Outcome of Photodynamic Therapy Using NPe6 for Bronchogenic Carcinomas in Central Airways >1.0 cm in Diameter


Abstract

Purpose: Most centrally located early lung cancers (CLELC) <1.0 cm in diameter do not invade beyond the bronchial cartilage, and photodynamic therapy (PDT) with Photofrin is currently recommended as a treatment option for such lesions. NPe6 is a second-generation photosensitizer, and because it has a longer absorption band (664 nm) than Photofrin (630 nm), we hypothesized that NPe6-PDT would exert a strong antitumor effect against cancer lesions >1.0 cm in diameter, which are assumed to involve extracartilaginous invasion and to be unsuitable for treatment with Photofrin-PDT.

Experimental Design: Between June 2004 and December 2008, 75 patients (91 lesions) with CLELC underwent NPe6-PDT after the extent of their tumors had been assessed by fluorescence bronchoscopy for photodynamic diagnosis and tumor depth had been assessed by optical coherence tomography.

Results: Seventy cancer lesions ≤1.0 cm in diameter and 21 lesions >1.0 cm in diameter were identified, and the complete response rate was 94.0% (66 of 70) and 90.4% (19 of 21), respectively. After the mass of large tumors and deeply invasive tumors had been reduced by electrocautery, NPe6-PDT was capable of destroying the residual cancer lesions.

Conclusion: NPe6-PDT has a strong antitumor effect against CLELCs >1.0 cm in diameter that have invaded beyond the bronchial cartilage, thereby enabling the destruction of residual cancer lesions after mass reduction of large nodular- or polypoid-type lung cancers by electrocautery. The PDT guidelines for lung cancers should therefore be revised because use of NPe6-PDT will enable expansion of the clinical indications for PDT. Clin Cancer Res; 16(7); 2198–204. ©2010 AACR.

Photodynamic therapy (PDT) consists of using a tumor-specific photosensitizer and laser irradiation to induce production of reactive oxygen species in cancer cells. It is used as a treatment modality for many cancers (1, 2), and it is widely used as a treatment option for solid cancers (3). Since the first modern clinical trial of PDT was reported by Dougherty et al., the photosensitizer Photofrin has been applied to the treatment of many kinds of cancers, and it has been approved by the U.S. Food and Drug Administration for the treatment of centrally located early lung cancer (CLELC) as well as advanced lung cancer. PDT allows lung function to be preserved and is recommended for CLELCs in the evidence-based clinical practice guidelines of the American College of Chest Physicians (4).

The second-generation photosensitizer mono-L-aspartyl chlorine e6 (talaporfin sodium, NPe6), which has a major absorption band at 664 nm, was recently approved for the treatment of CLELC by the Japanese Ministry of Health, Labour and Welfare (5, 6). A phase II clinical study of NPe6 and a diode laser for the treatment of CLELCs showed an excellent antitumor effect and safety, including significantly lower skin photosensitivity than with Photofrin-PDT (7). Because the mechanism of action of NPe6-PDT differs from that of Photofrin-PDT, because the absorption band of NPe6 is longer than that of Photofrin (5, 8–10), we hypothesized that NPe6-PDT would have a stronger antitumor effect on deeper lesions than Photofrin-PDT does.

Based on their analysis of the histopathologic features of CLELC, Furukawa et al. (11) concluded that it is important to accurately define tumor extent before doing Photofrin-PDT. In their study, the complete response (CR) rate of the group with lesions ≤1.0 cm and the group with lesions >1.0 cm in maximum diameter was 92.8% and 59.1%, respectively (11). In our previous study, we classified 264 lesions treated by PDT into four groups based on the maximum diameter of the longitudinal axis—≤0.5 cm group,
Translational Relevance

Photodynamic therapy (PDT) is recommended as a treatment option for centrally located early lung cancers (CLELC), meaning, roentgenographically occult squamous cell carcinomas that are located no more distally than segmental bronchi and, histologically, are either carcinoma in situ or carcinoma associated with only limited invasion. Because CLELC patients who are heavy smokers are at fairly high risk of developing a second primary lung cancer, they require treatment that will preserve their cardiopulmonary function. However, although PDT using Photofrin has not been recommended for large tumors or deeply invasive tumors, such as nodular-type lesions, in the past, if their mass is reduced by electrocautery, PDT with the NPe6 second-generation photosensitizer has been found to be capable of destroying the residual cancer lesion. Thus, the PDT guidelines for lung cancer need to be revised because the availability of NPe6-PDT will enable expansion of the clinical indications to many solid cancers.

0.5 to 0.9 cm group, 1.0 to 2.0 cm group, and >2.0 cm group (5, 6)—and their CR rates were 94.4%, 93.5%, 80%, and 44.1%, respectively. Miyazu et al. (12) examined the relationship between bronchoscopic appearance and the depth of tumor invasion estimated by endobronchial ultrasonography and found that most lesions >1.0 cm in diameter were diagnosed as extracartilaginous lesions by endobronchial ultrasonography and were considered unsuitable for treatment by PDT. In 2003, therefore, PDT was recommended only for small lesions (≤1.0 cm in diameter) in the guidelines established by the American College of Chest Physicians (4). Also in 2003, the Japan Photodynamic Association and the Japanese Society for Laser Surgery and Medicine established the following indications for PDT: (a) early-stage lung cancer based on an endoscopic evaluation, (b) normal chest X-ray and computed tomography findings, (c) no evidence of lymph node metastasis, and (d) tumor diameter no greater than 1.0 cm (5, 6).

Evaluation of tumor extent and tumor depth is very important to the success of PDT (6, 11, 13). We previously assessed the usefulness of a photodynamic diagnosis (PDD) system consisting of autofluorescence bronchoscopy SAFE-3000 (14) and NPe6 as a means of accurately defining the tumor margin before PDT (13). Although it was difficult to clearly identify tumor extent and to accurately radiate the tumor, we were able to clearly detect red fluorescence emanating from the tumor with the PDD system before PDT, and the PDD system consisting of SAFE-3000 and NPe6 allowed more accurate assessment of the tumor margin and the quality and efficacy of PDT (13).

Optical coherence tomography (OCT) is a new micron-scale resolution optical imaging method used in studies of the eye, gastrointestinal tract, and bronchial lesions. Coxon et al. (15) found that OCT can be used to measure airway wall dimensions. Tsuboi et al. (16) obtained high-resolution, cross-sectional microscopic images of tissue by OCT, potentially enabling optical biopsy to substitute for conventional excisional biopsy. Bronchial lumens were evaluated by inserting the OCT catheter into the working channel of the bronchoscope. In OCT images, the bronchial mucosal and submucosal layers appear in the presence of an extracellular matrix, and CLELCs are visualized as unevenly distributed high backscattering areas and loss of the normal layer structure. The depth range of OCT is sufficient to penetrate through the upper layers of exposed tissue on the airway surface (maximal depth average, 2–3 mm), where many endobronchial and bronchogenic carcinomas originate or spread. Ultrasound has been principally used to evaluate the degree of invasion by lung cancer, and OCT can provide high-resolution images of the bronchial surface, thereby enabling detailed examination of intraepithelial lesions (15, 16). Moreover, Lam et al. (17) reported that autofluorescence bronchoscopy-guided OCT imaging of bronchial lesions was feasible and OCT was a promising nonbiopsy tool for diagnosis of lung cancer.

In the present study, we assessed tumor extent by autofluorescence bronchoscopy (SAFE-3000; refs. 13, 14) and tumor depth by OCT, and we retrospectively evaluated the antitumor effect of NPe6 on tumors >1.0 cm in diameter to revise our indications for PDT and propose a new strategy for the treatment of centrally located lung cancers.

Materials and Methods

Photosensitizer. NPe6 (Meiji Seika) is a second-generation, water-soluble photosensitizer with a molecular weight of 799.69, and it has a chlorine annulus. Its maximum absorption peak is at a wavelength of 407 nm, and there is a second peak at 664 nm (5–7, 13). NPe6 has high tumor affinity, and it is excited by visible red light with a longer wavelength of 664 nm, enabling deeper and superior penetration into living tissues (5–7).

Laser unit. A diode laser (Matsushita Electric Industrial Co.) emitting continuous-wave laser light at a wavelength of 664 nm was used as the light source for excitation of NPe6 (5–7, 13). We can use two kinds of fiber-optic tips: a straight type and a cylindrical type. We usually use the straight-type fiber-optic tip. We use the cylindrical type for tumors that have spread to the bronchial wall.

Diagnostic criteria for CLELC. CLELCs were defined as a lung cancer located no more distally than the segmental bronchi, diagnosed histologically as squamous cell carcinoma, and determined to be carcinoma in situ or carcinoma associated with only limited invasion and no evidence of invasion beyond the bronchial cartilage (18–21). We routinely determined tumor depth by OCT to confirm that tumors had not invaded the bronchial wall beyond the level of the cartilage and were confined to the basal membrane of the mucosa, submucosa, or intracartilaginous...

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layers of the bronchial wall (15–17, 22, 23). Immediately before doing PDT, we accurately defined the tumor margin by using autofluorescence bronchoscopy (SAFE-3000) for PDD (6, 13).

**PDD procedure, PDT procedure, and follow-up.** Laser irradiation (664 nm) for NPe6-PDT was transmitted via quartz fibers inserted through the biopsy channel of the endoscope 4 to 6 h after administration of the photosensitizer NPe6 (40 mg/m²; refs. 5–7, 13). The total energy of the laser irradiation was 100 J/cm² (150 mW/cm²). Just before starting the PDT, we did PDD with SAFE-3000 and a diode laser (408 nm) to define the tumor margin based on the red fluorescence emitted by the tumor. Immediately after NPe6-PDT, we again did PDD with SAFE-3000 to compare the intensity of the red fluorescence with its intensity just before the PDT (13). As previous reports (5–7), skin photosensitivity after NPe6-PDT was low. Thus, patients were usually prohibited from going out into direct sunlight for 1 wk after administration of NPe6.

The Japanese government approved the use of PDT for CLELCs in 2003. NPe6 became available in Japan in June 2004 (5–7, 13), and we have been using NPe6 for PDT ever since then. Fiber-optic bronchoscopy with cytologic and histologic examination was done at 1, 2, and 3 mo after PDT and at 3-mo intervals during the first year after that, and 6-mo intervals during the second year. The antitumor effect of the initial treatment was rated based on endoscopic measurements of tumor size with forceps, the morphologic appearance of the tumors, and the pathologic findings in biopsy specimens according to the general rules of the Japan Lung Cancer Society and the Japan Society of Clinical Oncology (5–7, 13). Antitumor effect was evaluated again at 3 mo after PDT, and at that time, the tumors were classified as showing a CR (no microscopically demonstrable tumor in the brushings and or biopsy specimens over a period of 4 wk; refs. 5–7, 13). We used fluorescence bronchoscopy (SAFE-3000) as part of the follow-up examination after NPe6-PDT (6, 13).

**Patient selection.** At the Tokyo Medical University Hospital between June 2004 and December 2008, we found 75 patients with CLELC by bronchoscopic examination because of abnormal sputum production and/or sputum cytologic abnormalities. NPe6-PDT was used to treat patients who met the criteria for NPe6-PDT after obtaining their informed consent in accordance with institutional guidelines (4–6). The clinicopathologic characteristics of the patients are listed in Table 1. Their median age at diagnosis was 75 y (range, 67-84 y). All of the patients were men and heavy smokers with a smoking history of >30 pack-years.

**Statistics.** The relationship between tumor size and clinical response was statistically analyzed by using the Mann-Whitney test (24, 25). The local control after CR by NPe6-PDT until recurrence was plotted by the Kaplan-Meier method (26, 27). The log-rank test was used to compare the relapse-free probability of tumors ≤1.0 and >1.0 cm in diameter.

**Results and Discussion**

Between June 2004 and December 2008, 75 patients (91 lesions) with CLELCs underwent NPe6-PDT and PDD based on the diagnostic criteria indications (Table 1). The histologic type of all of the cancers was squamous cell carcinoma. In accordance with the guidelines for PDT for the treatment of lung cancer, we estimated tumor depth by OCT (15–17, 24) and tumor extent by fluorescence bronchoscopy (SAFE-3000; refs. 13, 14). The Japanese Lung Cancer Society classifies CLELCs on the basis of the endoscopic findings into a thickened type, polypoid type, and nodular type (5–7, 13). The thickened type is characterized by superficial lesions manifested by subtle mucosal changes on the bronchial surface, and it is the predominant type (5–7, 13). Of the 91 lesions examined in this study, 70 had a diameter ≤1.0 cm, and 69 of them were the thickened type and 1 was the polypoid type. Of

**Table 1. Clinicopathologic characteristics of the patients who underwent NPe6-PDT (2004.7-2008.12)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (lesions)</td>
<td>75 (91 lesions)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>67-83</td>
</tr>
<tr>
<td>Gender</td>
<td>Male: 75</td>
</tr>
<tr>
<td></td>
<td>Female: 0</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Positive: 75 (&gt;30 pack-years)</td>
</tr>
<tr>
<td>Histology</td>
<td>Squamous cell carcinoma: 91 lesions</td>
</tr>
</tbody>
</table>

**Table 2. Relationship between the size of tumor and outcome of NPe6-PDT (2004.7-2008.12)**

<table>
<thead>
<tr>
<th>Tumor size ≤1.0 cm</th>
<th>Tumor size &gt;1.0 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic findings</td>
<td>CR</td>
</tr>
<tr>
<td>Thickened type</td>
<td>69 (65) lesions</td>
</tr>
<tr>
<td>Polyloid type</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Nodular type</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CR rate</td>
<td>94% (66 of 70 lesions)</td>
</tr>
<tr>
<td></td>
<td>CR</td>
</tr>
<tr>
<td></td>
<td>17 (15) lesions</td>
</tr>
<tr>
<td></td>
<td>3 (3)</td>
</tr>
<tr>
<td></td>
<td>1 (1)</td>
</tr>
<tr>
<td></td>
<td>90.4% (19 of 21 lesions)</td>
</tr>
</tbody>
</table>
the 21 cancer lesions whose diameter was >1.0 cm, 17 were the thickened type, 3 were the polypoid type, and 1 was the nodular type (Table 2). The results of the evaluation of the efficacy of NPe6-PDT are shown in Table 2. The CR rate of centrally located lung cancers ≤1.0 and >1.0 cm in diameter was 94% (66 of 70) and 90.4% (19 of 21), respectively. We analyzed the relationship between tumor size and clinical response (Fig. 1), and there was no significant difference between tumor size and clinical response. Moreover, there was no significant difference between the efficacy of NPe6-PDT against tumors ≤1.0 and >1.0 cm in diameter (Table 2). The CR rate to NPe6-PDT is higher than that of Photofrin-PDT in our previous studies (5, 6), which suggests that NPe6-PDT has a stronger antitumor effect than Photofrin-PDT against large tumors >1.0 cm in diameter. In a previous study, we found that the CR rate to Photofrin-PDT of cancer lesions >1.0 cm in diameter was 58.1%, and the recurrence rate after a CR was 16.7% (11). Furuse et al. (28) found that longitudinal tumor extent was the only independent predictive factor of a CR after Photofrin-PDT. Based on their data, a CR after PDT requires that the following endoscopic conditions be satisfied: (a) no evidence of lymph node metastasis, (b) a superficial lesion having a maximum diameter of ≤1.0 cm, (c) no invasion of or beyond the cartilaginous layer, (d) a histologic diagnosis of squamous cell carcinoma, and (e) location of the lesion in a position where it can be easily irradiated with the laser (28). However, because NPe6-PDT requires a wavelength of 664 nm (red light), which is longer than the wavelength of 630 nm required by Photofrin-PDT, NPe6 can destroy deeper lesions (29, 30). Figure 2A shows an image of bronchoscopic finding of nodular-type, centrally located lung cancer. As shown in Fig. 2B, first, we did electrocautery by argon plasma coagulation (APC) to reduce the mass of the nodular tumor. Electrocautery has been reported to be the least expensive treatment for endobronchial tumors, and it enabled a CR rate of 80% in a small study (4, 31). Seven days after mass reduction, tumor extent was evaluated by autofluorescence bronchoscopy (SAFE-3000) for PDD, and red fluorescence was excited with the diode laser (408 nm) by using the SAFE-3000 system shown in Fig. 2C, as previously reported (6, 13). PDD revealed that the maximum diameter of the tumor was 1.5 cm, and the PDD system enabled us to clearly identify the tumor margin, independent of the endoscopic findings. We were able...
to accurately define the tumor margin, and immediately after PDT, we did PDD, which is the same as described in our previous report (13). Immediately after PDT, we were able to confirm loss of the red fluorescence from the tumor lesions, meaning that all of the NPe6 in the tumor had been excited by the laser irradiation (664 nm) and that red fluorescence by the tumor could no longer be detected. Thus, no irradiation with the diode laser (664 nm) after the PDT session was required, and the dosimetric assessment in relation of the doses of NPe6 and laser irradiation required for PDT was considered to be appropriate for treatment of the cancer.

Tumor depth was determined by OCT. In Fig. 2D, the tumor is depicted as an unevenly distributed high backscattering area and resultant loss of layer structure in the OCT image, which shows extracartilaginous invasion as previous reports (15–17, 24). However, chest computed tomography showed no evidence of lymph node metastasis. The tumor had been destroyed by NPe6-PDT, and a CR was achieved.

Figure 3A shows an image of a polypoid-type, centrally located lung cancer with a maximum tumor diameter of 2.0 cm obtained during fiber-optic bronchoscopy. As shown in Fig. 3B, we did electrocautery by APC to reduce the mass of the polypoid tumor. We determined the depth of the residual tumor by OCT and diagnosed the tumor as extracartilaginous, but no lymph node metastasis was detected. Although the patient was considered a candidate for surgical resection, the patient strongly desired to be treated by NPe6-PDT because of having poor cardiopulmonary function. For nodular-type tumors with a surface diameter of <0.5 cm, a CR can reportedly be achieved by using Photofrin-PDT (5, 6, 11). Akaoji et al. (32) showed that polypoid lesions and nodular lesions <1.0 cm were limited to within the cartilaginous layer and were unassociated with regional lymph node involvement. Miyazu et al. (12) stated that it is important to treat tumors by Photofrin-PDT with curative intent only if the tumors are intracartilaginous (i.e., limited to within the mucosa and submucosa). They examined the relationship between the bronchoscopic diameter of the tumors and depth of invasion estimated by endobronchial ultrasonography. The results showed that all tumors <1.0 cm in diameter were diagnosed as extracartilaginous, and no CRs were achieved when Photofrin-PDT alone was used to treat these lesions. Konaka et al. (33) examined the relationship between the greatest dimension of lesions and the depth of intrabronchial invasion after the surgery in 70 cases of centrally located lung cancer. The results showed that 77.8% of lesions whose greatest dimension was ≤4 mm were either an in situ carcinoma or a microinvasive tumor within the muscle layer and that 82.9% of lesions whose...
greatest dimension was ≥10 mm had invaded either the cartilaginous layer or the extracartilaginous layer. There was a statistically significant association between the greatest dimension and the depth of intrabronchial invasion in the study (34). It was possible to achieve a CR in nodular-type lesions with a diameter of >1.0 cm by treatment with NPe6-PDT. These results indicate that NPe6-PDT has a strong antitumor effect and can be used to achieve a CR in tumors with extracartilaginous invasion and a diameter of >1.0 cm if no lymph node metastasis is detected by chest computed tomography (34).

As shown in Table 2, a CR was not achieved in four lesions ≤1.0 cm in diameter and in two lesions >1.0 cm in diameter, and in two of these six lesions, the peripheral margin of the tumor was not observed. Figure 4 shows images of bronchoscopic findings of nodular-type, centrally located lung cancer of a 79-year-old man. The tumor was located at the bifurcation between the left B^9 and B^10 bronchi and had spread to the spur between B^{10a} and B^{10b}; the maximum extent of the tumor was >1.5 cm, and the peripheral margin was not observed. In this case, CR was not achieved by NPe6-PDT. These results suggest that accurate assessment of the peripheral margin of the tumor is important to the success of NPe6-PDT.

We examined the association between local control after a CR and tumor size. Figure 5 shows a local control after NPe6-PDT and analyzed the local control until recurrence after CR. There was no significant difference of local control after CR by NPe6-PDT between the groups whose tumor diameter was ≤1.0 and >1.0 cm (P = 0.778).

In conclusion, NPe6-PDT has a strong antitumor effect against centrally located lung cancers >1.0 cm in diameter that have invaded beyond the bronchial cartilage as estimated by OCT. For tumors >1.0 cm in diameter, mass reduction by electrocautery or a high-power laser may play an important role in the success of PDT in cases without lymph node metastasis. Thus, the PDT guidelines for lung cancers, which were established based on data obtained when Photofrin-PDT was used to treat lung cancer, may need to be revised. Finally, we recommend NPe6-PDT for the treatment of centrally located lung cancers >1.0 cm in diameter if there has been no lymph node metastasis. Moreover, a CR by large tumors, such as nodular-type lung cancers, which have invaded the extracartilaginous layer, can be achieved by using NPe6-PDT after mass reduction by APC or with a high-power laser such as Nd:YAG laser.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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