

Photodynamic therapy: Palliation and endoscopic technique in cholangiocarcinoma

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Abstract

Cholangiocarcinoma is the primary malignancy arising from the biliary epithelium. The disease is marked by jaundice, cholestasis, and cholangitis. Over 50 percent of patients present with advanced stage disease, precluding curative surgical resection as an option of treatment. Prognosis is poor, and survival has been limited even after biliary decompression. Palliative management has become the standard of care for unresectable disease and has evolved to include an endoscopic approach. Photodynamic therapy (PDT) consists of administration of a photosensitizer followed by local irradiation with laser therapy. Several studies conducted in Europe and the United States have shown a marked improvement in the symptoms of cholestasis, survival, and quality of life. This article summarizes the published experience regarding PDT for cholangiocarcinoma and the steps required to administer this therapy safely.

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Key words: Cholangiocarcinoma; Cholestasis; Jaundice; Neoplasia; Palliation; Photodynamic therapy; Photofrin

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INTRODUCTION

Cholangiocarcinoma is the primary neoplasia originating from the biliary system. The incidence rate is 1-2 per 100000 people per year in the United States^[1,2]. Initially thought to be an uncommon disease, the number of cases reported annually has been climbing^[2-4]. Nearly two-thirds of cases of cholangiocarcinoma occur in patients between the ages of 50 and 70, and the tumor appears to have a male predominance^[2,5]. Predisposing conditions include disorders such as primary sclerosing cholangitis, intrahepatic stones and choledocholithiasis, choledochal cysts, liver flukes, and previous exposure to the contrast agent thorium dioxide (Thorotrast)^[6-16].

Complete surgical resection is the only treatment with potential for a cure. Unfortunately, more than 50% of patients present with unresectable disease at the time of diagnosis^[17-19]. The prognosis at this stage is dismal, being approximately 3 mo without intervention, and 4-6 mo after palliative biliary decompression^[20-25]. Even after curative (RO) resection the 5-year survival rate is only 30%-40%^[26-28]. Successful palliation of biliary obstruction remains the main goal for reducing morbidity and mortality in these patients^[21,29].

PALLIATION OF CHOLANGIOCARCINOMA

The approach to biliary decompression has evolved from a surgical approach, to percutaneous drainage, and finally to endoscopic management. Hepaticojejunostomy is associated with a 30-d postoperative mortality rate of

between 7% and 24%^[30-34]. Furthermore, quality of life was only improved in a minority of patients undergoing surgery because of the time needed to recover^[24,35,36]. Biliary stenting only provides temporary relief^[37-42]. Adding chemotherapeutic agents has been largely unsuccessful; moreover, no standard chemotherapeutic regimen currently exists^[43]. Various chemotherapeutic agents have been studied, with limited improvement in survival rates^[44-46]. Radiotherapy is an area of great controversy regarding its efficacy in cholangiocarcinoma, and is associated with an increased incidence of cholangitis, gastro-duodenitis, and longer hospitalization^[47-49]. However, concurrent chemoradiotherapy with helical tomotherapy intensity modulated radiotherapy and capecitabine, in conjunction with photodynamic therapy, has been shown to be well tolerated in patients with hilar cholangiocarcinoma^[50,51].

PRINCIPLE OF PHOTODYNAMIC THERAPY

PDT is a two step process. during which a photosensitizer is initially administered, followed by photoradiation^[52]. Photofrin (porfimer sodium, Axcan Pharma Inc., Mont-Saint Hilaire, Canada) remains the most commonly used drug in this setting, since it has a selective nature and is preferentially retained by neoplastic tissue^[53]. Laser application at a specific wavelength starts the activation process by transforming the drug from its neutral ground state, into its activated state. In the presence of oxygen, cytotoxic singlet oxygen species are formed, destroying the dysplastic cells to which they are bound. These free radicals induce apoptosis and tumor necrosis to a depth of 4 mm to 6 mm^[54,55]. Synergistically, nearby vascular channels are also affected, indirectly accelerating the process by cutting off the supply of vital nutrients.

PDT has been shown to reduce xenografted human cholangiocarcinoma tumor volume by 60% in a mouse model^[56]. Recent reports and randomized controlled studies in which PDT was used as an adjuvant therapy, have shown a significant survival benefit in patients with unresectable cholangiocarcinoma, as well as a significant improvement in the quality of life after PDT and stenting^[57,58].

TECHNIQUES

The technique used to execute the procedure has become standardized. PDT has typically been offered to patients with nonresectable cholangiocarcinoma, or as a neoadjuvant therapy. Staging can be performed with computed tomography and/or magnetic resonance imaging^[58]. Resectability is usually defined according to the criteria of Vauthey and Blumgart^[59].

Each patient found to be a candidate for PDT undergoes a thorough educational process. Indeed, specific education regarding sun exposure and protection is necessary in order to avoid severe sun-related phototoxicity, and should be provided to all patients prior to the procedure^[58].

Endoscopic retrograde cholangiography (ERC) is performed using therapeutic duodenoscope (TJF-140, TJF-160, and TJF-160VF; Olympus America, Center Valley, PA). 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 realized selectively. Bougie and balloon dilation of the stricture(s) to be treated is performed, to facilitate diffuser placement within the malignant stricture.

After placement of the diffuser probe within the stricture to be treated, 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 s. One or more segments can be treated at the discretion of the endoscopist. When tumor length exceeds the maximal diffuser length, step-wise pull-back of the fiber under fluoroscopic guidance can be done. Placement of an endoprosthesis is performed systematically after the photodynamic treatment to prevent cholangitis. Our group has recently demonstrated the safety and efficacy of choledochoscopy-guided PDT, allowing specific intraductal visualization of the stricture(s) to be treated^[59].

For patients failing conventional ERC, a technique for photodynamic therapy using percutaneous biliary access can be used, in which a percutaneous drain is replaced with an 8French vascular sheath over a guidewire^[60]. PDT is typically repeated at 3-mo intervals at which time all stents should be replaced. Stents are exchanged earlier in the case of premature occlusion or migration, to maintain optimal biliary drainage. All patients should receive peri-operative antibiotic prophylaxis. Post-therapy, patients treated with PDT are advised to remain out of direct sunlight, since Porfimer sodium may cause prolonged photosensitivity lasting 30-90 d^[61].

ACCESSORIES

Though other photosensitizers are now available, porfimer sodium is the most studied, and the only photosensitizer approved by the FDA. It is administered intravenously at a dose of 2 mg/kg body weight 48 h prior to illumination. A diode laser system (InGaAlP Laser Diode; Diomed Inc., Andover, MA) with a maximum power output of 2000 mW and a wavelength of 630 nm is used as a light source, delivered through a 3.0-m length fiber having a 2.5-cm-long cylindrical diffuser at its distal end (Pioneer Optics, Windsor Locks, CT). The diffuser can be inserted into a 10 F sheath of a plastic stent delivery system (MAJ-1419; Olympus America) and placed at the level of the stricture being treated. Alternatively, our group has been using the single operator choledochoscope (Spyglass, Boston Scientific, Natick, MA) as a platform to administer PDT^[59].

RESULTS AND OUTCOMES

There have been several reports suggesting that PDT provides a survival benefit (Table 1)^[52,58,61-66]. In 2003, Ort-

Table 1 Table comparing studies performed by using endoscopic retrograde cholangiopancreatography with photodynamic therapy with photofrin sodium for palliation of cholangiocarcinoma

Study	Year	N	Study type	Median TB before and after PDT	Mean PDT sessions (range)	Median survival (mo)	Adverse events phototoxicity, cholangitis n (%)
Ortner <i>et al</i> ^[62]	1998	9	Single Arm	18.6 > 6	1.5 (1-2)	14.6	1 (11), 0 (0)
Berr <i>et al</i> ^[62]	2000	23	Single Arm	11.2 > 1.1	3.0 (1-5)	11.1	3 (13), 8 (35)
Rumalia <i>et al</i> ^[63]	2001	6	Single Arm	2.7 > 1.3	2.3 (1-2)	> 6	2 (33), 2 (33)
Dumoulin <i>et al</i> ^[64]	2003	24	Single Arm	13.3 > 2.6	1-2	9.9	2 (8), 5 (21)
Ortner <i>et al</i> ^[52]	2003	20	Randomized	NA (decreased)	2.4 (1-5)	16.4	2 (10), 5 (25)
Ortner <i>et al</i> ^[52]	2003	31	Nonrandomized	11.8 > 3.1	1.5 (1-4)	14.2	3 (10), 6 (19)
Harewood <i>et al</i> ^[65]	2005	8	Single Arm	7.7 > 1.1	2.0 (1-5)	9.2	2 (25), 2 (25)
Witzigmann <i>et al</i> ^[66]	2006	68	Single Arm	NA (decreased)	2.0 (1-6)	12.0	8 (12), 38 (56)
Prasad <i>et al</i> ^[61]	2007	25	Single Arm	6.1 > 3.5	1.6 (1-4)	13.4	1 (4), 2 (8)
Kahaleh <i>et al</i> ^[58]	2008	19	Comparative	6.3 > 3.5	1.6 (1-3)	16.2	3 (16), 7 (37)

TB: total bilirubin; NA: not available; PDT: photodynamic therapy.

ner *et al*^[52] conducted the first randomized controlled trial comparing survival rates in patients treated with biliary stenting alone with those treated with biliary decompression combined with photodynamic therapy. After 39 patients were enrolled in the study, improvement in survival and quality of life in the randomized PDT group was found to be so impressive [i.e. 493 d ($n = 20$) *vs* a median survival of 98 d ($n = 19$), $P < 0.0001$] that the trial was terminated prematurely. However, only patients failing conventional ERC were enrolled in that trial, making a repeat ERC indispensable, which might account for the benefit attributed to PDT.

In 2007, the Mayo team demonstrated that patients with unresectable cholangiocarcinoma without a visible mass benefited from early treatment with PDT^[61]. In 2008, our group published findings comparing stenting alone with a combination therapy of stenting and photodynamic therapy^[58]. Kaplan-Meier analysis demonstrated improved survival in the PDT group compared with the stent-alone group (16.2 *vs* 7.4 mo, $P < 0.004$). Mortality in the PDT group at 3, 6, and 12 mo 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 mo, but not at 12 mo. Although it was not entirely clear whether the benefit was directly related to PDT or the number of endoscopic retrograde cholangiopancreatography sessions, this study helped to strengthen the findings published by Ortner *et al*^[52] in 2003. Furthermore, adverse effects in the PDT group were minor, and largely related to mild phototoxicity managed conservatively. Other complications included cholangitis, hemobilia, cholecystitis, pancreatitis, duodenal perforation, hepatic abscess and myocardial infarction, and were a result of the endoscopic procedure and found in both groups treated^[57].

Recently, Wiedmann *et al*^[67] published their results using PDT as a neoadjuvant treatment for hilar cholangiocarcinoma. Seven patients were treated and underwent surgery after a median period of 6 wk (range, 3-44 wk). In all patients, tumor free resection margins were achieved with a 1-year recurrence free survival rate of 83%. Neoa-

djuvant PDT did not increase the rate of surgical complications and was well tolerated.

If PDT has become a standard of care in Europe, novel therapeutic approaches are still needed, such as a targeted molecular approach that may be used in conjunction to improve outcomes. For this therapy to become a more viable option alternative, photosensitizers are needed that provide deeper tumoricidal tissue penetration, shorter duration of phototoxicity, and more rapid onset^[68].

CONCLUSION

In summary, the majority of patients with cholangiocarcinoma present with advanced, unresectable disease and treatment options remain limited. 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, and to identify the optimal treatment regimen in these patients in order to improve their survival and quality of life.

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