Serial Fiberoptic Bronchoscopy during Chemotherapy for Small Cell Carcinoma of the Lung

Early Detection of Patients at High Risk of Relapse

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Serial fiberoptic bronchoscopic examinations were performed during intensive chemotherapy with a combination of drugs in 77 previously untreated patients with small cell carcinoma of the lung. Before treatment, bronchoscopic examination revealed evidence of cancer in 93 percent (70) of the 75 patients studied at that time, including 8 percent (six) in whom the tumor was not evaluable on the chest x-ray film. After therapy was initiated, 36 percent (29) of the 81 procedures performed in patients with a complete response radiographically and 62 percent (33) of the 53 bronchoscopic procedures in those with a partial response or no response showed evidence of tumor. In both of these groups, patients with abnormal findings on endoscopic examination had a much higher rate of relapsing tumor of the chest within a 12-week period. Progression of intrathoracic tumor was first detected solely by bronchoscopic examination in 22 percent (seven) of the 32 episodes of progression. In our hands, repeated fiberoptic bronchoscopic procedures during chemotherapy for small cell carcinoma have yielded information not apparent from the chest x-ray film in a significant number of patients.

In most patients with small cell carcinoma of the lung, treatment with either cytotoxic chemotherapy or radiotherapy leads to rapid regression of the tumor.† Complete clinical disappearance of disease is required for long survival in patients with this rapidly proliferating cancer.‡ Even so, most patients with a complete response to therapy will eventually suffer a relapse, implying that their tumor was not completely eradicated and suggesting that methods for detecting occult residual disease could identify patients who might benefit from alternative or additional forms of treatment.

Occult primary tumors of the lung occur only rarely in small cell carcinoma, and mediastinal involvement is almost universal.§ Therefore, the response of intrathoracic disease to therapy can be assessed radiographically in most patients.¶ Small cell carcinoma often occurs initially as a centrally located endobronchial tumor, but a characteristic which renders this cancer ideal for bronchoscopic observation. Indeed, the initial histologic diagnosis of small cell carcinoma is often made in this fashion. We therefore began to investigate the role of bronchoscopic examination in evaluating the response of this tumor to chemotherapy. The flexible fiberoptic bronchoscope was used because of visualization of a far greater portion of the tracheobronchial tree and because of the ease of repetitive examinations.

MATERIALS AND METHODS

Serial fiberoptic bronchoscopic examinations were performed before or during therapy (or at both times) in 77 previously untreated patients with small cell carcinoma. Most were referred to our unit for intensive treatment after diagnosis elsewhere. Treatment consisted of alternating regimens of chemotherapy with a combination of drugs; radiotherapy was initially given only for lesions of the central nervous system. Bronchoscopic examination was done before treatment, after 6 and 24 weeks of therapy, and whenever a new complete response in the chest or a progression of the tumor was suspected. Two hundred and thirty-four procedures (mean, three per patient; median, three; range, one to six) were done during this study.

A transnasally introduced flexible fiberoptic bronchoscope (Olympus BF B2) was used in these studies. The patients received premedication with diazepam (5 to 10 mg intramuscularly) and atropine (0.4 to 0.5 mg intramuscularly) and local anesthesia of the nasal cavity and pharynx, which was achieved by spraying with a 2 percent solution of lidocaine. The procedure was performed on an outpatient basis whenever possible. Only ambulatory patients or those with an arterial oxygen pressure of greater than 50 mm Hg while breathing room air were studied, unless tissue for initial

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Manuscript received February 27; revision accepted May 4.
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CHEST, 74: 5, NOVEMBER, 1978

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diagnosis was needed. The prothrombin time and the platelet count were required to be normal for elective endobronchial biopsies.

In all instances, visual inspection of the larynx, vocal cords, trachea, carina, and all segmental orifices of both lungs was performed. Lactated Ringer's solution was instilled through the bronchoscope, with aspiration for washings for cytologic examination. The washings were fixed in Saccomanno's fluid, concentrated by cytocentrifuge, and stained with hematoxylin-eosin (Fig 1). Visible endobronchial lesions were usually biopsied (Fig 2); bronchial brushings were not customarily obtained. White, often friable nodules of tumor are noted when endobronchial small cell carcinoma is observed bronchoscopically. \(^{11}\) Narrowing or obliteration of the bronchial lumen by swollen heaped-up mucosa, due to submucosal infiltration of the tumor (Fig 1), is also commonly seen. \(^{11}\) Bronchoscopic findings were considered abnormal if either visible endobronchial tumor or pathologically diagnostic (not "suspicious") cytologic washings or bronchial biopsy was present. Indirect effects of the tumor, such as extrinsic compression of the bronchial lumen without histologic confirmation of cancer, did not lead to the designation of abnormal findings. On the chest x-ray film, a complete response was defined as the disappearance of all evident tumor and its indirect effects. Postoperative changes, abnormalities due to preexisting pulmonary disease, and pleural changes in patients with resolving effusions were not required to disappear. A partial response was defined as a greater than 50 percent decrease in the products of perpendicular diameters of all measurable masses of tumor or a greater than 75 percent decrease in the size of all evaluable lesions. Progressive thoracic disease or a relapse from a prior response to chemotherapy was defined as the appearance of new radiographic or bronchoscopic lesions that were thought to be tumor or an increase of 25 percent or more in the size of a previously existing lesion.

**RESULTS**

No deaths and no hemorrhagic or major respiratory complications were observed after these elective bronchoscopic procedures, which included examinations with endobronchial biopsy before treatment in seven patients with the superior vena cava syndrome.

**Bronchoscopic Findings before Treatment**

Seventy-five of the 77 patients could be studied before chemotherapy was initiated. Endobronchial tumor was visualized in 62 patients (83 percent) and was central in location (main-stem or lobar bronchus) in 54 and more peripheral (segmental bronchus or more distal) in eight. Bilateral endobronchial tumor was seen in four instances (5 percent). Fifty-five (89 percent) of the 62 cases with bronchoscopically visible tumor were pathologically confirmed by washings, biopsy, or both. Among the 13 patients without visible carcinoma, extrinsic compression of the bronchial lumen was seen in six, and cytologic washings revealed cancer in eight (62 percent). In only four cases (including one patient with an extrathoracic primary tumor and two with purportedly curative pulmonary resections) was the
bronchoscopic examination entirely unrevealing. In bronchial biopsies with abnormal findings, the tumor was almost always limited to the submucosal tissues (Fig. 3). In only one instance was intraluminal spread of tumor visualized microscopically.

Visual findings and cytologic washings were almost equally sensitive in detecting tumor prior to therapy. Washings were abnormal in 78 percent (57) of the 73 specimens examined. A smaller frequency, 68 percent (45/66), of bronchial biopsies yielded pathologic proof of tumor, but multiple biopsies were not obtained in most patients. In 64 of these 75 patients complete visual inspection, cytologic washings, and bronchial biopsy were all performed. All three examinations showed evidence of tumor in 60 percent (38) of the 64 cases, while in only six patients (9 percent) were abnormal visual findings not confirmed pathologically. Only three (5 percent) of these fully evaluated patients did not have some evidence of tumor at bronchoscopic examination.

Correlation of bronchoscopic and radiographic findings in these 75 freshly diagnosed cases is presented in Table 1. In 64 patients (85 percent), evidence of tumor was noted both on the chest x-ray film and at bronchoscopic examination. The 70 patients (93 percent) with abnormal bronchoscopic findings included six (8 percent) in whom the bronchoscopic procedure provided the only evaluable evidence of tumor in the chest.

**Bronchoscopic Findings in Responders**

While our patients were receiving chemotherapy, the frequency of abnormal findings on bronchoscopic examinations was related to the response to chemotherapy as demonstrated on the chest x-ray film (Table 2). Of 81 procedures performed on 38 patients with a complete radiographic response at the time of examination, 36 percent (29) of the procedures demonstrated bronchoscopic evidence of residual tumor. In contrast, in the 31 patients studied on 53 occasions when a partial response or no change was noted on the chest x-ray film, the frequency of abnormal findings on the bronchoscopic procedures was 62 percent (33 procedures). Evidence of tumor in the cytologic washings or bronchial biopsy was found in 45 percent (13) of the 29 bronchoscopic procedures with abnormal findings in the patients with a complete radiographic response and in 67 percent (22) of the 33 procedures with abnormal findings in the patients without such a response.

The prognostic implications of residual bronchoscopic cancer not detected radiographically were evaluated by two methods. The frequency of relapse of the tumor in the chest within 12 weeks of the last bronchoscopic examination at which maximum response of tumor was observed was determined for all responding patients, including those responding to both initial and subsequent therapeutic programs. As may be seen from Table 3, both in patients with and those without a complete response on the chest x-ray film, abnormal bronchoscopic findings appeared to predict earlier relapse of tumor. Visual observation of residual carcinoma was predictive of relapse (even without pathologic confirmation) in patients with a complete response of their tumors radiographically. The 12-week rate of relapse in the chest in those cases with only visual evidence of tumor at bronchoscopic examination (50 percent; 4/8) was 2% times greater than in patients with completely normal results of endoscopic examination (19 percent; 6/31). The rate of relapse was even higher (71 percent; 5/7) when pathologic proof of residual cancer was obtained.

Since these episodes of progressive thoracic disease developed in patients receiving initial and subsequent therapeutic regimens for varying lengths of time, the usefulness of bronchoscopic findings after six weeks of initial therapy in predicting the status of

**Table 1—Findings before Treatment in 75 Patients**

<table>
<thead>
<tr>
<th>Bronchoscopic Results</th>
<th>Chest X-ray Film</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal findings</td>
<td>64 (85)</td>
</tr>
<tr>
<td>Normal findings</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

*Table values are numbers of patients; numbers within parentheses are percentages.

**Table 2—Correlation of Bronchoscopic Findings with Radiographic Response to Chemotherapy* |

<table>
<thead>
<tr>
<th>Data</th>
<th>Radiographic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>Complete or None</td>
</tr>
<tr>
<td>No. of bronchoscopic procedures</td>
<td>38</td>
</tr>
<tr>
<td>Procedures with abnormal findings</td>
<td>29 (36)</td>
</tr>
<tr>
<td>Procedures with normal findings</td>
<td>52 (64)</td>
</tr>
</tbody>
</table>

*Numbers within parentheses are percentages.

**Table 3—Relationship of Bronchoscopic Findings to 12-Week Rate of Relapse* |

<table>
<thead>
<tr>
<th>Bronchoscopic Results</th>
<th>12-Week Rate of Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal findings</td>
<td>Complete Radiographic Response</td>
</tr>
<tr>
<td>Normal findings</td>
<td>Partial or No Radiographic Response</td>
</tr>
<tr>
<td>Abnormal findings</td>
<td>9/12 (75)</td>
</tr>
<tr>
<td>Normal findings</td>
<td>6/31 (19)</td>
</tr>
</tbody>
</table>

*Table values are numbers of patients; numbers within parentheses are percentages.
the tumor in the chest at 24 weeks was also determined (Table 4). Adequate time for follow-up has elapsed in 59 patients. When assessed in this manner, especially among patients with a complete response on the chest x-ray film, the detection of residual tumor by the bronchoscopic procedure also implied a higher risk of relapse.

**Bronchoscopic Detection of Progression**

The relationship between radiographic and bronchoscopic findings in patients with progressive tumor in the chest is detailed in Table 5. Over two-thirds of the episodes of progression in approximately the same fraction of patients were associated with worsening of findings from both examinations, but in seven (22 percent) of the 32 episodes, only bronchoscopic findings showed deterioration while the findings on the chest x-ray film remained stable. Among the 29 episodes of progressive disease documented or confirmed at the bronchoscopic examination, visual findings worsened in 86 percent (25), while previously normal cytologic washings or bronchial biopsies became abnormal in 55 percent (16).

**DISCUSSION**

Evaluation of the response to therapy in patients with cancer of the lung was not mentioned in a recent review of the indications for fiberoptic bronchoscopic examination; however, at least two groups of authors have demonstrated superior survival in patients with lung cancer who are found to be without residual carcinoma at bronchoscopic examination performed after therapy with irradiation. Oka et al have utilized bronchoscopic examination to assess the effects of therapy with bleomycin in patients with various histologic types of lung cancer and have reported evidence of endoscopic improvement with therapy in 34 percent of the patients examined; however, the significance of this evidence was uncertain, since the drug was thought to be clinically "effective" in only 17 percent of all patients treated.

In our hands, serial fiberoptic bronchoscopic examinations performed during chemotherapy in patients with small cell carcinoma of the lung have yielded information not apparent from the chest x-ray film in a significant number of cases. The bronchoscopic procedure in our patients had minimal morbidity and could easily be repeated on an outpatient basis. Surveys of large numbers of procedures have previously documented the extremely low rate of complications associated with use of the flexible fiberoptic bronchoscope.

Prior to initiation of therapy, we have found that over 90 percent of the patients will have visual or pathologic evidence (or both) of tumor on the bronchoscopic examination; the procedure was especially useful in the small minority (8 percent; 675) in whom it provided the sole evaluable evidence of thoracic cancer. This high rate of bronchoscopically detectable tumor may partially reflect the fact that most of our patients were referred to us with an established diagnosis.

Our finding that 83 percent (62) of 75 small cell carcinomas were visible bronchoscopically exceeds the 45 percent rate of visibility reported in this histologic type by Kato et al, however, Kato et al utilized a rigid bronchoscope. Not surprisingly, we more often obtained pathologic confirmation of cancer in patients with a visible tumor than in those without one. Using the fiberoptic bronchoscope, pathologic proof of cancer in patients with endoscopically visible pulmonary tumors of all histologic types has been procured in 86 percent and 94 percent of the examinations performed, results quite similar to our figure of 89 percent (5562). In patients with small cell carcinoma of the lung who did not have a visible tumor, Kato et al reported that blind bronchoscopic biopsies were diagnostic of carcinoma in 30 percent of the cases. Our results in this group of patients (diagnosis of cancer in 62 percent [813]) can be attributed to the use of the flexible fiberoptic bronchoscope and the addition of bronchial washings.

We found bronchial washings to be more sensitive in detecting tumor than bronchial biopsy, in contrast

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**Table 4—Relationship of Six-Week Bronchoscopic Findings to 24-Week Rate of Relapse**

<table>
<thead>
<tr>
<th>Bronchoscopic Results</th>
<th>24-Week Rate of Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete Radiographic Response**</td>
</tr>
<tr>
<td>Abnormal findings</td>
<td>5/11 (45)</td>
</tr>
<tr>
<td>Normal findings</td>
<td>3/21 (14)</td>
</tr>
</tbody>
</table>

*Table values are numbers of patients; numbers within parentheses are percentages.

**At six weeks.

**Table 5—Bronchoscopic and Radiographic Findings at Time of Progression Disease in Chest**

<table>
<thead>
<tr>
<th>Data</th>
<th>Chest X-ray Film</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Worse</td>
</tr>
<tr>
<td>No. of patients</td>
<td>21</td>
</tr>
<tr>
<td>No. of bronchoscopic procedures</td>
<td>25</td>
</tr>
<tr>
<td>Procedures with worse bronchoscopic findings</td>
<td>22 (60)</td>
</tr>
<tr>
<td>Procedures with stable bronchoscopic findings</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

*Numbers within parentheses are percentages.
to others who have observed that washings do not increase the diagnostic yield obtained from brushings and biopsies; however, we did not routinely perform brushings or take multiple biopsies. Saltstein et al have reported that brushings, biopsies, and washings will each detect cases of cancer that would have been missed using only the other two techniques.

Because bronchial biopsies reveal that the cells of the tumor are almost always limited to the submucosal tissues, the masses of tumor visualized at bronchoscopic examination are covered by an intact mucosa. This may be the cause of the occasional normal findings from bronchial washings in patients with grossly visible endobronchial small cell carcinoma.

Serial bronchoscopic examinations in our patients were perhaps most helpful in revealing evidence of residual tumor in some patients who were thought to have a complete response to therapy on the basis of the chest x-ray film. The prognostic value of the procedure in these cases is suggested by the fact that the 12-week rate of thoracic relapse is four times higher in patients with persistent endoscopically demonstrable disease. Furthermore, our data in Table 4 demonstrate that the procedure can identify patients at an increased risk of early relapse as soon as six weeks after chemotherapy has begun.

Thus, in cases with complete radiographic resolution of tumor, the bronchoscopic examination detects a group of patients who are potential candidates for more aggressive or altered therapeutic strategies. The clinical benefit of such early identification to these patients will ultimately depend upon the success of the additional treatment. The patients with partial or no response on the chest x-ray film who have normal findings on bronchoscopic examinations may include some cases with clinical disappearance of thoracic carcinoma but with persistent pulmonary inflammation or other nonspecific radiographic changes that prevent the designation of a complete response.

In previous studies of patients with lung cancer who were treated with irradiation, bronchoscopic examination could distinguish two groups of patients with quite different prospects for short-term survival. This knowledge presumably could not have been obtained from chest x-ray films alone, since radiation-induced fibrosis would usually render them uninterpretable with regard to monitoring for the local recurrence of cancer. Our data are somewhat analogous, since the bronchoscopic procedure could identify some patients with small cell carcinoma who were at high risk for an early relapse, despite a normal chest x-ray film. The procedure may well be of less utility in evaluating the effects of chemotherapy in other types of cancer of the lung, since complete radiographic disappearance of the tumor occurs much less frequently than in small cell carcinoma.

A relatively high proportion of our patients with progressive cancer in the chest (almost one-fourth) were first detected solely by bronchoscopic examination. This fraction could well have been increased had routine examinations been done more frequently. The therapeutic value of such early awareness of relapsing disease will ultimately depend upon the availability of effective secondary treatment.

Based on our experience, we would suggest that serial fiberoptic bronchoscopic examinations should be considered during the treatment of small cell carcinoma in at least the following three situations. First, the procedure should be useful in assessing the response to treatment in the small minority of patients without radiographic evidence of evaluable tumor at diagnosis. It might also prove to be of value in patients whose chest x-ray films are rendered uninterpretable by early therapy with irradiation, which is included in the recent regimens of treatment by many investigators. Secondly, bronchoscopic examination should be a helpful tool in confirming a complete response to chemotherapy on the chest x-ray film and in monitoring for early detection of relapsing disease in experimental therapeutic protocols or other instances where such knowledge might be beneficial. Finally, since bronchoscopic examination in our hands revealed residual tumor in approximately one-third of the patients with a complete response to treatment (as judged by the chest x-ray film), bronchoscopic confirmation of remission should precede the discontinuation of therapy.

ACKNOWLEDGMENT: We thank Adi F. Gazdar, M.B., B.S., for reviewing some of the pathologic material and for supplying the illustrations.

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ANNOUNCEMENTS

Second National Congress, Emergency Medicine

The Second National Congress of the Services d’Aide Medicale Urgente will be held at the Palais des Congres, Toulouse, France, February 22-24, 1979. For information, write the President, Professor L. Lareng, Centre Hospitalier Universitaire de Toulouse, 31052 Toulouse Cedex, France.

Lung Disease in Children

The Postgraduate Course, Lung Disease in Children, will be held in Vail, Colorado, January 10-13. For information, contact the Office of Postgraduate Medical Education, University of Colorado School of Medicine, 4200 East Ninth Avenue, Denver 80262.

Advances in Selected Allergic and Immunologic Disease

This is the Seventh Annual combined National Asthma Center-National Jewish Hospital and Research Symposium, to be held in Keystone, Colorado, January 8-12, at the Keystone Ski Area Resort. For information, contact Hyman Chai, M.D., National Asthma Center, 1999 Julian Street, Denver 80204.