Published in final edited form as:

Photodiagnosis Photodyn Ther. 2009 June ; 6(2): 82–83. doi:10.1016/j.pdpdt.2009.06.002.

Cholangiocarcinoma: improving biliary drainage with PDT

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Cholangiocarcinoma is a disease that is challenging to both diagnose and treat. Only a minority of patients present at a stage suitable for attempted curative surgical resection and 5 year survival rates remain as low as 5% in most series [1]. Much of the morbidity of cholangiocarcinoma is caused by complications of biliary obstruction — a rationale for treatments such as PDT, which aim to optimise biliary drainage and thereby improve survival and quality of life.

In the comprehensive review by Allison et al in the current edition of the journal [2], the authors address the diagnostic and therapeutic challenges in cholangiocarcinoma. They also summarise the clinical trial data on PDT for cholangiocarcinoma and conclude that current evidence suggests PDT improves the outcome of patients with this difficult disease, but that further studies are required. In this respect, a phase III trial (PHOTOSTENT-02) is underway in the UK (EudraCT number 2005-001173-96) which aims to determine whether PDT improves the survival and quality of life of patients with locally advanced or metastatic biliary tract cancer.

However, a number of problems remain that limit the use of PDT in the management of patients with cholangiocarcinoma. As the authors point out, the classification and staging of cholangiocarcinoma can be complicated by confusing nomenclature and difficulties with imaging small volume tumours, which make comparison of trial data difficult. In their review, the authors classify hilar tumours as extra-hepatic, which differs from the intrahepatic classification of the International Classification of Diseases for Oncology (ICD-O-3). Indeed, there have been calls for alternatives to the ICD-O-3 staging system [3,4] which classify peripheral intrahepatic tumours, with their different biology and surgical management, separately to those arising from major bile ducts, which may be accessible by endoscopic or percutaneous biliary approaches and therefore amenable to PDT. There have been no studies in gallbladder cancer but obstructed major bile ducts due to local invasion may also be suitable for treatment using PDT.

Cholangiocarcinoma often invades by infiltrating along bile ducts and is thus commonly understaged by cross sectional imaging or cholangiography. There may be a role for extending PDT to treat areas of radiographically normal bile duct above and below the visible stricture, a question which could be addressed using emerging technologies such as cholangioscopy. As discussed in the review, a potential extension of this hypothesis is that intra- or peri-operative neoadjuvant or adjuvant PDT to bile ducts adjacent to planned resection margins may improve R0 resection rates.

Chemotherapy has been widely regarded as an ineffective treatment for biliary tract cancer. However, a meta-analysis of 2810 patients in 104 mostly small, non randomised studies reported a median response rate of 23% and a small survival advantage (1 month) in those undergoing chemotherapy, particularly using gemcitabine and platinum-based regimens [5].

A very recently reported phase III study of 410 patients with locally advanced or metastatic biliary tract cancer (ABC-02), has shown a significant survival advantage (without increased toxicity) of gemcitabine with cisplatin over gemcitabine alone (11.7 months v 8.2 months respectively, $p=0.002$) [6], so that chemotherapy should now be considered a standard palliative treatment option in BTC.

Our understanding of the biology and molecular markers of BTC still lags behind that of more common cancers, but is improving [7]. Allison et al refer to the evidence that interleukin 6 (IL-6) is over expressed in BTC, which may relate to its role in chronic inflammation, thought to be a trigger for cancer in the biliary tree. Epidermal growth factor receptor (EGFR) activation has also been shown to be upregulated in BTC but the impact of anti-EGFR agents on tumour biology and, more importantly, survival, have yet to be tested adequately. Other proteins or pathways implicated in BTC such as HGF, IGF1, VEGF, COX-2 and bcl-2 [7] also warrant further study in BTC. Future clinical studies of PDT will likely include combination treatment with chemotherapy and biological agents.

References

1. de Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. *N Engl J Med* 1999 Oct 28;341(18):1368–78. [PubMed: 10536130]
2. Allison RRZE, Sibata CH. Cholangiocarcinoma: An Emerging Indication for Photodynamic Therapy. *Photodiagnosis and Photodynamic Therapy*. 2009
3. Blechacz BR, Sanchez W, Gores GJ. A conceptual proposal for staging ductal cholangiocarcinoma. *Current opinion in gastroenterology* 2009 May;25(3):238–9. [PubMed: 19387257]
4. Matull, WR.; Khan, SA.; Pereira, SP. *Journal of the National Cancer Institute*. Vol. 99. 2007 Mar 7. Re: Impact of classification of hilar cholangiocarcinomas (Klatskin tumors) on incidence of intra- and extrahepatic cholangiocarcinoma in the United States; p. 407author reply -8
5. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. *British journal of cancer* 2007 Mar 26;96(6):896–902. [PubMed: 17325704]
6. Valle JWWH, Palmer DD, Cunningham D, Anthoney DA, Maraveyas A, et al. Gemcitabine with or without cisplatin in patients with advanced or metastatic biliary tract cancer: results of a multicenter, randomized phase III trial (the UK ABC-02 trial). *J Clin Oncol* 2009;27(15 supp) abstract 4503.
7. Sirica, AE.; Nathanson, MH.; Gores, GJ.; Larusso, NF. *Hepatology*. Vol. 48. Baltimore, Md: 2008 Dec. Pathobiology of biliary epithelia and cholangiocarcinoma: proceedings of the Henry M. and Lillian Stratton Basic Research Single-Topic Conference; p. 2040-6.

Abbreviations

BTC	biliary tract cancer
CC	cholangiocarcinoma
PDT	photodynamic therapy