

Photodynamic therapy for gastrointestinal disease

To promote the appropriate use of new or emerging endoscopic technologies and those technologies that have an impact on endoscopic practice, the ASGE Technology Committee presents relevant information to practicing physicians in the form of technology reviews. Evidence-based methodology is employed wherein a MEDLINE literature search is performed to identify pertinent clinical studies on the topic, a MAUDE (Food and Drug Administration Center for Devices and Radiological Health) database search is performed to identify the reported complications of a given technology, and both are supplemented by accessing the “related articles” feature of PubMed and by scrutiny of pertinent references cited in the identified studies. Controlled clinical trials are emphasized, but in many cases data from randomized controlled trials are lacking; in such cases, large case series, preliminary clinical studies, and expert opinion are utilized. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. Reviews are drafted by 1 or 2 committee members, reviewed in significant detail by the committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is appropriate, the most recent coding data and list prices at the time of publication are provided. For this review the MEDLINE database was searched through April 2006 for articles related to gastrointestinal photodynamic therapy by matching the keywords “photodynamic therapy” and “pdt” with “gastrointestinal disease,” “esophageal disease,” and “biliary disease,” “gastrointestinal cancer,” “esophageal cancer,” “Barrett’s esophagus,” and “cholangiocarcinoma.” Practitioners should continue to monitor the medical literature for subsequent data about the efficacy, safety, and socioeconomic aspects of these technologies.

BACKGROUND

Photodynamic therapy (PDT) is an ablative treatment for rapidly proliferating tissues, including dysplastic and malignant lesions. It employs administration of a photosensitizing drug followed by application of a specific wave-

length of light, leading to intracellular photoexcitation and injury. Photodynamic therapy has been applied to a variety of tissues that are accessible to light exposure, including the skin, retina, bronchial tree, and the majority of the gastrointestinal tract. This document covers the approved photosensitizing agents, light sources, and accessories used in the application of PDT to gastrointestinal lesions.

The technology

Principles. The basis for PDT is the propensity of some chemicals for photoexcitation when exposed to intense white or specific wavelength laser light. Upon light exposure, the production of singlet oxygen and other reactive chemical radicals cause local nonthermal cellular damage, vascular thrombosis, and necrosis, which evolve over hours to several days.^{1,2} Cellular localization and depth of injury are dependent upon the sensitizing agent, the interval between dosing and light stimulation, and the light dosimetry and wavelength.

Photosensitizing agents. There are a variety of candidate photosensitizing agents for use in PDT, based upon modifications of porphyrin, chlorine, and chlorophyll. Their macro-molecular nature contributes to preferential localization within and delayed clearance from neoplastic tissues, thus concentrating the major injury to these tissues when stimulated with light. Currently only 1 agent, porfimer sodium, is cleared for systemic use in the United States.³ Another, 5-aminolevulinic acid (5-ALA), is only cleared for topical use in the United States, but is used for gastrointestinal and other systemic applications outside of the United States.⁴ Both agents preferentially absorb light in the 630 to 635 nm range. Porfimer sodium also absorbs and becomes activated by 535 nm light.

Porfimer sodium (Photofrin, Axcam Scandipharm Inc, Birmingham, Ala), is a mixture of oligomers of up to 8 porphyrin units and is photoactivated by light at both 630 nm and 515 nm wavelengths. It is a freeze-dried brownish powder, requiring reconstitution in 5% dextrose or 0.9% NaCl before use. After reconstitution, porfimer sodium should be protected from bright light and administered immediately. Dosing is usually 2 mg/kg given via slow intravenous (IV) infusion over 3 to 5 minutes. After administration it is cleared from most tissues over 40 to 72 hours but retained for longer intervals in tumors, skin, and the reticuloendothelial system. Hence, light application is usually

scheduled at 40 to 50 hours after administration. Porphyrin sodium is contraindicated in patients taking other potential photosensitizing agents, including fluoroquinolones, griseofulvin, some hypoglycemic agents, phenothiazines, sulfonamides, sulfonyleurea, tetracyclines, and thiazides. There is no published experience with overdosage of porphyrin sodium, and the effect of overdosage on duration or intensity of photosensitivity is not known. Porphyrin sodium is not dialyzable. Laser light applications should be withheld in the event of overdosage.

Aminolevulinic acid (ALA) is a pro-drug of the photosensitizing compound protoporphyrin IX (PpIX), to which it is converted after administration. In the United States it is only cleared for use as a 20% solution (Levulan and Kerastick, DUSA Pharmaceuticals, Valhalla, NY) for topical therapy of cutaneous conditions.⁵ Systemic administration of ALA has been employed in numerous studies of PDT for ablation of Barrett's mucosa with⁶ and without⁷ dysplasia. Potential advantages of ALA specifically for Barrett's esophagus include greater mucosal concentrations compared to submucosal and stromal levels (yielding more superficial injury) and a much shorter half life (resulting in less photosensitivity reactions). When given orally it yields peak levels of PpIX in the esophageal mucosa in 4 to 6 hours.⁸ ALA toxicity includes transient (3-4 days) liver enzyme abnormalities in 50% of patients.

Light sources. Several commercial laser light sources can deliver appropriate wavelength light for application in the gastrointestinal tract, but only 1 is currently marketed for this application.⁹ The Diomed 630 PDT Laser Model 2TUSA (Diomed Inc, Andover, Mass), a 630 nm red light laser system, is the only light source that is FDA cleared for use with Photofrin porphyrin sodium. This portable device weighs 43 pounds, measures 19 × 8.5 × 6 inches, operates on standard 115 V AC current, has internal forced air cooling that does not require plumbing, and uses semiconductor diodes as a light source, thus avoiding the need for laser alignment and dye replenishment or disposal. It delivers up to 2000 mW of energy at the tip of the delivery fiber. The system incorporates an automated program for dosimetry (light power and duration) based on the operators input of the target organ, pathology, and fiber length to be used. Hence, for treatment of esophageal carcinoma using porphyrin sodium, the system's power output adjusts to yield a light dose of 300 joules (J)/cm of diffuser length, based on an assumed treatment duration of 12 minutes and 30 seconds, while for high grade dysplasia in Barrett's esophagus the power output adjusts to yield 130 J/cm of diffuser length, administered over 8 minutes. Custom treatment parameters can be based on adjustable treatment durations or J of energy to be delivered. The Diomed laser is marketed with autoclavable sterile cuvettes for calibration of the light output at the fiber tip. They can be sterilized and reused up to 10 times.

Other proprietary laser systems have been used for PDT therapy but are not specifically marketed for gastro-

intestinal applications or approved for use with Photofrin. They include systems from Lumenis, Ltd (Yokneam, Israel and Santa Clara, Calif; formerly Coherent Lasers Medical Group, Santa Clara, Calif)^{1,10} and Laserscope, Inc (San Jose, Calif).¹⁰ Laser light systems vary in their means of generating uniform wavelength light and in their requirements for electricity, plumbing, and replenishment of their light source.

Light delivery devices. One challenge in the endoscopic application of PDT is the delivery and even distribution of adequate doses of light to the tissue being treated. For hollow cylindrical organs, such as the gastrointestinal tract, light must be diffused evenly and circumferentially in a perpendicular orientation to the long axis of the fiber guide. Specific delivery catheters with tips that diffuse the light over carefully defined cylindrical lengths are available from a variety of sources (Table 1). The FDA-approved Diomed laser system employs a proprietary line of silica-core light delivery-diffusing fibers (Optiguide DCYL 200 Series) with an outer diameter of 1.65 mm and cylindrical diffuser tips available in 10, 15, 20, 25, and 50 mm lengths. Similar single-use fibers for delivery of laser light are available from other firms as well. Cylindrical centering balloons of various lengths and matched diffusion catheters (Xcell PDT Balloon with Fiber Optic Diffuser, Cook Endoscopy, Winston-Salem, NC) are available for positioning the laser delivery fiber within the lumen of the esophagus.¹¹ The balloon catheter is 81 cm long (working length 75 cm). The 25 mm diameter balloon distends the esophagus and centers the laser fiber, providing more complete and evenly distributed light exposure over 3, 5, or 7 cm lengths of mucosa. The centering balloon is marketed for use with the Diomed PDT laser as well as several laser models from Laserscope, Inc. It is important to confirm compatibility between laser sources, light guides, and centering devices.

Treatment regimens. Porphyrin sodium is used in the same dose of 2 mg/kg IV for all gastrointestinal applications. Total light doses of 150 to 200, 200, and 300 J/cm are used for Barrett's mucosa with high grade dysplasia, bronchogenic carcinoma, and esophageal carcinoma, respectively.^{1,3} To avoid generating a direct thermal effect of light on the tissue, a power density of 400 mW/cm is usually not exceeded. The relationship between total light dose in J/cm, power output from the diffusing fiber in watts, diffuser length in cm, and treatment time can be expressed as follows:

$$\begin{aligned} \text{light dose (J/cm)} \\ &= [\text{power output from diffuser (W)} \\ &\times \text{treatment time (s)}] / \text{diffuser length (cm)} \end{aligned}$$

Published dosimetry tables and computerized entry of the above elements assist with treatment planning for the common FDA-approved indications.³

Most tissues are treated with a single dose of photosensitizer followed by 1 application of 630 nm laser light 40 to 50 hours after infusion of the photosensitizing agent. For esophageal or endobronchial cancer, endoscopic debridement of the tumor can be performed 96 to 120 hours after injection and a second application of light can then be administered using the same dose as for the initial treatment. Subsequent full courses of PDT (photosensitizer and light), up to 3 total, can be used after 1 to 3 months or more.

For ablation of high-grade dysplasia in Barrett's esophagus, untreated "skip" areas can be treated with a second light application 96 to 120 hours after the porfimer sodium injection, using a lower dose of 50 J/cm of diffuser length and without a centering balloon. Additional full courses of PDT, up to 3 total, are allowed at 3-month intervals.

Indications

Photodynamic therapy using porfimer sodium (Photofrin II) is FDA cleared for (1) palliative treatment of patients with completely or partially obstructing esophageal cancer, (2) ablation of high-grade dysplasia in the setting of Barrett's esophagus in patients not undergoing surgery, and (3) reduction of endo-bronchial obstruction in patients with nonsmall cell lung cancer who are not candidates for surgery and radiotherapy. Outside of the United States, PDT is also approved for treatment of superficial gastric carcinoma. Miscellaneous investigational applications include ablation of nondysplastic Barrett's mucosa,¹² palliative treatment for nonresectable cholangiocarcinoma,¹³ and extensive FAP-associated adenomas of the duodenum or colo-rectum.¹⁴

Contraindications include the presence of any form of porphyria or known allergies to porphyrins, existing tracheoesophageal or broncho-esophageal fistula, tumors eroding into major vessels, the presence of esophageal or gastric varices, esophageal ulcers > 1 cm in diameter, and inability to comply with photosensitivity precautions.

Efficacy and comparison to available technologies

High-grade dysplasia in Barrett's esophagus. Porfimer sodium-based PDT eradicated high-grade dysplasia in 87% of 380 patients pooled from 4 large, prospective series.¹⁵⁻¹⁷ Eradication of intestinal metaplasia (nondysplastic Barrett's) is, however, achieved in only 50% to 70% of patients.¹⁸ In a large, multicenter, randomized, controlled trial, 208 patients were randomized to porfimer sodium-based PDT plus omeprazole 20 mg po BID versus omeprazole alone. At 2 years, high-grade dysplasia was ablated in 77% of study patients and 39% of omeprazole control patients.¹⁹ In a 5-year analysis of the same groups, 13% of the PDT group and 28% of the omeprazole control group had progressed to cancer ($P < .006$).¹⁹ There are several trials comparing 5-ALA-based PDT to argon

TABLE 1. Costs of components used in performance of PDT

Porfimer sodium	\$2336.58 per 75-mg vial
Diomed PDT laser system	
Diomed 630 PDT Laser, Model T2-USA	\$75,000
Reusable calibration cuvettes	\$120
Light diffusion catheters*	
10-mm diffuser	\$470
15-mm diffuser	\$525
20-mm diffuser	\$580
25-mm diffuser	\$605
50-mm diffuser	\$650
Protective eyewear for 630 nm light	\$150
Cook Endoscopy Xcell centering balloon and fiber optic diffuser	\$1000

*Bulk purchase can save 10% to 15% from list plus shipping.

beam coagulation of Barrett's mucosa with⁶ and without⁷ dysplasia, but none comparing PDT using the FDA-cleared agent to thermal ablative methods.

Esophageal carcinoma. Numerous small series have demonstrated successful palliation of dysphagia in patients with obstructing esophageal squamous cell carcinoma or adenocarcinoma.^{20,21} Two randomized, controlled trials have compared PDT versus Nd:YAG thermal ablative therapy for palliation of obstructing esophageal carcinoma. In one study of 42 patients, both therapies improved dysphagia but PDT yielded greater and more prolonged improvement in dietary intake and weight maintenance or gain.²² The second study, which enrolled 236 patients at 24 centers, reported equivalent improvement in early and late dysphagia scores and equivalent early improvements in objective tumor response, but more prolonged objective responses in the PDT group.²³ Both therapies failed to improve dysphagia scores in about 25% of patients.

Photodynamic therapy has also been studied in early stage nonobstructing esophageal carcinoma. Early studies employing less purified porphyrin preparations or aminolevulinic acid yielded complete response rates of only 50% to 80%.²⁴ More recent studies employing Photofrin have yielded cumulative response rates of about 88%,^{24,25} presumably due to the greater depth of injury compared to alternative agents.

In retrospective studies, porfimer sodium PDT coupled with endoscopic mucosal resection of focal dysplasia or superficial cancer compares favorably to esophagectomy,

TABLE 2. CPT codes for PDT ablation of tumor in the gastrointestinal tract**A. Endoscopy procedure**

43228: Esophagoscopy with ablation of tumor(s), polyp(s), or other lesion(s) not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique

B. Add photodynamic therapy code

96570: Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drugs(s); first 30 minutes (list separately in addition to code for endoscopy procedures of esophagus)

96571: Each additional 15 minutes (list separately in addition to code for endoscopy or bronchoscopy procedures of lung and esophagus)

C. Add Photofrin

J9600: Porfimer sodium, 75 mg (typically listed twice for 2 vials)

D. Administration of Photofrin (office setting, use only 1 code determined by technique of administration)

96409: Chemotherapy administration, intravenous, push technique, single or initial substance/drug

96413: Chemotherapy administration, intravenous infusion technique, up to 1 hour, single or initial substance/drug

with slightly lower disease-free survival at 19 months (20/24 for PDT vs 64/64 for esophagectomy) but also lower procedure-related morbidity despite greater comorbidities at the time of treatment (4/24 for PDT vs 31/64 for esophagectomy, $P < .01$).²⁶

Cholangiocarcinoma. Two small series of PDT for nonresectable cholangiocarcinoma suggested short-term improvement in jaundice in 9 patients and a slight survival benefit in 23 patients.^{13,27} This prompted a randomized, multicenter trial of optimal plastic stent management with or without porfimer sodium PDT in 39 patients.²⁸ Median survival was markedly improved with the addition of PDT to stent therapy (493 days vs 98 days, $P < .0001$).

Ease of use

Therapeutic dosing of radio-sensitizing agents is easily calculated and administered parenterally. Dosimetry and administration of the activating laser light is more involved but not technically demanding for esophageal applications. Balloons for centering the laser fiber within the lumen also provide radio-opaque barriers to limit the area of treatment more accurately than is possible by administration through bare fibers. The major challenge to patient management is provision of adequate counseling and patient adherence to light avoidance precautions designed to minimize skin photoreactions after administration of the radio-sensitizing agent.

Safety

Patient safety. The complications and toxicities occurring from PDT therapy for gastrointestinal disease are related to the associated endoscopic procedure, acute effects of the photosensitizing agent (constipation in 33%, rare allergic reactions), the local inflammatory and scarring effects in the region of therapy, and systemic phototoxicity.²⁹ After esophageal PDT, patients frequently experience odynophagia and chest pain; abdominal pain (20%), nausea and vomiting (15%-25%), fever (33%), and asymptomatic pleural effusions (33%-75%) are relatively common. Rare local toxicities include anemia related to mucosal ulceration, esophageal perforation,²⁹ atrial fibrillation, and respiratory compromise.

Esophageal stricture formation occurs in 15% to 58% of patients treated with PDT.^{11,17,29,30-33} Stricture formation is more common with higher light doses, focused pretreatment of localized lesions, overlapping treatment fields, and retreatment. Strictures generally present within 1 to 2 months of the therapy and most respond to serial esophageal dilation therapy.²⁹ Efforts to reduce stricturing with administration of prednisone have been disappointing.¹⁵ Aggressive acid suppression with proton pump inhibitors is indicated for several months after treatment.

Cutaneous phototoxicity occurs in about 30% of recipients of porfimer sodium,³⁴ with severe "sunburn" in 5% to 7%. There are no efficacious prophylactic therapies other than avoidance of exposure to bright light³⁵ using sunglasses, wide brimmed hats, and full coverage of the limbs, which should be employed for at least 30 days and often up to 90 days. Sunscreens do not protect against PDT-related phototoxicity. Exposure to dim interior light is useful in that it facilitates clearance and bleaching of porfimer sodium from the skin.

Personnel safety. Laser safety eyewear is the primary mechanism against ocular injury of staff members. Eyewear must be specific to the wavelength of the laser being used. The laser safety standard adopted by OSHA specifies that facilities using class 4 lasers (most medical applications) should designate a laser safety officer to oversee safety for all operational, maintenance, and servicing situations.

Financial

The costs for the various components required to deliver PDT to the gastrointestinal tract are outlined in

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Table 1. The photosensitizing agent, porfimer sodium (Photofrin), costs approximately \$2337 per 75 mg vial, and on average 2 vials are required per patient. Many centers lease the laser source on a per-use basis. Single-use fibers and diffusers add approximately \$1000 to the global expenses.

The Current Procedural Terminology (CPT®) codes for PDT ablation of gastrointestinal tumors during gastrointestinal endoscopy are provided in **Table 2**. The endoscopic code used in conjunction with the PDT codes is currently restricted to 43228 as instructed in the CPT manual (2006). The analogous EGD code (43258) has a correct coding edit precluding its use with the 96xxx series PDT codes. Although this edit can be overcome with a -59 modifier, this would not be appropriate since the site of service is the same for all of the codes that one would use. Administration of Photofrin in the office setting would include charges for the drug (typically a quantity of 2 vials) and the chemotherapy administration charges. The Center for Medicaid and Medicare Services (CMS) and most third party carriers cover PDT therapy for approved indications, but coverage varies greatly for the various off-label palliative applications in the gastrointestinal tract. As this therapy is both elective and expensive, coverage should be determined in advance of its use.

Summary

Photodynamic therapy using porphyrin sodium (Photofrin II) is FDA cleared for the palliation of malignant dysphagia secondary to esophageal carcinoma and for the treatment of Barrett's esophagus with high-grade dysplasia. It requires the administration of a photosensitizing agent that is avidly retained by neoplastic cells followed by light therapy to provide localized cell death. The major drawbacks to the therapy are its capital costs, per procedure expenses, and prolonged potentially severe cutaneous and ocular phototoxicity.

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Disclosure: This article was not subject to the peer review process of GIE.

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