Small Cell Carcinoma of the Lung*

By Robert B. Livingston

This variant of lung cancer accounts for about one-fourth of all primary tumors arising in that site, making it about as common as all lymphomas combined, according to 1979 estimates of the American Cancer Society. It is of particular interest to the internist who deals with cancer because of its unique responsiveness to chemotherapy and radiation therapy, and the possibility that some patients treated with these modalities may be cured.

Natural History, Growth Kinetics, and Pathology

Without specific treatment, small cell tumors have the worst prognosis of any form of lung cancer: the median survival is 7 wk from the time of diagnosis for patients with extensive disease and 14 wk for those with disease clinically limited to the hemithorax and its draining lymph nodes. About two-thirds of patients will present with extensive and one-third with limited involvement. There is no specific constellation of signs or symptoms that is characteristic for small cell carcinoma as compared to the other forms of lung cancer. In spite of the fact that paraneoplastic syndromes (other than those that produce hypercalcemia) are seen much more frequently with this type of tumor, the incidence of extrathoracic clinical manifestations (including paraneoplastic syndromes) at the time of diagnosis is quite low: 10% in one large series. Among patients with ectopic adrenocorticotropic hormone (ACTH) production or the syndrome of inappropriate antidiuretic hormone (ADH), on the other hand, small cell lung cancer is the most common underlying diagnosis. The Eaton-Lambert syndrome (pseudomyasthenia) is seen exclusively in these patients. On chest x-ray, the tumor is usually centrally placed, most often evident as a mass in the hilar area.

Occasionally, however, there may be only mediastinal widening or bilateral hilar enlargement that can be confused with Hodgkin’s disease, and the fact that a lesion is peripheral or “coin” in nature does not exclude small cell as a possibility. The frequency of metastatic involvement, at diagnosis and at autopsy, is summarized from several series in Table 1. About one-third of patients will have clinical evidence of systemic spread to multiple sites.

Growth kinetics of this tumor reveal a high thymidine labeling index (range, 11%-30%), comparable to that reported for solid specimens from patients with diffuse, non-Hodgkin’s lymphoma. This fact is probably related to its striking chemoresistance and to the relatively short duration of disease control by systemic or local therapy that still prevails in the majority of patients.

Pathologic subclassification of small cell undifferentiated carcinoma includes the “oat-cell” or “lymphocyte-like” variant (about 50%), intermediate forms (polygonal, fusiform, and tubular, about 33%), and mixed (the remainder). Whether this subclassification...
necessary to categorize the patient as having limited for diagnosis.

The appropriate tissue usually can be obtained from fiberoptic bronchoscopy; occasionally mediastinoscopy will be required if bronchoscopy is negative. The advent of the diagnosis already made. The procedures employed routinely for staging are based on a knowledge of known patterns of spread: bone, bone marrow, liver, and brain are the important organs to consider (see Table 1 and Fig. 1).

Frank lytic bone lesions evident on x-ray are uncommon in small cell carcinoma at any time. However, as many as two-thirds of patients will eventually have bone involvement. In a large study by the Southwest Oncology Group, which involved pretreatment bone scans in all patients, 21% had initial evidence of such involvement by scan. Nearly all had elevation of alkaline phosphatase. It would appear that any patient with elevation of alkaline phosphatase (or of the isoenzyme characteristic of bone, if available) should have a pretreatment bone scan. In the absence of such elevation or bone pain, a bone scan is probably superfluous, unless the patient is being staged for purposes of a research study.

Bone marrow involvement occurs in 15%-25% of patients at diagnosis based on series that involved a single aspirate and biopsy from the posterior iliac crest. The aspirate is more frequently positive than the biopsy. The absence of peripheral blood abnormality is not good evidence that the bone marrow is uninvolved. About 50% of patients with bone marrow metastasis have associated liver involvement. The frequency of bone marrow positivity without other evidence of metastatic disease is 4%-7%. In view of its low morbidity, this procedure should be carried out in most patients: not only is it important for staging, but occasionally it may provide the diagnosis in a critically ill patient. It is not required in the patient with clinically obvious extensive disease and a tissue diagnosis already made.

The role of liver scans is controversial. If liver function tests are all normal, the scan will almost certainly be normal (or nondiagnostic), as shown by Wittes and Yeh. Unfortunately, liver scans may be

### Table 1. Small Cell Carcinoma—Frequency of Metastatic Involvement at Diagnosis and at Autopsy

<table>
<thead>
<tr>
<th>Site</th>
<th>Frequency of Involvement (%)</th>
<th>At Diagnosis</th>
<th>Autopsy</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>9-12</td>
<td>15-24</td>
<td>60</td>
<td>16,21,22; 61-63</td>
</tr>
<tr>
<td>Bone</td>
<td>10</td>
<td>22</td>
<td>35-66</td>
<td>16-19; 3,4,61-63</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>4-7</td>
<td>11-23</td>
<td>35-66</td>
<td>16-19; 3,4,61-63</td>
</tr>
<tr>
<td>Brain</td>
<td>5</td>
<td>10-15</td>
<td>40</td>
<td>16,47; 14,38</td>
</tr>
</tbody>
</table>

DIAGNOSIS AND STAGING

Although sputum cytology will often yield a diagnosis, it may occasionally be in error. The advent of the fiberoptic bronchoscope has revolutionized the approach to diagnosis in this, as in other forms, of lung cancer. The appropriate tissue usually can be obtained from fiberoptic bronchoscopy; occasionally mediastinoscopy will be required if bronchoscopy is negative (70% or more of patients will have mediastinal node involvement at the time of diagnosis); only the rare patient with a peripheral coin lesion and no evidence of metastatic spread requires exploratory thoracotomy for diagnosis.

More controversial is the type and extent of staging necessary to categorize the patient as having limited versus extensive disease, a distinction with considerable prognostic importance and, possibly, differential therapeutic implications. It is important to realize that the history and physical examination are not sufficient. The role of liver scans is controversial. If liver function tests are all normal, the scan will almost certainly be normal (or nondiagnostic), as shown by Wittes and Yeh. Unfortunately, liver scans may be
false propensity for production of multiple, small metastatic lesions. In a patient with hepatomegaly and/or falsely negative in patients with this disease, which has a propensity for production of multiple, small metastatic lesions. In a patient with hepatomegaly and/or abnormal tests of liver function, the scan should always be performed, since it may provide information about location, extent, and response to treatment. Of the liver function tests, alkaline phosphatase is particularly sensitive: in 8 patients with proven hepatic involvement at peritoneoscopy, Margolis et al. reported alkaline phosphatase levels >150 mU/ml in 7. Dombernowsky et al.22 found increased alkaline phosphatase levels in 24/34 with documented liver involvement. They reported that alkaline phosphatase, lactate dehydrogenase (LDH), and SGOT were all elevated in 18/34 (52%), and 32/34 had abnormality of at least one. Only 3% of patients with disease that proved to be limited to the thorax had 2 or more abnormal liver function tests in Dombernowsky's series, compared to 68% of those with liver metastases. Given the low frequency of metastatic involvement in patients with a normal battery of liver chemistries, peritoneoscopy is not indicated in this group. But peritoneoscopy with directed liver biopsy may be useful for confirmation in the small minority of patients (< 10%) who have abnormal liver function tests(s), an equivocal or normal liver scan, and no other evidence of extensive disease. The role of abdominal ultrasound and computerized tomography remains to be determined.

"Routine" brain scans are probably not indicated in patients with normal neurologic examinations and no complaint of headache or history of seizures. In 35 consecutive patients with oat-cell carcinoma who underwent "screening" brain scans, only 1 yielded new information about possible organ involvement.20 Another series of 35 patients with all forms of lung cancer showed 7 (20%) with scans positive for tumor, but 6/7 had neurologic deficits corresponding to the scan abnormality.21

At completion of the staging process (shown as an algorithm in Fig. 1), a patient's disease may be categorized as limited (confined to the hemithorax, with or without involvement of supraclavicular nodes) or extensive (spread beyond the hemithorax and adjacent nodes, and/or recurrent disease after radiation to the primary tumor, or pleural effusion with positive cytology). Clinically, this is a very important distinction, since complete response and prolonged survival (more than a year) are much more likely if a patient has limited disease. It is noteworthy that patients with supraclavicular node involvement and/or superior vena caval syndrome appear to have the same response rate and overall prognosis as patients with "lesser" limited disease, while those with pleural effusion "only" as evidence of extensive disease seem to have response and survival characteristics like those of the extensive disease population as a whole.16

A factor that is just as important as the clinical stage of disease in determining prognosis is the pretreatment performance status. As in other forms of lung cancer, patients with fully ambulatory status (out of bed most of the time during the day, capable of complete self-care) live longer than those who are less than fully ambulatory, whether receiving no specific treatment2 or on various forms of therapy.

TREATMENT

Limited Disease

Takita et al. reviewed the experience with surgery alone as treatment of apparently resectable small cell carcinoma: among 806 cases, there were 5 long-term survivors after surgery alone, and 2 additional patients who lived 5 yr after surgical resection plus treatment with radiation or chemotherapy. Since the incidence of surgical cure is less than the expected morality from a major procedure, resection as definitive treatment is almost never carried out in a patient with small cell carcinoma.

Radiation therapy became the standard treatment for limited disease in the 1960s. Regardless of whether split course or continuous fractionation is employed, the median survival of such patients, treated with definitive irradiation to the primary tumor and mediastinum, is 5–7 mo; 1-yr and 2-yr crude survivals (including deaths from other causes) are 18%–30% and 5%–10%, respectively.24,25 Almost 90% of patients will show greater than 50% regression of measurable tumor.26,27 However, survival beyond 2 yr after radiation therapy is quite rare: 3/62 (5%) in the British Medical Research Council trial25 (in a subgroup defined as "potentially operable") and 3% in Lee's series24 had survival to 5 yr. The majority of patients treated with radiation therapy alone will relapse in sites outside the field,28 implying that disseminated micrometastases were present at the outset and/or the primary tumor was not sterilized.

Table 2 summarizes results of randomized trials and other studies involving more than 50 patients with limited disease in the English-language literature. Three trials, those of the VA Lung Study Group,28 the Eastern and Radiation Therapy Oncology groups combined,29 and the Southeast Group,30 prospectively compared radiation alone to the same radiation and chemotherapy (CCNU and hydroxyurea, CCNU and cyclophosphamide, and cyclophosphamide, Adriamycin, and dacarbazine, respectively). There was a
significant difference in median survival in the VA study that favored the group receiving combined treatment (9 versus 5 mo, \( p < 0.05 \)) but no difference in survival at 1 yr. Unfortunately, neither CCNU nor hydroxyurea are among the drugs of initial choice to treat the disease. The radiation therapy and drug treatment were given concomitantly, as they were in the ECOG-RTOG trial that showed no effect on median survival but some improvement in response duration for the combined modality group. In the Southeast Group study, chemotherapy was given first and radiation therapy in “sandwich” fashion between courses of drug treatment. Response duration and median survival of responders were both improved in the combined modality group. All these trials may have suffered from the choice of suboptimal chemotherapy.

Two trials have now been reported in which combination chemotherapy alone was prospectively compared to the same chemotherapy plus chest irradiation. That of Hansen et al. reported no difference in response duration, but an actual advantage in median survival for the group that received chemotherapy alone: 14 versus 11 mo (\( p < 0.01 \)). Stevens et al. found a slight, statistically insignificant advantage for the combined approach. Both groups concluded that radiation therapy to the chest was of no value. However, the radiation therapy used in each study involved an unorthodox, high-dose fraction shortened split course; a similar program in regional non-small cell lung cancer was recently found by Perez et al. to be inferior to other, more orthodox fractionation schemes.

The issue of whether to give chest irradiation revolved around one’s opinion of its value in local control at the primary tumor site. All are agreed that local control is a major problem: in a representative study by the Southwest Oncology Group, initial

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### Table 2. Treatment of Limited Disease: Studies With More Than 50 Patients

<table>
<thead>
<tr>
<th>Investigator(s)</th>
<th>Regimen</th>
<th>No. Pts.</th>
<th>Median Survival</th>
<th>1-yr Survival (%)</th>
<th>2-yr Survival (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fox et al.(^2)</td>
<td>&quot;Radical&quot; XRT</td>
<td>73</td>
<td>7</td>
<td>22</td>
<td>10</td>
<td>Randomized comparison to surgery: all deemed operable pretreatment</td>
</tr>
<tr>
<td>Lee et al.(^3)</td>
<td>4700 rad: split vs. continuous</td>
<td>58</td>
<td>7</td>
<td>20</td>
<td>8</td>
<td>Randomized comparison: no difference</td>
</tr>
<tr>
<td>Petrovich et al.(^4)</td>
<td>5000–6000 rad in 4–6 wk vs. Same XRT + CCNU and hydroxyurea</td>
<td>69</td>
<td>5</td>
<td>30</td>
<td>—</td>
<td>Difference in median survival significant</td>
</tr>
<tr>
<td>Livingston et al.(^5)</td>
<td>ADR + CTX + VCR (\rightarrow) XRT (split to 4500 rad total) (\rightarrow) ADR + CTX + VCR</td>
<td>104</td>
<td>12</td>
<td>50</td>
<td>15</td>
<td>Randomized comparison</td>
</tr>
<tr>
<td>Maurer et al.(^6)</td>
<td>CTX (\pm) VCR + MTX (\rightarrow) XRT</td>
<td>(\sim) 100</td>
<td>10.5</td>
<td>—</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>(cited by Weiss)</td>
<td>(3200 rad in 2 wk) (\rightarrow) same chemo</td>
<td>Hansen et al.(^7)</td>
<td>CTX + CCNU + MTX + simultaneous local XRT vs. CTX + CCNU + MTX + simultaneous extended field XRT (brain and abdomen)</td>
<td>53</td>
<td>11.5</td>
<td>—</td>
</tr>
<tr>
<td>Lowenbraun et al.(^8)</td>
<td>CTX + ADR + DTIC (no XRT)</td>
<td>61</td>
<td>10.6</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Hansen et al.(^9)</td>
<td>CTX + CCNU + MTX + VCR vs. CTX + CCNU + MTX + VCR and XRT to chest</td>
<td>69</td>
<td>14</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Feld et al.(^1)</td>
<td>CTX + ADR + VCR (\rightarrow) XRT to chest (\rightarrow) CTX + MTX + PROC</td>
<td>66</td>
<td>11</td>
<td>—</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Creech et al.(^1)</td>
<td>XRT:4500 rad in 5–6 wk (\pm) WBI vs. Same XRT + CTX + CCNU</td>
<td>94</td>
<td>4.6</td>
<td>13</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Krauss et al.(^1)</td>
<td>XRT:4500 rad in 5–6 wk + WBI vs. Same XRT + CTX + ADR + DTIC</td>
<td>30</td>
<td>6.2</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>White et al.(^1)</td>
<td>XRT:3000 rad or 4500 rad to (1^\circ) + WBI + comb. chemo. (\pm) BCG</td>
<td>90</td>
<td>9–15</td>
<td>20–30</td>
<td>—</td>
<td>(proj.)</td>
</tr>
</tbody>
</table>

XRT, radiation therapy; CCNU, Lomustine; ADR, Adriamycin (doxorubicin); VCR, vincristine; MTX, methotrexate; CTX, cyclophosphamide; DTIC, Dacarbazine; BCG, bacillus of Calmette and Guerin; WBI, whole brain irradiation; PROC, procarbazine; HDMTX, high-dose methotrexate; VP-16, 4′-demethylpipodophyllotoxin; HMM, hexamethylmelamine; 5FU, 5-fluorouracil.
failure occurred in the chest in 57%, and one-third were in the irradiated field. There is, however, a body of uncontrolled data that suggests a strong dose–response for radiation, with respect to control of the primary tumor in a setting of effective systemic chemotherapy. Inadequate dosage may be related to poor results. A common additional problem may be the treatment of inadequate field sizes to sterilize foci of residual microscopic tumor (e.g., treatment of apparent disease after delivery of chemotherapy, rather than of the original tumor area).

Although the debate is by no means settled about whether to radiate the chest, the best long-term survival results appear to be from those investigators who used simultaneous radiation and effective chemotherapy. Kent et al. reported disease-free survival of 36% at 2 yr in their group of 36 patients, albeit at a cost of deaths during the period of remission induction in 22% and some irreversible complications of concomitant treatment in the surviving patients, including especially esophageal stricture and skin toxicity. Using a similar basic program but with reduction in the dosage of both modalities, Greco et al. have reported 70% survival to 1 yr in a small group, with markedly reduced toxicity. Their experience demonstrates that it is possible to give Adriamycin and chest irradiation without unacceptable esophagitis and skin reactions, but not at full dose of each.

**Extensive Disease**

There are several established indications for radiation therapy in the treatment of extensive disease. It usually is the treatment of choice against clinically evident brain metastases (which, in the case of small cell, are most often multiple). Unfortunately, the treatment of grossly apparent brain metastasis with presently available radiation therapy achieves palliation in only about 50% of patients, with median survival in the range of 3–4 mo. It appears that 3000 rad delivered to the whole brain over a 2–wk period is as effective as any other regimen. There may be some improvement in the survival of patients who present with brain metastasis since the advent of effective systemic chemotherapy, but the majority will die with uncontrolled disease in the central nervous system. The outlook for patients who develop brain metastasis as the initial manifestation of relapse, after an initial response of systemic disease to therapy, is probably even worse: in Einhorn’s series, all 5 patients who developed brain metastasis were dead within a month, and Holoye reported a median survival of 10 wk from the time brain recurrence became apparent in 8 patients; this was in spite of whole-brain irradiation and steroids on an “emergency” basis, in both series.

The most important current role of radiation therapy is probably in the elective treatment of presumed microscopic metastatic disease, before it becomes clinically apparent. The frequency of brain metastases as the initial manifestation of recurrence has been dramatically reduced (from 22% to 2% overall) by the use of elective, whole-brain irradiation, usually to a total of 3000 rad in 2 wk, at some time between the initiation of treatment and 12 wk into therapy. In addition 2 prospective controlled trial demonstrated a decrease in the frequency of brain recurrence among patient receiving “prophylactic” whole-brain irradiation. Two points bear emphasis here: (1) only those patients (today a small minority) who have prolonged control of systemic disease will demonstrate real survival improvement, while the median survival of all patients treated is not likely to be altered; and (2) since “reseeding” of the brain may occur if systemic disease is not immediately controlled, it is probably better to delay the administration of elective whole-brain irradiation until clinically evident response of systemic disease has occurred. This is quite feasible since almost all responses are evident by 6 wk (including the majority of complete responses), and the median time to development of brain relapse is about 6 mo (first seen at 16–18 wk). Those patients who fail to show systemic disease response by 6–12 wk on treatment should probably not have elective whole-brain irradiation.

A third established role for radiation therapy is in the treatment of extradural (or other) metastases that threaten to produce spinal cord compression. Classically, these lesions present first as back pain (as in lymphoma), then as sensory and/or motor changes with a pattern of subacute to acute evolution. With the advent of effective systemic treatment, relapses have been shown to occur with increasing frequency in dural and intramedullary sites and as diffuse, meningeal carcinomatosis: as many as 10% of initial relapses in patients with extensive disease may be in these locations. Until we develop effective systemic agents with good penetration into the central nervous system, these sites will require innovative “local” approaches to management and, perhaps more importantly, elective treatment aimed at eradication of subclinical micrometastasis. These may include irradiation of the neuraxis and/or intrathecal chemotherapy. The latter is a subject of a current randomized trial in the Southwest Oncology Group.

Controversy exists about the role of radiation therapy in the management of superior vena caval syndrome, obstruction of a major bronchus, and treat-
ment of the primary lung tumor. Chemotherapy appears to be as successful as irradiation in the initial treatment of these problems. In the studies of Cancer and Leukemia Group B and the Southwest Oncology Group, the routine sequential addition of therapy to the primary tumor and mediastinum (3000 rad in 2 wk for patients with extensive disease) did not improve median or long-term survival time over that achieved by similar combinations of chemotherapy alone. However, it may be argued that the dose of radiation used was suboptimal, or that only responders to systemic chemotherapy should receive chest irradiation. Also, investigators at the National Cancer Institute have reported that response and palliation with radiation delivered after failure on chemotherapy regimens is considerably inferior to that expected with radiation therapy delivered de novo, suggesting that it might be more useful to radiate the chest “up front” in the therapeutic sequence.

Experimental roles for radiation therapy that are undergoing evaluation in patients with extensive disease include its use in the “consolidation” of chemotherapy response (i.e., sequential “involved-field” radiation to areas of known previous tumor spread) and hemibody therapy.

Chemotherapy has become the major approach to

Table 3. Treatment of Extensive Disease: Studies With More Than 40 Patients

<table>
<thead>
<tr>
<th>Investigator(s)</th>
<th>Regimen</th>
<th>Median Survival (months)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zelen et al.</td>
<td>CTX 700 mg/m q 3 wk + CCNU 70 mg/m PO q 6 wk</td>
<td>106</td>
<td>4.5</td>
<td>12</td>
<td>43</td>
</tr>
<tr>
<td>Hansen et al.</td>
<td>CTX 700 mg/m q 3 wk + CCNU 70 mg/m PO + MTX 10 mg/m q 2 wk</td>
<td>52</td>
<td>5.8</td>
<td>—</td>
<td>78</td>
</tr>
<tr>
<td>Cohen et al.</td>
<td>CTX 500 mg/m q 3 wk + CCNU 50 mg/m q 6 wk + MTX 10 mg/m q 2 wk</td>
<td>42</td>
<td>6-8</td>
<td>—</td>
<td>45-56</td>
</tr>
<tr>
<td>Hansen et al.</td>
<td>CTX 700 mg/m q 3 wk + CCNU 70 mg/m q 4 wk + MTX 20 mg/m q days 18 and 21, q 4 wk vs. CTX + CCNU + MTX + VCR weekly x 4, then q 4 wk</td>
<td>53</td>
<td>7.6</td>
<td>—</td>
<td>75</td>
</tr>
<tr>
<td>Cohen et al.</td>
<td>CTX 1500 mg/m q 1 mo; then 1000 mg/m q 3 wk + CCNU 100 mg/m q 3 wk + MTX 15 mg/m q 2 wk; then vcr 2 mg</td>
<td>42</td>
<td>9</td>
<td>36</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Livingston et al.</td>
<td>ADR 50 mg/m q 1 mo + CTX 750 mg/m + VCR 1 mg + 60 mg/m q 42 + 63 + PROC 100 mg/m q/m day x 10, varied</td>
<td>250</td>
<td>6</td>
<td>14</td>
<td>56</td>
</tr>
<tr>
<td>Mauer et al.</td>
<td>CTX + VCR + MTX + XRT (3200 rad in 2 wk) same chemo</td>
<td>&gt;100</td>
<td>6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Oldham et al.</td>
<td>CTX + ADR + VCR + HMTX — VP-16 + PROP + HMM</td>
<td>45</td>
<td>7+</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>Dombernowsky et al.</td>
<td>CTX + CCNU + MTX + VCR vs.</td>
<td>73</td>
<td>9</td>
<td>81</td>
<td>—</td>
</tr>
<tr>
<td>Feld et al.</td>
<td>CTX + ADR + VCR — XRT (1+ only) — CTX + MTX + PROP</td>
<td>81</td>
<td>8</td>
<td>8*</td>
<td>65</td>
</tr>
<tr>
<td>McCracken et al.</td>
<td>CTX + VCR + MTX + 5FU vs. VCR + MTX + VP-16 — CTX + ADR + VCR ± BCG (all pts. received WBI)</td>
<td>138</td>
<td>6-8</td>
<td>&gt;20</td>
<td>66</td>
</tr>
</tbody>
</table>

*Response assessed at 6 wk. Abbreviations as in Table 2.
the patient with extensive disease, and the weight of evidence is that combinations are superior to the single agent cyclophosphamide (see Table 3). The most effective regimens include cyclophosphamide plus vincristine or methotrexate, with or without Adriamycin or CCNU. As shown in Table 4, the most effective single agents are VP-16, cyclophosphamide, Adriamycin, vincristine, methotrexate, and hexamethylmelamine. The study of Cohen et al. in which high-dose CCNU, cyclophosphamide, and methotrexate were followed by vincristine, Adriamycin, and procarbazine after 2 induction cycles, resulted in an increase in the complete response rate from 20% to 36%. This was an exciting result and has led to further exploration of intentionally alternating, non-crossresistant combinations in other series. It appears that the achievement of clinical complete response by 6 wk is a favorable prognostic sign: in Cohen’s experience, relapse was observed in 1/17 who were in complete response at 6 wk and 8/16 who required an additional 6 wk (2 courses of VAP) to achieve complete response. It should be emphasized that the 36% complete response rate cited was achieved by very aggressive chemotherapy. The lower complete response rates reported by others, in the studies cited in Table 3, reflect less aggressive approaches tailored to “outpatient” chemotherapy. These approaches, with a variety of combinations, produce complete response in 5%–15% of patients with extensive disease, a median survival of 5–7 mo, and 1-yr survival in 15%–20%. Sustained complete response has been observed in 3%–5% even with this “low-dose” approach, suggesting the possibility of cure in a very small minority. Perhaps more aggressive chemotherapy, and/or the alternation of effective combinations to kill resistant cells, will produce marked improvements in long-term survival. It is certain that the trend toward more aggressive chemotherapy means increased morbidity and carries with it the risk of greater treatment-related mortality.

The experience of the Southwest Oncology Group is fairly representative of problems from “outpatient” approaches with combination therapy. Alopecia and drug-related gastrointestinal disturbance were virtually universal. Nausea and vomiting were in general limited to the first 12 hr after administration of cyclophosphamide or Adriamycin (with hexamethylmelamine, which is available only in an oral formulation and must be administered on a relatively prolonged basis, this problem may be dose-limiting). Life-threatening side effects occurred in 10% of patients related to leukopenia (fever and presumed infection, with or without bacteriologic confirmation), and drug-related death on this basis in 3%. Thrombocytopenia is rarely severe with the agents commonly employed (except CCNU), and hemorrhage quite unusual (0.6% of patients in the Southwest Oncology Group study required platelet transfusions). Vincristine neuropathy is related both to total dose and to dose level, as well as the patient’s age. The dependence of vincristine and Adriamycin on liver function and of methotrexate on renal function for their excretion dictates appropriate dose modification of these agents with compromise of the respective organs. Urate nephropathy from tumor lysis can be avoided by the routine administration of allopurinol, 300 mg/day, starting the day before the first induction course and continued for 5–7 days. It is unnecessary to give allopurinol prophylaxis in most patients after the first course. Rarely, severe electrolyte derangements can result from rapid tumor destruction.

As mentioned previously, the major thrust of investigation in chemotherapy of extensive disease involves a shift toward very aggressive, “acute leukemia style” induction therapy and emphasis on the alternation of non-crossresistant regimens. The only significant new drug to emerge is VP-16, an epipodophyllotoxin derivative that is probably cell-cycle specific. The concepts of reinduction, as well as early and late intensification, which have been pioneered in acute leukemia, will undoubtedly be applied to the treatment of small cell lung cancer. Intrathecal “prophylaxis” of some kind

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### Table 4. Small Cell Carcinoma: Single Agent Activity* of Drugs Tested in ≥ 20 Patients

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>189</td>
<td>52 (28)</td>
<td>4</td>
<td>Intermittent</td>
<td>74</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>36</td>
<td>11 (31)</td>
<td></td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>73</td>
<td>22 (30)</td>
<td></td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>Vincristine</td>
<td>43</td>
<td>18 (42)</td>
<td>7</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>VP-16</td>
<td>167</td>
<td>75 (45)</td>
<td>9</td>
<td></td>
<td>74–76</td>
</tr>
<tr>
<td>CCNU</td>
<td>76</td>
<td>11 (14)</td>
<td>4</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>Hexamethylmelamine</td>
<td>69</td>
<td>21 (30)</td>
<td>7</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td>55</td>
<td>24 (44)</td>
<td></td>
<td></td>
<td>74</td>
</tr>
</tbody>
</table>

*Most patients had extensive disease.

CR, complete response; PR, partial response (≥50% regression of all measurable disease for ≥4 wk).
will become more and more common. Autologous bone marrow reinfusion has already been reported and may see more widespread use, especially in the treatment of refractory disease with massive doses of chemotherapy. A potential problem here is the possibility that tumor cells may be reinfused also, due to clinically apparent residual involvement of the marrow.

**SUMMARY**

**Present Management and Trends in Treatment**

The patient with limited small cell carcinoma of the lung at diagnosis is a candidate for potentially curative treatment, with a probability of long-term, disease-free survival approximating that of an adult with acute myelogenous leukemia. The “best” treatment has not yet evolved, and many research protocols presently in progress will shed light on this question. Because microscopic dissemination of disease is present in the majority of patients, chemotherapy must be an important component of their management. Cyclophosphamide-based combinations, especially those involving vincristine with or without Adriamycin, methotrexate, or VP-16, currently appear to be the most effective. The role of radiation therapy to the primary tumor, once considered “standard,” is now being questioned. But increased dose, better treatment planning, advances in technique, and/or particle (e.g., neutron) therapy may lead to an increase in efficacy of this modality. In those programs that involve combined radiation and chemotherapy, both theory and experience suggest that agents with marked overlapping toxicity (e.g., Adriamycin and methotrexate) should not be administered simultaneously with full-dose radiation. The use of chemotherapy, followed by radiation, followed by chemotherapy in a “sandwich” fashion, is better tolerated than a concomitant approach. However, it may also be less effective. Local therapy to the brain by irradiation will by necessary to prevent relapse in this “sanctuary” site as long as systemic chemotherapy remains ineffective. In extensive small cell disease, elective whole-brain radiation should be carried out also, at least in those patients who show a partial or complete response after 2–4 courses of combination chemotherapy. The experience with relapse in nonbrain CNS sites indicates that these will require some form of local “prophylactic” treatment in such patients, either intrathecal chemotherapy or neuraxis irradiation.

The only hope of prolonged disease-free survival for patients with extensive disease at presentation lies in achieving a complete response with systemic chemotherapy. Present trends are toward very intensive regimens, often alternating and complex, to achieve that goal. This means more treatment-related morbidity and the need for excellent supportive care if mortality is to be avoided. Many, if not all, patients will require treatment on an inpatient basis, and at least one in five will probably require additional hospitalization for the management of complications. For all these reasons, the best treatment for most patients will be entry on a research protocol and management by a skilled multidisciplinary team.

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Small cell carcinoma of the lung

RB Livingston