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Photodynamic Therapy for Cancers: A Clinical Trial of Porfimer Sodium in Japan

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Photodynamic therapy utilizing Photofrin has proven to be an effective modality that can be used in the treatment of a wide variety of solid tumors and luminal cancers. An argon pumped dye laser or excimer dye laser was used to deliver 630 nm light via quartz fibers passed through the biopsy channel subsequent to i.v. injection of photosensitizer. In this study, 64 patients with superficial cancers were treated in this manner but only 58 patients, including 21 with roentgenographically occult lung cancer, 8 with stage I lung cancer, 5 with esophageal cancer, 12 with gastric cancer, 8 with cervical cancer and 4 with bladder cancer were evaluable. Complete remission was obtained in 48 out of 58 cases (82.8%). There was no serious complication except skin photosensitivity, which was seen in 13 patients. We conclude that photodynamic therapy is efficacious in the treatment of superficial cancers where complete remission may be achieved.

Key words: Photodynamic therapy — Photofrin — Argon dye laser — Excimer dye laser

It has been known for nearly a century that a photochemical reaction occurs when photosensitizing compounds are exposed to light.[1] In 1961, a hematoporphyrin derivative (HpD) was prepared from hematoporphyrin hydrochloride by treatment with acetic acid and was shown to have great affinity for malignant tissue by Lipson *et al.*[2] The effectiveness of photodynamic therapy (PDT) in the treatment of malignant tumors was established by Dougherty *et al.*[3] for the treatment of skin metastatic lesions of breast carcinoma. Since then increasing attention has been paid to this new diagnostic and therapeutic modality. A wide variety of malignancies have been treated by this method and according to the literature, over 3000 patients worldwide have been treated with photodynamic therapy.[4]

Fluorescent materials for clinical use in cancer therapy must be safe and have an affinity for malignant tumors. There have been many investigations of candidate fluorescent materials. However, on the basis of its safety, low toxicity, stability, and tumor selectivity, Photofrin (commercial name of porfimer sodium) is the most commonly used clinically. However, no proper clinical trial has been designed, because PDT involves many complicated factors, such as the photosensitizer itself and light source. In this paper, we describe and evaluate our experience obtained in the first nationwide clinical trial in Japan utilizing PDT in the treatment of superficial cancers in a variety of organs, such as the lung, esophagus, stomach, bladder and cervix.

PATIENTS AND METHODS

All patients were required to have histopathologically and cytologically proven superficial cancer of the lung, esophagus, stomach, uterine cervix or bladder. Except for cervical and bladder cancer, each patient had a bidimensionally measurable lesion. Details of the eligibility criteria are shown in Table I. Informed consent was obtained from all patients or their relatives. Reasons why PDT was conducted in the enrolled patients with lung, esophageal or gastric cancer were refusal of surgery, inoperability because of poor organic functions, serious concomitant disease or advanced age. In patients with cervical and refractory multifocal bladder cancer, PDT

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Table I. Patient Selection Criteria

Criteria	Lung A[a]	Lung B[b]	Esophagus	Stomach	Cervix	Bladder
Age (years)	≧79	≧79	No limit	No limit	No limit	≦18
PS[c] (ECOG)	0–2	0–2	No limit	No limit	No limit	0–2
Clinical stage (UICC TMN)	TX, is N0 M0	T1, 2 N0 M0	Tis, 1 N0 M0	Tis, 1 N0 M0	Dysplasia, CIS or stage Ia	Tis N0 M0
Staging	Chest X-ray, endoscopy, CT, US, bone scintigraphy		Endoscopy, US EUS		Colposcopy, smear, punch biopsy	Endoscopy, cytology, histology
Tumor location	Vocal cord–Subsegmental bronchi				Cervix–Cervical canal	
Endoscopical findings	Superficial thickening or small protrusion		Mucosal or submucosal type	Mucosal or submucosal type		
Tumor area	Entire tumor visible with endoscope	No limit	≦2×2 cm Entire tumor visible with endoscope	Diameter of ≦3 cm Area of ≦7 cm² Entire tumor visible with endoscope	Entire tumor visible with endoscope	No limit
Prior treatment	No	No limit	No	No	No	No
Others	PaO_2 of ≧60 Torr Chest X-ray: occult	PaO_2 of ≧60 Torr				Bladder capacity of ≧200 ml

CT, computed tomography; US, ultrasonography; EUS, endoscopic ultrasonography.
a) Roentgenographically occult lung cancer.
b) Stage I lung cancer.
c) Performance status.

was chosen mainly to preserve fertility and as an alternative to cystectomy, respectively.

Photofrin (photosentitizer) was administered intravenously at 2 mg/kg and photoradiation was performed at 630 nm with an argon dye laser or excimer dye laser 48–72 h after injection of this agent. The laser light transmitted endoscopically via quartz fiber was applied at doses of >200 J/cm^2 for lung cancer, >90 J/cm^2 for esophageal and stomach cancer and 10–30 J/cm^2 for bladder cancer. When the excimer dye laser was used, the dose was >100 J/cm^2 in lung and cervical cancer. After administration of this agent, patients were restricted from exposure to bright illumination or direct sunlight for at least 4 weeks.

Responses and toxicity, as well as histological and cytological findings, were evaluated periodically according to the "WHO Handbook for Reporting Results of Cancer Treatment." However, we made a partial response (PR) rating if abnormalities in these findings were seen despite apparent complete response (CR) endoscopically. Tumor responses of lung, esophageal and gastric cancers were evaluated as follows: complete response (CR), no evidence of tumor both endoscopically and histologically for at least 4 weeks; partial response (PR), 50% or more reduction in tumor volume for at least 4 weeks; no change (NC), less than 50% reduction to less than 25% increase in tumor volume 4 weeks after PDT; progressive disease (PD), 25% or more increase in tumor volume. As for cervical cancer, tumor response was evaluated at 2 or 4 months after PDT endoscopically, histologically and cytologically. Negative results in all 3 categories indicated CR, while negative results in 2 categories received a PR rating. No change in 2 of the 3 categories was classified as NC. Progression in one or more categories was classified as PD. As for bladder cancer, tumor response was evaluated as follows: CR, results of endoscopy, histology and cytology were all negative; PR, results of both endoscopy and histology were negative, but cytology was positive; NC, histolgoy was positive.

Photofrin and the excimer dye laser used in this trial were kindly supplied by Lederle Japan Ltd. (Tokyo) and Hamamatsu Photonics K.K. (Hamamatsu), respectively.

RESULTS

A total of 64 patients were enrolled between June 1989 and September 1991. Of these, 3 failed to meet the eligibility criteria. Two patients were treated concomitantly with therapies other than PDT during the evaluation term and one died due to another disease. Responses and toxicity were evaluated in 58 and 64 cases, respectively.

Characteristics of evaluable cases are shown in Table II. CR was observed in a total of 48 cases (82.8%). As shown in Table III, CR rates were 95.2% for roentgenographically occult lung cancer, 75.0% for stage I lung cancer, 80.0% for esophageal cancer, 66.7% for gastric

Table II. Characteristics of Evaluable Patients

		Lung A[a]	Lung B[b]	Esophagus	Stomach	Cervix	Bladder
Sex	Male	21	8	4	9		4
	Female			1	3	8	
Age	–39					6	
	40–49	2	1			1	
	50–59	1					
	60–69	9	2	1	7		1
	70–79	9	5	3	4	1	3
	80–			1	1		
PS[c] (EOCG)	0	11	2	3	1	8	4
	1	10	5	2	9		
	2		1		2		
Tumor length(cm)	–1.0	16	8	1	7		
	1.1–2.0	3		2	3		
	2.1–3.0	1					
	3.1–	1		2	2		
Histology	Dysplasia					2	
	Squamous cell					6	
	Wel. dif.[d]	8	8				
	Mod. dif.[e]	9		5			
	Por. dif.[f]	4					
	Adenocarcinoma						
	Wel.dif.[d]				9		
	Mod. dif.[e]				2		
	Signet ring cell				1		
Tumor invasion	CIS[g]	8	Mucosal	2	8		
	Early invasive	8	Submucosal	3	4		
	Unknown	5					
Tumor location							
(Lung)	Vocal cord	4					
	Trachea	2					
	Bronchi						
	Main						
	Lobor	4	3				
	Segmental	9	4				
	Subsegmental	1	1				
	Vocal cord + Main	1					
(Esophagus)	Cervical			1			
	Upper intrathoracic			1			
	Middle intrathoracic			3			
(Stomach)	Upper third				1		
	Middle third				6		
	Lower third				4		
	Pylorus ring				1		
Laser	Argon dye	17	8	5	12		3
	Excimer dye	4				8	1
Total		21	8	5	12	8	4

a) Roentgenographically occult lung cancer. *b*) Stage I lung cancer. *c*) Performance status.
d) Well differentiated. *e*) Moderately differentiated. *f*) Poorly differentiated. *g*) Carcinoma *in situ*.

cancer, 100.0% for cervical cancer and 50.0% for bladder cancer. Excimer dye laser produced CR in roentgenographically occult lung cancer and cervical cancer. No relationship was seen between patients' characteristics and responses in any type of tumor.

Main toxic effects were photosensitivity and cutaneous reactions, seen in 20.3% and 14.1% of patients, respectively. They lasted several weeks. In laboratory tests, transient elevations of GOT and GPT were observed in 10.9% and 12.5% of cases, respectively. Organ- or

Table III. Response Rate for Evaluable Cases

	Number	CR[a]	PR[b]	NC[c]	PD[d]	Response rate (%) CR[a]	Response rate (%) CR[a]+PR[b]
Lung A[e]	21 (4)[g]	20 (4)[g]	1			95.2 (100.0)[g]	100.0 (100.0)[g]
B[f]	8	6		2		75.0	75.0
Esophagus	5	4		1		80.0	80.0
Stomach	12	8	3	1		66.7	91.7
Cervix	8 (8)[g]	8 (8)[g]				100.0 (100.0)[g]	100.0 (100.0)[g]
Bladder	4 (1)[g]	2		2 (1)[g]		50.0 (0.0)[g]	50.0
Total	58 (13)[g]	48 (12)[g]	4	6 (1)[g]		82.8 (92.3)[g]	89.7 (92.3)[g]

a) Complete response. *b*) Partial response. *c*) No change. *d*) Progressive disease.
e) Roentgenographically occult lung cancer. *f*) Stage I lung cancer. *g*) Excimer dye laser.

Table IV. Side Effects of Porfimer Sodium (64 Cases)

	Incidence (%)	Grade[a] 1	2	3	4
Erythrocyte ↓ [b]	1 (1.6)				
Hemoglobin ↓	1 (1.6)	1			
Hematocrit ↓ [b]	1 (1.6)				
Leucocyte ↓	1 (1.6)		1		
Platelet	1 (1.6)				1[c]
GOT ↑	7 (10.9)	6	1		
GPT ↑	8 (12.5)	6	2		
γ-GPT ↑ [b]	3 (4.7)				
Al-p ↑	2 (3.1)	1	1		
LDH ↑ [b]	1 (1.6)				
Total protein ↓ [b]	2 (3.1)				
Urinary protein	1 (1.6)	1			
Urinary sediment[b]	3 (4.7)				
Photosensitivity	13 (20.3)	11	2		
Efflorescence	9 (14.1)	8	1		
Pigmentation	1 (1.6)	1			

a) WHO grade.
b) Not graded.
c) Pretreatment: $6.5\times10^4/mm^3$ → nadir: $2.3\times10^4/mm^3$.

tumor-specific adverse reactions were not seen, as shown in Table IV.

DISCUSSION

The mechanisms by which PDT exerts its cytotoxic effects have been reported.[5] Singlet oxygen is known to play an important role in inducing lethal damage to the cell. Previous reports have shown that HpD is absorbed in the cytoplasm and tends to accumulate in mitochondria, where the first cellular changes take place.[6,7] Cytocidal effects are thought to result from biochemical lesions causing severe disturbances in the tricarboxylic acid cycle. The preferential retention of HpD by malignant tissue makes it possible selectively to induce tumor-specific cytotoxic effects with less damage to surrounding normal tissue.[8] The most effective excitation wavelength for HpD is at the Soret band, at 405 nm. Excitation of HpD at this wavelength produces maximal fluorescence and initiates the photochemical reaction, producing lethal reactive oxygen species such as singlet oxygen, superoxide anion and the hydroxyl radical. Other bands capable of exciting HpD to a lesser extent, Q bands, exist at 488, 514 and 630 nm. A wavelength of 405 nm is therefore used to elicit fluorescence for diagnostic purposes, whereas 630 nm light, although less efficient for excitation, is used for treatment, due to its greater depth of penetration through tissue.

Although PDT already has a history of more than a decade and good results have been reported with cancers of lung,[9] female genital tract,[10] esophagus,[11,12] stomach,[13] bladder,[14] no proper Phase II study has been designed and performed. The main reason is difficulty in the supply of Photofrin, and various investigators have used different drugs or purified hematoporphyrin derivative. Another reason is that it is impossible to evaluate the toxicity of PDT itself because the drug alone has no pharmacological properties that would be useful against tumors.

In Japan, before the start of the current study, the efficacy and safety of PDT were investigated by Kato *et al.*[15] in a multicenter research study project (7 institutions) on PDT organized by the Ministry of Health and Welfare mainly using 2.0 mg/kg Photofrin. One hundred thirty-three cases of gastric cancer (including 120 cases of early stage cancer), 209 cases of lung cancer (69 cases of early stage cancer), 66 cases of esophageal cancer (22 cases of early stage cancer), and 86 cases of other organ cancers were treated. Among early stage cancer cases 77.3% showed a complete response (CR). Concerning safety, 81.4% showed photosensitivity, but in almost all cases it was slight, and only 2.65% needed treatment for dermatitis due to sunburn. Therefore we considered that these results demonstrated the safety and

efficacy of PDT using 2.0 mg/kg of Photofrin for early stage cancers. Based on those results, we designed the present clinical trial for various early stage cancers such as lung, esophagus, stomach, cervix and bladder using Photofrin as a photosensitizer.

In this study, we evaluated the effectiveness of PDT in the treatment of superficial cancers from various organs for the first time nationwide in Japan. Fortunately, patients with cancers of the esophagus, stomach, lung and cervix are generally diagnosed and treated at relatively early stages in Japan owing to systematic screening programs. Presently, PDT is primarily indicated for early stage lesions that are inoperable because of poor general health or poor cardiopulmonary function or refusal of surgery. It is very encouraging that we were able to obtain CR in 82.8% of such patients. The reasons why complete remission was not obtained in all cases were primarily technical problems such as failure to recognize endoscopically the entire extent of cancerous lesions and insufficient photoradiation due to tangential submucosal invasion by the tumor.[10] Improvements of the laser system, quartz fibers and endoscopic equipment are still necessary. Unlike the lung, with its numerous bifurcations making endoscopic maneuvering difficult, and the stomach, with its many folds and pits, the esophagus and cervix are ideal for PDT in that they are straight with a relatively smooth mucosal surface. However, in the lung, esophagus and stomach, there is a possibility of insufficient irradiation with the laser beam due to respiratory movement of the target site. From this point of view, the cervix is ideal for PDT. In bladder cancer, irradiation of the entire bladder wall is necessary for the treatment of refractory multifocal tumors. Usually patients receive only 10–30 J/cm^2 of laser light irradiation because it takes too many hours for irradiation and there is a possibility of causing severely contracted bladder. These problems appear to be related to the different CR rates in different organs.

PDT has proven most beneficial in patients with central-type early stage lung cancers readily accessible to the endoscope. In addition, another advantage of this form of therapy is that it can be used repeatedly, with no apparent side effects from multiple injection of Photofrin. There is no apparent contraindication to using it in patients who have had previous therapy or who are receiving radiotherapy or chemotherapy.[16]

As regards side effects, there were no seriously abnormal laboratory data. GOT and GPT were elevated in 7 and 8 cases out of 64 cases respectively, but none of these were serious. Photosensitivity was the only disadvantage of this modality and required the patients to avoid direct sunlight for at least 4 weeks; however, not all patients followed instructions and photosensitivity was manifested in 13 cases out of 64 cases (20.3%), but all cases were under grade 2 and the percentage of skin photosensitivity cases was lower than in another report.[17]

In conclusion, we have defined indications for endoscopic PDT in esophageal, stomach, lung, bladder and cervical cancers to include patients with inoperable early superficial disease, without lympho-node involvement, where complete remission may be achieved. We hope the results of this study will stimulate further investigation and contribute to the next phase study.

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