking sorafenib for advanced HCC had a 10 week improvement in survival compared to placebo (4). The benefit for patients with advanced pancreas cancer taking erlotinib along with gemcitabine was a mere 2 weeks (5). After taking into account side effects and toxicity, one has to question whether these drugs are right for everyone, or do we need to improve patient selection?

The rarity of the disease, and perhaps its histologic heterogeneity, further complicate the application of MTT to biliary tract cancer. Clinical studies assessing single agents have been conducted with limited sample sizes ranging from 2 to 53 patients and with varying outcome measures (response rate, progression-free survival, and/or overall survival) (6). A recent Lancet Oncology publication by Lee and colleagues (7), however, describes an impressive multi-center effort to assess the impact of gemcitabine and oxaliplatin with and without erlotinib, a targeted tyrosine-kinase inhibitor of the epidermal growth factor receptor (EGFR). This randomized phase III trial included patients with gallbladder and ampullary cancer along with patients with cholangiocarcinoma, thus highlighting the heterogeneity in studies of biliary tract malignancy. Although the authors did not demonstrate an overall survival benefit, the addition of erlotinib to chemotherapy in the subset of patients with cholangiocarcinoma did prolong median progression-free survival as compared to chemotherapy alone (5.9 *vs.* 3 months, P=0.049), an improvement of 12 weeks.

The real question, however, is: Do we have the correct target? Is erlotinib, an EGFR inhibitor, the best drug for this disease? Is EGFR mutated in biliary tract malignancy and does it represent one of the main pathways for tumor proliferation? Or, should we be looking at other pathways such as the PI3K-AKT-mTOR pathway or the WNT/β-catenin pathway? Is there a downstream activating mutation in *KRAS* that might negate any potential positive effect of erlotinib or other drugs that target the EGFR pathway? This concept is best demonstrated in colorectal cancer, in which cetuximab, a monoclonal antibody to EGFR, although initially thought to have efficacy in all patients with advanced disease, was found to have no clinical benefit in patients whose tumors have a downstream *KRAS* mutation (8,9). *EGFR* activating mutations and gene amplifications are present in 15% and 6% of biliary tract cancers, respectively, and *KRAS* mutations have been identified in 6.1% to 56% of biliary tract cancers (10).

The mutation status of *EGFR* and/or *KRAS* was unfortunately unavailable for the entire population in the Lee *et al.* study. Amongst the small subset of patients tested, however, there was distinct variability in response rate. Given the limited number of patients in whom tissue was available for analysis, no conclusions can be made on the basis of mutation status and further investigation is necessary. Therefore, the true role of erlotinib for advanced biliary tract malignancy remains to be evaluated.

As we attempt to move towards personalization of cancer therapy and introduce new agents that target specific pathways, we should strive to understand and characterize the molecular basis of these tumors. Clearly, one single targeted agent will not be the answer for everyone. There is too much variation and redundancy in the pathways of tumor proliferation for the answer to be that easy. Tissue-based correlative studies should be routinely incorporated into clinical trials in order to adequately stratify patients and truly understand which patients are best selected for which type of therapy. When dealing with rare cancer types such as biliary tract malignancy, it is especially important for the oncology community to come together through multi-institutional or cooperative group studies. Others have also advocated for more phase II trials to assess activity of molecular targeted therapy in the context of relevant molecular marker analysis (11). Simply performing one randomized trial after the next testing different targeted agents without correlative tissue studies will be time consuming, costly, and unlikely to produce meaningful practice-altering results.

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## References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. de Groen PC, Gores GJ, LaRusso NF, et al. Biliary tract cancers. N Engl J Med 1999;341:1368-78.
3. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273-81.
4. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
5. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960-6.
6. Jensen LH, Jakobsen A. Combining biological agents and chemotherapy in the treatment of cholangiocarcinoma. Expert Rev Anticancer Ther 2011;11:589-600.
7. 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. Lancet Oncol 2012;13:181-8.
8. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357:2040-8.
9. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757-65.
10. Marino D, Leone F, Cavalloni G, et al. Biliary tract carcinomas: From chemotherapy to targeted therapy. Crit Rev Oncol Hematol 2012. [Epub ahead of print].
11. Jensen LH. Biliary-tract cancer: improving therapy by adding molecularly targeted agents. Lancet Oncol 2012;13:118-9.

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