Cyclophosphamide, Vincristine and Sequential Split-Course Radiotherapy in the Treatment of Small Cell Lung Cancer*

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Thirty-nine patients with small cell lung cancer were treated with large dose intravenous cyclophosphamide combined with vincristine. Sequential split-course radiotherapy was added when the gross disease was limited to one hemithorax and draining scalene nodes. Fifteen of 16 patients in the limited disease category showed objective response, eight of which were complete. Fourteen of 23 patients in the extensive disease category yielded an objective response, six of which were complete. The median survival for complete responders was 48 weeks, 38 weeks for partial responders and 14 weeks for non-responders. The difference between responders and non-responders was statistically significant. The major toxicity was myelosuppression with a median leukocyte nadir of 500/mm³ noted on treatment day no. 15. Prompt recovery was the rule. Toxicity appeared to be cumulative for patients receiving radiotherapy. These results are superior to those evolving from treatment with cyclophosphamide as a solitary agent.

The median survival of untreated small cell lung cancer varies from 4 to 22 weeks depending on extent of the disease and disability as measured by performance status. Radiotherapy has not improved survival, although it has unequivocal palliative value. Chemotherapy trials have demonstrated striking responsiveness to many drugs, especially alkylating agents. Mechlorethamine, procarbazine, hexamethylmelamine, nitrosoureas, and cyclophosphamides have all shown clear activity. However, survival time does not appear to be significantly improved when these agents are used individually. The major exception is large dose intravenous cyclophosphamide which the Veterans Administration Lung Cancer Study Group reported to be superior to mechlorethamine, low-dose oral cyclophosphamide, or placebo in prolonging survival. Furthermore, the Veterans Administration Surgical Adjuvant Group has shown an improved survival at four years for those patients treated with two courses of large dose parenteral cyclophosphamide following resection. Therefore, cyclophosphamide should be considered an integral part of any chemotherapy program. Since the remission rate of cyclophosphamide as a solitary agent is less than 50 percent, the addition of other agents with qualitatively different mechanisms of action and toxicity is necessary. Vincristine, an alkaloid derived from the Vinca rosea Linn, acts as a mitotic spindle poison and is only minimally myelosuppressive. Also there is experimental evidence to suggest synergism with cyclophosphamide. Vincristine, therefore, appeared ideal for combination with cyclophosphamide since full doses of each agent could be used.

In our experience with chemotherapy alone, tumor escape usually first occurs at the site of primary disease and draining mediastinal nodes. For this reason, radiotherapy has been added to the protocol with the aim of preventing or delaying recurrence within the chest.

### MATERIALS AND METHODS

All new patients seen in the outpatient clinic between June, 1971 and May, 1973 with a proved diagnosis of small cell bronchogenic carcinoma were entered in the study in a prospective fashion. Table 1 describes the patient population.

<table>
<thead>
<tr>
<th>Total Number of Evaluable Patients</th>
<th>Median Age</th>
<th>Male/Female</th>
<th>Prior to Diagnosis</th>
<th>Previous Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>60</td>
<td>30/9</td>
<td>8</td>
<td>None XRT Surgery therapy*</td>
</tr>
<tr>
<td>(37-70)</td>
<td></td>
<td></td>
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</tbody>
</table>

*Nitrogen mustard, 0.4 mg/kg x 1

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The separation of the clinical presentations into limited disease and extensive disease categories has been found to be a major factor affecting survival.\textsuperscript{14,15} The criteria of the Veterans Administration Lung Study Group is considered the most pragmatic for clinical usage. Limited disease is defined as tumor confined to one hemithorax and may include positive scalene nodes. Extensive disease includes all the remaining patients.

Of equal importance is the degree of disability, termed performance status, at initial presentation. This is rated on a scale of zero to 3 as follows: 0—no disability or symptoms; 1—has symptoms but works full time; 2—requires assistance, in bed less than 50 percent of time; 3—in bed more than 50 percent of time. Table 2 summarizes performance status and presentation and correlates performance status with response.

Response was determined both at the completion of the first course of chemotherapy and then at the completion of radiotherapy. A partial response is defined as a decrease in the maximum diameter of tumor mass by at least 50 percent, and a complete response exists when all clinical evidence of disease has disappeared for at least two more months.\textsuperscript{16} A reduction of tumor mass by less than 50 percent was considered a nonresponse.

Therapy consisted of intravenous cyclophosphamide at a dosage of 10 mg/kg/day for a total of eight to ten days, or until the total white count fell to 2000/mm\textsuperscript{3}. Each dose was diluted in 200 ml of 5 percent glucose in water and administered over 30 minutes. Vincristine 2 mg intravenously, was given on days one and seven (Fig 1). Twenty-eight days from day one of the first chemotherapy course, radiotherapy was initiated and 3000 rads tumor dose was delivered over a two week period for patients with limited disease. The portals included the primary, mediastinum, and both supraclavicular areas. After one month, the patient was re-evaluated and if there was no evidence of metastatic disease, the patient was retreated with an additional 2500 to 3000 rads. The spinal cord was excluded for the last 1500 rads tumor dose. Following the completion of the second fraction of radiation, the patients were given a two week rest period, and then chemotherapy with cyclophosphamide and vincristine was re instituted. An additional four courses were programmed at six to eight week intervals depending on tumor status and patient tolerance.

Five patients presented with superior vena caval syndrome. Radiotherapy was given prior to chemotherapy in this situation. In patients who presented with extensive disease, chemotherapy alone was used.

**Results**

Twenty-nine patients of the total population of 39 evaluable patients demonstrated objective tumor response. Table 3 details response by presentation.

### Table 2—**Performance Status and Response**

<table>
<thead>
<tr>
<th>Performance Status</th>
<th>Limited Disease</th>
<th>Extensive Disease</th>
<th>Number Responses</th>
<th>Median Duration Response (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>16</td>
<td>15</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>5</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See text.

**Table 3—** *Tumor Presentation and Response*

<table>
<thead>
<tr>
<th>Tumor Presentation and Response</th>
<th>Number Evaluable Patients</th>
<th>Number Complete Response</th>
<th>Number Partial Response</th>
<th>Number of Response</th>
<th>Median Survival Time (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Limited Disease</strong></td>
<td>16</td>
<td>8</td>
<td>7</td>
<td>94</td>
<td>51 (6-156)</td>
</tr>
<tr>
<td><strong>Extensive Disease</strong></td>
<td>23</td>
<td>6</td>
<td>8</td>
<td>64</td>
<td>25 (1-90)</td>
</tr>
</tbody>
</table>

Figure 1. Treatment plan. Patients with extensive disease presentation did not receive radiotherapy to the primary lesion.

The limited disease category showed a total response rate of 95 percent, half of which were complete, while the extensive disease category yielded a 64 percent response rate but only 25 percent were complete. Thus, the rate of response and quality of response are related to presentation. The overall complete response rate to chemotherapy is 36 percent and increases to 44 percent at completion of radiotherapy. The duration of response is clearly related to performance status, increasing from a median of 17 weeks for symptom status 2 to median of 32 weeks for symptom status 0-1 (Table 2).

Patients with limited disease received a median of three chemotherapy courses, while patients with extensive disease received a median of two courses. The major reason for the abbreviated number of courses was not patient intolerance to drug therapy but the development of new metastatic disease. The pattern of recurrence is as follows: brain 9 (23 percent), spinal cord 3 (7.6 percent), liver 6 (15.4 percent).
Survival was studied by the life table analysis method. The median survival time for complete responders is 48 weeks, while it is 38 weeks for partial responders and 14 weeks for nonresponders (Fig 2). The difference in survival between complete responders and nonresponders is statistically significant (P < 0.01), as is the difference between partial responders and nonresponders (P = 0.05). Survival curves were also compared for limited and extensive disease (Fig 3). The median survival for limited disease is 51 weeks versus 25 weeks for extensive disease. Using a modified Wilcoxon test, we found that there is a highly significant difference between the two curves (P < 0.01).

Seven patients survived beyond one year in complete remission. Three have subsequently died from widespread metastasis while the remaining four continue with no evident disease. The mean survival time for this small group is 81-plus weeks.

Toxicity
All patients experienced nausea and vomiting during chemotherapy, not, however, severe enough to interfere with further administration of treatment. Only one instance of chemical cystitis secondary to cyclophosphamide was noted. Reversible alopecia was seen in all patients who received more than one course and was usually complete. Severe leukopenia was the rule with a median nadir of 500/mm³ at day 15. Recovery was prompt, the leukocyte level rising beyond 2000/cu mm by day 21. Repeat courses did not result in cumulative toxicity for patients in the extensive disease category. However, delayed recovery from myelosuppression was seen in the limited disease category after radiation therapy had been completed (Table 4). The interval between courses as measured from day one to day one increased from a median of seven weeks to 11 weeks, primarily because of a delay in platelet recovery.

Included among the ten nonresponders are two patients who died following chemotherapy. These deaths occurred in patients with initial thrombocytopenia secondary to massive bone marrow invasion by tumor and were attributed to sepsis.

Discussion
Although it is agreed that cyclophosphamide has striking activity in small cell lung cancer, the schedules of administration and dosage have varied with different investigators. Thus, Bergsagel 17 gave 1 to 2.5 gm/M² intravenously as a single dose every 17 to 21 days to 40 patients with lung cancer excluding...
adenocarcinoma and noted a 40 percent objective remission rate with a median survival of 18 weeks. Maurer compared cyclophosphamide 2.0 gm/M² intravenously every 28 days with cyclophosphamide, vincristine, methotrexate and sequential 3200 rads megavoltage radiotherapy given over 12 days. Cyclophosphamide alone gave a complete plus partial response rate of 23 percent versus 37 percent for the combination. Although survival data was not given for this study, a previous report of 16 patients gave a mean survival of 5.6 months for the three-drugs-plus-radiotherapy combination.

Since Bruce has shown that cyclophosphamide is a cycle active agent, working best on cells in mitosis (but not in any specific phase), we have preferred to administer the drug daily over eight to ten days in order to cover one or more mitotic cycles. The exact cell cycle time of the anaplastic small cell is not known, but is presumed to be three to four days if similar to other human tumor cells. Unlike most alkylating agents, the half-life of cyclophosphamide is long, and active metabolites may persist in the circulation for up to 24 hours.

The importance of radiotherapy in the protocol seems very clear since only one of the 16 patients with limited disease had recurrence within the chest in the previously irradiated area. However, distant metastases were noted to occur in 25 percent of the patients while receiving radiotherapy. The time allotted to complete the split-course radiotherapy program is ten weeks, and it is apparent that this is too long an interval without chemotherapy. Thus, further programs will schedule chemotherapy to follow each course of radiation.

The improved response rate of 75 percent noted in this report suggests that large dose cyclophosphamide plus vincristine is more efficacious than cyclophosphamide alone in remission induction. Further, the median survival of the limited disease group is significantly prolonged. However, survival time for extensive disease has not been significantly improved over cyclophosphamide alone, and long term survival beyond one year continues to remain poor. Thus, combination chemotherapy trials will proceed with the addition of a third active agent, Adriamycin, to the protocol.

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REFERENCES
1 Zelen M: Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 4:31-41, 1973
4 Oat Cell Lung Cancer in Lung Cancer: A study of five-thousand Memorial Hospital cases (William L Watson, ed.). St Louis, CV Mosby Co, 1968, pp 394-405
12 Schabel FM, Jr: Synergism and antagonism among anti-
tumor agents. Twenty-Seventh Annual Symposium on Fundamental Cancer Research: Pharmacological Basis of Cancer Research, MD Anderson Hospital, Houston, Texas 1974


A Look Into the Future

Even the gloomiest demographers cannot foresee a world of 100 billion people until sometime in the second quarter of the twenty-second century. We are therefore entitled, by the experience of history, to assume that a number of technological advances will take place in the interim which will enhance the capacity to cater to the food needs (and whims) of the 100 billion. We may learn to peel away the cloud over the agricultural lands to increase the quantity of light available for photosynthesis. Or what amounts to the same thing, we may decide, as has already been done experimentally, to illuminate our fields at night with high energy laser beams. Or we may do both, and apply various other food-related technologies now being given a try and those still to come. All would tend to reduce crop-acreage, and so free more and more areas for less functional, pleasurable uses. In the United States, for example, advances in agricultural technology have permitted a 20 percent reduction of farm acreage between 1930 and 1970.

Katz R: A Giant in the Earth.
New York, Stein and Day, 1973

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