REVIEW

The Effects of Photodynamic Therapy in Upper-Gastrointestinal Malignant Diseases

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Photodynamic therapy (PDT) is a promising new modality that utilizes the combination of a photosensitizing chemical and visible light for the management of various solid malignancies, including gastrointestinal (GI) cancer. PDT has some advantages over chemotherapy in terms of its greater safety and lower toxicity in the treatment of malignant lesions. However, PDT has not been used widely for treating upper GI cancer due to its relatively low cost-effectiveness and anatomical characteristics of the GI system. Nevertheless, PDT may be an effective alternative therapy for early upper-GI cancer patients who are at a high risk of curative surgical resection or systemic chemotherapy. In some clinical studies, PDT for various upper GI cancer showed positive results. To improve the efficacy of PDT for upper GI cancer, development of photosensitizer and light delivery system is needed. (*Gut Liver* 2010;4(Suppl. 1):S39-43)

Key Words: Photodynamic therapy; Photosensitizer; Upper-gastrointestinal cancer

INTRODUCTION

Photodynamic therapy (PDT) utilizes the unique characteristics of photosensitizer which accumulates in tumor and uses light energy to destroy malignant neoplasm. It was first adopted in treatment of esophageal malignancies since early 1980s and is now increasingly used in treatment of gastric cancer, biliary cancer and colon cancer.¹ The PDT accurately delivers light energy to the target lesion which enables selective tissue destruction and minimizes adjacent normal tissue damage.² Therefore it is possible to maintain gastrointestinal system's mechanical

function and is suitable for repeated treatment of small lesions of immunocompromised patients.³ Since the advent of this novel treatment modality, PDT has yet to prove its superiority to other treatment methods and development of newer photosensitizer and improvement of light delivery system remains an unsolved, ongoing problem. Nevertheless, the PDT remains a useful and noteworthy treatment modality because of the recent increasing needs for a minimal invasive treatment method. In this review, we will discuss the principles and mechanisms of PDT and its clinical applications, especially on esophageal cancer, Barrett's esophagus, and gastric cancer.

PRINCIPLES AND MECHANISMS

PDT is defined as the therapeutic use of photosensitizers which are activated by light.⁴ The three main steps for PDT include injection of photosensitizer, activation of photosensitizer by endoscopy guided red light application, and cell death by production of active oxygen.⁵ Fig. 1 is a typical energy level diagram for photosensitizer activation.⁶ A photon of light, of an appropriate wavelength, is absorbed by the photosensitizer molecule, raising it from ground state to a short-lived (singlet) excited state. The next step is intersystem crossover in which internal rearrangement to a longer-lived (triplet) state porphyrin takes place (Fig. 2). Finally, the reactive oxygen is produced which provides biological effects (Fig. 3).

EQUIPMENTS

PTD involves three separate components. The photosensitizer, light source, and light delivery systems. A brief

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Fig. 1. Energy absorption and excitation: singlet (short-lived) excited-state porphyrin.

Fig. 2. Intersystem crossover (electron spin conversion): internal rearrangement to a longer-lived (triplet-state) porphyrin.

Fig. 3. Production of highly active singlet oxygen.

lists of current PDT drugs are given in Table 1.⁶ Hematoporphyrin derivatives (HPD), the 1st clinical photosensitizer, commercially available as Photoprin is currently widely in use. However, due to its limitation such as instability at room temperature, long skin photosensitivity and weak light absorption at wavelengths above 600 nm, 2nd generation drugs are now undergoing clinical trial. They are benzoporphyrin derivatives, mTHPC, purpurines and chlorin derivatives and ALA.⁷ Most clinical drugs have optimal activity in 530-700 nm range. In this wavelength range, Laser has been the preferred light source. Ideal source should generate enough light with the correct wavelength, in a convenient, flexible way for delivery to the tissues. For delivery of light, a radially diffusing cylindrical or frontal diffuser or a bal-

loon-diffuser system can be used to adapt the light irradiation to the shape of the target tissue. The balloon-diffuser system has been shown to be successful in centering the rays of radiation and providing a uniform circumferential and predictable light delivery.

PHOTODYNAMIC THERAPY FOR UPPER GASTROINTESTINAL CANCER

Possible Indications for PDT are obstructing esophageal cancer, superficial esophageal cancer, Barrett's esophagus with HGD, gastric cancer, duodenal/ampullary neoplasm, cholangiocarcinoma/pancreatic cancer, small bowel cancer, colorectal cancer.

In Barrett's esophagus and esophageal cancer, the

Table 1. Examples of Photodynamic Therapy Drugs

Class	Examples	Commercial drugs
Porphyrins	Hematoporphyrin derivative (HpD) Protoporphyrin IX (PpIX) Benzoporphyrin Derivative (BPD-MA) Meso-tetra(hydroxyphenyl) chlorin (porphyrin) (mTHPC)	Photofrin* (QLT Phototherapeutics, Canada) Levulan* (DUSA, USA) Vertofrin* (QLT Phototherapeutics, Canada) Foscan* (Scotia Quanta Nova, UK)
Purpurins	Tin Etiopurpurin (SnET2)	Purlytin* (Miravant, USA)
Phthalocyanines	Aluminumchlorosulfonated phthalocyanine, AIPcS	
Texafrins	Lutetium texafrin, LuTex	Lutrin* (Pharmacyclics, USA)
Chlorins	Chlorin-e6	NPe6* (Nippon Chemical, Japan)

*Currently in clinical trials.

Table 2. Summary of Reported Cases of Esophageal Cancer Treated by Photodynamic Therapy

Reference	No. of patient	Stage of tumor	Complete response/ Remission rate, %	Duration of follow-up, mo
Early esophageal cancers				
Fujimaki and Nakayama	11	Early	82	13-48
Patrice <i>et al.</i>	8	Early	50	10.8
Calzavara <i>et al.</i>	20	Superficial	40	5-20
Monnier <i>et al.</i>	15	Superficial	80	6-60
Sibille <i>et al.</i>	123	Small	74	5 years
Kato <i>et al.</i>	66	Early	80	36
Overholt <i>et al.</i>	14	Superficial	100	6-22
Tian <i>et al.</i>	13	Superficial	92	21-32
Gossner <i>et al.</i>	22	Early	77	1-30
McCaughan <i>et al.</i>	8	Stage I	87	62% 5-year survival
Hayata <i>et al.</i>	6	Early	66	19-41
Spinelli <i>et al.</i>	20	Superficial	73	5 years
Advanced esophageal cancer				
McCaughan <i>et al.</i>	11	Stage II	100 (initial/1 mo)	Median survival 12 months
	26	Stage III	100 (initial/1 mo)	Median survival 6.2 months
	32	Stage IV	97 (initial/1 mo)	Median survival 3.5 months
Thomas <i>et al.</i>	15	Advanced	100 (initial)	24
Heier <i>et al.</i>	32	Advanced	91 (initial)	Median relief of symptoms (84 days)
Jin <i>et al.</i>	207	Advanced/Recurrent	16.40	8 years

Reference: Role of Photodynamic Therapy in the Management of Gastrointestinal Cancer. Digestion. 1999;60:1-10.

standard treatment is surgery but it has substantial morbidity and postoperative complications. In shallow, early dysplastic lesions, PDT can be an effective treatment option.^{8,9}

As for early gastric cancer, PDT is technically more difficult and its use has been limited due to stomach's unique geometry like gastric folds, peristalsis, etc. Therefore at the moment, endoscopic submucosal dissection has been a mainstay of the curative treatment but also carries the risk of complications like perforation and bleeding. Although PDT has limitation on deep lesion, it has proved to be effective for the treatment of certain shallow and small-diameter early gastric cancer without disturbing the stomach geometry.¹⁰ PDT can also be useful in early, shallow gastric cancer in elderly and immunocompromised patients.

CLINICAL DATA

Table 2 is a summary of reported cases of esophageal cancer treated by PDT showing variable complete remission rate ranging 40% to 100% for early and 91% to 100% for advanced cancer.¹¹ For the treatment of Barrett's esophagus, PDT can be effective in many cases. The reported rate of successful ablation of combined low grade dysplasia or Barrett's esophagus itself ranges from 82% to 100%, and successful ablation rate in high grade dysplasia or cancer was 77% to 91% (Table 3).^{9,12-16} However, these studies confirmed the feasibility, safety of the PDT, and obtained mixed success as well in terms tumor response. Some report complete histologic response in "advanced" tumors, whereas others report only partial response even in "early" tumors.

Unfortunately the analysis of PDT for gastric cancer is plagued by mixed and varied results with low patient numbers and inadequate follow-up. In several studies in Japan, The largest series by Mimura *et al.*¹⁷ included 27 patients with early gastric cancer: After PDT using photoprin administration two days before procedure, the complete remission rate was 88%, whereas a smaller study including seven patients using same photosensitizer, showed 100% of complete remission rate. Another study using 2nd generation photosensitizer, the rate of complete remission was 73%.¹⁰

During the past four years, PDT was performed 14 patients with gastric cancer in Korea University Guro Hospital, Seoul, Republic of Korea. Study patients included seven patients for curative treatment: six with early gastric cancer and one high grade dysplasia, who were inoperable due to either severe comorbidities or refusal of resection either by surgery or endoscopic submucosal dissection, and five patients for adjuvant therapy after endoscopic submucosal dissection due to either incomplete resection in two patients and positive margin in three. In the rest 2 patients, PDT was done for palliation of symptoms. PDT was done using photozem, near identical with photofrin, in dose of 2-3 mg/kg, as a photosensitizer. one patient completed therapy after one session and other 13 patients underwent two sessions with average interval of 2 days. Follow-up upper GI endoscopy and tissue biopsies were done at 1, 3, and 6 months after the therapy. The CR rate in curative treatment group was 57% with PDT only and 67% with combination of local therapy. And 60% in the adjuvant therapy group after ESD. In palliative treatment group, although small in number, all showed symptomatic improvement, resulting

Table 3. Summary of Randomized Controlled Trials of Photodynamic Therapy in Barrett's Esophagus

Investigator	No. of patients	Treatment agent	Follow up, mo	Residual BE	Residual dysplasia
Ackroyd <i>et al.</i> (2000) ¹²	30 (LGD)	1 session ALA-PDT OMP alone	24	ALA-PDT: 100% OMP: 100%	ALA-PDT: 0% OMP: 80%
Kelty <i>et al.</i> (2004) ¹³	68 (No dysplasia)	2 session ALA-PDT 3 sessions APC	24	ALA-PDT: 50% APC: 97%	-
Hage <i>et al.</i> (2004) ¹⁴	40 (8 LGD)	1 session ALA-PDT (100J) 1 session ALA-PDT (20+100J) 2 sessions APC	12	ALA-PDT (100): 18% ALA-PDT (20+100): 0% APC: 33%	ALA-PDT (100): 0% ALA-PDT (20+100): 10% APC: 0%
Wang <i>et al.</i> (2005) ¹⁸	167 (90 HGD, 22 EC)	Photofrin-PDT	54	50%	9%
Overholt <i>et al.</i> (2005) ¹⁵	208 (HGD)	Photofrin-PDT+OMP OMP alone	24	48% 93%	23% 61%
Overholt <i>et al.</i> (2007) ¹⁶	208 (HGD)	Photofrin-PDT+OMP OMP alone	60	-	10% 31%

LGD, low grade dysplasia; EC, esophageal cancer; HGD, high grade dysplasia.

in a total of 71% of response rate as expected.

CONCLUSION

In conclusion, PDT for gastric cancer is one of the treatment options in selected cases. However, how to maximize clinical efficacy is unclear. With the development of light delivery system and new photosensitizer, more energy and high dose of photosensitizer than usual may be the "answer". We also need new trials aimed at improving efficacy.

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