Photodynamic Therapy: An Emerging Treatment for GI Neoplasia

by S. Patel, B. Katanyutanon and J. Levey

Photodynamic therapy (PDT) is an emerging endoscopic technique used to treat a variety of gastrointestinal neoplasms. PDT is a safe and effective way to ablate neoplastic tissue within the gastrointestinal tract and elsewhere in the body using a photosensitizing agent and exposure to laser light. The following is a review of PDT including basic concepts, its use in Barrett’s esophagus, esophageal cancer, and cholangiocarcinoma.

INTRODUCTION

Photodynamic therapy (PDT) is an emerging therapy for the localized treatment of cancers. Its potential use was first suspected nearly 100 years ago when visible light was noted to have a lethal effect on paramecia treated with acridine dye (1). More recently, PDT’s use has been extended to the treatment of cancers of the esophagus, stomach, colon, bronchus, bladder, brain, and biliary tree (2–8). Experience and expertise with PDT is rapidly growing. Currently, it is FDA approved for the treatment of Barrett’s esophagus with high-grade dysplasia and superficial cancer as well as for the palliation of dysphagia in patients with advanced esophageal cancer. The place of PDT within the therapeutic armamentarium is rapidly evolving. It is clear that PDT affords an alternative treatment option for patients with various cancers who are not suitable candidates for other therapies. This article will review the current knowledge of PDT as a treatment modality.

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BASICS

PDT utilizes a two-step process to achieve localized tissue destruction. The essential components of PDT include a tumor-localizing photosensitizing agent, laser light activation, and the presence of oxygen gas.

Photosensitizer

The first step in PDT is the administration of a photosensitizing agent. The photosensitizer is inert in its native state and can be administered orally, intravenously, or topically. Although taken up by all tissues in the body, most available photosensitizers have a 2–4 fold higher affinity for tumor cells than normal cells and therefore achieve higher tissue concentrations within neoplastic tissue. This selectivity is thought to be due to multiple factors including variations in cellular uptake and metabolism between neoplastic and normal cells, differences in proliferation rates, and a more permeable vasculature within neoplastic tissues. This selective uptake is subsequently exploited in the activation step of PDT.

At present, the majority of photosensitizers available for use in clinical practice are derivatives of porphyrin compounds. The two most frequently used pho- (continued on page 51)
tosensitizers are sodium porfimer and 5-aminolevulinic acid (5-ALA). Although these compounds disperse to all tissues of the body upon administration, it has been shown that normal tissues tend to retain the porphyrin compounds for only several hours. On the other hand, neoplastic tissues maintain measurable drug concentrations for up to several days after administration.

Sodium porfimer (Photofrin®) is the most commonly used photosensitizer in the U.S. and the only one approved by the FDA. It is administered as an intravenous infusion over 3–5 minutes approximately 48 hours prior to laser application. Sodium porfimer tends to accumulate in the submucosal layers of various tissues, including the skin where it can remain for up to thirty days and lead to photosensitivity reactions. On the other hand, 5-ALA is a prodrug that must first be converted via the heme synthetic pathway to protoporphyrin IX which then serves as the active photosensitizer. 5-ALA is administered orally or topically 4–6 hours before laser activation and accumulates predominantly in the mucosa. It tends to have a significantly shorter period of potential photosensitivity (1–2 days). Because sodium porfimer accumulates to a greater degree in the deeper layers of the neoplastic tissue as compared to 5-ALA, the subsequent depth of treatment is correspondingly greater with its use. This finding has clinical implications that will be discussed.

Laser Light Activation

Approximately 48 hours (4–6 hours with 5-ALA) after photosensitizer administration, laser light is applied leading to a photochemical reaction. Both sodium porfimer and protoporphyrin IX (derived from 5-ALA) can be activated with visible red light at 630–635 nm. An optical fiber is passed through the accessory channel of a video endoscope to deliver the activating light. Upon laser application, the initially non-toxic photosensitizer is activated to become cytotoxic which then leads to subsequent local tissue destruction. With the ability to target light delivery to certain areas and therefore confine activation, a second level of selectivity in treatment is possible.

Oxygen Free Radicals

The mechanism of cytotoxicity (or phototoxicity) is primarily mediated by the generation of singlet oxygen and oxygen-derived free radicals (9–11). The process begins with the absorption of light energy by the photosensitizer followed by the transference of this energy to molecular oxygen. The latter step results in the production of the high-energy oxygen species that can interact with the tissue to induce necrosis. Damage to the tissues is thought to result from direct singlet oxygen-induced injury to the cellular machinery such as mitochondria, mitochondrial enzymes, lysosomes, and cell membrane as well as to the surrounding vasculature (9,12,13). Ultimately, this injury leads to cellular apoptosis and vascular ischemia (14–17). Because of the integral role that oxygen and its derivatives play in PDT, tissues with higher blood flow are considered better targets for treatment and the desired tissue destruction.

TREATMENT

Although use of PDT in the local treatment of several cancers has been investigated, it has been most extensively studied in the setting of esophageal dysplasia and cancer.

Newer data has also shown that PDT can be beneficial in patients with non-resectable cholangiocarcinoma. Lastly, PDT has received attention for its potential applications in the treatment of non-small cell lung cancer.

Barrett’s and Esophageal Disease

Barrett’s esophagus (BE) is a condition in which the normal, stratified squamous epithelium of the distal esophagus is replaced by abnormal, intestinal-type epithelium called specialized intestinal metaplasia. This condition develops in the setting of chronic gastroesophageal reflux disease and is considered an important premalignant precursor to esophageal adenocarcinoma. In fact, the relative risk of developing esophageal adenocarcinoma in patients with BE appears to be 30–125 times that of the general population. Over the past three decades, there has been a dramatic 5%–10% rise in the incidence of adenocarcinoma of the distal esophagus with the majority of cases arising from BE (18). It is postulated that the development of cancer progresses through a series of molecular events in the unstable metaplastic epithelium leading to progressive dysplasia and ultimately carcinoma.
The understanding of the malignant potential associated with BE has led to periodic endoscopic surveillance with random biopsies for dysplasia. In theory, this approach allows gastroenterologists the opportunity to detect dysplastic changes prior to the development of advanced malignancy. Once high-grade dysplasia (HGD) is found, the current recommendation is that patients should undergo an esophagectomy. Proponents of this strategy argue that such patients with HGD have a 30% likelihood of having concurrent, undiagnosed invasive carcinoma that may have been missed due to biopsy sampling error (19). Unfortunately, esophagectomy is associated with significant morbidity (20%–47%) and mortality (average 4%) even at experienced centers (18). A further complicating matter is that many patients are unsuitable surgical candidates based on significant comorbidities.

Clearly, there is a need for the development of minimally invasive treatment modalities for HGD or superficial cancer within BE. In the past several years, several endoscopic ablative modalities have been explored including thermal, mechanical, and photodynamic (20–24). PDT has shown particular promise in this area (Table 1). Multiple case series evaluating PDT use have shown significant regression in the length of BE including complete BE eradication in select patients (25–31). In addition, these studies have

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Photosensitizer</th>
<th>Pts w/ residual dysplasia and/or CA (%)</th>
<th>Complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barr (25)</td>
<td>5 (HGD)</td>
<td>5-ALA</td>
<td>40</td>
<td>None</td>
</tr>
<tr>
<td>Gossner (28)</td>
<td>32 (10 HGD, 22 CA)</td>
<td>5-ALA</td>
<td>NR</td>
<td>Nausea-47, Mild ALT/AST elevation-65</td>
</tr>
<tr>
<td>Overholt (26)</td>
<td>100 (14 LGD, 73 HGD, 13 CA)</td>
<td>Porfimer</td>
<td>50 LGD, 57 HGD, 70 CA</td>
<td>Chest pain-NR, Strictures-34, Atrial fibrillation-3, Pleural effusions-NR, Phototoxicity-4</td>
</tr>
<tr>
<td>Ackroyd (30)</td>
<td>18 (LGD)</td>
<td>5-ALA</td>
<td>100</td>
<td>Chest pain-100, Phototoxicity-6</td>
</tr>
<tr>
<td>Wolfsen (31)</td>
<td>48 (34 HGD, 14 CA)</td>
<td>Porfimer</td>
<td>44*</td>
<td>Stricture-23, Phototoxicity-15, Atrial fibrillation-2, Congestive heart failure-2, Esophageal perforation-2</td>
</tr>
<tr>
<td>Overholt (27)</td>
<td>103 (14 LGD, 80 HGD, 9 CA)</td>
<td>Porfimer</td>
<td>29 LGD, 46 HGD, 66 CA</td>
<td>Strictures-30</td>
</tr>
<tr>
<td>Overholt (29)</td>
<td>138 (HGD)</td>
<td>Porfimer</td>
<td>NR</td>
<td>Strictures-37</td>
</tr>
</tbody>
</table>

LGD, low grade dysplasia; HGD, high-grade dysplasia; CA, cancer; NR, not reported; *not further specified.
shed light on PDT’s ability to eliminate dysplasia and superficial cancer (25–31). Numerous studies have also confirmed that the use of PDT in conjunction with acid suppressive therapy can result in the regrowth of squamous epithelium in the esophagus (25–28,30).

Overholt, et al followed 103 patients [77.7% with HGD, 13.6% with low-grade dysplasia (LGD), and 8.7% with early stage carcinoma] for a mean follow-up period of 50.7 months after PDT with porfimer sodium (27). This intention-to-treat analysis showed complete eradication of BE in 54% of patients and a mean reduction in length of BE of 6.92 cm. Success in elimination of LGD, HGD, and cancer was 92.9%, 77.5%, and 44.4% respectively. Esophageal strictures were seen in 30% of patients overall. Of concern, metaplastic glands were found beneath the regenerated squamous mucosal in 4 patients and subsquamous cancer developed in 3 patients with initial HGD.

In attempt to reduce the risk of post-PDT stricture formation, Gossner, et al evaluated PDT using 5-ALA in 32 patients (10 with HGD and 22 with early adenocarcinoma) (28). HGD and cancer were eliminated in 10 of 10 patients and 17 of 22 patients respectively. Notably, PDT had particular difficulty in treating cancerous lesions that were thicker that 2 mm which likely reflects the predilection for superficial obliteration with this photosensitizer. Complete BE eradication was not seen in any patients, however, partial squamous reepithelialization was seen in 68% of patients. Once again, residual BE was observed beneath the newly formed squamous epithelium. No esophageal strictures were seen.

FDA approval for the use of PDT in the treatment of HGD within BE was granted based on a follow-up study presented in abstract-form by Overholt, et al (29). They evaluated the efficacy of PDT using porfimer sodium plus omeprazole (PO) versus omeprazole (O) alone in a multicenter, partially blinded, randomized study that included 208 patients with HGD in BE. Patients were randomized in 2:1 ratio to the PO and O groups respectively. All patients received omeprazole 20 mg po BID and were followed for a minimum of 24 months. The results impressively showed statistically significant differences in favor of the PO group with regards to complete ablation of all areas of HGD (76.8% vs. 38.6%) and disease progression to cancer (13.0% vs. 28.0%). Strictures were seen in 37.1% of patients following PDT with the vast majority (98%) resolving after dilation procedures.

Lightdale, et al evaluated PDT with porfimer sodium versus Nd:YAG thermal ablation for the palliation of dysphagia in advanced esophageal cancer using a prospective, multicenter, randomized study design (32). Thermal tumor ablation with high-power Nd:YAG laser was considered the most efficacious endoscopically guided palliation technique available at that time for patients with malignant dysphagia. A total of 236 patients with either squamous cell or adenocarcinoma were randomized either to treatment with PDT or Nd:YAG laser therapy, and efficacy determinations were based on symptom palliation and objective tumor response. PDT showed comparable efficacy to Nd: YAG therapy with nearly 50% in both groups reporting an improvement in swallowing at 1 week post-treatment, however PDT was also noted to have a statistically significant effect on objective tumor response (32% vs. 20%—p <0.05). PDT was found to be technically easier to perform, better tolerated by patients, and required fewer treatment sessions to achieve a similar effect. PDT was also more efficacious for treatment of longer tumors (>10 cm), tumors located in the upper and lower third of the esophagus, and for patients who had undergone previous cancer treatment or experienced tumor recurrence. Photosensitivity was the most common adverse event (19%) seen in the PDT group. Based on this data, PDT use in malignant esophageal dysphagia received FDA approval.

Cholangiocarcinoma

Cholangiocarcinoma, or cancer of the bile ducts, is a rare tumor with a generally dismal prognosis. It accounts for approximately 3 percent of all gastrointestinal malignancies and has been recognized to have a rising incidence on three separate continents (33). Early, presymptomatic detection and the potential for curative surgical resection are exceedingly uncommon. Most patients are diagnosed after they manifest symptoms reflective of biliary obstruction, most prominently jaundice. As obstruction of the bile ducts is a consequence of advanced disease, curative surgical resection is generally no longer a viable option in
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Table 2

PDT and non-resectable cholangiocarcinoma series

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Photosensitizer</th>
<th>Pts w/ reduction of cholestasis (%)</th>
<th>Improvement in QOL indices</th>
<th>Median survival (mo.)</th>
<th>Complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ortner (6)</td>
<td>9</td>
<td>Porfimer</td>
<td>100</td>
<td>Yes</td>
<td>14.4</td>
<td>Skin hyperpigmentation-100 Fever-11</td>
</tr>
<tr>
<td>Berr (7)</td>
<td>23</td>
<td>Porfimer</td>
<td>100</td>
<td>Yes</td>
<td>11.0</td>
<td>Epigastric distress-NR Mild rise in ALT-NR Hemobilia-4 Cholangitis-35 Phototoxicity-17</td>
</tr>
<tr>
<td>Ortner (8)</td>
<td>54</td>
<td>Porfimer</td>
<td>73.8</td>
<td>Yes</td>
<td>14.4</td>
<td>Photosensitivity-10 Fibrotic stricture-4 Cholangitis-4 Bleeding-2</td>
</tr>
</tbody>
</table>

NR, not reported; * as compared to median survival between 1.5–4.2 months in matched historical controls.

these patients. Unfortunately, the role of chemotherapy and radiation therapy has yet to be defined with the literature containing disappointing and conflicting data (34–37). For these patients with inoperable tumors, palliation is the primary focus of medical management including consideration of biliary drainage options.

At present, two approaches are routinely utilized to enhance biliary drainage: endoscopic retrograde cholangiography (ERC) and percutaneous transhepatic cholangiography (PTC). Both approaches allow for the subsequent placement of plastic or expandable metal stents into the large intrahepatic ducts and common bile duct to facilitate flow of biliary contents into the duodenum. Unfortunately, both types of stents are prone to occlusion secondary to tumor infiltration and biofilm formation. Despite our best attempts to ensure adequate biliary drainage, patients remain at risk for infectious complications and hospital admissions due to recurrent biliary obstruction.

Several recent reports have shown the potential usefulness of PDT with sodium porfimer in the palliation of non-resectable cholangiocarcinoma (6–8,38) (Table 2). The initial was a case report by McCaughan, et al, which showed the potential benefit of this modality in a single patient with cholangiocarcinoma who received 7 sessions of PDT over a 4-year period (38). This was followed by two studies by Ortner, et al. The first was an uncontrolled pilot study of PDT in nine patients with advanced non-resectable cholangiocarcinoma (6). The authors demonstrated that PDT induced a rapid decline in serum bilirubin levels and improved quality of life indices. In addition, its use was associated with significantly longer median survival times as compared to historical controls (439 days versus 70 days). As a follow-up to this study, Ortner, et al performed the first randomized, prospective, controlled trial of PDT use in thirty-nine patients with non-resectable cholangiocarcinoma (8). Patients were randomized to either PDT plus stenting (group A) versus stenting alone (group B). They were once again able to show that PDT significantly prolongs median survival time (493 days in group A vs. 98 days in group B) as well as improves biliary drainage and quality of life. In fact, the survival benefit was so impressive that the investigators terminated the study early as they deemed continued patient randomization to stenting alone to be unethical. Photosensitivity was noted in 10% of patients treated with PDT and post-PDT biliary strictures were seen in 2 patients.

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Non-small Cell Lung Cancer

Lung cancer is currently the leading cause of cancer-related mortality in both men and women in developed countries. Surgical resection is considered the treatment of choice for patients with early stage lung malignancies. However, a significant number of these patients are not favorable operative candidates in light of cardiopulmonary comorbidities and the high risk of operative mortality as well as post-operative reduction in functional lung capacity. In this setting, PDT has shown promise as an alternative treatment option. Remission rates have ranged from 70%–81% in various reports evaluating PDT’s efficacy in the treatment of early stage non-small cell lung cancers, with better outcomes seen with smaller, more superficial lesions (39–42). Five-year survival rates for patients with early stage non-small cell lung cancers treated with PDT have varied widely ranging from 43%–93% (39,43). In patients with more advanced, obstructing, endobronchial lesions, PDT has been shown to safely improve airway patency in 74%–90% of treated patients (44,45). Based on this body of literature, PDT has been approved by the FDA for the treatment of microinvasive, endobronchial non-small cell lung cancers in patients who are not candidates for other therapies as well as for the palliation of obstructing, endobronchial non-small cell lung masses.

ADVERSE EVENTS

To date, the literature regarding PDT has shown that it is a generally safe and well-tolerated treatment modality. The most commonly seen adverse events include cutaneous and ocular photosensitivity (20%–68%) (46), esophageal stricture formation (0%–37.1%) (26–29,31), as well as non-specific gastrointestinal symptoms (5%–30%) (46). Photosensitivity reactions are predominantly mild and include skin erythema, edema, and blistering as well as ocular discomfort, erythema, and photophobia. All patients who receive sodium porfimer may be photosensitive for up to thirty days post-infusion. A significantly shorter photosensitivity period (24–48 hours) is seen with the use of 5-ALA as the photosensitizer. Operating room lamps, unshaded light bulbs at close proximity, etc.) during this time. The photosensitivity is a result of uptake of this drug by all parts of the skin and activation by visible light. The vast majority of these reactions can be prevented with the proper use of protective gear including clothing, sunglasses, and hats. Ultraviolet sunscreens are of no value in protecting against photosensitivity reactions because photoactivation occurs via exposure to visible light.

As described above, esophageal stricture formation is commonly seen after PDT treatment of esophageal disease, especially with the use of sodium porfimer as the photosensitizer. In greater than 90% of cases, such strictures were successfully treated with esophageal dilation and patients experienced improvement in dysphagia (27–29). The most frequently observed, gastrointestinal symptoms with PDT include abdominal pain, nausea, constipation, and diarrhea. These complaints tend to be self-limited and can be generally controlled with over-the-counter and/or prescription medications.

THE FUTURE

Clearly, PDT has been shown to be an attractive, local cancer treatment option that has many advantages over other conventional therapies. As many cancer patients are debilitated from their underlying malignancy as well as comorbidities, treatment options may be limited. The growing experience with this novel therapy has confirmed PDT’s vast potential as a safe and effective therapeutic modality for various cancers. Future areas of investigation include developing newer photosensitizers to optimize therapy for a given cancer, determining other cancers that are amenable to treatment, and defining the role of combination therapy with other modalities. Undoubtedly, PDT’s ease of application, favorable safety profile, and promising results merit consideration for use in select patients. Indeed, the future of PDT, just like the laser light that is essential to the phototoxic process, is considerably bright.

References
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