Photodynamic Therapy: Application for Upper GI Diseases

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Introduction

Photodynamic therapy has been available for treatment for UGI disease in the United States since its initial approval for obstructing esophageal cancer. This was primarily a palliative therapy and was found to be superior to thermal laser therapy (Nd:YAG) because it had less complications. Subsequently, it was approved for Barrett’s esophagus with high-grade dysplasia. Additional usages in the UGI tract that have been explored include cholangiocarcinoma, pancreatic cancer, early mucosal cancer therapy, and hepatocellular cancer. The usage of this therapy in the United States was primarily for Barrett’s esophagus. The advent of radiofrequency ablation has substantially decreased the popularity of PDT due to its unusual side effect profile including cutaneous photosensitivity and severe esophageal strictures. In addition, costs of treatment in particular the drug were prohibitive.

1. PDT: Mechanism of Action

Photodynamic therapy operates through the absorption of light of a specific wavelength (630 nm for sodium porfimer) by a large chemical, a photosensitizer. The approved drug in the US is sodium porfimer which can then in turn pass this energy onto molecular oxygen producing singlet oxygen. The singlet oxygen has a very short half life and interacts with proteins and nucleic acids in its immediate vicinity producing cell death through apoptosis, necrosis, even through immune mediated injury. This unusual requirement of needing sufficient drug concentration and light to achieve a threshold effect allows photodynamic therapy to be more selective than traditional thermal therapy. In addition, there is a vascular effect that causes tissue hypoxia very early on in the treatment. Theoretically, this could be easily tailored to the condition in the tissue as the photosensitizer is photobleached during the treatment. This means that as the treatment is continued, the amount of drug present will decrease at a relatively constant rate. This can be monitored as the photosensitizers, by their very nature, are fluorescent and can be detected by relatively simple optical instruments. None of the monitoring is available clinically although it has been shown to be possible clinically.

The mechanisms of action have clinical consequences. In very hypoxic tumors, photodynamic therapy is not as effective due to the lack of oxygen to form singlet oxygen. Patients are often given supplemental oxygen to enhance the effect of therapy. In addition, the photodynamic effect does not lead to visible changes in the tumor...
other than surface hypoxia such that the gastroenterologist must gauge therapy solely on the amount of light energy that is placed on the tumor. Also, since light must reach the tumor cells, laser probes must be inserted into larger tumors to ensure adequate light delivery. Red light is selected primarily because it penetrates deeper into the tissue. However, sodium porfimer is not the ideal agent as its absorption of red light is not very efficient, its peak absorption is in the blue-green light wavelength and unfortunately overlaps the hemoglobin absorption spectrum so this light wavelength is not used clinically.

2. Disease Applications

**Esophageal Cancer:** The earliest clinical application of photodynamic therapy was for the treatment of esophageal cancer that had advanced and was producing dysphagia. The primary advantage of photodynamic therapy is the reproducibility of the results. PDT requires very little advanced endoscopic technical skills and only requires the positioning of a photoradiation catheter into the central lumen. In areas such as obstructing tumor, it is very well tolerated and is effective with 32 percent palliated 1 month after PDT versus 20% with thermal laser palliation. In addition, before the development of resection techniques, PDT was used as a single therapy for smaller esophageal cancer (<2 cm diameter). There was surprisingly reasonable results from these early trials with disease-specific survival in the majority of patients.

**Barrett’s Esophagus:** This was an approved indication for PDT in patients with high grade dysplasia with a 77% response rate. These patients had reasonable response rates but developed severe strictures in 30% of patients treated which were often difficult to dilate. This primarily occurred in patients with longer lengths of Barrett’s esophagus. Responses to photodynamic therapy was much more common in individuals with intact p16. This seems to be related to effects of the INK4a locus within the gene that regulates cellular senescence. Unfortunately, with recent increases in costs of PDT, this treatment is now predominantly secondary therapy for Barrett’s esophagus.

**Cholangiocarcinoma:** There has been multiple studies on the treatment of cholangiocarcinoma with photodynamic therapy. In small randomized trials, there was a suggestion that PDT could significantly increase survival in patients with advanced disease. However, careful assessment of these studies has found that there is not substantial evidence that this treatment is beneficial given the low number of patients. The major difficulty is that the equipment for PDT in the biliary has not been produced until this year. Smaller flexible fibers are necessary to access the bile duct and the dosages of light used for photoradiation of the bile duct is much larger than in the luminal GI tract. The photoradiation must be done blind to the endoscopist so that if there is any breakage of the photoradiation catheter, this is not observable during the treatment.

**Pancreatic Cancer:** Photodynamic therapy has been used in obstructing pancreatic cancer to relieve the stenosis. This has been done using a fairly aggressive photosensitizer mTHPC that has deep tissue penetration. Even more intriguing, photodynamic therapy has been reported to be used for IPMN where it has been able to eliminate neoplasia in the proximal pancreatic duct. Interestingly, despite the degree of tissue injury with PDT, pancreatitis from PDT has not been reported which may be due to the type of injury that PDT produces.

**Gastric Neoplasm:** Photodynamic therapy has been used for superficial gastric cancers as well. The challenge in this area for mucosal resection techniques is just the inability to reach these areas with the endoscope in certain locations such as the high fundus or in the incisora. In these areas, using photodynamic therapy is an option to radiate this area.
**Future Applications**: With new photosensitizers and more selectivity, it is possible that photodynamic therapy applications will increase particularly in areas like the bile duct and pancreas. In the luminal GI tract, it is more likely to remain a second line therapy.

**Conclusions**

Photodynamic therapy is reasonable as a second-line therapy for esophageal lesions such as Barrett’s esophagus and high-grade dysplasia and adenocarcinoma. Applications in the pancreatic and biliary tree is intriguing and would be an area for future development.

**References**


