Published in final edited form as:

Photodiagnosis Photodyn Ther. 2012 December ; 9(4): 287–292. doi:10.1016/j.pdpdt.2012.03.005.

Safety and long term efficacy of porfimer sodium photodynamic therapy in locally advanced biliary tract carcinoma

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Abstract

Background—In patients with unresectable cholangiocarcinoma, photodynamic therapy (PDT) with porfimer sodium promotes biliary drainage and may improve survival and quality of life.

Aim—To prospectively evaluate the safety and efficacy of PDT in patients with locally advanced biliary tract carcinoma.

Methods—Eligible patients had unresectable, histologically confirmed disease, a Karnofsky performance status of $\geq 30\%$ and life expectancy >12 weeks. Patients received 2mg/kg i.v. of porfimer sodium, followed by endobiliary laser activation and stent replacement 48 hrs later. Patients were assessed clinically and radiologically before treatment and on day 28, and followed up thereafter at three-monthly intervals until death.

Results—36 patients were entered over an 18 months period: 14 males, 22 females, with a median age of 65 (30–79) yr and performance status of 80 (50–100). PDT was technically successful in all cases and was generally well tolerated; there was no grade 4 toxicity and no treatment-associated mortality. The median survival was 12 (1–84) months.

Conclusions—Porfimer sodium PDT can be delivered safely to patients with biliary tract cancer and is suitable for testing in phase III studies (UKCRN ID 1218).

Keywords

photodynamic therapy; biliary tract cancer; porfimer sodium

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Conflict of interest statement for all authors: "No conflicts of interest exist"

INTRODUCTION

Cholangiocarcinoma and carcinoma of the gall bladder are tumours of the biliary tract that are considered as one pathological entity (biliary tract carcinoma, BTC). BTC has a poor prognosis, with an overall five-year survival of less than 5% [1]. The only curative option is margin-free surgical resection, but this is achievable in less than 20% of cases and even then, the disease recurs in at least 70% and the 5-year survival is no greater than 10-30% [2]. Although most patients with unresectable disease can be palliated at least temporarily by endoscopic or percutaneous placement of one or more biliary stents, the prognosis remains poor, with a median survival of less than six months in patients with complex hilar lesions [3, 4]. Oncological opinion supports the use of palliative chemotherapy, with the recently published ABC-02 study reporting that cisplatin plus gemcitabine, compared with gemcitabine alone, was associated with a significant survival advantage (11.7 vs 8.1 months, $p < 0.001$) without the addition of substantial toxicity [5]. However, novel palliative approaches are needed to improve quality of life and survival in this patient group.

Photodynamic therapy (PDT) is a way of producing localised tissue necrosis or apoptosis. Light (most conveniently from a low-power, red laser) after prior administration of a photosensitising agent, initiates a localised, non-thermal, cytotoxic effect and tissue necrosis [6]. PDT has been used for palliation in patients with unresectable cholangiocarcinoma, with small single-centre studies reporting an improvement in cholestasis, quality of life and survival of patients treated with stenting plus PDT compared with historical controls treated with stenting alone [7, 8]. These results have been supported by two small randomised controlled trials from Germany [9, 10], both of which reported a survival benefit for PDT with stenting over stenting alone for unresectable cholangiocarcinoma. Given these encouraging reports, a phase II prospective single-arm study based in three UK centres was designed to address the safety and long-term efficacy of this treatment modality in patients with locally advanced, unresectable, disease.

PATIENTS AND METHODS

Patients

Patients over 18 years of age with a histopathological/cytological diagnosis of locally advanced biliary tract carcinoma within the previous 8 weeks were screened for trial eligibility. All patients underwent multidisciplinary team assessment and had either unresectable disease (as defined by a Bismuth grade of III - IV and TNM tumour stage of III or IV) or were unfit for surgery. Patients with gallbladder cancer were required to have disease extension to the liver hilum requiring palliative stenting. Additional inclusion criteria were a Karnofsky performance status of $> 30\%$ and an estimated life expectancy of at least 12 weeks. Patients were also required to have radiologically assessable, measurable or non-measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST) criteria [11].

Patients were excluded from entry into the trial if they had received treatment with curative intent (ie, a prior resection, radical radiotherapy or chemotherapy), had a history of prior malignancy that could interfere with response evaluation, or if there was any evidence of severe or uncontrolled systemic disease or laboratory findings that made it undesirable for the patient to enter the trial. Additional exclusion criteria included porphyria, pregnancy or breast-feeding, or lack of informed consent.

Study entry

The initial patient evaluation included a history and physical examination, laboratory studies (complete blood count, biochemistry panel including liver function tests and tumour

markers) and chest x-ray. In women of child bearing age, a negative serum pregnancy test was required. If not already done within the previous 8 weeks, tumour staging was performed by CT or MRI/MRCP and diagnosis confirmed by endoscopic brush cytology or biopsy. If cytology or histology were negative at the first endoscopy, a repeat intervention (ERCP, CT- or ultrasound-guided percutaneous needle biopsy, or endoscopic ultrasound-guided fine needle aspiration) was performed. All patients received either endoscopic or percutaneous biliary drainage and insertion of endoprosthesis into the right and left intrahepatic biliary tree as necessary. The placement of endoprosthesis was defined as technically successful when the stent bridged the main stricture to the right and/or left hepatic ducts ensuring sufficient passage of contrast medium through the stent into the duodenum (endoscopic plastic endoprosthesis, 10 French diameter, Cotton-Huibregtse type, Cook Ireland Ltd, Limerick). In some cases where it was not possible to place 10F stents across tight biliary strictures or during bilateral stenting, 7F stents were used. Oral ciprofloxacin 500 mg twice daily was given before the ERCP and continued for at least 24 hours.

All eligible patients were registered with the Cancer Research UK & UCL Cancer Trials Centre. The inclusion and exclusion criteria were checked at the registration telephone call and once eligibility was confirmed, a unique trial number was allocated. All study data were recorded on the Case Report Forms supplied by the Trials Centre.

Photodynamic therapy

Once trial eligibility had been confirmed, patients received intravenous porfimer sodium (Photofrin®; Axcan Pharma Incorporated, Mont Saint-Hilaire, Canada) at a dose of 2 mg/kg bodyweight. At ERCP 48 hours later, the previously placed endoprostheses were removed, and endoluminal photoactivation performed through a clear 10F Huibregtse-Cotton endoscopic catheter introduced proximally above the stricture, which we had previously shown in phantom studies to result in less than 5% of light energy being dissipated. Alternatively, we used an opaque Soehendra dilator (Cook Ireland Ltd) to traverse tight strictures, after which the dilator was pulled back to leave the laser quartz fibre (Medlight SA, Ecublens, Switzerland; 400µm core diameter, 20-50 mm cylindrical diffuser tip with an x-ray marker on both ends of the diffuser) directly across the stricture.

Photoactivation was performed at 635 nm using a light from a diode laser (Diomed, Ltd. Cambridge, UK), using a linear diffuser exit dose of 186 J/cm, at linear irradiance of 300 mW/cm. During the procedure, all patients received oxygen via a nasal catheter and conscious i.v. sedation with midazolam and fentanyl or pethidine. The appropriate length fibre was chosen to span the stricture with an overlap of approximately 5 mm on either side. Where tumour length exceeded the maximal diffuser length, the first segment of tumour length was illuminated, then the fibre was repositioned under radiological control using the markers viewed on the x-ray screen to the next segment of the bile duct. In Bismuth IV strictures, a guide wire was inserted into the duct while treating one side before repeating treatment on the other side. Care was taken to avoid overlapping treatment fields, either by using different fibre lengths, or more commonly the opaque Soehendra catheter to reduce the effective fibre length on the second side treated to avoid having to use multiple fibres in the same patient. A new set of endoprosthesis was inserted after the completion of treatment.

Patients remained on the ward in subdued lighting after administration of the photosensitiser, followed by re-adaptation to indirect sunlight for increasing periods during the morning and late afternoon of each day. Bright indoor light was permitted after the initial 2-3 day period.

Assessment during and after treatment

The primary objective of this study was to evaluate the safety and efficacy of delivering porfimer sodium PDT to patients with locally advanced BTC. Secondary objectives were to evaluate the impact of PDT on serum bilirubin and the tumour markers carcinoembryonic antigen (CEA) and cancer antigen CA 19-9 (CA19-9), as well as tumour response rate and patient performance status, quality of life and overall survival. Clinical and laboratory assessments, including full blood count, urea and electrolytes, liver function tests, Karnofsky performance status, weight and clinical examination, were repeated at 7 and 28 days after light activation. Thereafter, all patients were followed up at 3-monthly intervals. Formal tumour response evaluation by serum tumour markers and abdominal CT or MRI/MRCP (using RECIST criteria) was performed at 28 days and again at 6 and 12 months following administration of porfimer sodium.

Endoprostheses exchange was performed at 6-monthly intervals or earlier if clinically indicated. In some patients with evidence of tumour progression at follow-up CT/MRI and/or worsening strictures with positive cytology at ERCP, a second PDT was performed at least 6 months after initial treatment. During the study period, patients could receive chemotherapeutic agents upon disease progression at the oncologist's discretion. As per RECIST criteria, any evidence of progression of assessable lesions, measurable lesions, or the development of new lesions, qualified as disease progression.

Assessment of adverse events and quality of life

Treatment-related toxicity was assessed at discharge and at each subsequent follow-up visit. All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0) and were reported to the Trial Centre for documentation.

The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) was used to evaluate the impact of PDT on patient's performance status. Patients completed the QLQ-C30 at study entry then at three-monthly intervals.

Statistical analysis

Descriptive statistics were expressed as means $\pm$ standard deviations or medians with ranges. Survival curves were based on Kaplan-Meier estimates. Group comparisons were made either by t-test (2-tailed) or Mann Whitney U-test as appropriate. Results were considered to be statistically significant if significance level reached <0.05 . Statistical analyses were performed using the statistical package SPSS version 14.0.

Ethical guidelines

The study was approved by the Northern and Yorkshire Main Research Ethics Committee and conducted in accordance with the recommendations for physicians involved in research on human subjects, as outlined in the Declaration of Helsinki (1964, revised 2000). Written informed consent was obtained from all patients participating in the trial. The study protocol was developed with the help of the UK National Cancer Research Institute Upper GI Studies Group and adopted into the UK Clinical Research Network Study Portfolio (www.ukcrn.org.uk, UKCRN ID 1218).

RESULTS

Patient characteristics

Over an 18 month period, 36 patients were recruited to the trial from three centres (University College Hospital and King's College Hospital, London, and Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK). There were 14 males and 22 females, with a median age of 65 (range 30-79) years. All patients had undergone multidisciplinary review and were considered to have unresectable disease (n=33) or be unfit for surgery. The clinicopathologic characteristics of the patients are shown in Table 1.

Treatment details

PDT was technically successful in all patients, with light delivery performed after a median drug light interval of 48 (range 41-72) hours. Eighteen patients (50%) underwent PDT to one site, while the remaining 18 patients received bilateral PDT followed by stent insertion. Patients were discharged a median of 6 (range 1-33) days after treatment.

Adverse events

In general, PDT was well tolerated in all 36 patients; there was no grade 4 toxicity and no treatment associated mortality. The most commonly reported early (less than 1 month) adverse event was mild (grades 1 & 2), transient abdominal pain post-ERCP in 17 patients, although none of the patients developed ERCP-induced pancreatitis. Biliary sepsis was reported in 5 patients — one grade 1, two grade 2 and three grade 3 (severe infection requiring intravenous antibiotics), and all recovered with conservative treatment. Four of the 36 patients (11%) reported mild photosensitivity reactions (painless erythema); all recovered fully with conservative management.

Serum bilirubin concentrations

The mean serum bilirubin levels before and after PDT are shown in Figure 1. Among the 35 patients with available data, bilirubin levels decreased in 19 patients (54%), remained stable in 14 patients (40%) and increased in 2 patients (6%) during the initial 3 months after PDT. In the 6 patients with a baseline serum bilirubin level of $>80 \mu\text{mol/L}$, the median bilirubin level fell from 143 (range 97-706) $\mu\text{mol/L}$ before PDT, to 111 (45-312) $\mu\text{mol/L}$ on day 7 and to 31 (23-49) $\mu\text{mol/L}$ on day 28. Overall, significant decreases in mean serum bilirubin concentrations were noted only at the 28-day and 3-month periods when compared with the baseline level ($p<0.05$). At subsequent time points, bilirubin levels fluctuated in most patients, with a $>50\%$ increment in serum bilirubin concentrations in 14 of the patients during follow-up, due either to stent occlusion or disease progression.

Serum tumour markers

Of the 21 patients with elevated serum CA19-9 concentrations at diagnosis, the levels decreased or remained stable in 14 (67%), with 11/14 patients having a $>50\%$ decline at some stage during follow-up, and 6/14 having subsequent rises in association with CT evidence of disease progression. In the other 7 patients, serum CA19-9 levels remained elevated throughout the follow-up period. There was no statistically significant difference in mean CA19-9 levels at any of the follow-up time points, in part because of the high variability of CA19-9 results (Figure 1b). Serum CEA levels were elevated at diagnosis in 10 patients, which decreased in 6 patients and increased in 4 during follow-up (data not shown).

Response to treatment

Of the 36 patients enrolled, 23 had assessable disease radiologically prior to therapy and follow-up imaging available for assessment of tumour response. Tumour load was assessed by experienced radiologists and compared with the baseline scans. Eleven patients (48%) had stable disease and one patient had a partial response (4%). The other 11 (48%) patients had progressive disease.

15 of the 36 patients (42%) were offered chemotherapy, usually upon evidence of disease progression, and received additional treatment with either gemcitabine in combination with cisplatin or gemcitabine alone as part of a randomised phase II trial (ABC-01) [12]. Five patients received repeat PDT at least 6 months after their initial treatment.

Performance status and quality of life

The median Karnofsky performance score at baseline was 80 (range 50-100), and remained unchanged at 7 and 28 days. EORTC QLQ-C30 quality of life scores were also stable throughout the follow-up period. The only parameter which changed significantly over time was an improvement in role functioning (50.8 ± 7.4 , at baseline vs. 64.4 ± 8.8 at 1 month, $p = 0.04$). There were marginal declines in global health and functional parameters, and slight increases in symptom and single item scores over time, but, none of them reached statistical significance.

Survival time and causes of death

34 patients had complete follow-up data and were suitable for the survival analysis. At five years follow-up, all but one patient had died. Most patients died due to tumour progression but 3 died due to uncontrolled biliary sepsis between 4 and 24 months after PDT. There were no early (< 30 days) deaths, but one patient died at 31 days after PDT due to disease progression, which was not considered to be treatment related. One patient survived more than 7 years after PDT for histologically proven locally advanced (stage 4A) cholangiocarcinoma. Three years after PDT, she had persistent hilar stricturing but no mass lesion or cytological evidence of malignancy and underwent orthotopic liver transplantation for intractable pruritis. The explant liver showed no evidence of cancer at the site treated with PDT, but had a solitary metastasis < 10 mm diameter on the surface of the liver. She remained well for 3 years after transplantation before developing biopsy proven metastatic disease.

(Figure 2). Chemotherapy had no demonstrable impact on overall patient survival, with median survivals of 13 months (95% CI 5.3 to 20.7) in PDT with chemotherapy and 12 months (95% CI 5.4 to 18.6) in PDT without chemotherapy ($p = 0.957$) (data not shown).

DISCUSSION

Biliary tract cancer is a lethal disease with limited treatment options. The cancers uncommonly metastasise to distant organs and most deaths are attributable to local tumour progression and sepsis secondary to biliary outflow obstruction. Insertion of plastic or metal endoprosthesis can alleviate biliary obstruction, at least temporarily, but stent occlusion with recurrent cholangitis is a frequent problem. Thus, maintenance of biliary drainage is a key factor in the palliation of patients with locally advanced BTC.

PDT is a relatively new concept in the treatment of BTC, with the first description of its use for this indication in 1991 [13]. In small (9-24 patients) phase II studies from Germany [7, 8, 14], Korea [15] and the USA [16], stenting plus porfimer sodium PDT resulted in an improvement in cholestasis, quality of life and survival compared with historical controls

treated with stenting alone. The 30-day mortality in the studies ranged from 0 to 4%, with median survival times of 10 [14] to 16.2 [16] months in the PDT groups. These results are consistent with those of a randomised controlled trial from Germany of porfimer sodium PDT + stenting versus stenting alone for unresectable cholangiocarcinoma [9]. The trial was discontinued early by the monitoring group due to the marked survival advantage of the PDT group, with a median survival of 493 days after PDT, compared with 98 days in the stent alone PDT group. The patients in this study were those in whom jaundice could not be relieved by stenting, so it remains unclear whether PDT may also improve the survival of the majority of patients whose cholestasis can be relieved, at least temporarily, by biliary stenting. In a randomised study of 32 patients with unresectable cholangiocarcinoma (histologically proven in 63%) using Photosan-3 (a haematoporphyrin derivative) [10], the median survival time after randomisation was 21 months for the PDT group compared with 7 months for the control group.

Similarly, in the present study, the low toxicity and median survival of 12 months after PDT is consistent with previous studies showing that PDT + stenting is a safe treatment modality which may confer significant palliation including preservation of quality of life. Witzigmann *et al* reported a comparable survival in patients with attempted curative surgery but positive (R1/R2) resection margins and those treated palliatively with PDT plus stenting [17] — similar findings to our own group [18]. Thus, a careful selection of patients for PDT may also avoid the morbidity and mortality associated with noncurative surgical resection.

In all the previous studies, adverse events related to PDT were minor (mainly cholangitis) and there was no early mortality. We also demonstrated a low adverse event profile, with no grade 4 toxicity and a significant improvement in serum bilirubin levels up to 3 months after PDT, associated with stable performance status and quality of life scores. Infectious complications occurred in 17%, despite the routine use of antibiotic prophylaxis and regular stent changes — a similar rate to the 6-56% incidence of cholangitis after ERCP plus PDT reported in other studies [19].

In conclusion, the results of this prospective non-randomised study indicate that PDT can be delivered safely to patients with locally advanced BTC. Following on from these encouraging results, a multi-centre phase III study was set up in the UK using the same treatment parameters as the current study [20]. The preliminary results indicate that patients with biliary tract cancer who received PDT plus stenting actually had a poorer overall survival than those who had stenting alone, which was only partly explained by fewer PDT plus stenting patients receiving subsequent palliative chemotherapy. Technical aspects of future studies will be to control for the effects of chemotherapy, to match the distribution of laser effects to the extent of diseased tissue being treated, and ideally to extend the treated area beyond the tumour margins identified on pretreatment scans while ensuring that treated areas heal safely without unacceptable effects on structure or function. This requires optimal imaging to establish the extent of disease and to ensure that appropriate light doses are delivered to all relevant sites. Much current research is focusing on ways to improve the extent of tumour necrosis by monitoring PDT in real time during light delivery. Other approaches include better delivery of photosensitisers to tumour tissue, the development of new photosensitisers with enhanced tumour specificity, and optimisation of drug-light intervals.

Acknowledgments

This study was supported in part by an unrestricted educational grant from Axcan Pharma. SP is a recipient of NIH grant P01 P01CA84203. The work was undertaken in part at UCLH/UCL which receives a proportion of funding from the Department of Health's National Institute for Health Research (NIHR) Biomedical Research Centres funding scheme.

We thank the patients and their families; Steve Bown and Sandy Mosse from the National Medical Laser Unit, and Jonathan Ledermann from the CRUK & UCL Cancer Trials Centre, for their help with the trial.

Abbreviations used in this paper

BTC	biliary tract carcinoma
CT	computerised tomography
ERCP	endoscopic retrograde cholangiopancreatography
MRI/MRCP	magnetic resonance imaging / cholangiopancreatography
PDT	photodynamic therapy

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Figure 1. Serum concentrations of: (a) bilirubin and (b) CA 19-9 before and for up to three months after photodynamic therapy.

Figure 2.
Kaplan–Meier estimate of survival function after PDT plus stenting.

Table 1

Patient characteristics and tumour location

Age (years) *	64.5 ± 11.8
Gender (male:female)	14:22
Serum bilirubin (μmol/L) *	71.2 ± 130.5
CA19-9 (IU/L) *	2124.5 ± 6493.8
CEA (ng/ml) *	21.4 ± 65.9
Median Karnofsky score (range)	80 (50 – 100)
Distant metastasis	
Yes	2
No	32
Unknown	2
Bismuth classification	
1	1
2	2
3	12
4	17
Unknown	2
Gallbladder cancer	2

* Values are mean ± SD