Photodynamic Therapy for Airway Malignancies: The Ohio State University Experience Since 1998

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Abstract

Although treatment of cutaneous breast and lung cancers with photodynamic therapy (PDT) was initiated in the 1970s and 1980s, approval of its use in the United States for non–small cell lung cancer (NSCLC) came in 1998. That same year, the first PDT procedure for NSCLC was performed at The Ohio State University (OSU), and since then, approximately 1000 cases of airway malignancies have been treated with PDT there. Based on this extensive experience at OSU, PDT has emerged as an effective alternative for the palliative treatment of hemoptysis, obstructive metastatic disease to the lungs, and tracheal lesions, with a low rate of complications. Moving beyond its role for symptomatic relief, PDT also may prove to be useful in the curative setting as induction therapy in conjunction with other modalities, such as surgery and chemotherapy, and for early airway cancer. Further investigation into the indirect systemic effects and associated inflammatory reactions with PDT may make the term photoimmunotherapy a more accurate designation. (JNCCN 2012:10[Suppl 2]:S9–S13)

“Photodynamic therapy (PDT) is not just a palliative treatment,” declared Patrick Ross, Jr, MD, PhD, Director, Division of Thoracic Surgery, The Ohio State University (OSU), Columbus, Ohio. “The real bang for the buck with PDT has got to be curative attempt.” PDT first emerged on the scene at OSU primarily as an effective palliative tool for symptom management in patients with advanced non–small cell lung cancer (NSCLC), with very few complications. Now many researchers and clinicians are considering the role of PDT for curative indications, such as primary treatment of early airway cancer and induction therapy in combination with other modalities. This article offers a backward glance at the early results with PDT at OSU since 1998, a contemporary look at the various indications for PDT in treating airway malignancies, and a future perspective on the next steps for PDT as it moves forward.

The Growing Thoracic PDT Experience at OSU

McCaughan et al1 were the pioneers of PDT at OSU, performing the novel treatment for patients with esophageal malignancy from 1982 to 1994. All of these patients had experienced failed response to, refused, or were ineligible for surgical intervention, ionizing radiation therapy, or chemotherapy. Among their findings were a 5-year survival rate of 62% in 7 patients with stage I disease and a median survival of 3.5 months for those with stage IV disease.1 “As a palliative intervention, these are sort of the numbers you would expect,” stated Dr. Ross. With few complications and no procedure-related deaths, McCaughan et al1 deemed PDT an alternative treatment for patients with Barrett esophagus with severe dysplasia.

During this same period, McCaughan and Williams2 (a thoracic surgeon who is still on the faculty at OSU) performed PDT on 175 patients with bronchogenic and esophageal tumors. They treated patients with all stages of disease and achieved excellent palliation, revealed Dr. Ross. For 16 patients with stage I disease, the...
5-year disease-related estimated survival was 93%. For those with more advanced disease (stages IIIA, IIIB, and IV), the median survival was between 5 and 6 months. Dr. Ross called these “great results” in long-term survival in patients with advanced-stage disease. “What they didn’t recognize, because they didn’t know [at the time], was that there was a systemic effect with PDT,” he revealed.

PDT was approved for treating early-stage lung cancer in Japan in 1994; its approval in the United States for NSCLC came in 1998. The first PDT procedure performed at OSU was in March 1998, and Dr. Ross reported that another 999 patients have been treated with PDT at OSU since then. Then in 2008, the job description of PDT began to expand, as its use in conjunction with other modalities, such as surgery, targeted therapy, and cell-based nanotherapy, was explored. By 2010, OSU established the Photodynamic Medicine Program. This year (2012), OSU hosted the inaugural Photodynamic Therapy Symposium (attended by the brain trust of PDT researchers and clinicians).

Symptomatic Treatment With PDT: From Hemoptysis to Metastatic Disease

Dr. Ross discussed the rationale behind using PDT in thoracic oncology and the clinical scenarios ideally suited for this technique. Effective in multiple cell types, PDT is useful throughout the aerodigestive tract. Its clinical versatility makes it possible to treat symptoms such as hemoptysis and obstructive lesions from metastatic disease. Moreover, PDT interventions can be repeated as symptoms or lesions recur.

“PDT is perfect for treating hemoptysis,” pronounced Dr. Ross. He shared his experience with PDT in managing hemoptysis from a right upper lobe lesion. The reason why PDT works for these lesions is based on the interplay among photochemistry, membrane binding, and damaging effects (eg, apoptosis, immune reaction, inflammatory reaction, microvascular injury). The technique for PDT used at OSU is summarized in Table 1. Dr. Ross explained the reason for general anesthesia: “If you are trying to treat a superficial lesion of the airway and the patient is coughing or moving, you don’t know what you are treating.” In addition, he alluded to the benefit of a second application of light: “Trying to pick up any additional depth of penetration is valuable, to my mind.”

PDT can also be used to treat metastatic lesions in the airway, such as from Hodgkin lymphoma, renal cell cancer, breast cancer, and melanoma. Kiani et al used PDT in a patient with endobronchial vasculitis and associated hemoptysis from nodular sclerosing Hodgkin lymphoma. In this case, the patient initially responded to PDT before induction of tumor-specific therapy. More recently, Dr. Ross and colleagues applied PDT to ameliorate symptoms of metastatic airway obstruction in 9 patients with primary carcinomas of the colon, breasts, kidneys, and tongue. After 2 PDT treatments, all but 1 patient had a complete response.

PDT for Primary Tracheal Carcinoma

“I do think that PDT has a role in definitive management of airway lesions,” revealed Dr. Ross. For example, autofluorescence bronchoscopy is an alternative for treating tracheal lesions. Sharing the indications and outcomes of thoracic PDT in 500 patients, Dr. Ross said this group contained “all comers” with complex esophageal and airway malignancies.

In this group of patients, mortality rates of 1.6% in those treated with PDT between 1998 and 2000 and 1% in those treated with PDT between 2001 and 2004 were noted. “Now mortality rates with PDT are well under 1%,” he added. “Basically, patients do not die after PDT; they die of their disease down the road.” In terms of morbidity in this group of patients, the rate was between 6% and 8% for all patients treated from 1998 to 2004. “The most common complication is stricture of the esophagus, but with good dosimetry, it is limited,” explained Dr. Ross. Although naysayers of PDT point to photosensitization as a complication, Dr. Ross says they are wrong. “We just do not see problems with photosensitivity because of good patient education,” he pronounced.

The take-home message regarding PDT for primary tracheal cancers is that with experience, it is an easy technique to perform and is associated with few complications. “We have become comfortable using PDT for complex end-stage problems and some of the early airway issues,” he said.
**Induction PDT: A Multidisciplinary Approach to NSCLC**

Dr. Ross and colleagues have expanded the role of PDT into the realm of multidisciplinary treatment of NSCLC. They have incorporated PDT as an induction modality in 86 patients with nonmetastatic NSCLC. Reporting on their first 41 patients, they used induction PDT with chemotherapy and/or radiotherapy. Fifty percent of patients initially deemed unresectable based on their preoperative evaluation were able to undergo definitive surgical resection after trimodality induction therapy. In addition, 27% of patients considered to require pneumonectomy were able to have a lobectomy as a result of this induction therapy. After PDT, the pathologic stage was also lowered from the preinduction clinical stage in 14 of 22 cases.

Dr. Ross offered a few cases from his own clinical practice to highlight the benefits of PDT in a multidisciplinary framework. In the case shown in Figure 1, PDT was used preoperatively to improve outcomes in a patient who had an obstructing left upper lobe lung abscess. In another case, a dyspneic patient with an obstruction in the right main stem from NSCLC who was not initially a good candidate for chemotherapy underwent PDT (Figure 2). “For us, the quickness with which you can get the airway open with PDT can clear the pneumonia,” he explained. After PDT, the main stem was cleared, chemotherapy could be started, and the patient underwent subsequent surgical resection. With this approach, the complications associated with sepsis were avoided. Figure 3 shows another example of the use of PDT before chemotherapy and then pneumonectomy in a patient with NSCLC of the right main stem.

Dr. Ross emphasized the need for a multicenter clinical trial to define strict criteria (perhaps based on pulmonary function) for symptoms before therapy with PDT is undertaken. In many cases, Dr. Ross and colleagues found they were able to downstage the cancer through using PDT, thereby lowering the rate of pneumonectomy. Some patients no longer required this procedure after PDT, and for those who still needed pneumonectomy, the extent of surgery is sometimes reduced.

**Curative PDT for Early Airway Cancers**

Although the primary indications for PDT may center on symptom relief, induction in conjunction with other modalities, and palliative improvement in quality of life, the future of PDT may be as a curative option for early airway cancers. The rationale behind PDT as definitive therapy may have emerged from a case study back in the 1980s. Kato et al treated a woman with a malignant squamous cell carcinoma with PDT alone. She responded well to the treatment, and within a week the lesion had disappeared. Five years after endoluminal therapy, she was apparently disease-free. “This was an important paper, showing that we could successfully treat these patients,” stated Dr. Ross.

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**Table 1 The Photodynamic Therapy Technique at The Ohio State University**

| Porfimer sodium is used as a photosensitizer. |
| The dose of the photosensitizer is 2 mg/kg given intravenously. |
| All patients are treated while under general anesthesia. |
| At 48 hours after injection of the photosensitizer, the first light therapy is given. |
| At 96 hours after injection of the photosensitizer, the second light application is given. |
| Quartz diffusing fibers of 1.0–2.5 cm are used. |
| Dosimetry: |
| • 200 J for the first application |
| • 100–200 J for the second application |
Isolated superficial, synchronous, metachronous, and recurrent lesions are several types of early-stage airway cancers for which PDT may offer a cure, according to Dr. Ross. “No one is at greater risk of developing a second lung cancer than the patient who had a first lung cancer to begin with,” reasoned Dr. Ross. Improving significant impairment of pulmonary function as a result of medical comorbidities is another goal in the treatment of early airway malignancies with PDT. For instance, an elderly person with a synchronous primary NSCLC who also has chronic obstructive pulmonary disease and coronary artery disease “defines” minimally invasive surgery, he said. In terms of safety, PDT for early-stage airway cancers is associated with few complications, in Dr. Ross’s experience. “In the airway, PDT is almost a completely safe treatment,” he declared.

Dr. Ross raised a few questions regarding thoracic PDT. Would it be possible to evaluate PDT responder and nonresponders through genetic profiling of tumors to discover a genetic pattern to predict outcomes? Would better tools for autofluorescent bronchoscopy enable physicians to visualize more early lesions and treat more patients? Could patient outcomes be optimized through treating early-stage synchronous airway lesions that might not require surgical resection?

What Next? Future Steps for PDT

Dr. Ross envisioned the road ahead for PDT and some of the necessary steps along the way. First, what’s in a name may play a part in moving PDT from a niche technique into mainstream medicine. Perhaps rebranding PDT as photodynamic medicine may serve to highlight the other aspects connected with PDT beyond therapy. “It is more than therapy and more than just about a local effect,” revealed Dr. Ross. “It can be used for diagnosis, quality of life, palliative therapy at low risk.” Dr. Ross’s personal favorite designation is photoimmunotherapy, which encompasses more of the indirect systemic effects and associated inflammatory reactions with PDT still under investigation.

Second, “this inflammatory or immune biologic response probably accounts for more of the long-term success story [with PDT] than we currently realize,” stated Dr. Ross. “By identifying a mechanism, we can identify an adjunct to make it work better.” Immunobiology is the direction for the next generation of PDT, and “it will be our basic science colleagues who will help us figure this out,” he predicted.

Third, a Web-based PDT registry would be a critical tool for assembling data and linking institutions. Each center could enter its own data through the Web and have access to retrospective cases. Addressing the participants of the 2012 Photodynamic Medicine Symposium at OSU this past May, Dr. Ross called for a pooling of the aggregate outcomes of all who have years of expertise in treating patients using PDT. “Although it may not include all patient details,” he admits, “it would still represent the largest single accumulation of data that can be analyzed and stratified.” Furthermore, Dr. Ross is calling on all participants from centers that want to contribute to this PDT registry prospectively or to collaborate on randomized controlled trials. Finally, to keep the
PDT ball rolling, Dr. Ross foresees making this 2012 symposium an annual event, with more representatives from various disciplines with expertise in PDT in attendance to connect the bench and the bedside.

Conclusions

PDT is a versatile alternative for several clinical scenarios in the treatment of airway malignancies. As a palliative tool, it is an effective way to manage obstructive and bleeding symptoms in patients with advanced NSCLC with few complications. As a component of multidisciplinary therapy, PDT can be used as induction with other modalities or as a potential systemic adjunct to enhance patient outcomes. For patients with early-stage airway cancers, PDT may be considered an effective curative approach along with surveillance bronchoscopy. With good patient and staff education, the rate of photosensitivity is low. Finally, development of a Web-based PDT registry could be home to the largest single accumulation of data on outcomes with PDT and may guide the bright future for PDT.

References