

Chemotherapy for advanced cholangiocarcinoma: what is standard treatment?

Danish Mazhar[†],
Justin Stebbing
& Mark Bower

[†]Author for correspondence
Chelsea & Westminster
Hospital, Department of
Oncology, 369 Fulham Road,
London SW10 9NH, UK
Tel.: +44 208 237 5054;
Fax: +44 208 746 8863;
d.mazhar@imperial.ac.uk

Cholangiocarcinoma is a relatively uncommon malignancy, that presents late in the vast majority of cases. Overall survival rates are extremely poor and treatment options remain limited in patients with inoperable, recurrent or metastatic disease. Systemic chemotherapy has historically had little impact on the natural history of this disease, owing to both the absence of agents with substantial activity and the overall morbidity of treatment in this patient population. Response rates with 5-fluorouracil have been 10% at best, with a median survival of 6 months. However, there has been interest in the use of newer cytotoxic drugs and combination regimens in advanced cholangiocarcinoma, and Phase II trials have reported much improved results. This review examines this data and assesses whether a new standard of care for advanced cholangiocarcinoma can be found.

Cholangiocarcinoma was first described by Durand-Fardel [1]. It is a malignancy arising from the ductular epithelium of the biliary tree, either within the liver (intrahepatic cholangiocarcinoma) or, more commonly, from the extrahepatic bile ducts (extrahepatic cholangiocarcinoma). Generally, it remains a rare malignancy, although the incidence of intrahepatic cholangiocarcinoma is rising [2]. In the vast majority of patients the prognosis is poor. At the time of diagnosis, more than two-thirds of cholangiocarcinomas are unresectable [3]. Even patients with operable tumors have high recurrence rates of up to 80% [4]. Overall survival rates, even including patients with operable diseases, are extremely disappointing, with less than 5% of patients surviving 5 years [5].

Primary sclerosing cholangitis (PSC) is the most commonly known predisposing condition for cholangiocarcinoma in the West. Cholangiocarcinoma rates of up to 40% have been reported in patients with PSC in follow-up studies and explant specimens [2]. Two-thirds of patients with PSC have associated inflammatory bowel disease, but no association has been found between the risk of cholangiocarcinoma and inflammatory bowel disease. Early diagnosis of cholangiocarcinoma in PSC is particularly difficult, as presentation can mimic benign dominant biliary stricturing. The only treatment option that has been shown to extend survival is liver transplantation in a selected group of patients.

Chemotherapy has traditionally been used in the settings of inoperable, recurrent and metastatic cholangiocarcinoma. Biliary bypass or stenting is often required if chemotherapy is to be contemplated. To date, chemotherapy has

had a limited impact on the natural history of this disease, owing to both the absence of agents with substantial activity and the overall morbidity of treatment in this patient population. No standard chemotherapy has been identified that can clearly prolong survival. However, a number of recent Phase II trials using newer chemotherapeutic agents and combination regimes have suggested a level of chemosensitivity not previously seen. This review examines the available data with the aim of answering the question; 'Are we close to finding a consensus chemotherapeutic standard for advanced cholangiocarcinoma?'

Use of 5-fluorouracil

In the past, chemotherapy in advanced disease has demonstrated only very limited success in terms of objective responses or survival benefit. Much of this experience is based on 5-fluorouracil (5-FU), either alone or in combination with other drugs. Many of the studies with 5-FU have been small and uncontrolled. Moreover, some included patients with primary gallbladder or pancreatic cancer, complicating the analysis further. Overall response rates with 5-FU alone have been up to 10%, with a median survival of approximately 6 months [6]. However, Glimelius and colleagues demonstrated there was improved quality of life for biliary cancer patients treated with 5-FU-based chemotherapy versus best supportive care, although median survival remained low [7].

Combining 5-FU with other agents may improve efficacy. The addition of leucovorin (LV) gave a response rate of 32% in one study [8]. The addition of doxorubicin, and mitomycin C with methyl-1,(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) or streptozotocin to 5-FU

Keywords: 5-fluorouracil, chemotherapy, cholangiocarcinoma, extrahepatic, gemcitabine, intrahepatic

future
medicine

has not demonstrated any improvement in either response rate or survival time [9]. The combination of cisplatin with 5-FU resulted in a response rate of 24% with a median survival time of 10 months [10]. The combination of cisplatin, epirubicin and 5-FU (ECF) produced a response rate of 40% with a median survival time of 11 months in one study [11]. However, in another study the response rate was only 10% and the median survival time was 5 months [12].

Interferon (IFN)- α combined with 5-FU has been reported to give a partial response rate of up to 34% [13]. The addition of other drugs (cisplatin, doxorubicin) to the 5-FU/IFN- α combination did not improve response rates and resulted in considerably higher toxicities [14]. The oral 5-FU prodrugs, uracil–tegafur (UFT) and capecitabine, have been evaluated in advanced biliary tract cancer. Stabilization of disease was observed in two out of 14 patients when UFT was given with LV, with a median survival time of 5 months [15]. In 18 patients with cholangiocarcinoma, an overall partial response rate of 6% was observed with capecitabine, and 28% of patients achieved stable disease with a median survival of 8.1 months [16]. Capecitabine plus cisplatin demonstrated an overall response rate of 21.4% with a median overall survival of 9.1 months [17]. A Phase II study of epirubicin, cisplatin and capecitabine in 43 patients with advanced biliary tract adenocarcinoma gave a partial response rate of 40%, mirroring the response observed in the study by Ellis and colleagues with ECF a decade earlier. Median survival time was 8 months with acceptable toxicity [18].

Use of gemcitabine & gemcitabine-based combinations

In recent years, given the lack of success of 5-FU-based regimens, there has been interest in the use of gemcitabine (2,2-dideoxyfluorocytidine) in cholangiocarcinoma. Gemcitabine has demonstrated activity in several other solid tumors (including non-small cell lung, bladder, pancreatic, breast and ovarian cancers) while having a relatively favorable toxicity profile. Studies using gemcitabine, either alone or in combination with other cytotoxic agents, in advanced cholangiocarcinoma have been conducted. Once again, investigators have often included other hepatobiliary malignancies, hampering the assessment of the benefit in cholangiocarcinoma. The studies also have generally been relatively small. One further problem here is that patients with advanced cholangiocarcinoma,

particularly those who are not amenable to palliative stenting, often have deranged liver function tests, which makes them ineligible for such studies which have restrictive inclusion criteria. The standard of management in patients with significant hepatic dysfunction who are not amenable to palliative stenting is limited essentially to supportive care, with low dose 5-FU the only cytotoxic agent that may be considered in selected cases where performance status is acceptable.

Several single agent gemcitabine dosing schedules have been tested in studies, with varying results. In a Phase II trial of 1200 mg/m² gemcitabine given weekly for 3 weeks followed by 2 weeks off treatment, three out of 19 patients (16%) with biliary tract or gallbladder carcinoma achieved a partial response (PR). The median survival period was 6.5 months and the time to disease progression was 2.5 months [19]. A Phase II trial of gemcitabine given every other week at a dose of 2200 mg/m² reported a response rate of 22% and a median survival period of 11.5 months [20]. Arroya and colleagues reported a 36% response rate in 39 patients treated with gemcitabine at 1000 mg/m² weekly for 3 weeks followed by 2 weeks off treatment, although the overall survival was 6.5 months [21]. However, in a separate Phase II trial of 13 patients with biliary tract or gallbladder carcinoma, no significant responses were observed with gemcitabine [22].

The combination of gemcitabine and a fluoropyrimidine in biliary cancers is worthy of further evaluation. The toxicity profiles of these agents are known to be non-overlapping. Moreover, both drugs interfere with the pyrimidine biosynthesis pathways and may act synergistically. Indeed, pre-clinical studies including xenograft models support this notion [23]. The combination of gemcitabine, 5-FU and LV has been evaluated in three Phase I trials to date [24,25,26]. All these studies demonstrated antitumor activity with few significant side effects. In the study by Berlin and colleagues the combination of gemcitabine, 5-FU and LV was given weekly for 3 weeks in a 4-week cycle. The recommended Phase II doses from that study were 1000 mg/m² gemcitabine, 600 mg/m² 5-FU and 25 mg/m² LV. At these doses, Grade 3 absolute neutrophil count was observed but no other Grade 3/4 hematological toxicities. Non-hematological toxicities were described as mild [26]. Alberts and colleagues carried out a Phase II trial where they evaluated the 6-month survival, response and toxicity associated with a combination of gemcitabine (1000 mg/m²), 5-FU (600 mg/m²) and LV (25 mg/m²) in

patients with unresectable or metastatic cholangiocarcinoma or gallbladder carcinoma. Of the 42 patients studied, 24 (57%) survived for 6 months or longer. There were five PRs (12%) and the median time to progression was 4.6 months with a median survival of 9.7 months. There were no treatment-related deaths, although Grade 3 thrombocytopenia was seen in six patients and Grade 3 or 4 neutropenia in 19 patients [27].

Knox and colleagues have recently reported on a Phase II study of gemcitabine and capecitabine in patients with locally advanced or metastatic cholangiocarcinoma or gallbladder cancer [28]. Patients were treated on a 3-week cycle consisting of capecitabine at 650 mg/m² orally twice a day for 14 days and gemcitabine at a fixed dose of 1000 mg/m² intravenously over 30 min on days one and eight. A total of 45 patients were enrolled, in which 53% had cholangiocarcinoma, 47% had gallbladder cancer and 89% had metastatic disease. The overall objective response rate was 31%, with an additional 42% of patients with stable disease, for a disease control rate of 73%. The median overall survival time was 14 months, and the median progression-free survival time was 7 months. Therapy was generally well-tolerated. Transient neutropenia, thrombocytopenia, fatigue and hand-foot syndrome were commonly observed, but were easily managed without discontinuing further treatment.

The combination of gemcitabine with cisplatin has demonstrated promising results in patients, with a good performance status and adequate hepatic function. With this combination, a response rate between 27.5 and 50% has been reported, with median overall survival ranging from 5–11.3 months [29,30,31]. The study with the best response rate and most optimistic overall survival only included 11 subjects [29]. Again, there was considerable variation in chemotherapeutic dosing and scheduling, and several studies included other hepatobiliary malignancies.

Thongprasert and coworkers have reported on one of the largest series of trials for the combination of gemcitabine and cisplatin [31]. In their Phase II study, 43 patients were enrolled to receive gemcitabine 1250 mg/m² on day 1 and 8, and cisplatin 75 mg/m² on day 1 every 3 weeks. To be eligible, patients had to have a Karnofsky Performance Status of 60% or better, as well as serum bilirubin of less than 5 mg/dl, serum transaminases of no more than 2.5-times normal limits, albumin levels of at least 2.5 mg/dl and serum creatinine levels of 1.5 mg/dl or less. In total, 40 patients were

assessable (3 patients chose to discontinue chemotherapy after the first cycle). It was found that 39 patients had cholangiocarcinoma and one had primary gallbladder cancer. The overall response rate was 27.5% (PR in 11 patients), with 32.5% with stable disease. Median survival time was 36 weeks. Grade 3 hematological toxicity was not common (leucopenia was seen in only 1.73% of patients) and non-hematological toxicity (i.e., rash, nausea, vomiting, neuropathy and myalgia) ranged from mild to moderate.

Recently, Andre and colleagues studied the combination of gemcitabine and oxaliplatin (GEMOX) [32]. Patients with advanced biliary tract cancer (34 cholangiocarcinoma, 19 primary gallbladder and 3 ampulla of Vater) were recruited from four centers. Those in the first group (A) had a Performance Status (PS) of 0–2, bilirubin of less than 2.5 the normal and received GEMOX as first-line chemotherapy. Those in the second group (B) had a PS of more than 2 and/or bilirubin of more than 2.5 the normal and/or prior chemotherapy. All received gemcitabine 1000 mg/m² as a 10 mg/m²/min infusion on day 1, followed by oxaliplatin 100 mg/m² as an infusion on day 2, every 2 weeks. In group A (n = 33), objective responses were observed in 36%, stable disease in 26% and progressive disease 39% of patients. The median progression-free survival was 5.7 months and overall survival 15.4 months. Results for the poorer prognosis group B (n = 23) were objective response in 22%, stable disease in 30% and progressive disease in 48%, with a median progression-free survival of 3.9 months and overall survival of 7.6 months. Grade 3–4 toxicities were neutropenia observed in 14%, thrombocytopenia in 9%, nausea and vomiting in 5% and peripheral neuropathy in 7% of patients. Results indicate that GEMOX has some activity, even in patients with a poor prognosis who have received previous chemotherapy. Tolerability of GEMOX in group B did not differ significantly from that in group A patients, indicating that this combination is safe in patients with a poor prognosis or pretreated by chemotherapy.

Therefore, current opinion is that gemcitabine-based chemotherapy regimens are superior compared with schedules based on 5-FU. The combination of gemcitabine with cisplatin or oxaliplatin may be superior to single agent gemcitabine, although there is lack of published randomised data. A Phase III trial addressing the comparison of gemcitabine compared with gemcitabine and cisplatin is underway in the UK.

Use of taxanes

The combination of gemcitabine and docetaxel gave a response rate of only 9% in a study of 43 patients with advanced cholangiocarcinoma or gallbladder cancer, although the median overall survival was 11 months [33]. Docetaxel, given as a single agent, induced one complete response and three PRs in 21 patients with inoperable or metastatic cholangiocarcinoma [34]. However, another study reported no objective responses in 17 patients [35]. Preliminary data suggest that paclitaxel has no activity in biliary tract carcinoma [36].

Conclusions

There is no current standard chemotherapy for advanced cholangiocarcinoma and it may be sometime before a consensus is found. Table 1 outlines some of the existing data regarding the use of cytotoxics for advanced biliary tract malignancy. Practices vary considerably and range from not offering patients chemotherapy owing to concern over lack of efficacy and detrimental toxicity, to offering patients multiple-drug regimens. The recent surge of new Phase II trials in cholangiocarcinoma reflects not only the lack of consensus on the best treatment, but also an increase in research interest on how to manage this challenging disease. Data from Phase II studies suggest that gemcitabine monotherapy represents an active and well-tolerated treatment. The

combinations of gemcitabine and cisplatin and gemcitabine and oxaliplatin demonstrate promising activity. The role of 5-FU and LV with cisplatin also merits further study. There are difficulties in making comparisons between many of the studies to date since inclusion criteria and study design vary greatly. Moreover, only a few studies have addressed the issue of treatment of patients who have progressed after previous chemotherapy. The possible benefit of combining regional chemoembolization with chemotherapy has been recently suggested for inoperable cholangiocarcinoma [37]. There may also be merit in investigating systemic targeted therapies such as bevacuzimab (a monoclonal antibody against vascular endothelial growth factor receptor), cetuximab (monoclonal antibody against endothelial growth factor receptor) and tyrosine kinase inhibitors, administered either alone or coadministered with chemotherapeutic agents. At present, there is interest in the use of such agents in a variety of malignancies, although there is no clinical data on the use of such agents in cholangiocarcinoma as yet. Finally, the relative benefit of chemotherapy in this disease is called into question given the promising results of photodynamic therapy in the palliative setting. In a prospective study, 39 patients with inoperable cholangiocarcinoma were randomized to treatment with either biliary stenting plus photodynamic therapy or stenting alone. The photodynamic therapy

Table 1. Selected chemotherapy for advanced biliary tract cancer.

Treatment	Patients (n)	Overall response (%)	Median survival	Ref.
5-FU	30	10	26 weeks	[6]
5-FU/LV	28	32	6 months	[8]
5-FU/cisplatin	25	24	10 months	[10]
5-FU/epirubicin/cisplatin	20	40	11 months	[11]
5-FU/epirubicin/cisplatin	20	10	5 months	[12]
Capecitabine	18	6	8.1 months	[16]
Capecitabine/epirubicin/cisplatin	43	40	9.1 months	[18]
Gemcitabine (1000 mg/m ² day 1, 8, 21 q28)	39	36	6.5 months	[21]
Gemcitabine (2200 mg/m ² day 1 q14)	32	22	11.5 months	[20]
Gemcitabine/5-FU/LV	42	9.5	9.7 months	[27]
Gemcitabine/cisplatin	40	27.5	9 months	[31]
Gemcitabine/oxaliplatin	33	36	15.4 months	[32]
Gemcitabine/capecitabine	17	33	Not reported	[28]
Gemcitabine/docetaxel	43	9	11 months	[33]

5-FU: 5-fluorouracil; LV: Leucovorin.

group had a far superior median survival (493 vs 98 days), as well as better quality of life scores and less cholestasis than the stenting group, although the benefit may be largely attributed to relief of obstruction rather than a reduction in tumor mass [38]. Is the future of advanced cholangiocarcinoma management a combination of chemotherapy and photodynamic therapy?

Future perspective

Treatment options for advanced cholangiocarcinoma remain limited. However, the results of several recent Phase II studies have led to renewed interest in the use of gemcitabine-based

combination chemotherapy regimens. We believe that the coming years will provide further evidence of the benefit of the use of two or more cytotoxic drugs compared with using just one. We believe that the enthusiasm surrounding novel targeted therapies, we believe, will extend to the use of such agents in this disease-setting in clinical trials. The promising initial results of photodynamic therapy also merit further study. However, there clearly needs to be a focus on the processes involved in the development of cholangiocarcinoma, and in methods of enhancing early diagnosis and prevention of this devastating disease.

Executive summary

Introduction

- Cholangiocarcinoma is a rare malignancy, which usually presents late.
- Prognosis of cholangiocarcinoma remains poor.
- There is no current standard chemotherapeutic regimen for advanced cholangiocarcinoma.

Use of 5-fluorouracil

- Traditionally, chemotherapy with 5-fluorouracil (5-FU) in advanced cholangiocarcinoma has demonstrated limited survival benefit.
- Combining 5-FU with other cytotoxics may improve efficacy.

Use of gemcitabine & gemcitabine-based combinations

- Recent Phase II studies using gemcitabine, either alone or in combination with other cytotoxics (e.g., cisplatin and oxaliplatin), have demonstrated promising response rates.
- However, there are several problems in the analysis of such studies, including the inclusion of other hepatobiliary malignancies in many studies and the relatively small number of patients included.
- There is no published, randomized study of gemcitabine versus gemcitabine combined with other cytotoxic agents to date.

Use of taxanes

- Data suggests that paclitaxel has no activity in cholangiocarcinoma and that the gemcitabine and docetaxel combination gives disappointing results.

Future perspective

- The use of targeted therapies in cholangiocarcinoma remains largely unexplored.
- Photodynamic therapy has demonstrated some promising initial results in the palliation of advanced cholangiocarcinoma.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Olnes MJ, Erlich R: A review and update on cholangiocarcinoma. *Oncology* 66, 167–179 (2004).
2. Khan SA, Thomas HC, Davidson BR, Taylor-Robinson SD: Cholangiocarcinoma. *Lancet* 366, 1303–1314 (2005).
- Good overview of cholangiocarcinoma etiology, epidemiology, diagnosis and treatment.
3. Khan SA, Davidson BR, Goldin R *et al.*: Guidelines for the diagnosis and treatment of cholangiocarcinoma. *Gut* 51(Suppl. 6), 1–9 (2002).
4. Kopelson G, Gunderson LL: Primary and adjuvant radiation therapy in gallbladder and extrahepatic biliary tract carcinoma. *J. Clin. Gastroenterol.* 5, 43–50 (1983).
5. Khan SA, Taylor-Robinson SD, Toledano MB, Beck A, Elliott P, Thomas HC: Changing international trends in mortality rates for liver, biliary and pancreatic tumours. *J. Hepatol.* 37, 806–813 (2002).
6. Falkson G, MacIntyre JM, Moertel CG: Eastern Cooperative Oncology Group experience with chemotherapy for inoperable gallbladder and bile duct cancer. *Cancer* 54, 965–969 (1984).
7. Glimelius B, Hoffman P, Sjoden PO *et al.*: Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann. Oncol.* 7, 593–600 (1996).
8. Choi CW, Choi IK, Seo JH *et al.*: Effects of 5-fluorouracil and leucovorin in the treatment of pancreatic-biliary tract adenocarcinomas. *Am. J. Clin. Oncol.* 23, 425–428 (2000).
9. Thongprasert S: The role of chemotherapy in cholangiocarcinoma. *Ann. Oncol.* 16(Suppl. 2), 93–96 (2005).
- Useful summary of trials using gemcitabine-based regimens for treatment of advanced cholangiocarcinoma.
10. Ducreux M, Rougier P, Fandi A *et al.*: Effective treatment of advanced biliary tract carcinoma using 5-fluorouracil continuous infusion with cisplatin. *Ann. Oncol.* 9, 653–656 (1998).

11. Ellis PA, Norman A, Hill A *et al.*: Epirubicin, cisplatin and infusional 5-fluorouracil (5-FU) (ECF) in hepatobiliary tumours. *Eur. J. Cancer* 1594–1598 (1995).
12. Lee MA, Woo IS, Kang JH *et al.*: Epirubicin, cisplatin and protracted infusion of 5-FU (ECF) in advanced intrahepatic cholangiocarcinoma. *Cancer Res. Clin. Oncol.* 130, 346–350 (2004).
13. Patt YZ, Jones DV Jr, Hoque A *et al.*: Phase II trial of intravenous fluorouracil and subcutaneous interferon α -2b for biliary tract cancer. *J. Clin. Oncol.* 14, 2311–2315 (1996).
14. Patt YZ, Hassan MM, Lozano RD *et al.*: Phase II trial of cisplatin, interferon α -2b, doxorubicin, and 5-fluorouracil for biliary tract cancer. *Clin. Cancer Res.* 7, 3375–3380 (2001).
15. Chen JS, Yang TS, Lin YC, Jan YY: A Phase II trial of tegafur-uracil plus leucovorin (LV) in the treatment of advanced biliary tract carcinomas. *Jpn. J. Clin. Oncol.* 33, 353–356 (2003).
16. Patt YZ, Hassan MM, Aguayo A *et al.*: Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. *Cancer* 101, 578–586 (2004).
17. Kim TW, Chang HM, Kang HJ *et al.*: Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced biliary cancer. *Ann. Oncol.* 14, 1115–1120 (2003).
18. Park SH, Park YH, Lee JN *et al.*: Phase II study of epirubicin, cisplatin, and capecitabine for advanced biliary tract adenocarcinoma. *Cancer* 106, 361–365 (2006).
19. 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* 56, 177–180 (1999).
20. Penz M, Kornek GV, Raderer M *et al.*: Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. *Ann. Oncol.* 12, 183–186 (2001).
21. Arroyo G, Gallardo J, Rubio B: Gemcitabine (GEM) in advanced biliary tract cancer (ABTC). Experience from Chile and Argentina in Phase II trials. *Proc. Am. Soc. Clin. Oncol.* 20, 157 (2001).
22. Mezger J, Sauerbruch T, Ko Y *et al.*: Phase II study with gemcitabine in gallbladder and biliary tract carcinomas. *Oncology* 21, 232–234 (1998).
23. Schulz L, Schalhorn W, Wilmanns W *et al.*: Synergistic interaction of gemcitabine and 5-fluorouracil in colon cancer cells. *Proc. Am. Soc. Clin. Oncol.* 17, 251 (1998).
24. Poplin E, Roberts J, Tombs M *et al.*: Leucovorin, 5-fluorouracil, and gemcitabine: a Phase I study. *Invest. New Drugs* 17, 57–62 (1999).
25. Hidalgo M, Castellano D, Paz-Ares L *et al.*: Phase I-II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer. *J. Clin. Oncol.* 17, 585–592 (1999).
26. Berlin JD, Alberti DB, Arzooarian RZ *et al.*: A Phase I study of gemcitabine, 5-fluorouracil and leucovorin in patients with advanced, recurrent, and/or metastatic solid tumors. *Invest. New Drugs* 16, 325–330 (1998).
27. Alberts SR, Al-Khatib H, Mahoney MR *et al.*: Gemcitabine, 5-fluorouracil, and leucovorin in advanced biliary tract and gallbladder carcinoma. *Cancer* 103, 111–118 (2005).
28. Knox JJ, Hedley D, Oza A *et al.*: Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a Phase II trial. *J. Clin. Oncol.* 23, 2332–2338 (2005).
29. Carraro S, Servienti PJ, Bruno MF: Gemcitabine and cisplatin in locally advanced or metastatic gallbladder and bile duct adenocarcinomas. *Proc. Am. Soc. Clin. Oncol.* 20, 146 (2001).
30. Doval DC, Sekhon JS, Gupta SK *et al.*: A Phase II study of gemcitabine and cisplatin in chemotherapy-naïve, unresectable gallbladder cancer. *Br. J. Cancer* 90, 1516–1520 (2004).
31. Thongpansert S, Napapan S, Charoentum C, Moonprakan S: Phase II study of gemcitabine and cisplatin as first line chemotherapy in inoperable biliary tract carcinoma. *Ann. Oncol.* 16, 279–281 (2005).
- **One of the largest Phase II trials of gemcitabine and cisplatin in advanced cholangiocarcinoma to have been conducted to date.**
32. Andre T, Tournigand C, Rosmorduc O *et al.*: Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. *Ann. Oncol.* 15, 1339–1343 (2004).
- **First published study of gemcitabine and oxaliplatin in advanced biliary tract cancer.**
33. Kuhn R, Hribaschek A, Eichelmann K *et al.*: Outpatient therapy with gemcitabine and docetaxel for gallbladder, biliary, and cholangiocarcinomas. *Invest. New Drugs* 20, 351–356 (2002).
34. Papakostas P, Kouroussis C, Androulakis N *et al.*: First-line chemotherapy with docetaxel for unresectable or metastatic carcinoma of the biliary tract. A multicenter Phase II study. *Eur. J. Cancer* 37, 1833–1838 (2001).
35. Pazdur R, Royce ME, Rodrigues GI *et al.*: Phase II trial of docetaxel for cholangiocarcinoma. *Am. J. Clin. Oncol.* 22, 78–81 (1999).
36. Jones DV, Lozano R, Hoque A *et al.*: Phase II study of paclitaxel therapy for unresectable biliary tree carcinomas. *J. Clin. Oncol.* 14, 2306–2310 (1996).
37. Kirchoff T, Zender L, Merksdal S *et al.*: Initial experience from a combination of systemic and regional chemotherapy in the treatment of patients with nonresectable cholangiocellular carcinoma in the liver. *World J. Gastroenterol.* 11, 1091–1095 (2005).
38. Ortner ME, Caca K, Berr F *et al.*: Successful photodynamic therapy for non-resectable cholangiocarcinoma: a randomized prospective study. *Gastroenterol.* 125, 1355–1363 (2003).
- **Prospective study exploring the use of photodynamic therapy in the palliation of cholangiocarcinoma.**

Affiliations

- **Danish Mazhar**
Specialist Registrar in Medical Oncology, Chelsea & Westminster Hospital, Department of Oncology, 369 Fulham Road, London SW10 9NH, UK
Tel.: +44 208 237 5054;
Fax: +44 208 746 8863;
d.mazhar@imperial.ac.uk
- **Justin Stebbing**
Chelsea & Westminster Hospital, Department of Oncology, 369 Fulham Road, London SW10 9NH, UK
Tel.: +44 208 237 5054;
Fax: +44 208 746 8863;
j.stebbing@imperial.ac.uk
- **Mark Bower**
Chelsea & Westminster Hospital, Department of Oncology, 369 Fulham Road, London SW10 9NH, UK
Tel.: +44 208 237 5054;
Fax: +44 208 746 8863;
m.bower@imperial.ac.uk