Photodynamic Therapy (PDT) for Lung Cancers

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Photodynamic therapy (PDT), a treatment for cancer, uses a photosensitizer and laser irradiation to produce reactive oxygen in cells. In Japan, the United States, and many other countries, PDT is a treatment option for stage 0 (TisN0M0) and stage I (T1N0M0) centrally located early stage lung cancer. PDT can preserve lung function, can be repeated, and can be combined with other therapeutic modalities such as chemotherapy. Recently, mono-L-aspartyl chlorine e6 (NPe6, Laserphyrin), a second-generation photosensitizer with lower photosensitivity than Photofrin (porfimer sodium), was approved by the Japanese government and a phase II clinical study using NPe6 with a new diode laser demonstrated an excellent antitumor effect and low skin photosensitivity. We expect PDT to be widely employed in many fields and the applications of PDT to be extended because of the decreasing cost of laser equipment and lower systemic photosensitivity induced by the photosensitizer. The purpose of this review is to introduce not only recent clinical trials of PDT for centrally located early lung cancer, but also new applications of PDT for cases of peripheral-type, early-stage lung cancers. We also discuss the applications of PDT for advanced lung cancer and combined therapy using PDT and other treatments for lung cancer.

Key Words: Photodynamic therapy, Lung cancer.

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INTRODUCTION TO PHOTODYNAMIC THERAPY AND CELL DEATH

Photodynamic therapy (PDT) is a novel treatment for cancer and certain noncancerous conditions that are generally characterized by proliferation of unwanted or malignant cells.[1,2] The procedure requires exposure of cells and tissues to a photosensitizing drug followed by irradiation with visible light of appropriate wavelength, usually in the red or near-infared region and compatible with the absorption spectrum of the photosensitizer drug. Upon absorption of a photon, the photosensitizer undergoes one or more energy transitions and usually emerges in its excited triplet state. The triplet can participate in a one-electron oxidation-reduction reaction (type I photochemistry) with a neighboring molecule, producing free radical intermediates that can react with oxygen to produce peroxyradicals and various reactive oxygen species (ROS).[3,4] Alternatively, the triplet-state photosensitizer can transfer energy to ground state oxygen (type II photochemistry), generating singlet molecular oxygen, a highly reactive form of oxygen that reacts with many biological molecules, including lipids, proteins, and nucleic acids. The photosensitizers for PDT are primarily porphyrins or porphyrin-related derivatives with hydrophobic aromatic ring structures, and they localize in one or more cellular membranes.[5] Most photosensitizers do not accumulate in cell nuclei, and the potential of PDT to cause DNA damage, mutations, and carcinogenesis is low. The photosensitizer Photofrin (porfimer sodium) preferentially binds to mitochondrial membranes, endoplasmic reticulum, and Golgi complexes in cancer cells. Singlet oxygen species and other ROS that are produced by PDT in the membranes cause photo-oxidative damage to proteins and lipids that reside within a few nanometers of the photosensitizer binding sites. PDT rapidly induces apoptosis, inflammatory reaction, tumor-specific and/or -nonspecific immune reaction and damages the microvasculature of the tumor bed.[2,6–9] With some photosensitizers, the effect on the vasculature is the most important mechanism of their therapeutic effect.

BACKGROUND

In 1978, Dougherty et al.[1] reported the first clinical case of PDT in a patient with metastatic breast cancer to the skin, and in 1978 we began our study of PDT and photodynamic diagnosis using hematoporphyrin derivative and a krypton ion laser or argon dye laser.[10,11] In 1980, we performed the first endoscopic PDT procedure for human lung cancer in a patient with poor cardiopulmonary function in whom surgery was not possible. This was an advanced squamous cell carcinoma obstructing the right main bronchus, resulted in opening of the bronchus by PDT. The second case was an early stage squamous cell carcinoma of the right upper bronchus in March of 1980.[12,13] The patient was a 74-year-old man who refused surgery, and this became the first case in the world in which PDT was performed for an early-stage

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lung cancer. A complete cure was obtained, and he remained disease free for >5 years.[14]

PHOTOSENSITIZER

For lung cancer patients, two kinds of photosensitizers are used. The most common is Photofrin (porfimer sodium). The first health agency approval of PDT with Photofrin was obtained in Canada in 1993 for the treatment of bladder cancer. Subsequently, approval of Photofrin was obtained in The Netherlands and France for the treatment of advanced lung cancers, in Germany for the treatment of early stage lung cancer, and Japan for early-stage lung cancer. Currently, approvals are being sought in >10 additional countries in Europe.[1]

The major side effect of Photofrin itself is skin photosensitivity, which can last as long aso 4 to 6 weeks.[1,2,15] Photofrin remains in cancer cells longer than in normal cells, thus providing some tissue selectivity. When the cancer cells are exposed to 630-nm red light, Photofrin absorbs the light and in the presence of oxygen for toxic radicals.

Phase II clinical trials using Photofrin for early-stage lung cancer were conducted from June of 1989 to March of 1992.[15] The Japanese government approved PDT using Photofrin in October of 1994, and authorized reimbursement through the National Health Insurance began in April of 1996.[16]

In 1995, the U.S. Food and Drug Administration (FDA) approved Photofrin for esophageal cancer, and in 1998, it was approved for the treatment of early non-small cell lung cancer.[1,16]

The other photosensitizer used for lung cancer, is mono-L-aspartyl chlorine e6 (talaporfin sodium, Laserphyrin, NPe6), which was approved by the Japanese government in 2003.[16] Laserphyrin, another effective photosensitize has a major absorption band at 664 nm and with a molecular weight of 799.69. A phase I clinical study using NPe6 suggested that the optimal conditions in terms of safety and efficacy were intravenous administration of 40 mg/m^2 and laser irradiation at 4 hours after administration.[17] A phase II clinical study demonstrated excellent antitumor effects and safety, including lower skin photosensitivity, compared with Photofrin.[18]

LASER EQUIPMENT AND PROCEDURE

In Photofrin PDT, we use either an excimer dye laser (EDL) system, which was developed by the authors and Hamamatsu Photonics Inc. (Shizuoka, Japan), or a YAG-OPO (Ishikawajima Harima Industry Co., Ltd., Tokyo, Japan) laser system. These 630-nm wavelength light beams are transmitted via a quartz fiber inserted through the instrumentation channel of the channel of a fiber-optic bronchoscope. In the EDL system, the frequency was 20 to 60 Hz, and the energy was adjusted to a 4 mJ/pulse. The illumination time generally ranged from 10 to 40 minutes, giving energy densities of 100 to 800 J/cm^2. Outside Japan, a diode laser is currently used for activation of Photofrin.

For Laserphyrin PDT, we use an aluminum gallium indium phosphorus (AlGaInP) diode laser system (Panalas 6405, Matsushita Electric Industrial Co., Ltd., Osaka, Japan).[17,18] The laser wavelength is adjusted to 664 nm, and the power output can be varied from 50 to 500 mW at the fiber tip in a continuous wave mode. The laser system weighs 20 kg and is portable.[17,18]

CRITERIA OF EARLY-STAGE LUNG CANCER

In Japan, the criteria of early-stage lung cancer were strictly defined in 1975.[16] Early-stage lung cancer should be divided into two categories: central type or peripheral type, according to the site of origin. In the central type early-stage lung cancer, most patients have symptoms such as cough, sputum production, or blood-tinged sputum. The tumor must be located only as far as the segmental bronchi and be carcinoma in situ or with only limited invasion into the bronchial wall. The histologic type should be squamous cell carcinoma. In the peripheral type, the tumor should be located in the subsegmental or more peripheral bronchi, <2 cm in diameter, and without evidence of metastasis.

PDT FOR CENTRALLY LOCATED EARLY-STAGE LUNG CANCER

In the United States, the National Cancer Institute has recommended PDT as a treatment option for stage 0 (TisN0M0) and stage I (T1N0M0) centrally located early-stage lung cancer.[1]

In 1997, Cortese et al.[19] reported on a group of 21 patients with 23 centrally located early-stage lung cancers. These patients received 200 to 400 J/cm^2 of 630 nm irradiation after injection of hematoporphyrin derivative. Fifteen patients showed a complete response (CR) after PDT. A CR lasting longer than 12 months was noted in 11 patients (52%). They concluded that PDT may be an alternative to surgery for patients with early-stage squamous cell carcinoma.[19]

In 1988, a multicenter study on PDT for centrally located early-stage lung cancer was performed by the PDT cancer group of the Japanese Ministry of Health, Labor, and Welfare.[20] This study demonstrated a CR rate of 77.3% (51 of 66 lesions), and for cases with lesions <1 cm in diameter, the CR rate was 100% (28 lesions), and the overall recurrence was 15.7 % (eight of 51 lesions).

A prospective phase II study on PDT with Photofrin for centrally located early-stage lung cancer was conducted using either an argon dye laser or EDL from June of 1989 to February of 1992 in Japan.[15,16] In the study, 54 patients with 64 early-stage lung cancers were treated using Photofrin (2.0 mg/kg) and 630-nm illumination of 100 to 200 J/cm^2. Of 59 assessable cancers, 50 were shown to have a CR (84.8%), six had partial response, and three had no response.

While the effectiveness of PDT using Photofrin has been recognized clinically, it is not widely employed. This is due in part to the cost of the laser equipment and the problems posed by the skin photosensitization.[16] Many investigators have shown interest in the synthesis of new photosensitizers that possess lower skin photosensitivity for use in PDT.[21,22]

From April of 1995 to December of 1996, we performed a phase I clinical study of centrally located early-stage lung cancer using Laserphyrin. This second-generation photosensitizer has low photosensitivity and uses a small

diode laser. The results were analyzed in eight eligible patients, and CR was obtained in 87.5%. A phase II clinical study was then conducted to investigate antitumor effects and the safety of Laserphyrin and the diode laser.[18] A total of 10 institutions participated in this study from October of 1997 to March of 2000. Laser irradiation (100 J/cm^2) using a diode laser was performed 4 hours after administration of Laserphyrin (40 mg/m^2). Among 41 patients with 46 lesions, 40 with 45 lesions were eligible for efficacy evaluation. Disappearance of skin photosensitivity was reported within 2 weeks in 28 of 33 patients (84.8%) and in the other seven patients first tested at 15 to 18 days. CR was obtained in 84.6% of lesions (82.9% patients).

In 2002, therapeutic guidelines for lung cancer were established by the Japanese Ministry of Health, Labor, and Welfare using the principles of evidence-based medicine.[16] PDT was recommended as a treatment option for centrally located early-stage lung cancer. Our criteria for the treatment of centrally located early-stage lung cancer using PDT are (1) patients with endoscopically assessable early-stage lung cancer, (2) patients with normal chest x-ray and computed tomography scan, (3) no metastasis to lymph nodes and no distant metastasis revealed by routine clinical diagnostic methods (N0M0), (4) tumor size not >1 cm in greatest diameter.

One can see the important correlation between response rate and tumor size based on better staging methods. For PDT to be successful, it is necessary that tumor growth is limited to the mucosa and submucosa. It has been reported that the depth of tumor invasion as estimated by surface diameter was not always accurate when histopathologic specimens were examined and that some tumors ≤ 1.0 cm may show extracartilaginous invasion.[16] Usuda et al.[23] reported that tumor invasion in layers of bronchial wall deeper than 3 mm may already have tumor spread to regional lymph nodes. To evaluate the depth of tumor is very important for excluding N1 disease. Furukawa et al.[24] reported that the CR rate was 92.8% for lesions <1.0 cm in diameter and 58.1% for lesions ≥ 1.0 cm. Recurrence after CR was observed in nine of 77 lesions (11.7%). The recurrent lesions were treated with a repeat course of PDT in seven patients and an operation in two patients. The overall 5-year survival rate was 57.9%, reflecting the advanced age and comorbidities of this group. Table 1 summarizes the clinical trials done for PDT.

We now can clearly determine the tumor margin using autofluorescence endoscopy, but it is still difficult to evaluate this using conventional bronchoscopy. Improving the assessment of tumor margin and depth of invasion into the bronchial wall using endobronchial ultrasound imaging and optical coherence tomography may greatly improve the quality and efficacy of PDT[25] (Fig. 1). If the tumor recurs, we generally perform PDT again. When additional systemic or local treatment is needed, we administer chemotherapy or radiation or perform an operation for recurrent lesions.

TABLE 1. Centrally Located Early-Stage Lung Cancers Treated with PDT

Study Group	Photosensitizer	CR Rate, % (No. of CR Lesions/Total Lesions)
Furuse et al.[15]	Photofrin	84.8% (50/59)
Cortese et al.[19]	Photofrin	69.6% (16/23)
Kato et al.[18]	Laserphyrin	82.9% (33/39)
Furukawa et al.[17]	Photofrin	92.8% (77/83) (lesions <1.0 cm in diameter)

CR, complete response.

PDT FOR PERIPHERAL LUNG CANCER

Computed tomography screening for lung cancer has attracted much attention for its ability to detect peripheral-type early-stage lung cancer.[26,27] Okunaka et al.[28] reported interstitial PDT for peripheral-type lung cancer by placing an optical fiber inside the tumor using a percutaneous needle. In their study, nine patients were deemed unsuitable for surgery or radiotherapy because of poor cardiopulmonary function. The procedure was carried out with local anesthesia infiltrated into the chest wall, 48 hours after Photofrin administration. Needles containing an internal catheter were inserted percutaneously under computed tomographic guidance. The needles were then extracted and a diffuser fiber with a

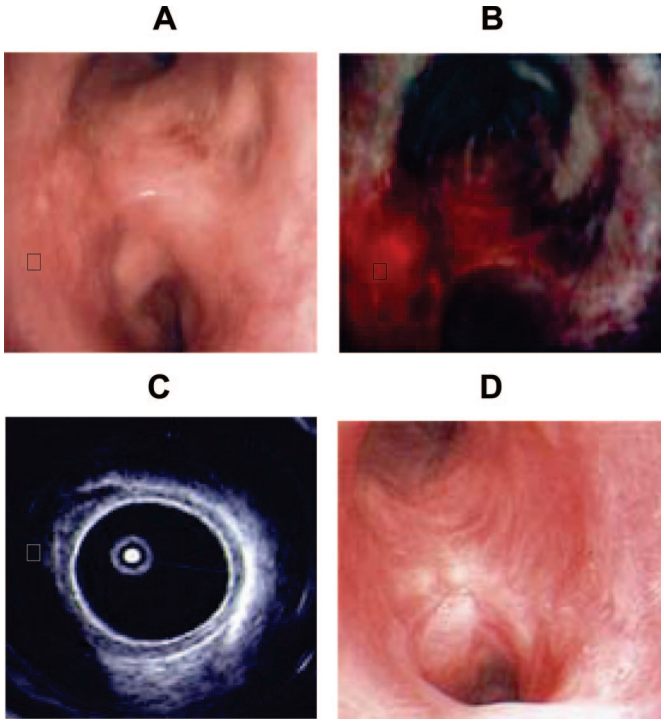

FIGURE 1. A case of 82-year-old man with primary squamous cell carcinoma. The *star* indicates the tumor lesion. (*A*) Hypertrophic-type squamous cell carcinoma located at the left upper bronchus. (*B*) Photodynamic diagnosis using fluorescence bronchoscopy before Laserphyrin PDT. Photodynamic diagnosis image of area of tumor shows red fluorescence. (*C*) Endobronchial ultrasound imaging shows a small tumor before Laserphyrin PDT. The tumor appears as an isoechoic area and was diagnosed as intracartilaginous. (*D*) Three months after Laserphyrin PDT. Complete response was obtained.

2-cm-long tip for light delivery was positioned in the tumor through the catheter. Nine patients were enrolled in this trial, and none had serious complications. Two patients had pneumothorax, in one of which chest drainage was necessary, while the other patient recovered spontaneously. Although no CR was obtained, partial response was achieved in seven cases. Recently, other treatments for peripheral-type lung cancer such as radiofrequency ablation and microwave coagulation were reported to be feasible and safe.[29,30] However, these treatments need to be examined further and discussed. In the future, we need to conduct randomized trials comparing PDT and surgical resection for peripheral lung cancer.

PDT FOR ADVANCED LUNG CANCER WITH AIRWAY OBSTRUCTION

The majority of patients diagnosed with lung cancer have advanced disease, and most patients with inoperable tracheobronchial lesions will require palliative treatment to open an obstructed airway. Diaz-Jimenez et al.[31] reported that PDT and conventional Nd-YAG laser therapy appeared to be equally effective and safe in relieving airway obstruction in advanced lung cancer. An advantage of PDT is the longer time to treatment failure. PDT was found to achieve a lower rate of immediate reopening, and it is thought to be unsuitable when tracheobronchial obstruction requires rapid relief.[32–35] Furukawa et al.[36] reported that overall effective opening of bronchi was achieved in 61 of 81 lesions (75%) treated by PDT, compared with 143 of 177 lesions (81%) treated by Nd-YAG laser. PDT seemed to be useful for obstruction of lobar and segmental bronchus.

PREOPERATIVE PDT

For lung cancer patients with low pulmonary function, it is very important to reduce the extent of lung resection. In 1985, we began using PDT before surgery.[37,38] Okunaka et al.[39] reported that preoperative PDT was performed in 32 patients with lung cancer for the purpose of either reducing the extent of resection or increasing operability. An operation was performed 3 to 9 weeks after PDT. In their study, conversion to an operable condition was achieved in four of five inoperable cases, whereas 23 of 27 patients who were originally candidates for pneumonectomy were managed with lobectomy or sleeve lobectomy. They concluded T4 primary squamous cell carcinoma cases with superficial invasion extending to the upper lobe bronchus are good candidates for combination therapy.

NEW APPLICATIONS OF PDT FOR THE TREATMENT OF LUNG CANCER

It has been reported that PDT induces oxidative stress, localized inflammation, and vascular injury within treatment fields, and these responses can lead to increased expression of angiogenic factors and cytokines. Recently, PDT using Photofrin increased expression of vascular endothelial growth factor and prostaglandin E_2 in murine tumors.[40–42] Ferrario et al.[43] reported that the combination of vascular endothelial growth factor inhibitors or cyclooxygenase-2 improved the therapeutic efficacy of PDT. They demonstrated that PDT-treated tumors have increased expression of matrix metalloproteinases and that pharmacologic inhibition of matrix metalloproteinases can increase the antitumor effect of PDT in vivo. In the future, the combination therapies using PDT and molecule-targeted agents such as vascular endothelial growth factor inhibitors or matrix metalloproteinase inhibitors may become treatment options for patients with lung cancer.

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