REVIEW

Photodynamic Therapy for Cholangiocarcinoma

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Cholangiocarcinoma is the primary malignancy arising from the biliary epithelium, and it presents as jaundice, cholestasis, and cholangitis. Over 50 percent of patients present with advanced-stage disease, and the prognosis is poor with the survival measured in months even after biliary decompression. Palliative management has become the standard of care for unresectable disease, and this involves an endoscopic approach. Photodynamic therapy (PDT) involves the administration of a photosensitizer followed by local irradiation with laser therapy. The use of PDT for palliation of bile-duct tumors has produced promising results. Several studies conducted in Europe and the United States have shown that PDT produces a marked improvement in the symptoms of cholestasis, survival, and quality of life. This chapter summarizes the principle of PDT, the technique employed, and the published experience regarding PDT for cholangiocarcinoma. (**Gut Liver 2010;4(Suppl. 1):S62-66**)

Key Words: Cholangiocarcinoma; Photodynamic therapy; Biliary cancer

INTRODUCTION

Cholangiocarcinoma is a malignancy that arises from the epithelial cells of the biliary tree. It can affect the intrahepatic and extrahepatic bile ducts and is associated with significant morbidity and mortality.¹ Tumor formation appears to be the result of an underlying chronic inflammatory state of the biliary tract. There are multiple possible predisposing conditions, which include primary sclerosing cholangitis, intrahepatic stones and choledocholithiasis, choledochal cysts, liver flukes, and prior exposure to thorium dioxide.²⁻⁹

The average 5-year survival rate of patients with cholangiocarcinoma is 5-10%.¹⁰ The incidence of cholangiocarcinoma is increasing¹¹ and is currently thought to be one to two cases per 100,000 patients in the United States, with the majority of patients being predominantly male and older than 65 years of age.¹⁰ The only hope for cure is surgical resection. Even after curative resection, the 5-year survival rate is only 30-40%.¹²⁻¹⁴ Unfortunately, greater than 80% of patients present at an unresectable stage,¹¹ with a median survival time of 3-6 months from the time of diagnosis.¹⁵ These patients require palliative management.

Surgical decompression of the biliary tract involves a hepatico-jejunostomy, which has a 30 day post-operative mortality rate between 7% and 24%.¹⁶⁻¹⁹ Recovery time is a limiting factor in quality of life improvement in a majority of patients who undergo surgery.²⁰⁻²² Presently, biliary decompression is most frequently accomplished through endoscopic biliary stent placement. This has been shown to relieve obstructive jaundice, but has not been shown to improve survival.¹¹ The addition of chemotherapy to biliary decompression has been largely unsuccessful.²³ Various chemotherapeutic agents have been studied with overall minimal improvement in survival.²⁴⁻²⁶ The survival benefit of palliative radiation therapy is considered controversial.¹⁰ It has been associated with an increased incidence of cholangitis, gastroduodenitis, and longer hospitalizations.²⁷⁻²⁹ Concurrent chemotherapy with radiation therapy, including helical tomotherapy intensity modulated radiotherapy and capecitabine, in conjunction with photodynamic therapy (PDT) has been shown to be well tolerated in patients with hilar cholangiocarcinoma.^{30,31} Wiedmann *et al.*³² published their results using PDT as a neoadjuvant treatment for hilar cholangio-

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carcinoma. Seven patients were treated and underwent surgery after a median period of 6 weeks (range, 3-44 weeks). In all patients tumor free resection margins were achieved with a 1-year recurrence free survival rate of 83%. Neoadjuvant PDT did not increase the rate of surgical complications and was well tolerated. Additionally, proximal obstruction of the bile ducts by malignant tissue can prevent successful endoscopic stenting. Photodynamic therapy has recently been introduced to circumvent this problem.¹¹

PRINCIPLE OF PHOTODYNAMIC THERAPY

This therapy includes the use of, a photosensitizing agent administered before the photoradiation process can occur.³³ Photofrin (porfimer sodium; Axcan Pharma Inc., Mont-Saint Hilaire, Canada) has a selective nature and is preferentially retained by neoplastic tissue.³³ At a specific wavelength of light, laser application begins the activation process by transforming the drug from its neutral ground state into its excited state. In the presence of oxygen, cytotoxic radical species are formed, which destroy dysplastic cells by directly inducing apoptosis and tumor necrosis. Local vascular channels are also affected.^{34,35} PDT was demonstrated to reduce xenografted human cholangiocarcinoma tumor volume by 60% in a mouse model.³⁶ PDT has been shown to have a significant survival benefit in patients with unresectable cholangiocarcinoma as well as a significant improvement in the quality of life after PDT and stenting.^{37,38}

Though other photosensitizers are now available, porfimer sodium is the most studied and the only photosensitizer approved by the FDA.

STAGING AND TISSUE DIAGNOSIS

All patients must have clinical and radiological features of cholangiocarcinoma. Staging can be performed by computed tomography (CT) or magnetic resonance imaging (MRI). Staging can be performed with CT and/or MRI.³⁷ Resectability is usually defined according to the criteria of Vauthey and Blumgart.³⁹

Bismuth classification should be documented for all patients.¹ In our experience and others,^{37,40} definitive pathological diagnosis of cholangiocarcinoma is established in approximately 60% of cases.^{37,40}

TECHNIQUE

Each patient undergoes a detailed educational process on PDT after which informed consent is obtained. Pa-

tients treated with PDT receive Porfimer sodium (Photofrin; Axcan Pharma Inc.) at a dosage of 2 mg/kg body weight intravenously 48 hours before laser activation.

Endoscopic retrograde cholangiography (ERC) is performed using a large channel duodenoscope (TJF-140, TJF-160, and TJF-160VF; Olympus America, Center Valley, PA, USA). After cannulation into the biliary tract, a cholangiogram is performed to help define the anatomic distribution of malignant tissue and the extent of disease within the biliary ducts. Careful opacification of the dilated segments is performed selectively. Next, selective bougie and balloon dilation of the stricture(s) to be treated is performed to facilitate diffuser placement within the malignant stricture.

Photodynamic therapy is delivered through a 3.0-m length fiber with a 2.5-cm-long cylindrical diffuser at its distal end (Pioneer Optics, Windsor Locks, CT, USA). The diffuser can be inserted into a 10 F sheath of a plastic stent delivery system and placed at the level of the stricture being treated.³⁷ Alternatively, our group has been using the single operator cholangioscopy (SOC) as a platform to administer PDT (Spyglass; Boston Scientific, Natick, MA, USA).⁴⁰

A diode laser system (InGaAlP Laser Diode; Diomed Inc., Andover, MA, USA) with a maximum power output of 2,000 mW and a wavelength of 633±3 nm is used as a light source.

Photoactivation is performed at 630 nm with a light dose of 180 J/cm², fluence of 0.250 W/cm² and irradiation time of 750 seconds. Multiple segments can be treated at the discretion of the endoscopist. When tumor length exceeds the maximal diffuser length, overlap of treated areas should be avoided by a stepwise pull-back of the fiber under fluoroscopic guidance. Placement of endoprotheses is performed systematically after the photodynamic treatment to prevent cholangitis.³⁷

PDT is typically repeated at 3-month intervals at which time all stents should be replaced; stents are exchanged earlier in the case of premature occlusion or migration to maintain optimal decompression. All patients should receive peri-operative antibiotic prophylaxis. Post-operatively, patients treated with PDT are advised to remain out of direct sunlight since Porfimer sodium may cause prolonged photosensitivity lasting 30-90 days.⁴¹

REVIEW OF THE LITERATURE

There have been several uncontrolled reports that suggest that PDT can provide for a survival benefit (Table 1). In 2003, Ortner *et al.*³³ conducted the first randomized controlled trial comparing survival between biliary stent-

Table 1. Table Comparing Studies Performed by Using ERCP with PDT with Photofrin Sodium for Palliation of Cholangiocarcinoma

Study	Year	No. of patients	Study type	Median TB before and after PDT	Mean PDT sessions (range)	Median survival, mo	Adverse events phototoxicity, cholangitis
Ortner <i>et al.</i> ⁴¹	1998	9	Single arm	18.6>6	1.5 (1-2)	14.6	1 (11%), 0 (0%)
Berr <i>et al.</i> ³⁶	2000	23	Single arm	11.2>1.1	3 (1-5)	11.1	3 (13%), 8 (35%)
Rumalla <i>et al.</i> ⁴⁸	2001	6	Single arm	2.7>1.3	2.3 (1-2)	>6	2 (33%), 2 (33%)
Dumoulin <i>et al.</i> ⁴⁹	2003	24	Single arm	13.3>2.6	1-2	9.9	2 (8%), 5 (21%)
Ortner <i>et al.</i> ³³	2003	20	Randomized	NA (decreased)	2.4 (1-5)	16.4	2 (10%), 5 (25%)
Ortner <i>et al.</i> ³³	2003	31	Nonrandomized	11.8>3.1	1.5 (1-4)	14.2	3 (10%), 6 (19%)
Harewood <i>et al.</i> ⁵⁰	2005	8	Single arm	7.7>1.1	2 (1-5)	9.2	2 (25%), 2 (25%)
Witzigmann <i>et al.</i> ⁵¹	2006	68	Single arm	NA (decreased)	2 (1-6)	12	8 (12%), 38 (56%)
Prasad <i>et al.</i> ⁴⁴	2007	25	Single arm	6.1>3.5	1.6 (1-4)	13.4	1 (4%), 2 (8%)
Kahaleh <i>et al.</i> ³⁷	2008	19	Comparative	6.3>3.5	1.6 (1-3)	16.2	3 (16%), 7 (37%)

ERCP, endoscopic retrograde cholangiopancreatography; PDT, photodynamic therapy; TB, total bilirubin; NA, not available.

ing alone vs biliary decompression combined with photodynamic therapy. After enrolling 39 patients in the study, a median survival of 493 days (n=20) was noticed in the group treated with PDT and stenting vs. a median survival of 98 days (n=19) in the stent-alone group ($p < 0.0001$). The trial was terminated prematurely as continued data collection and randomization was thought to be ethically unacceptable. This study was criticized since only patients failing conventional ERC were enrolled in the study, making a repeat ERC indispensable which might account for the benefit attributed to PDT. Another randomized study by Zoepf *et al.*³⁸ showed similar improvement of survival time in the PDT group (21 vs 7 months). Three recent reviews that analyzed the contribution of photodynamic therapy to the treatment of cholangiocarcinoma all confirmed these data.^{11,42,43}

In 2007, Prasad *et al.*⁴⁴ found that patients with unresectable cholangiocarcinoma without a visible mass benefited from early treatment with PDT. They described a technique for photodynamic therapy using percutaneous biliary access. Patients that failed biliary cannulation or those with pre-existing biliary drains were successfully treated using this method. The percutaneous biliary drain was replaced with an 8 F vascular sheath over a guide-wire. PDT was administered by fluoroscopically guided placement of the cylindrical diffusing fiber. After the treatment was completed, a standard 10 Fr biliary drain was placed to facilitate biliary drainage.

In 2008, our group compared stenting alone vs combination therapy of stenting and photodynamic therapy.³⁷ Kaplan-Meier analysis demonstrated improved survival in the PDT group compared with the stent-alone group (16.2 vs 7.4 months, $p < 0.004$). Mortality in the PDT group at 3, 6, and 12 months was 0%, 16%, and 56%, respectively. The corresponding mortality in the stent

group was 28%, 52%, and 82%, respectively. The difference between the two groups was statistically significant at 3 and 6 months, but not at 12 months. Although it was not entirely clear whether the benefit was directly related to PDT or the number of endoscopic retrograde cholangiopancreatography (ERCP) sessions, this study helped to strengthen the findings published by Ortner *et al.* in 2003.³³ Importantly, adverse effects in the PDT group were minor, largely related to self-limiting phototoxicity.

FUTURE DIRECTION

Successful PDT under cholangioscopic guidance has been previously reported by Ortner *et al.*^{33,41} Although past efforts at cholangioscopy were generally time consuming and technically demanding, the development of SOC has allowed the procedure to become more feasible. SOC is a platform initially designed to enhance diagnostic accuracy during ERCP by allowing guided biopsy.^{45,46}

Recently, our group compared patients who underwent PDT alone with patients who underwent PDT using SOC.⁴⁰ A total of forty-five patients (24 male, aged 67.3 ± 10.6 years) were treated with PDT during a five-year period. Thirty-two patients were treated with PDT alone, and 13 patients were treated with PDT using SOC. The two groups did not differ significantly in regards to age, gender, serum bilirubin, or MELD score. No significant difference existed between the two groups regarding the number of ERCP sessions ($p=0.71$), the number of PDT sessions ($p=0.36$) or the PDT procedure time ($p=0.76$). The median fluoroscopy time was 21.1 minutes in the PDT only group and 11.1 minutes in the PDT using SOC group ($p < 0.0001$). Median survival for the PDT only group was 200 days, and median survival for the

PDT using SOC group was 386 days ($p=0.45$). There was no significant difference in total adverse affects between the groups ($p=1.0$). SOC permits targeted therapy during PDT and can be successfully performed without adverse events while simultaneously reducing exposure to radiation.

In the near future novel therapeutic approaches such as targeted molecular therapies may be used in conjunction with PDT to improve outcomes. Finally, alternative photosensitizers are needed that provided deeper tumoricidal tissue penetration, shorter duration of phototoxicity, and more rapid onset.⁴⁷

CONCLUSION

In summary, the majority of patients with cholangiocarcinoma present with advanced, unresectable disease and treatment options are generally limited to palliation. Photodynamic therapy in conjunction with stenting has shown very promising outcomes; Further multicenter, randomized, prospective controlled trials are needed to confirm the benefit of PDT and stenting compared to stenting alone, to confirm the role of SOC in PDT, and to identify the optimal treatment regimen in these patients in order to improve survival and quality of life.

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