Photodynamic Therapy in the Palliation of Late Stage Obstructing Non-Small Cell Lung Cancer*

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Photodynamic therapy selectively destroys malignant tumors by laser activation of injected hematoporphyrin derivative. Between July 1985 and January 1989, ten patients underwent 13 courses of PDT for relief of endobronchial tumor obstruction due to endstage primary non-small lung cancer. Initial biopsy specimens demonstrated squamous carcinoma in eight patients and adenocarcinoma in two. At the time of treatment, all patients were considered surgically unresectable: T4N2M1 (one), T4N2M0 (one), T3N3M1 (two), T3N2M0 (five), and T2N1M0 (one). This latter patient had exclusionary medical conditions. The average Karnofsky status was 75 (worst was 60, best was 90). Obstruction was mainstem for six, bronchus intermedius in one, and left upper lobe in three. The average obstruction was 86 ± 2 percent. Following treatment, the average obstruction was 57 ± 3 percent. Responses were >50 percent reduction in four and <50 percent in six. Half of the patients still had more than 70 percent obstruction following PDT. However, all patients had a decrease in symptoms, especially coughing. Six of ten patients subsequently received external beam radiation. Three of these patients developed significant problems during and following radiation. Side effects of HPD were minimal and included burns in two and mild anasarca in one patient. PDT appears to offer palliation of obstructive symptoms in patients with late stage lung cancer. Since life span is so short in these individuals, physicians must weigh carefully the potential side effects of combination therapy. (Chest 1990; 98:97-100)

Photoactivation of light-sensitive compounds to produce chemical reactions, a recognized phenomenon since 1908, has been applied to human cancer since 1966.1 To date, an estimated 3,000 patients benefited from such treatment.2 With the addition of fiberoptic delivery systems, physicians are treating tumors of virtually any organ system including the integument, central nervous system, aerodigestive tract, pulmonary, and genitourinary tract.3-6

Many of the articles on PDT for lung cancer deal with early stage disease.9-11 One report by Hugh-Jones and Gardner12 concentrates on those patients considered to have inoperable disease. Few, if any, reports address patient problems when PDT is an adjunct to other palliative modalities. Pass and colleagues14 recently reported on a series of ten patients with late stage disease who exhibited improvement immediately following therapy. This report chronicles our long-term experience with PDT in patients who have advanced stage lung cancer undergoing additional treatment modalities. Particular attention is given to the quality of life for these terminally-ill patients.

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Materials and Methods

Between July 1985 and January 1989, ten patients underwent 13 courses of PDT for relief of endobronchial tumor obstruction due to primary end-stage non-small cell lung cancer. During the period of study, all patients with obstructing lesions were treated. Although Nd:YAG laser capability was available, it was used only as a second line therapy or as the first treatment in patients with severe acute respiratory compromise. Initial biopsy specimens demonstrated squamous carcinoma in eight patients and adenocarcinoma in two. Patients had initial evaluation by chest roentgenogram and computed tomography scans. Eight patients demonstrated roentgenographic evidence of obstruction. Five patients showed evidence of segmental or subsegmental collapse, while two had lobar collapse. One patient with a right mainstem lesion had volume loss of the right lung without complete collapse. In cases of indeterminate regional disease, surgical mediastinal exploration was performed. No patient required thoracotomy to determine unresectable status. Patients were then staged by the TNM classification as described by the American Joint Committee for Cancer staging and end results reporting.2

With the exception of one patient who was inoperable due to exclusionary medical conditions, all had locally extensive nonsurgical disease at the time of diagnosis. One patient had T4N2M1 disease, two had T3N2M1 disease, one had T4N2M0 disease, five had T3N2M0 disease, and one had T2N1M0 disease. At initial presentation, all patients were able to perform daily activities. The average Karnofsky status recorded at initial evaluation was 75. The worst Karnofsky status was 60 and the best 90. Six patients had no therapy prior to PDT, while four had prior therapeutic radiation to the primary tumor and mediastinum. One of these had also received preradiation chemotherapy.

Patients most commonly complained of cough (seven out of ten). Patients also complained of fatigue (five of ten), dyspnea (four of
trolled with topical epinephrine.

Pulmonary function pre-PDT and one week post-PDT showed no significant changes (Table 3). Some patients improved, but most remained the same. However, all patients had a decrease in symptoms, especially coughing. Dyspnea also lessened in most patients. Repeat bronchoscopy performed at one week and every three months remained positive in every case, even if no gross lesion was visible.

Six of ten patients subsequently received external beam radiation averaging 60 Gy. During therapy, one patient became significantly worse with severe fatigue and dyspnea and died one month following completion of 45 Gy radiation. One patient had further regression of his tumor with no visible evidence of obstruction, but within one month of completing 64 Gy, he developed dyspnea and fatigue compatible with radiation fibrosis partially responsive to steroids. He died four months later after a downhill course. Another patient was readmitted five months postradiation and died in cardiogenic shock. Autopsy showed extensive cardiac metastases. In the other three patients, x-ray therapy made no change in their condition.

Complications of HPD were minimal and predictable. One patient developed a minor sunburn. One

### Table 1—Anatomic Data of Advanced Bronchogenic Tumors

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Cell Type</th>
<th>Stage</th>
<th>Location*</th>
<th>Tumor Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adenocarcinoma</td>
<td>T3N2M0</td>
<td>RBI</td>
<td>1.77 cm³</td>
</tr>
<tr>
<td>2</td>
<td>Squamous</td>
<td>T2N1M0</td>
<td>LUL</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>Squamous</td>
<td>T3N2M0</td>
<td>RMS</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>Squamous</td>
<td>T3N2M0</td>
<td>LMS</td>
<td>1.8</td>
</tr>
<tr>
<td>5</td>
<td>Squamous</td>
<td>T3N2M0</td>
<td>LMS</td>
<td>3.1</td>
</tr>
<tr>
<td>6</td>
<td>Squamous</td>
<td>T3N2M0</td>
<td>LMS</td>
<td>2.3</td>
</tr>
<tr>
<td>7</td>
<td>Squamous</td>
<td>T3N2M1</td>
<td>LUL</td>
<td>0.78</td>
</tr>
<tr>
<td>8</td>
<td>Squamous</td>
<td>T4N2M1</td>
<td>LMS</td>
<td>(Tumor studding)</td>
</tr>
<tr>
<td>9</td>
<td>Adenocarcinoma</td>
<td>T3N2M1</td>
<td>LUL</td>
<td>1.0</td>
</tr>
<tr>
<td>10</td>
<td>Squamous</td>
<td>T4N2M0</td>
<td>RMS</td>
<td>6.28</td>
</tr>
</tbody>
</table>

*RBI, right bronchus intermedius; LUL, left upper lobe; RMS, right mainstem; and LML, left mainstem.

ten, fevers and pain (two of ten), and hemoptysis (one of ten). Table 1 summarizes the preoperative anatomic data. Most tumor obstructions were mainstem lesions. Three patients had left upper lobe lesions, and one patient had a lesion in the bronchus intermedius. The predominance of left-sided lesions (seven of ten) may be due to the small sample size.

Endobronchial tumor volumes were estimated by measuring the size of the lesion with the biopsy forceps at the time of bronchoscopy. Since most tumors were not completely obstructing, an estimate of the spherical or cylindrical nature of the tumor mass could be made and size calculated. The percentage of obstruction was determined by measuring from a transbronchoscopic photograph the area of the bronchus and comparing it to the projected area of the tumor at its widest point. The volume of tumor within the airway averaged 2.36 ± 0.2 cm³. The average obstruction was 86 ± 2 percent.

All patients had bronchoscopic photodynamic therapy using a standard protocol. Details of treatment have been published elsewhere. Briefly, dihematoporphyrin ether, 2 mg/kg, was given in a single intravenous dose delivered 46 to 50 hours prior to laser treatment. Using an Argon pumped dye laser set at 630 nm of red laser light, 300 J/cm energy was delivered to the tumor by cylindrical fiber placed directly in the tumor mass. Exposure times were always 12.5 minutes. The power output of the fiber was chosen based upon the length of the tumor and matched to one of three fiber lengths: 0.5, 1.0, or 1.5 cm. The wattage was 200, 400, or 600 mW, respectively. All treatments were performed using local anesthesia and intravenous sedation. Following therapy, repeat bronchoscopy was performed two days later.

### RESULTS

Prior to debridement at posttherapy bronchoscopy, percentage of obstruction was estimated and compared to pretreatment obstruction (Table 2). The average obstruction was 86 ± 2 percent pretreatment compared to 57 ± 3 percent posttreatment for an average decrease in the obstruction of one third. Two patients had essentially no change in the lesion, while one patient's lesion actually enlarged. Four patients had a tumor reduction of >50 percent. Figures 1 and 2 illustrate one such patient. Three patients had a reduction of <50 percent. Half of the patients still had more than a 70 percent obstruction following photodynamic therapy. Only debridement of devitalized tissues was performed. As soon as bleeding was encountered, debridement was discontinued. Only one patient had significant bleeding which was

### Table 2—Bronchoscopic Obstruction Pre + Post PDT

<table>
<thead>
<tr>
<th>Case No.</th>
<th>% Tumor Obstruction</th>
<th>% Change</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Pre PDT</td>
<td>Post PDT</td>
</tr>
<tr>
<td>1</td>
<td>95</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>99</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>40(esp)</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Average</td>
<td>86 ± 2</td>
<td>57 ± 3</td>
</tr>
</tbody>
</table>
I had residual obstruction of 40 percent. He subsequently received radiation and lived four months dying of metastatic disease.

**Table 3—Pulmonary Function Testing Pre and Post PDT**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>FVC, L*</th>
<th>FEV₁, L</th>
<th>FEF (L/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>1</td>
<td>2.59</td>
<td>2.75</td>
<td>1.76</td>
</tr>
<tr>
<td>2</td>
<td>2.18</td>
<td>2.04</td>
<td>1.27</td>
</tr>
<tr>
<td>3</td>
<td>1.72</td>
<td>1.62</td>
<td>1.04</td>
</tr>
<tr>
<td>4</td>
<td>1.85</td>
<td>1.74</td>
<td>1.34</td>
</tr>
<tr>
<td>5</td>
<td>2.83</td>
<td>4.39</td>
<td>1.85</td>
</tr>
<tr>
<td>6</td>
<td>1.75</td>
<td>1.75</td>
<td>1.53</td>
</tr>
<tr>
<td>9</td>
<td>1.55</td>
<td>1.55</td>
<td>0.93</td>
</tr>
</tbody>
</table>

*FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; and FEF, forced mid-expiratory flow rate.

uncertain whether this is a complication of the drug or part of the patient's disease.

Three patients subsequently were retreated with PDT an average of nine months following initial therapy for increasing symptoms and regrowth of their tumor. In each case, minimal improvement was documented. One patient required YAG laser resection twice more prior to death at 22 months following the first photodynamic therapy.

Overall survival was 8.3 months. Only three patients lived more than one year and all patients in this group were retreated for recurrent disease. The median survival was four months. With the exception of one patient who became ill during radiation, all patients remained out of hospital and able to perform daily activities until two to three weeks prior to death.

**Discussion**

Late-stage lung cancer carries a dismal prognosis. Hara and colleagues demonstrated in 1984 a 12 percent two-year survival regardless of therapy for stage III patients. Mountain showed similar poor results for these late stage lesions. Radiation therapy has been the usual definitive therapy for locally extensive disease. However, the five-year survival rate in this group of patients is only 7 percent as reported in several series.

No good data exist for relative survival in patients who have locally extensive disease with endobronchial obstruction. In a group of similar patients with inoperable local disease at thoracotomy, a cohort which may be comparable, Shields notes that 15 percent survive only three months, and one half are dead within six months. These patients with advanced disease have only a very short time to live and are miserable due to complications of their local-regional disease.

Three of the six patients who received follow-up radiation therapy had major complications. This is in contrast to the four pre-PDT patients who had no radiation complications. Although this may be due to the extensive nature of the disease, there is the
potential that ionizing radiation therapy may also activate hematoporphyrin derivative, thus enhancing the side effects. This idea has been proposed by Kostron and associates after studying gamma radiation to a rat glioma model. Although this is highly unlikely, no experimental data exist to show one way or the other the effect of ionizing irradiation on HPD loaded tumors. We are studying currently in vitro several human lung cancer cell lines to evaluate this theory.

Photodynamic therapy appears to offer palliation of the most significant problem for these patients (ie, endobronchial obstruction). In this series, all had symptomatic improvement and one half had decrease in tumor obstruction. The treatment, however, is not without significant consequences and potential complications. Although they may be mobile, sun exposure severely limits patients' activity for at least a month of their shortened life span. Patients with late stage lesions and their physicians must weigh this carefully when deciding among alternative therapies. Since the treatments can be performed as an outpatient with local anesthesia, there is less hospital time than with Nd:YAG therapy. Also, bleeding complications appear less frequent with PDT. No treatment in this group of patients is ideal and the decision for a particular therapy should remain individualized.

REFERENCES