Photodynamic Therapy of Non–Small Cell Lung Cancer

Narrative Review and Future Directions

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Abstract

Photodynamic therapy (PDT) is an established treatment modality for non–small cell lung cancer. Phototoxicity, the primary adverse event, is expected to be minimized with the introduction of new photosensitizers that have shown promising results in phase I and II clinical studies. Early-stage and superficial endobronchial lesions less than 1 cm in thickness can be effectively treated with external light sources. Thicker lesions and peripheral lesions may be amenable to interstitial PDT, where the light is delivered intratumorally. The addition of PDT to standard-of-care surgery and chemotherapy can improve survival and outcomes in patients with pleural disease. Intraoperative PDT has shown promise in the treatment

of non–small cell lung cancer with pleural spread. Recent preclinical and clinical data suggest that PDT can increase antitumor immunity. Crosslinking of signal transducer and activator of transcription-3 molecules is a reliable biomarker to quantify the photoreaction induced by PDT. Randomized studies are required to test the prognosis value of this biomarker, obtain approval for the new photosensitizers, and test the potential efficacy of interstitial and intraoperative PDT in the treatment of patients with non–small cell lung cancer.

Keywords: photodynamic therapy; non–small cell lung cancer; intraoperative photodynamic therapy; interstitial photodynamic therapy

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Photodynamic therapy (PDT) has been approved for the treatment of non–small cell lung cancer (NSCLC) for more than 15 years (1, 2). In PDT, systemic administration of a light-sensitive drug (i.e., photosensitizer), is followed by illumination of the target tissue with visible light that leads to the generation of reactive oxygen species, notably singlet oxygen (3). This results in the destruction of the tumor by a combination of direct cellular and secondary vascular effects (4). In addition to local tumor ablation, PDT has been shown to enhance antitumor immunity in both preclinical and clinical settings (5–7). PDT can be used as solo

therapy or in combination with surgery, chemotherapy, or standard radiation therapy (8–10). The primary indications are for obstructive disease and symptom palliation in patients with tumors that are not eligible for standard surgery and radiation therapy.

Currently, the most commonly used photosensitizer is porfimer sodium (Photofrin; Pinnacle Biologics Inc., Bannockburn, IL). After intravenous injection, porfimer sodium is retained in tumor and to a lesser degree in normal tissue (11). The therapeutic effect is obtained by illuminating the target tumor tissue and margins with activating laser light with

630 ± 3 nm wavelength, about 48 hours after photosensitizer administration (12–14). The light is transmitted through optical fibers with either a lens or a cylindrical diffuser (CD) end for superficial or circumferential illumination, respectively. The procedure is usually performed with flexible bronchoscopy under moderate sedation and topical anesthesia to prevent coughing. Rigid bronchoscopy under general anesthesia is reserved for patients with marginal lung function to prevent hypoxia or in those requiring a prolonged procedure. This is followed by a repeat bronchoscopy in 2 days to remove any tissue debris and

retained secretions distal to the lesion, which is often inflamed as a consequence of the cytotoxic reaction.

In the case of porfimer sodium illumination, additional illumination can be performed within 6 to 7 days for any residual tumor, when the photosensitizer concentration is still in the therapeutic range. It should be emphasized that when PDT is used to achieve complete pathological response, the extent of the tumor should be mapped and any synchronous airway lesion should be confirmed or excluded before the procedure. This is done by endobronchial ultrasonography and bronchoscopy (13, 14).

The major complications of PDT with porfimer sodium are photosensitivity and hypoxia. The photosensitivity usually lasts for 4 to 6 weeks. During that time, the patients are instructed to use sunglasses and cover the skin when exposed to direct sunlight or bright indoor light. Patients are also instructed to expose their skin to ambient indoor light, to allow for a slow and controlled photobleaching of the porfimer sodium. After PDT treatment, hypoxia may result from tissue debris and retained secretions within the first 24 to 48 hours after illumination, when the airway narrowing or obstruction caused by inflammation and associated edema is greatest (12, 13). A follow-up bronchoscopy is performed as soon as manifestations of bronchial obstruction emerge.

Several groups reviewed the use of PDT in the treatment of lung cancer. Recently, Simone and Cengel published a review paper on the mechanism of and rationale for using PDT to treat lung cancer and malignant pleural mesothelioma (15). An earlier review by Simone and colleagues focused on the use of PDT in the treatment of roentgenographically occult, early-stage, and endobronchial NSCLC (16). Ernst and LoCicero published a review paper that provides a short summary on the use of PDT in the treatment of lung cancer (14). Kato reported the experience of a single center in the use of PDT and photodiagnosis in Japan (17). Allison and colleagues described the mechanism of action of PDT and different photosensitizers and light sources in the treatment of head and neck, lung, gynecological, gastrointestinal, and genitourinary cancer (18). Chen and

colleagues reviewed the use of PDT in unresectable esophageal and lung cancer (19). Loewen and colleagues reviewed the use of porfimer sodium and 2-[1-hexyloxyethyl]-2 devinyl pyropheophorbide-a (HPPH) in the treatment of early-stage lung cancer and reported early results with HPPH (20). Banerjee and George reviewed the use of bronchoscopy in photodynamic diagnosis and therapy in lung cancer (21).

This review is tightly focused on palliative and curative PDT in lung cancer. It highlights a new technique for interstitial PDT, examines a new approach for targeted PDT in lung cancer, and includes a description of a promising biomarker for quantifying PDT-induced photoreaction. It presents the principles that can allow the use of PDT in combination with new immunotherapies. The overall objective of this focused review paper is to offer new perspectives for the use of PDT in the treatment of NSCLC.

Current Indications for PDT

In palliative settings, PDT effectively reduces airway obstruction and improves respiratory function (22–26). One retrospective study that included 529 operations on 133 patients reported that PDT is safe and effective in the treatment of bleeding tumors that block the tracheobronchial tree, in particular (22). These researchers reported that PDT was effective even in severely debilitated patients with profound shortness of breath from advanced malignancy who failed conventional core-out or laser treatments. A pilot study, using PDT with hyperbaric oxygen for enhanced oxygen-dependent tumor lysis, demonstrated a significant improvement in controlling bleeding and obstructive symptoms (27, 28).

In the last 10 years, several clinical studies yielded encouraging results in the treatment of locally advanced NSCLC with airway obstruction. Weinberg and colleagues combined porfimer sodium-mediated PDT with high-dose-rate brachytherapy and obtained local tumor control in 78% (29). Ross and colleagues performed porfimer sodium-mediated PDT as additional induction modality alone or in combination with chemotherapy and/or radiation. They achieved partial response in 100%, and

down-staging for surgery was possible in 54% (30). No specific explanation was provided for the rationale and sequence of this multimodality approach. Akopov and his team demonstrated that preoperative induction PDT combined with neoadjuvant chemotherapy and additional intraoperative PDT of the resection margins can be beneficial in the treatment of advanced stages of NSCLC using Radachlorin as photosensitizer (31, 32). Ji and colleagues reported that PDT with Radachlorin as solo therapy can induce complete response in 20% of the cases and partial response in 70% of the cases (33).

Other studies reported that PDT can effectively reduce tumor size of inoperable tumors to make them operable or allow the treating physician to change the intended pneumonectomies to lesser anatomical lung resections (34–36). In a prospective randomized study in 42 patients with stage IIIA and IIIB disease, the efficacy and safety of PDT with chlorin e6 in combination with standard chemotherapy was compared with that of chemotherapy alone (37). The results of this study suggest that neoadjuvant PDT is safe and effective in converting inoperable into operable tumors and that neoadjuvant PDT can improve the completion of surgical resection in patients with stage III NSCLC.

Although surgical resection remains the standard treatment in early-stage NSCLC, PDT is also used with curative intent in patients with centrally located early-stage NSCLC (without cartilage involvement), either occult or overt on currently available imaging (15). The occult lesions are usually detected on screening sputum cytology in high-risk groups and subsequently confirmed by bronchoscopy. In Figure 1 we show typical bronchoscopic images during and after PDT of carcinoma *in situ* in the left upper lobe and distal left main stem. This patient was successfully treated with PDT using 1 mg/kg porfimer sodium and 630-nm laser light delivered through CD at 400 mW/cm for 500 seconds to administer 200 J/cm.

PDT was also used in the treatment of early-stage NSCLC in patients who were otherwise fit enough for surgical resection (13). Ono and colleagues demonstrated an impressive safety profile of PDT in 30 patients with roentgenographically occult lung cancer who did not experience any major treatment complications (38). In

Figure 1. (A) An optical fiber with 20-mm cylindrical diffuser end (Optiguide Fiber Optic; CuraScript/ Pinnacle Biologics, Chicago, IL). (B) This bronchoscopic image shows the photodynamic therapy (PDT) catheter (arrow) during illumination of the left upper lobe and distal left main stem to treat the carcinoma *in situ*. (C) Bronchoscopic image showing the mucus sloughing of the distal left main stem and the left upper lobe (arrow) 2 days post PDT. (D) Bronchoscopic image showing the distal left main stem and left upper lobe 4 weeks post PDT.

another study, a complete response was seen in 100% of 33 patients with roentgenographically occult lesions 1 cm or smaller, whereas only 38% of lesions with larger than 1 cm diameter had complete remission (39). Imamura and colleagues used PDT with porfimer sodium to treat 29 patients with 39 roentgenographically occult lesions of less than 1 cm (40). Complete response was much higher in superficially infiltrative lesions (76%) than in nodular lesions (43%). Disease recurrence was seen in 23% of patients, and the 5-year survival rate was 56%. In a very similar later study by Endo and colleagues, with 48 patients, the complete response was as high as 94%, and the 5-year and 10-year survival rates were 81 and 71%, respectively (41).

The response to PDT of more infiltrative and larger early-stage lesions is not as impressive as that of roentgenographically occult lesions less than or equal to 1 cm. A Mayo Clinic study on 10 patients achieved complete response only in the lesions with invasion depth of less than 5 mm (42). Later, as an

expansion of the same study, complete response was seen only in 48% of lesions with surface area of 3 cm² or less (43). In another study from the Mayo Clinic, PDT was used in 21 patients with early-stage lung cancer who had declined surgical resection. Complete response was observed in 70% of lesions, and 48% of patients required subsequent surgery for incomplete response, recurrence, or second primary (44). A number of other studies have demonstrated similar pathological response and safety profile for PDT in early-stage lesions larger than 1 cm (45–48).

PDT for centrally located early lung cancer has shown promise in several clinical studies. Furukawa and colleagues reported complete response in 92.8% for lesions that were less than 1 cm in thickness and 58.1% response in thicker lesions, in a study that included 93 patients (49). Moghissi and colleagues reported complete response in 100% of their patients treated with porfimer sodium PDT (50). Corti and colleagues, in 40 patients, used two different photosensitizers, porfimer sodium II and

hematoporphyrin derivative, and reported complete and partial response of 72 and 20%, respectively (51). Usuda and colleagues conducted three studies using talaporfin sodium as sole photosensitizer. They obtained complete response rates ranging from 90.4 to 100% (52–54).

In the past 10 years, a total of 493 patients participated in prospective clinical studies that evaluated and validated the benefit of PDT, with different photosensitizers, in the treatment of early-stage (n = 370) and advanced (n=123) NSCLC as detailed in Tables 1 and 2. The complete response for early-stage disease ranged from 72% to an impressive 94% and 100% (Table 1). In the case of advanced disease, the range of local control and partial response was reported to vary from 78 to 100%, respectively (Table 2).

Targeted and Low-Phototoxicity Photosensitizers

Although PDT with the approved drug porfimer sodium is highly effective, the persistence of the photosensitizer in skin and the associated photosensitization necessitates prolonged complete protection from bright light. HPPH was identified as a photosensitizer with reduced phototoxicity and promising clinical outcomes (20, 55–57). HPPH has been shown to be specifically retained by tumor cells as compared with stromal fibroblastic cells. This feature is demonstrated in Figure 2, by the example of a reconstituted coculture of cells derived from lung squamous carcinoma (58). The enhanced loss of HPPH from stromal cells is probably the main reason for the relatively short-time photosensitivity (7–14 d) of HPPH, in comparison to porfimer sodium.

Other second-generation photosensitizers, like temoporfin (Foscan), talaporfin sodium, and chlorin e6, have been explored for PDT of NSCLC (37, 54, 59, 60). All of these are associated with short-time photosensitivity (2–14 d). In two phase II studies involving 41 and 75 patients, respectively, talaporfin sodium was used to treat early-stage central superficial tumors 2 cm or smaller, with promising results. In the first study, 85% of patients achieved complete response, and in the second study, complete response rates were 94% for lesions 1 cm or

Table 1. Photodynamic therapy studies for early-stage non-small cell lung cancer in the last 10 years

Publication	Indication	Photosensitizer	No. of Patients	Outcome
Furukawa et al., 2005 (49)	CLELC	Porfimer sodium	93	CR: 92.8%/58.1% (less/greater than 1-cm lesion)
Corti et al., 2007 (51)	CLELC	Porfimer sodium II (50%), hematoporphyrin derivative (50%)	40	CR: 72%, PR: 20%, NR: 6%
Usuda et al., 2007 (52)	CLELC	Talaporfin sodium	29	CR: 92.1%, PR: 7.9%
Moghissi et al., 2007 (50)	CLELC	Porfimer sodium	21	CR: 100%
Endo et al., 2009 (41)	CLELC	Porfimer sodium	48	CR: 94%
Usuda et al., 2010 (54)	CLELC	Talaporfin sodium	75	CR: 94%/90.4% (less/greater than 1-cm lesion)
Usuda et al., 2010 (53)	CLELC	Talaporfin sodium	64	CR: 100%

Definition of abbreviations: CLELC = centrally located early lung cancer; CR = complete response; NR = no response; PR = partial response.

smaller and 90% for lesions larger than 1 cm (54, 60).

Intraoperative PDT

Local recurrence of NSCLC remains a significant problem despite modest improvement in survival from adjuvant chemotherapy (61). The rate of recurrence increases with higher tumor, nodal, or overall pathologic stage (62–64). It has been postulated that the presence of microscopic residual disease after surgical resections is a significant cause for local recurrence that will decrease survival of patients (65–67). One possible solution is the use of intraoperative PDT, where the margins in the surgical bed are illuminated before wound closure to treat undetected viable

cancer cells, which could lead to a reduction in local recurrence (68, 69). Several studies reported that intraoperative PDT with porfimer sodium or temoporfin (Foscan) can potentially improve survival of patients with malignant pleural mesothelioma (59, 68, 69).

Outcomes from small phase I and II studies demonstrated that intraoperative PDT can result in median survival of 31.7 to 41.2 months in patients with malignant mesothelioma, who typically have median survival of about 12 months (15, 70). In a phase II study on 22 patients with cT4 NSCLC and pleural spread, intraoperative hemithoracic pleural PDT using porfimer sodium was used after partial or complete tumor debulking. Statistical analysis revealed a 73.3% local control rate at 6 months and overall median

survival of 21.7 months (69). A very recent retrospective study evaluated the benefit of adding intraoperative PDT in the treatment of patients with thymoma and those with pleural spread of NSCLC (71). This study compared the mean survival of 51 patients who underwent surgery and chemotherapy to 18 who received intraoperative PDT with porfimer sodium, in addition to these standard therapies. It was found that the mean survival of the PDT group was 39 versus 17.6 months of the standard therapy group. Thus, intraoperative PDT has shown promise in improving survival in patients who can undergo a macroscopically complete resection in a lung-sparing procedure.

Our research group is currently evaluating the potential benefit of intraoperative temoporfin PDT in

Table 2. Photodynamic therapy studies for advanced non-small cell lung cancer in the last 10 years

Publication	Indication	Photosensitizer	No. of Patients	Outcome	Comments
Ross et al., 2006 (30)	IIA–IIIB	Porfimer sodium	41	PR: 100%	Induction PDT: PDT alone, PDT with Chemo and/or RT followed by surgery
Weinberg et al., 2010 (29)	IA, IIA, III, IV	Porfimer sodium	9	Local tumor control: 78%	Combined PDT and HDR
Ji et al., 2013 (33)	IIIA	Radachlorin	10	CR: 20%, PR: 70%	PDT as unique treatment modality
Akopov et al., 2013 (32)	IIIA and IIIB	Radachlorin	20	PR: 100%	Induction PDT with Chemo, followed by surgery and intraoperative PDT of the resection margins
Akopov et al., 2013 (31)	II–III	Radachlorin	22	PR: 95%	Induction PDT with Chemo, followed by surgery and intraoperative PDT of the resection margins
Akopov et al., 2014 (37)	IIIA and IIIB	Radachlorin	21	PR: 90%/76% (with/without PDT)	Prospective randomized study: Induction Chemo with PDT compared with Chemo alone, followed by surgery

Definition of abbreviations: CR = complete response; Chemo = chemotherapy; HDR = high-dose-rate brachytherapy; PDT = photodynamic therapy; PR = partial response; RT = radiotherapy.

Figure 2. Tumor epithelial cells were isolated and enriched by proliferation under selective culture conditions *in vitro*. (A) Phase contrast image of tumor cell and fibroblast ($\times 100$). (B) Fluorescence image of the fibroblast stained with carboxyfluorescein succinimidyl ester dye. (C) Fluorescence image of the 2-[1-hexyloxyethyl]-2 devinyl pyropheophorbide-a. The image on the right shows preferential retention of this photosensitizer 24 hours after the initial exposure.

patients with resectable primary NSCLC with ipsilateral thoracic nodal (N1 or N2) or T3/T4 disease (NCT 01854684). In this pilot study, after the surgical removal of the primary tumor and immediately before PDT, detection fibers are placed within the cavity (Figure 3). Before illumination, warm saline is poured into the pleural cavity, to match the refractive index of the optical fiber and tissue. A therapeutic red light is delivered to the thoracic cavity with an optical fiber sheathed within a balloon device (CDB-30; Medlight SA, Ecublens, Switzerland) inflated with sterile saline (Figure 3B). The light dose is measured

with isotropic detectors that are placed in the thoracic cavity (Figures 3C and 3D). A total of five subjects were treated with low-dose temoporfin (0.04 mg/kg) at 10 J/cm^2 with no serious adverse events.

Interstitial PDT

If PDT is to be used for deep-seated and large tumors ($>1 \text{ cm}$), interstitial PDT (I-PDT) is necessary (72). The laser fiber is inserted into the tumor through a needle or a catheter that was placed under computed tomography (CT) or ultrasound imaging guidance. The light is delivered

from the diffuse tip of a CD. Typically, multiple CD fibers are used to illuminate the target tumor (72). The number and location of the CDs depends on the tumor size and location. Image-based pretreatment planning is often used to determine how many CDs are needed for complete and safe illumination of the clinical target volume (73–75). Recent advancements in computer simulations enable near real-time planning and dosimetry (74–79).

It is conceivable that I-PDT would be suitable for the treatment of locally advanced and large NSCLC. One pilot study in Japan included nine patients with peripheral lung tumors treated with I-PDT through catheters placed percutaneously under CT guidance (80). Depending on tumor size, up to six catheters were placed into the tumor. In large tumors, more than one I-PDT session was conducted. All patients underwent histological assessment at 1 and 4 weeks post therapy using CT-guided needle biopsy and/or brush cytology. Seven of the nine patients (78%) demonstrated partial response, and no patient had progressive disease at 4 weeks. Two of the nine patients developed pneumothorax, with one patient requiring chest tube placement.

Biomarkers for Quantifying Photoreaction

Significant efforts have been made to find a biomarker for the early PDT response. Several preclinical and clinical studies, at our institution, have shown that covalent homodimeric crosslinking of signal transducer and activator of transcription-3 (STAT3) is highly sensitive and proportional to the photosensitizer-mediated photoreaction (56, 81, 82). The photosensitizer-dependent photoreaction produces singlet oxygen and other reactive oxygen species, which oxidize cellular substrates such as lipids and proteins. The photoreaction results in a proportional formation of cross-linked proteins with a particularly high specificity for STAT3 (82). The fact that all cells of the body contain approximately the same amount of STAT3 renders its PDT-dependent crosslinking to be a universal marker for the photoreaction achieved during PDT. The assay must be performed on tissue collected from the treatment site

Figure 3. (A) Procedure involving light illumination of the thoracic cavity during intraoperative photodynamic therapy (PDT). (B) Balloon device used to deliver diffused laser light within the cavity. Although this is a therapeutic red light, the high intensity is shown as bright white light. (C) The isotropic probes (arrow) in a transparent tube secured with a suture within the cavity, before PDT. (D) Portable laser and light dosimetry system. Each detector is marked with its location, in this exemplary case (from left to right): Apex, posterior mediastinum (PM), pericardium (PERI), diaphragm (DIA), pulmonary hilum (PH), posterior diaphragmatic sulcus (PS), anterior diaphragmatic sulcus (AS), anterior mediastinum (AM).

immediately after PDT. The tissue can be fresh or snap frozen. This rather standard assay can be completed within 24 hours post PDT. It has the potential to assist physicians in evaluating the response to PDT early enough to consider other options. However, more prospective studies are required to test the prognosis value of this biomarker.

In a recent clinical study in using PDT to treat early-stage oral cancer, we detected STAT3 dimers only in head and

neck squamous cell carcinoma biopsies collected immediately after PDT (56). A threshold level of 10% STAT3 crosslinking appeared to be associated with an effective and durable response of SCC to HPPH-PDT (56). In Figure 4 we present preliminary results for the degree of STAT3 crosslink as a function of HPPH-mediated PDT in lung cancer cells. These data are in agreement with a report from another group (83), and demonstrate that STAT3 crosslinking may be used to

detect photoreaction and the response to PDT treatment within 24 hours (56, 82).

PDT and Immune Response

Several studies have demonstrated that PDT can enhance antitumor immunity (5, 6, 84). Early studies conducted by Canti and colleagues (85) and Korbelik and colleagues (86) in murine models showed that mice whose tumors had been ablated by PDT

Figure 4. Response of TEC-1-2 lung tumor epithelial cells to 2-[1-hexyloxyethyl]-2 devinyl pyropheophorbide-a (HPPH) photodynamic therapy by (A) crosslinking signal transducer and activator of transcription-3 (STAT3), and (B) inducing cell death as measured 24 hours later. Ctl = control; PS = photosensitizer.

were able to resist subsequent tumor challenge and possessed immunologic memory. Clinical PDT also increases antitumor immunity. PDT of multifocal angiosarcoma of the head and neck resulted in increased immune cell infiltration into distant untreated tumors that was accompanied by tumor regression (87). PDT of basal cell carcinoma increased immune cell reactivity against a basal cell carcinoma-associated antigen (7). Finally, a recent study combining radical lung-sparing pleurectomy with PDT for treatment of malignant mesothelioma indicated that disease recurrence in these patients was more indolent and occurred locally rather than at distant sites (70), leading investigators to speculate on the possibility of PDT-enhanced antitumor immunity.

PDT can activate both humoral and cell-mediated adaptive antitumor immunity (88); however, most studies have shown that enhanced antitumor immunity after PDT is dependent on CD8⁺ T cells (86). Therefore, the importance of the humoral arm of antitumor immunity after PDT

remains unclear, and most mechanistic studies to date have focused on PDT modulation of cell-mediated antitumor immunity. Activation of CD8⁺ T cells is primarily dependent on dendritic cell maturation and activation. Activated dendritic cells stimulate the differentiation and activation of T cells through expression of antigenic peptide: MHC complexes, costimulatory molecules, and cytokines, resulting in induction of antitumor immunity. PDT results in the maturation and activation of dendritic cells (89) and migration to the draining lymph nodes, where they are believed to stimulate T-cell activation (89, 90). Dendritic cell maturation after PDT is believed to be due in part to recognition of PDT-induced immunologic tumor cell death (88, 91–94).

Interestingly, several studies have suggested that PDT efficacy is dependent, in part, on the presence of an active immune response. Long-term tumor response is diminished or absent in immunocompromised mice (86, 95). Reconstitution of these mouse strains with bone marrow or T cells from

immunocompetent mice resulted in increased PDT efficacy. Clinical PDT efficacy also appears to depend on antitumor immunity. Patients with vulvar intraepithelial neoplasia who did not respond to aminolevulinic acid were more likely to have tumors that lacked major histocompatibility complex class I molecules (MHC-I) than patients who responded to aminolevulinic acid (96). MHC-I recognition is critical for activation of CD8⁺ T cells, and tumors that lack MHC-I are resistant to cell-mediated antitumor immune reactions (97). Patients with vulvar intraepithelial neoplasia who responded to PDT had increased CD8⁺ T cell infiltration into the treated tumors as compared with nonresponders. Immunosuppressed and immunocompetent patients with actinic keratoses and Bowen disease had similar initial response rates to PDT; however, immunosuppressed patients exhibited greater persistence of disease or appearance of new lesions (98). These studies suggest that combination therapies of PDT and immune-modulating agents could lead to improved overall responses. This hypothesis is supported by recent work showing that epigenetic agents that increase MHC-I expression on tumor cells increase PDT efficacy (99).

In addition to epigenetic mechanisms, antitumor immunity is frequently inhibited in patients with cancer as a result of local immune suppression mediated by suppressive cells and immune checkpoints (100). Suppressive cells include regulatory T cells; preclinical studies have shown that inhibition of regulatory T cells can enhance PDT-induced antitumor immunity and overall efficacy (101). Importantly, blockade of the immune checkpoint (anti-programmed death-1 and one of its ligands) axis has proven to be effective in clinical trials of NSCLC (102–105). Given that checkpoint blockade cannot create tumor-specific T-cell responses in the absence of an existing response, it is logical to assume that therapies that increase tumor-specific T cells will benefit/synergize with checkpoint blockade therapies. The proven ability of PDT to enhance antitumor immunity makes it an ideal therapy to combine with checkpoint blockade therapy. A future challenge will be demonstrating to what extent the PDT of NSCLC will engage the adaptive immune system to control

Table 3. Key indications of photodynamic therapy in the treatment of lung cancer

Indication	Suggested PDT Procedure
Palliative	
Locally advanced and peripheral tumors	Interstitial PDT using image guidance and treatment planning.
Pleural disease and margin control	Intraoperative PDT by transthoracic or thoracoscopic irradiation after tumor resection and complete removal of the macroscopic disease.
Definitive	
Early stage, superficial, and centrally located endobronchial NSCLC tumors	Bronchoscopic irradiation with lesser phototoxicity using new efficient photosensitizers

Definition of abbreviations: NSCLC non-small cell lung cancer; PDT = photodynamic therapy.

cancer recurrence and whether combination therapies that include PDT and therapeutics targeting immune suppression enhance overall survival of patients.

Summary

Multiple clinical studies have demonstrated that PDT is an effective palliative therapy for relieving airway obstruction from NSCLC. It is effective for eradication of thin (<1 cm) noninvasive endobronchial lesions that are accessible to conventional bronchoscopes. Thicker and deeper lesions will not respond well because of limited light penetration (<1 cm). In these lesions, I-PDT may hold promise. This technique allows delivering light intratumorally; thus, it can be used to treat large tumors. Although feasible, more studies are required to test its safety and efficacy. Pretreatment planning and real-time dosimetry could further improve the administration of I-PDT that can also be used for the treatment of peripheral lung tumors.

PDT can be used in combination with other therapeutic modalities, such as chemotherapy, radiotherapy, and surgery, in the treatment of lung cancer (15). Many clinical studies have shown that PDT may also have a role as a neoadjuvant therapy to reduce the proximal extent of tumors and the management of malignant pleural effusions from NSCLC. Therefore, the key indications for the use of PDT in clinical care for palliation of NSCLC are: locally advanced and peripheral tumors, pleural disease, and margins control. The key indications for the use of PDT for definitive treatment of NSCLC include: early stage, superficial, and centrally located endobronchial tumors. The palliative and definitive indications are summarized in Table 3.

Phototoxicity is the main side effect limiting the widespread clinical acceptability of PDT. Introduction of second-generation photosensitizers, such as temoporfin, HPPH, and chlorin e6, has decreased the duration of light avoidance for patients from 40 to 60 days to 14, 7, or 1 to

2 days, respectively. Another limiting factor in the use of PDT is the need to wait 24 to 96 hours from the time of the photosensitizer administration to the laser light illumination, also known as drug–light interval. This obstacle may be minimized with the use of vascular-targeted photosensitizer (e.g., chlorin e6) that reduces the drug–light interval to 3 hours, which has shown promise in the treatment of NSCLC.

Recent preclinical and clinical data suggest that PDT effectively triggers the immune response to obtain distant control of a metastatic cancer. It has been postulated that the immune response may be responsible for the improved outcomes of patients with mesothelioma after intraoperative PDT (15). This approach could be used to develop new PDT regimens in the treatment of metastatic lung cancer in combination with checkpoint blockade (such as the PD-1 axis), which have shown promise in patients with advanced-stage NSCLC (106).

Preclinical and clinical studies demonstrated that the degree of crosslinking of STAT3 molecules is a reliable biomarker to quantify the PDT-induced photoreaction. Additional prospective studies will have to confirm that STAT3 crosslinking is a reliable marker for the early PDT response. Multicenter randomized clinical studies are required to support new indications for the use of these new photosensitizers in the treatment of lung cancer. ■

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