Lung cancer: A review

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Lung cancer is one of the most common malignancies diagnosed in the United States. It is also one of the most preventable. As with all cancers, the greatest hope for a cure with lung cancer is when the disease is detected early in its course. However, many people with lung cancer are diagnosed at advanced—and usually incurable—stages. In these patients, radiation therapy and chemotherapy play a major role. Several antineoplastic agents have recently become available that show more promise in the management of patients with advanced lung cancer than has been seen for some time. This article reviews the frequency, risk factors, pathophysiology, diagnosis, and management of lung cancer.

Anatomy and physiology

The right lung consists of three lobes and the left lung of two (Figure 1). The trachea is the major airway that carries air to and from the lungs. At its distal end, the trachea branches into two main bronchi, each of which enters a lung at the hilum. The area of the bifurcation of the trachea is known as the carina, an important anatomical landmark. Spread of cancer to within 2 cm of the carina may make surgical resection impossible. One of the first areas of spread beyond the lungs is the regional lymph nodes. For staging purposes, the regional lymph nodes are classified into mediastinal and intrapulmonary groups. Mediastinal nodes include peritracheal, pretracheal and retrotracheal, aortic, subcarinal, periesophageal, and pulmonary ligament nodes. The intrapulmonary nodes consist of the hilar, peribronchial, intralobar, lobular, and segmental nodes. The most common locations for lymphatic spread are the hilar, mediastinal, and para-aortic nodes. Identification of disease in regional nodes plays a major role in staging the disease and in determining the prognosis for surgical resection.
Frequency
The American Cancer Society estimated that 169,500 new cases of lung cancer would be diagnosed in 2001 and that 157,400 people would die of the disease that year. In men, lung cancer is second in frequency only to prostate cancer, accounting for 14% of newly diagnosed cancers. Lung cancer is also the second most common cancer in women (after breast cancer), accounting for 12% of newly diagnosed cancers. Lung cancer is the number one cause of death from cancer in both men and women. Approximately one of three men who die of cancer die of lung cancer, while one of four women who die of cancer die of cancer of the lungs and bronchi.

Although the frequency of lung cancer in both men and women increased for many decades, the frequency in men peaked in 1984 at 86.5 cases per 100,000 population and declined by 1.4% annually through 1996. Deaths among men peaked in 1990 at 75.2 per 100,000 and were lower from 1994 to 1996 than in the preceding three years. The rate of lung cancer among women may have peaked in 1994 at 43.4 per 100,000. Rates declined by 1.3% per year from 1994 to 1996. There has been no decline in lung cancer death rates among women.

Etiology and risk factors
The major risk factor for lung cancer is smoking. An estimated 75–80% of lung cancer-related deaths are due to smoking. A 1995 survey estimated that 47 million U.S. adults smoke. Smoking is more common among men (27%) than women (23%). The risk of lung cancer increases with the number of cigarettes smoked per day, as well as with the number of years spent smoking. Once someone quits smoking, the risk gradually declines. Doll and Peto, in a 20-year survey, found that mortality declined among British male physicians who stopped smoking compared with those who did not. The overall mortality of ex-smokers resembled that of nonsmokers 15 years after smoking ceased. The overall mortality of ex-smokers resembled that of nonsmokers 15 years after smoking ceased. Garfinkel and Stellman reported that the risk of lung cancer among women also declined after they stopped smoking. The relative risk of lung cancer in women who had never smoked was defined as 1.0. Women who smoked 1–20 cigarettes per day had a relative risk of 10.3, which declined to 3.3 after they had quit smoking for 6–10 years. After 16 years of nonsmoking, the risk fell to 1.3. A considerable decline was also noted among women who smoked 21 or more cigarettes per day who quit: a relative risk of 21.2 for current smokers versus 4.0 for those who had quit for 16 years.

People who live or work with smokers may inhale cigarette smoke as a result of their proximity to smokers. Passive inhalation of cigarette smoke increases the risk of lung cancer. About a third of the cases of lung cancer among nonsmokers who live with smokers can be attributed to passive smoking.

Asbestos is a known carcinogen that increases the risk of lung cancer in people exposed to airborne fibers. The risk increases with the amount of exposure and is even higher in exposed smokers. About 3–4% of lung cancers are due to asbestos exposure. Radon is a gas produced by the decay of radium 226. The decay of this isotope leads to the production of substances that emit α particles. These particles may cause cell damage that increases the potential for malignant transformation. Radon may become trapped in houses and buildings with poor ventilation, especially in the basement. Exposure to radon may increase the risk of lung cancer. Additional exposures that may increase this risk of lung cancer include chromium, nickel, polycyclic aromatic hydrocarbons, inorganic arsenic compounds, and bis-(chloromethyl) ether. There is some evidence that people who carry an α1-antitrypsin deficiency allele may be at greater risk for lung cancer.

There is no clear evidence that substances in the diet increase the risk of lung cancer. However, some dietary substances may be involved in prevention, including vitamins C and E, selenium, and carotenoids.

Pathology
Lung cancers can be broadly clas-
sified into two forms, small-cell carcinomas and non-small-cell carcinomas. The non-small-cell carcinomas are further divided into squamous-cell carcinomas, adenocarcinomas, and large-cell carcinomas.

Squamous-cell carcinomas account for approximately 30% of lung cancers. This type of tumor is one of the two most commonly associated with smoking; the other is small-cell carcinoma. Squamous-cell tumors are usually found in the central part of the chest and tend to grow relatively slowly, doubling in size every 88 days. Tumors may be present for several years before they grow large enough to produce signs or symptoms. Squamous-cell carcinomas are the most likely to remain centrally located.

Adenocarcinomas are the most common form of lung cancer found in nonsmokers and in women. About 30–40% of lung cancers are adenocarcinomas. They tend to grow toward the periphery of the lung and double in size every 161 days. Adenocarcinomas have a higher tendency to metastasize than squamous-cell carcinomas.

Large-cell carcinomas are the least common form, accounting for about 10–15% of lung cancers. These tumors tend to grow in a peripheral location at a rate comparable to that of squamous-cell cancers, doubling in 86 days. Like adenocarcinomas, large-cell cancers are more likely to metastasize than squamous-cell carcinomas.

Small-cell carcinomas account for some 20–25% of lung cancers. They tend to originate in central locations and grow very rapidly; the doubling time is approximately 29 days. A large majority of patients with small-cell carcinomas have metastatic disease at the time of diagnosis.

Signs and symptoms

There are no signs or symptoms that are specifically diagnostic of lung cancer. Some symptoms seen in patients with lung cancer are also found in people who smoke or have other disorders, including upper-respiratory-tract infections. Signs and symptoms are related to the size and location of the primary tumor and to the presence of metastatic disease. Common symptoms include cough, hemoptysis, wheezing, and dyspnea, although it is not unusual for a lesion to be discovered by chest radiography in an asymptomatic patient. Additional symptoms may appear as the lesions enlarge and begin to spread. Growth within a bronchus often leads to coughing and wheezing and occasionally produces stridor. Hemoptysis is usually mild, consisting of blood-streaked sputum. Obstruction of an airway may also result in pneumonia and fever. Involvement of a pleura could produce pleuritic pain, as well as pleural effusion. Additional signs associated with local spread include superior vena cava syndrome (with edema in the face, neck, and shoulders), due to compression of the superior vena cava by an enlarging tumor, and Pancoast’s syndrome (shoulder or arm pain), due to compression of the brachial plexus by extension of an apical tumor. Enlargement of the tumor or mediastinal nodes may cause pressure on the laryngeal nerve, leading to hoarseness. Various nerve palsies may also occur.

Symptoms of metastatic disease are related to the location of the tumor. The most common sites of distant metastases are the liver, brain, bones, and adrenal glands. Patients with brain involvement may have headaches, decreased mental capacity, seizures, and even signs of encephalopathy. Bone lesions are generally very painful. Lesions in the liver may result in abdominal pain and eventually jaundice. Nonspecific symptoms of metastatic disease include fatigue and weight loss.

Diagnosis

A complete medical history and physical examination may reveal signs and symptoms suggestive of lung cancer. Many smokers cough and produce sputum daily. Any change in the amount or consistency of the sputum may be important. Shortness of breath, wheezing, chest pain, blood in the sputum, or frequent respiratory infections may be helpful in diagnosis. Patients should always be questioned about smoking and exposure to environmental toxins and irritants, such as asbestos. Bone pain, fatigue, and unintentional weight loss also increase the index of suspicion.

One of the first tests used to evaluate a patient suspected of lung cancer is chest radiography. The results may reveal a mass, lymph node enlargement, pleural effusion, or lung collapse. Chest computed tomography and magnetic resonance imaging may also assist in the detection of physical abnormalities suggestive of cancer. Imaging of symptomatic areas may identify metastases to the bones, liver, and other locations.

The easiest way to obtain samples of malignant cells for cytologic examination is to collect sputum. Collection for three days is usually sufficient. Difficulties that may arise include the patient’s inability to produce sputum and the size and location of the tumor. Small tumors and tumors that are not close to an airway may not shed cells into the sputum. Tumors in the lung periphery may not yield positive results on sputum examination. About 80% of central tumors will be diagnosed by sputum cytology.

Bronchoscopy is also a valuable diagnostic tool. Samples of lesions found within the bronchi can be obtained by using forceps, brushes, and washings; lung cancer is present in 90% of cases in which a visible lesion is found. Bronchoscopy is limited to lesions located within airways. Lesions deep within the bronchial tree or in small airways may be beyond the reach of bronchoscopy.

Fine-needle biopsy of a lesion in the lung or a lymph node or of a
metastatic lesion is another technique, yielding a positive result up to 95% of the time. Needle biopsy is especially useful for peripheral lesions beyond the reach of a bronchoscope.

Mediastinoscopy is used to evaluate the superior mediastinal nodes. An incision is made at the suprasternal notch, and the mediastinoscope is inserted. The scope can be used to visualize and sample the nodes. It is usually not needed to make the diagnosis and is primarily used to determine nodal involvement as part of a staging workup.

Most patients can be correctly diagnosed with the procedures discussed above. Rarely, a thoracotomy may be necessary to make the diagnosis.

**Staging**

Two major staging systems are used for lung cancer. The TNM system stages lung cancer on the basis of the primary tumor (T), the extent of lymph node involvement (N), and distant metastases (M). Each letter is assigned a number that specifies the extent of tumor involvement (Table 1). In the numerical staging system, a numerical designation from 0 to IV is assigned on the basis of TNM characteristics (Table 2). The TNM system is primarily used for patients with non-small-cell lung cancer. Patients with small-cell lung cancer are commonly staged with the Veterans Affairs lung cancer classification system, which classifies the disease into two stages, limited and extensive. Limited disease is defined as disease involved in one hemithorax, including ipsilateral mediastinal, ipsilateral supraclavicular, and contralateral hilar nodes. Anything beyond limited disease is designated as extensive disease.

**Management of non-small-cell lung cancer**

**Stages I and II.** Stage I and II disease accounts for about 15% of newly diagnosed cases of non-small-cell lung cancer. These patients are candidates for surgical resection, which offers the best opportunity for a cure. The type of surgery performed is based on the location and extent of the disease and on the patient’s ability to tolerate the procedure. The most common surgical procedure is lobectomy, in which the entire lobe containing the tumor is removed. Limited resections, such as wedge resections, are associated with a greater risk of local recurrence and are reserved for patients who cannot tolerate a more extensive procedure. Occasionally, a patient may have such extensive disease that a total pneumonectomy is necessary. The five-year survival rate for patients with surgically confirmed stage Ia disease is about 70%, while patients with stage Ib disease have a 60% five-year survival rate. Patients with stage Ia and stage Ib disease have 55% and 40% five-year survival rates, respectively. Some patients with localized disease may not be candidates for surgery because of comorbid conditions. These patients may be offered radiation therapy with curative intent. Survival rates after such irradiation are in the 15–20% range.

**Adjuvant therapy.** Although patients with stage I and II non-small-cell lung cancer may undergo resection with curative intent, many relapse and eventually die of their disease. These patients most likely had cancer cells left behind, either locally or at distant sites, that redeveloped into clinical disease. Adjuvant therapy is applied after the primary form of therapy in an effort to eradicate residual disease or to prevent recurrence. For patients with early disease, the primary therapy is surgery, with adjuvant therapy available as irradiation or chemotherapy.

### Table 1. TNM Staging System for Lung Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1$</td>
<td>Tumor demonstrated by the presence of malignant cells in bronchopulmonary secretions but not visible radiographically or bronchoscopically; also includes any tumor that cannot be assessed.</td>
</tr>
<tr>
<td>$T_2$</td>
<td>Tumor of $\leq 3$ cm in greatest dimension, surrounded by lung or visceral pleura and without evidence of invasion proximal to a lobar bronchus at bronchoscopy.</td>
</tr>
<tr>
<td>$T_3$</td>
<td>A tumor of $&gt;3$ cm in greatest dimension, or a tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region; on bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2 cm distal to the carina; any associated atelectasis or obstructive pneumonitis must involve less than an entire lung.</td>
</tr>
<tr>
<td>$T_4$</td>
<td>A tumor of any size with direct extension into the chest wall, diaphragm, or mediastinal pleura or pericardium without involving the heart; great vessels, trachea, esophagus, or vertebral body; or a tumor in the main bronchus 2 cm from the carina without involving the carina.</td>
</tr>
<tr>
<td>$N_0$</td>
<td>Regional lymph nodes cannot be assessed.</td>
</tr>
<tr>
<td>$N_1$</td>
<td>Metastasis to nodes in the ipsilateral peribronchial or ipsilateral hilar region and involvement of intrapulmonary nodes by direct extension of the primary tumor.</td>
</tr>
<tr>
<td>$N_2$</td>
<td>Metastasis to ipsilateral mediastinal lymph nodes or subcarinal lymph nodes.</td>
</tr>
<tr>
<td>$N_3$</td>
<td>Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, or ipsilateral or contralateral scalene or supraclavicular lymph nodes.</td>
</tr>
<tr>
<td>$M_0$</td>
<td>No known distant metastases.</td>
</tr>
<tr>
<td>$M_1$</td>
<td>Distant metastases present—specify sites.</td>
</tr>
</tbody>
</table>
CLINICAL REVIEWS Lung cancer

Table 2. Numerical Staging System for Lung Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>T\textsubscript{0}N\textsubscript{0}M\textsubscript{0}</td>
</tr>
<tr>
<td>Ia</td>
<td>T\textsubscript{1}N\textsubscript{0}M\textsubscript{0}</td>
</tr>
<tr>
<td>Ib</td>
<td>T\textsubscript{1}N\textsubscript{0}M\textsubscript{0}</td>
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<tr>
<td>Ila</td>
<td>T\textsubscript{1}N\textsubscript{0}M\textsubscript{0}</td>
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<td>Iib</td>
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</tr>
<tr>
<td>IIIa</td>
<td>T\textsubscript{1}N\textsubscript{1}M\textsubscript{0}</td>
</tr>
<tr>
<td>IIIb</td>
<td>T\textsubscript{1}N\textsubscript{1}M\textsubscript{0}</td>
</tr>
<tr>
<td>IV</td>
<td>T\textsubscript{1}N\textsubscript{2}M\textsubscript{1}</td>
</tr>
</tbody>
</table>

See Table 1.

No survival advantage was conferred by adjuvant radiation therapy among patients who had undergone resection for stage I lung cancer. Therefore, adjuvant therapy is usually not recommended for stage I disease. The use of adjuvant therapy for stage II or III disease is controversial. The Lung Cancer Study Group randomly assigned 230 patients who had had a complete surgical resection of stage II or IIIa squamous-cell carcinoma to postoperative irradiation or no additional therapy. Patients who received irradiation had a local first recurrence rate of 3%, versus 41% for those who did not. However, there was no difference in survival between the two groups. A high rate of systemic recurrence may explain the lack of a survival difference. Fifty-nine percent of the nonirradiated patients and 97% of the irradiated patients had a systemic recurrence as their first recurrence. Stephens et al. randomized 308 patients with T\textsubscript{1–2}N\textsubscript{1–2}M\textsubscript{0} disease to either postoperative irradiation or observation. The local recurrence rate was 41% with observation, versus 29% after irradiation. However, there was no difference in survival.

A meta-analysis of nine randomized trials involving 2128 patients also failed to find a survival advantage with postoperative radiation therapy. The researchers found an inverse relationship between death in irradiated patients and stage of disease and nodal involvement. The highest death rates were among irradiated patients with stage I or N\textsubscript{0} disease; radiation had no significant effects in patients with stage III or N\textsubscript{2} disease. In summary, the data available to date indicate that adjuvant radiation therapy may reduce local recurrence and prolong the disease-free survival period but not prolong overall survival.

Relapses at distant sites play a major role in the recurrence of lung cancer after complete resection. Radiation therapy, which is a localized treatment, would not be expected to have an impact on distant recurrence. Chemotherapy, a systemic form of treatment, might. Most randomized trials comparing adjuvant chemotherapy with observation fail to demonstrate a survival advantage for chemotherapy, however. A meta-analysis of these trials revealed that the outcome may be due, in part, to the type of chemotherapy used. Older studies that employed alkylating agents were associated with a negative effect on survival of -5% at five years. Cisplatin-containing regimens were associated with a 5% improvement in survival at five years. Several randomized trials of adjuvant therapy with newer antineoplastic agents are under way. These trials are designed to eliminate some of the problems the older trials had, such as small numbers of patients, inadequate delivery of drugs, and the drugs themselves.

Stage III. Stage III non-small-cell lung cancer accounts for approximately 25% of patients at diagnosis. Stage III is divided into sub-stages IIIa and IIIb. IIIa includes tumors designated by size and spread as T\textsubscript{1–3}, with concurrent N\textsubscript{0} nodal involvement or T\textsubscript{4} with N\textsubscript{1} nodal spread. About one third of patients with stage IIIa disease may be candidates for surgical resection. Stage IIIb disease includes tumors of any size with N\textsubscript{1} nodal involvement or T\textsubscript{4} tumors. These patients are usually managed nonsurgically.

After careful staging, IIIa disease is classified as resectable or unresectable. Patients with chest-wall involvement may be surgical candidates. The major determinants of survival in these patients are the extent of the resection and the amount of nodal involvement. Patients without nodal disease have a better prognosis than patients with nodal spread. In the largest series involving surgical resection for chest-wall involvement, 125 patients were treated. Seventy-seven had complete resection, the rest partial or no resection. The five-year survival rate, among patients with complete resection, was 56% for those without nodal disease and 21% for those with N\textsubscript{1} or N\textsubscript{2} disease. Patients with partial resection had all died by 2.5 years. Piehler et al. reported a 33% five-year survival rate among 56 patients who had complete resection of chest-wall tumors. Survival rates were 54% for patients without nodal involvement and 7% for patients with N\textsubscript{1} or N\textsubscript{2} disease.

Surgical treatment of N\textsubscript{2} disease is controversial. Involvement of mediastinal nodes greatly reduces the possibility of long-term survival. The extent of nodal involvement is also a major factor in survival. Patients with limited N\textsubscript{2} disease (confined to one nodal site) fare much better than patients with advanced N\textsubscript{2} disease (anything beyond limited disease). Complete resection in patients with limited N\textsubscript{2} disease is associated with five-year survival rates of 19–30%. Advanced N\textsubscript{2} disease is usually considered inoperable.

For many years, radiation therapy was considered standard for patients with unresectable locally advanced disease. Despite the extensive use of radiation therapy in these patients, control of localized disease was poor and patients frequently died as a result of distant metastases. Long-term survival rates with this approach were 5–10%. A few uncontrolled trials indicated that survival might be
improved by combining radiation therapy with chemotherapy. Randomized trials were conducted to determine if such combined therapy would improve survival over irradiation alone. Although several earlier trials did not indicate a survival advantage of chemotherapy plus radiation therapy over radiation therapy alone, more recent trials did. Chemotherapy and radiation therapy can be administered either sequentially or concurrently; there is uncertainty as to which is the better schedule. In three of the trials in which chemotherapy and radiation therapy were used concurrently, the major benefit was a reduction in locoregional disease. When the two therapies were administered sequentially, one trial found a major reduction in the development of distant metastases. Only two trials comparing sequential and concurrent schedules have been published. Furuse et al. randomized 320 patients to receive radiation therapy and either concurrent or sequential chemotherapy with mitomycin, vincristine, and cisplatin. There were 314 evaluable patients. After a median follow-up of five years, the authors reported that the median survival time for the patients who received concurrent therapy was 16.5 months, compared with 13.3 months for the patients who received sequential treatment \( (p = 0.039) \). The yearly survival figures were as follows for concurrent and sequential therapy, respectively: one year, 64% and 55%; two years, 35% and 27%; three years, 22% and 15%; four years, 17% and 10%; and five years, 16% and 9%.

The Radiation Therapy Oncology Group conducted a Phase III comparison of concurrent and sequential chemotherapy and radiation therapy. Six hundred eleven patients with stage II or III disease were entered into the study between 1994 and 1998 and randomized to receive one of two concurrent regimens or sequential therapy. One of the concurrent regimens consisted of once-daily irradiation plus cisplatin and vinblastine, while the other involved lower dosages of cisplatin and etoposide and twice-daily irradiation. In the sequential regimen, patients received cisplatin and vinblastine. After a minimum follow-up period of 15 months (median, 40 months), the median survival times for the sequential, once-daily irradiation, and twice-daily irradiation groups were 14.6, 17.0, and 15.6 months, respectively. The differences were not significant.

Both the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommend chemotherapy with cisplatin-based regimens plus radiation therapy for patients with unresectable stage III disease. Neither organization states a preference for sequential or concurrent schedules. ASCO recommends two to eight cycles of chemotherapy, while NCCN does not specify the length of treatment.

**Neoadjuvant therapy.** Neoadjuvant therapy is administered before the primary form of therapy. Three small studies found increased survival with neoadjuvant chemotherapy. Rosell et al. randomly assigned 60 patients with stage IIIa disease to receive surgery and postoperative radiation therapy or preoperative chemotherapy. The median survival time for the group that received chemotherapy was 26 months, versus 8 months for the group that did not \( (p < 0.001) \). Roth et al. randomized patients with stage IIIa disease to chemotherapy and surgery or to surgery alone. Patients who responded to preoperative chemotherapy also received postoperative chemotherapy. A major response (complete or partial) was seen in 35% of the patients who received chemotherapy. Thirty-nine percent of the patients who received chemotherapy underwent complete resection, while 31% of those who were not given chemotherapy had complete resection. The median survival time for patients who received chemotherapy was 64 months, compared with 11 months for the nonchemotherapy group \( (p < 0.008) \). Projected three-year survival rates were 56% in the chemotherapy group and 15% in the surgery-only group.

Andre et al. reported on 686 patients with stage N_M0 disease resected with curative intent. The patients were classified as having minimal N2 disease (mN2, no preoperative detection of N2 involvement) or clinically apparent disease (cN2, detected preoperatively). Fifty-two percent had mN2 disease, and 48% had cN2 disease. Twenty-nine of the patients with mN2 disease and 95 with cN2 disease had preoperative chemotherapy. The five-year survival rate after neoadjuvant chemotherapy and surgery for patients with cN2 disease was 18%, versus 5% for patients treated with surgery alone \( (p < 0.0001) \). These studies provide evidence that neoadjuvant chemotherapy may improve survival in patients with resectable stage IIIa disease. A study by Depierre et al. added to the controversy when no significant survival advantage was found for neoadjuvant chemotherapy in patients with N2 disease.

**Stage IV.** Approximately 50% of newly diagnosed patients with non-small-cell lung cancer have advanced metastatic disease (stage IV disease). These patients are candidates for chemotherapy. Although many agents have been evaluated in patients with stage IV disease, six newer drugs that have shown significant activity \( (a \geq 15\% \text{ response rate}) \) are emphasized in this discussion: paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, and topotecan. Studies involving cisplatin and carboplatin are also reviewed.

The use of chemotherapy in patients with advanced or unresectable non-small-cell lung cancer is controversial. Although several studies have
demonstrated an improvement in survival with combination chemotherapy relative to best supportive care (BSC), there is still skepticism about the value of chemotherapy for these patients, perhaps because any survival advantage is likely to be very small. Advanced disease is associated with a 2% five-year survival rate.\(^2\)

Several meta-analyses of chemotherapy in these patients have been conducted. Marino et al.\(^49\) reviewed therapy in these patients have been for chemotherapy. Six of these studies involved cisplatin-containing regimens. A total of 712 patients with stage IIIb or IV disease were included. The endpoint was the survival rate at six months. Only three trials found a significant survival benefit for chemotherapy. Overall, there was a 20% difference in survival time in favor of chemotherapy at 6 months: 3.9 months for BSC versus 6.7 months for chemotherapy.

The Non-Small Cell Lung Cancer Collaborative Group reviewed the literature for the period from 1965 to 1991.\(^30\) The review involved four comparisons: surgery versus surgery plus chemotherapy for patients with early disease; surgery plus radiation therapy versus surgery, radiation, and chemotherapy for patients with early disease; surgery plus radiation therapy versus radiation therapy plus chemotherapy for patients with locally advanced disease; and chemotherapy versus BSC for patients with advanced disease. The last comparison involved a review of 11 trials, 8 of them using cisplatin, in a total of 1190 patients. The major endpoint was survival. Chemotherapy was associated with a 27% overall reduction in the risk of death compared with BSC. A 10% survival advantage was seen at one year in favor of chemotherapy. However, the overall median survival time in patients who received cisplatin-containing regimens was increased by only 1.5 months. This study indicated some advantage of chemotherapy over BSC in patients with advanced disease.

Lilenbaum et al.\(^51\) compared single-agent chemotherapy with combination chemotherapy in patients with stage III or IV disease. They reviewed 25 trials published between 1974 and 1996 and involving 5156 patients. The study endpoints were response, toxicity, and survival. Combination chemotherapy was associated with an almost twofold increase in response over single agents but was also more toxic. There were 15 treatment-related deaths among 1976 patients who received single agents (0.8%), versus 71 among the 2869 who received combination chemotherapy (2.5%). Combination chemotherapy was associated with more leukopenia, febrile neutropenia, nausea and vomiting, nephrotoxicity, and peripheral neuropathy. At six months, 51% of those who received combination chemotherapy were still alive, compared with 49% of those who received single agents (a 10% difference). At one year, 24.6% of the combination chemotherapy group patients were still alive, compared with 21.7% of the single-agent group.

The most active single agents against non-small-cell lung cancer are listed in Table 3.\(^52\) A direct comparison of the clinical activity of these agents is impossible because of the number of agents that would have to be compared. However, several generalizations concerning single-agent chemotherapy for non-small-cell lung cancer can be made: (1) Non-small-cell lung cancer is not very sensitive to chemotherapy, (2) few agents demonstrate even minimally acceptable activity, (3) the most active agents are associated with response rates of <50%, (4) few responses are complete, (5) response duration is short, on the order of 16–18 weeks, and (6) few patients survive even one year.

Chemotherapy is unlikely to cure patients with advanced lung cancer. The current achievable goals are to palliate symptoms and prolong survival with an acceptable level of toxicity. In 1999, Shepherd\(^53\) suggested that response rate alone is not an adequate measure of the value of a combination regimen. Response should be accompanied by a demonstration of meaningful survival. One year of survival was suggested as a measure of activity.

Early platinum-based chemotherapy. In the 1980s, cisplatin became the backbone of combination chemotherapy regimens for stage IV disease. One of the first combinations to demonstrate significant activity was cyclophosphamide, doxorubicin, and cisplatin. Response rates of 38–48% were reported. Many trials of combination therapy followed. The most successful regimens were cisplatin based and produced responses in 20–50% of patients, with a median survival time of 20–30 weeks.\(^32\) Another popular combination was cisplatin and etoposide, which achieved a 38% response rate among 94 patients with advanced disease.\(^34\) The response rate among patients without prior chemotherapy was 56%. In general the combination of cisplatin and etoposide has been associated with response rates of 20–30% and little, if any, impact on survival.\(^16\) The median survival time with these regimens was around six months; 15–20% of patients lived for one year. Both ASCO and NCCN recommend
cisplatin-based combination chemotherapy for patients with advanced disease. However, neither group recommends a specific regimen.

Although carboplatin is less toxic than cisplatin, only three trials have evaluated the combination of carboplatin and etoposide. Aitini et al. administered both carboplatin and etoposide at 60 mg/m²/day for five days to 44 patients with advanced disease. The response rate was 27%, and the median survival time was 10.4 months. Alopecia was the only significant adverse effect. Pronzato et al. reported a response rate in 4 of 24 patients who received carboplatin 300 mg/m² on day 1 and etoposide 120 mg/m² per day for three days every three weeks. The median survival time was eight months. Toxicity was moderate, with no nephrotoxicity, neurotoxicity, or ototoxicity reported. The largest trial involved 76 patients who received both agents at maximum tolerated dosages. Despite the intensive therapy, only 11% of the patients had an objective clinical response. The median survival time was 7.4 months, with 37% of the patients surviving for one year. Severe or life-threatening toxicity was reported in 74% of the patients.

Only one randomized trial has compared cisplatin plus etoposide with carboplatin plus etoposide. Cisplatin was administered at a dose of 120 mg/m², carboplatin at 325 mg/m², and etoposide at 100 mg/m² per day for three days. There were 27 responses among 100 evaluable patients who received cisplatin plus etoposide and 16 responses among 102 patients who received carboplatin plus etoposide; the difference was not significant. Median survival times were also not significantly different: 30 weeks with the cisplatin-containing regimen and 27 weeks with the carboplatin-containing combination. The cisplatin–etoposide regimen was significantly more toxic with respect to myelosuppression, nausea and vomiting, diarrhea, and renal dysfunction.

These trials indicate that the clinical activity of carboplatin plus etoposide is comparable to that of cisplatin plus etoposide, with considerably less toxicity. Recently, several newer agents, including paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan, have been combined with cisplatin or carboplatin (Table 4).

Paclitaxel. Paclitaxel is one of the more active agents against advanced disease (Table 5). Single-agent trials have found response rates of 10–56%, with six median survival times of 5.5–11 months and one-year survival rates of 22–53%. Ranson et al. compared paclitaxel plus BSC with BSC alone in 157 patients with stage IIIb or IV disease. Paclitaxel 200 mg/m² was administered over three hours every three weeks. Patients who received paclitaxel had a significantly longer median survival time (6.8 months) than those who received BSC alone (4.8 months) (p = 0.037). There were no differences in quality-of-life measurements, except for a significantly better functional activity score for patients who received paclitaxel.

The Eastern Cooperative Oncology Group compared cisplatin plus etoposide with two cisplatin–paclitaxel regimens, one involving paclitaxel 250 mg/m² with filgrastim and the other paclitaxel 135 mg/m², both administered over 24 hours. The cisplatin–paclitaxel regimens were associated with higher response rates—28% for high-dose paclitaxel and 25% for low-dose paclitaxel. There was a 12% response rate with cisplatin–etoposide (p < 0.001). The combined median survival time for the paclitaxel groups was 9.9 months, versus 7.6 months for the etoposide regimen (p = 0.048). There were no differences in one-year survival rates between any of the regimens. Patients in the low-dose paclitaxel group had significantly more neutropenia than patients in the etoposide–cisplatin group or those who received high-dose paclitaxel plus filgrastim. However, there were no differences among the three regimens regarding febrile neutropenia or infection. Both paclitaxel-containing regimens were associated with significantly more myalgia and arthralgia than the cisplatin–etoposide regimen. Patients taking high-dose paclitaxel also had more serious cardiac events.

Other trials of cisplatin and paclitaxel involved cisplatin doses of 60–120 mg/m² administered over one or two days plus paclitaxel at doses of 110–225 mg/m² administered over three hours (Table 5). Response rates ranged from 35% to 43%, with a median survival time of 10 months and one-year survival rates of 35–43%. The most common adverse effects associated with cisplatin and paclitaxel were myelosuppression, alopecia, myalgia, arthralgia, and peripheral neuropathy. The neurotoxicity appeared to be cumulative.

Table 4.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Response Rate (%)</th>
<th>Median Survival Time (mo)</th>
<th>One-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>21–46</td>
<td>8–11</td>
<td>33–48</td>
</tr>
<tr>
<td>Etoposide</td>
<td>17–37</td>
<td>5–8.3</td>
<td>15–20</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>26–54</td>
<td>8–14</td>
<td>35–61</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>29–59</td>
<td>10–11</td>
<td>37</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>25–43</td>
<td>9.5–10</td>
<td>32–43</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>25–57</td>
<td>8–16</td>
<td>33–56</td>
</tr>
<tr>
<td>Carboplatin and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>45–51</td>
<td>7–16</td>
<td>30–62</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>22–62</td>
<td>6.5–13</td>
<td>31–55</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>31–40</td>
<td>9.5–12</td>
<td>36</td>
</tr>
</tbody>
</table>
Paclitaxel has also been administered in combination with carboplatin (Table 6). Paclitaxel doses ranged from 135 to 280 mg/m² administered over 1, 3, or 24 hours. The carboplatin dose was calculated on the basis of the desired area under the concentration-versus-time curve (AUC) of 5–7.5 mg/mL · min (most commonly 6 mg/mL · min). Overall objective response rates ranged from 22% to 62%, and median survival times were 6.5–13 months. One-year survival rates ranged from 31% to 55%. The duration of the paclitaxel infusion did not affect the outcome, nor was there evidence of a superior AUC for carboplatin. The dose-limiting adverse effect associated with 24-hour infusions of paclitaxel with carboplatin was myelosuppression, while the one- to three-hour paclitaxel infusions were primarily limited by neurotoxicity or myalgia. Paclitaxel is currently approved for use as a first-line agent along with cisplatin in patients who are not candidates for potentially curable surgery or radiation therapy.

**Docetaxel.** Docetaxel was evaluated as a single agent in several trials (Table 7). The most common regimen was 100 mg/m² administered every three weeks. The response rate was 20–54%. Median survival times ranged from 5 to 12 months, and one-year survival rates were 21–71%. Docetaxel has also been evaluated in combination with cisplatin. Five trials involving 200 evaluable patients found response rates of 21–46%, median survival times of 8–11 months, and one-year survival rates of 33–48%. The most common adverse effects associated with cisplatin 75–100 mg/m² and docetaxel 75 mg/m² every three weeks included neutropenia (up to 87%) and febrile neutropenia (8.5–15%). Additional grade 3 or 4 toxicities included nausea (7–12%), vomiting (4–7%), diarrhea (3–6%), and neuropathy (2%).

In a Phase III trial, Rozkowski et al. compared docetaxel 100 mg/m² (137 patients) with BSC alone (70 patients). Twenty percent of the patients responded to docetaxel and had a median survival time of 6 months, which was no different from the 5.7-month median survival time associated with BSC alone. However, docetaxel recipients achieved higher one- and two-year survival rates. Twenty-five percent of docetaxel recipients lived one year, versus 16% of those given BSC alone. At two years, the survival rate was 12% with docetaxel; none of the patients who received BSC alone survived more than 20 months. Overall survival was significantly longer with docetaxel (p = 0.026).

There have been several trials of docetaxel as second-line therapy (Table 8). When second-line docetaxel was administered at 100 mg/m² every three weeks, the response rate was 6.3–22%. The median survival time ranged from 5.5 to 10 months, and the one-year survival rate was 19–44%. Myelosuppression was the dose-limiting toxicity. Grade 3 or 4 neutropenia occurred in 80–88% of patients who received the drug at a dose of 100 mg/m²; infections were seen in 11–16%. In an effort to reduce toxicity, Fossella et al. compared 100 mg/m² with 75 mg/m² administered every three weeks. There were 120 patients in each group. No significant differences in response rate, median survival time, or one-year survival rate were seen. At the higher dose, grade 4 myelosuppression was seen in 77% of the patients, there was a 12% infec-

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**Table 5. Activity of Paclitaxel Alone and with Cisplatin against Non-Small-Cell Lung Cancer**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. Patients</th>
<th>Regimen (mg/m²)</th>
<th>Response Rate (%)</th>
<th>Median Survival Time (mo)</th>
<th>One-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>24</td>
<td>250/24 hr</td>
<td>21</td>
<td>5.5</td>
<td>42</td>
</tr>
<tr>
<td>60</td>
<td>25</td>
<td>200/24 hr</td>
<td>24</td>
<td>9.2</td>
<td>33</td>
</tr>
<tr>
<td>61</td>
<td>51</td>
<td>175/3 hr</td>
<td>10</td>
<td>6.7</td>
<td>40</td>
</tr>
<tr>
<td>62</td>
<td>60</td>
<td>210/3 hr</td>
<td>38</td>
<td>11.2</td>
<td>48</td>
</tr>
<tr>
<td>63</td>
<td>60</td>
<td>210/3 hr</td>
<td>32</td>
<td>6.9</td>
<td>22</td>
</tr>
<tr>
<td>64</td>
<td>25</td>
<td>175/3 hr</td>
<td>56</td>
<td>NR</td>
<td>53</td>
</tr>
<tr>
<td>65</td>
<td>50</td>
<td>225/3 hr</td>
<td>24</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>66</td>
<td>53</td>
<td>135 or 200/1 hr</td>
<td>25</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>69</td>
<td>40</td>
<td>CIS 75, PAC 175/3 hr</td>
<td>35</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>70</td>
<td>20</td>
<td>CIS 50 days 1 and 2, PAC 175/3 hr</td>
<td>35</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>71</td>
<td>29</td>
<td>CIS 100–120, PAC 135–225/3 hr</td>
<td>38</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>72</td>
<td>40</td>
<td>CIS 60, PAC 110/3 hr q 2 wk</td>
<td>43</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>73</td>
<td>155</td>
<td>CIS 80, PAC 175/3 hr</td>
<td>41</td>
<td>9.7</td>
<td>43</td>
</tr>
<tr>
<td>86</td>
<td>162</td>
<td>CIS 80, TEN 100 days 1, 3, and 5</td>
<td>28</td>
<td>9.9</td>
<td>41</td>
</tr>
</tbody>
</table>

*NR = not reported, CIS = cisplatin, PAC = paclitaxel, TEN = teniposide.
*Regimens administered on day 1 of cycle and repeated every three weeks unless noted otherwise.
*Administered weekly for the first six weeks of an eight-week cycle.
*Significantly different from corresponding value for CIS 80, PAC 175/3 hr (p = 0.018).
tion rate, and two patients died. Among patients who received the lower dose, there was a 56% rate of grade 4 myelosuppression, an infection rate of 4%, and no deaths.

Shepherd et al.106 studied docetaxel versus BSC alone in 104 patients. Docetaxel was initially administered at 100 mg/m², but the dose was reduced to 75 mg/m² after 49 patients were treated for drug-related toxicity. There were no significant differences in response rates, median survival times, or one-year survival rates between the two docetaxel doses. However, of patients who received the higher dose, 86% had grade 3 or 4 neutropenia, 22% developed infections, and 10% (5) died (three due to drug-induced neutropenia, two due to uncertain causes). At the lower dose, the frequency of grade 3 or 4 neutropenia was 67%, the infection rate was 1.8%, and one patient (2%) died of uncertain causes. Patients who received the 75-mg/m² dose had a significantly longer median survival time and one-year survival rate than patients given BSC alone.

It appears that docetaxel has an advantage over BSC as a second-line treatment in patients with advanced non-small-cell lung cancer. Docetaxel administered at a dose of 75 mg/m² every three weeks has much less toxicity than 100 mg/m² and no loss of toxicity rate, and two patients died. Among patients who received the lower dose, there was a 56% rate of grade 4 myelosuppression, an infection rate of 4%, and no deaths.

Table 6.
Activity of Paclitaxel and Carboplatin against Non-Small-Cell Lung Cancer

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. Patients</th>
<th>Regimen (mg/m²)</th>
<th>Response Rate (%)</th>
<th>Median Survival Time (mo)</th>
<th>One-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>60</td>
<td>CAR AUC = 5, PAC 200/1 hr</td>
<td>29</td>
<td>9.5</td>
<td>38</td>
</tr>
<tr>
<td>75</td>
<td>25</td>
<td>CAR AUC = 5, PAC 200/3 hr q 4 wk</td>
<td>52</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>76</td>
<td>63</td>
<td>CAR AUC = 6, PAC 200/1 hr q 4 wk</td>
<td>25</td>
<td>7.4</td>
<td>NR</td>
</tr>
<tr>
<td>77</td>
<td>144</td>
<td>CAR AUC = 6, PAC 225/1 hr</td>
<td>36</td>
<td>8</td>
<td>42</td>
</tr>
<tr>
<td>78</td>
<td>53</td>
<td>CAR AUC = 6, PAC 200/3 hr</td>
<td>55</td>
<td>12.7</td>
<td>55</td>
</tr>
<tr>
<td>79</td>
<td>35</td>
<td>CAR AUC = 6, PAC 175-225/1 hr</td>
<td>29</td>
<td>6.5</td>
<td>31</td>
</tr>
<tr>
<td>80</td>
<td>41</td>
<td>CAR AUC = 6, PAC 150-250/3 hr</td>
<td>41</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>81</td>
<td>53</td>
<td>CAR AUC = 7.5 day 2, PAC 135–215/24 hr</td>
<td>62</td>
<td>12.3</td>
<td>54</td>
</tr>
<tr>
<td>82</td>
<td>51</td>
<td>CAR AUC = 6 or 300 day 2, PAC 135 or 175/24 hr q 4 wk</td>
<td>27</td>
<td>8.8</td>
<td>32</td>
</tr>
<tr>
<td>83</td>
<td>22</td>
<td>CAR AUC = 7.5, PAC 175–280/1 hr</td>
<td>55</td>
<td>10.8</td>
<td>45</td>
</tr>
<tr>
<td>84</td>
<td>46</td>
<td>CAR AUC = 6 day 1, PAC 200/3 hr day 1</td>
<td>22</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>85</td>
<td>48</td>
<td>GEM 1000 days 1 and 8, PAC 200/3 hr day 1</td>
<td>37.5</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

CAR = carboplatin, AUC = area under the concentration-versus-time curve (mg/mL · min), PAC = paclitaxel, NR = not reported, GEM = gemcitabine.

Table 7.
Activity of Docetaxel Alone and with Cisplatin against Non-Small-Cell Lung Cancer

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. Patients</th>
<th>Regimen (mg/m²)</th>
<th>Response Rate (%)</th>
<th>Median Survival Time (mo)</th>
<th>One-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td>75</td>
<td>60/1–2 hr</td>
<td>19</td>
<td>9.8</td>
<td>41</td>
</tr>
<tr>
<td>87</td>
<td>20</td>
<td>75/1 hr</td>
<td>25</td>
<td>9.1+</td>
<td>71</td>
</tr>
<tr>
<td>88</td>
<td>35</td>
<td>100/1 hr</td>
<td>23</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>89</td>
<td>35</td>
<td>100/1 hr</td>
<td>34</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>91</td>
<td>29</td>
<td>100/1 hr</td>
<td>38</td>
<td>6.3</td>
<td>21</td>
</tr>
<tr>
<td>92</td>
<td>39</td>
<td>100/1 hr</td>
<td>33</td>
<td>10.8</td>
<td>45</td>
</tr>
<tr>
<td>93</td>
<td>54</td>
<td>100/1 hr</td>
<td>31</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>94</td>
<td>41</td>
<td>100/1 hr</td>
<td>54</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>95</td>
<td>35</td>
<td>100/1 hr</td>
<td>20</td>
<td>10</td>
<td>42</td>
</tr>
<tr>
<td>96</td>
<td>91</td>
<td>100/1 hr</td>
<td>26</td>
<td>8.4</td>
<td>36</td>
</tr>
<tr>
<td>97</td>
<td>38</td>
<td>36/wk × 6</td>
<td>18</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>98</td>
<td>22</td>
<td>CIS 75–100, DOC 75–85</td>
<td>46</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>99</td>
<td>47</td>
<td>CIS 75, DOC 75</td>
<td>21</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>100</td>
<td>36</td>
<td>CIS 75, DOC 75</td>
<td>39</td>
<td>9.6</td>
<td>33</td>
</tr>
<tr>
<td>101</td>
<td>42</td>
<td>CIS 100 q 3 wk × 3, then q 6 wk plus DOC 75 by same schedule</td>
<td>33</td>
<td>8.4</td>
<td>35</td>
</tr>
<tr>
<td>102</td>
<td>53</td>
<td>CIS 80 day 2, DOC 100 day 1</td>
<td>45</td>
<td>11.1</td>
<td>48</td>
</tr>
</tbody>
</table>

NR = not reported, CIS = cisplatin, DOC = docetaxel.

Regimens administered every three weeks unless noted otherwise.

Responders received docetaxel weekly for up to 32 weeks.
activity. This agent has FDA-approved labeling for use in patients with locally advanced or metastatic non-small-cell lung cancer after cisplatin-containing regimens have failed.\(^{107}\) The docetaxel package insert contains a “black-box” warning of increased mortality in patients with non-small-cell lung cancer who receive the drug at a dose of 100 mg/m\(^2\) every three weeks as a second-line agent after platinum-based chemotherapy. The approved schedule is 75 mg/m\(^2\) administered over one hour every three weeks.

Docetaxel has also been administered on a weekly schedule in an attempt to reduce toxicity. A Phase I trial established the maximum tolerated weekly dose at 43 mg/m\(^2\) and recommended 36 mg/m\(^2\) per week for future studies.\(^{108}\) Only one Phase II trial has been completed. In this study, docetaxel was administered as first-line therapy at 36 mg/m\(^2\) per week to 39 patients with advanced disease. The response rate was 20%. The actuarial one-year survival rate was 28%. No patients had grade 4 neutropenia or febrile neutropenia. Grade 3 neutropenia occurred in three patients (8%).\(^{109}\) By comparison, docetaxel administered as a first-line agent at a dose of 100 mg/m\(^2\) every three weeks has produced response rates of 23–54%, with one-year survival rates of 21–45% (Table 7). Grade 3 or 4 neutropenia was seen in 28–97% of patients at some time during their treatment. Febrile neutropenia was reported in 3.6–41% of the patients and in 1.2–11% of the courses of therapy.\(^{108,109,110}\) These studies demonstrate that, when docetaxel is used as a first-line agent, lower weekly doses may be as active as higher doses given every three weeks, with much less toxicity. Additional studies are needed to confirm this.

Preliminary results on the use of weekly docetaxel as second-line therapy are available. Docetaxel was administered at 35–43 mg/m\(^2\) per week in three trials with a total of 45 evaluable patients and produced response rates of 12–27%.\(^{110-112}\) There were no incidents of grade 4 neutropenia. Grade 3 neutropenia was reported in two trials and occurred in 1 (0.04%) of 24 patients who received a dose of 35 mg/m\(^2\) and in 3 (13%) of 22 patients given 36 mg/m\(^2\). These response rates are better than those reported for docetaxel 75 mg/m\(^2\) every three weeks (5.5–6.7%). However, no survival data were available from the weekly trials. Although early data indicate that weekly docetaxel may be therapeutically equivalent to higher every-three-week doses, randomized studies comparing these regimens are needed before any firm conclusions can be made.

**Gemcitabine.** Gemcitabine has usually been administered at 800–1250 mg/m\(^2\) every week for three doses, with one week off per four-week cycle (Table 9).\(^{113,114}\) The response rates were 7–27%, the median survival times 5.7–11 months, and the one-year survival rates 27–42%.

Table 10 summarizes six Phase II trials of cisplatin plus gemcitabine.\(^{122-127}\) The response rates in the five trials that used cisplatin 100 mg/m\(^2\) plus gemcitabine 1000–1200 mg/m\(^2\) were 37–54%, and the median survival time was 8.4–14.3 months. When cisplatin was administered at 30 mg/m\(^2\) per day for three days with gemcitabine 1500 mg/m\(^2\) per week, the response rate was 26%. The most common adverse effect reported for the combination of cisplatin and gemcitabine was myelosuppression. Thrombocytopenia may be cumulative with continued administration.

Anderson et al.\(^{128}\) compared gemcitabine plus BSC with BSC alone in 300 patients with locally advanced or metastatic disease. Gemcitabine 1 g/m\(^2\) was administered on days 1, 8, and 15 of a 28-day cycle. Although there were no survival differences, the gemcitabine recipients had a significant improvement in quality of life and improved symptom control.

Sandler et al.\(^{129}\) compared gemcitabine plus cisplatin with cisplatin alone. Two hundred sixty evaluable
In a Phase III trial, gemcitabine alone achieved a significantly higher response rate (38%) versus 26% (p ≤ 0.029); however, there was no difference in median survival time: 8.6 months for gemcitabine–cisplatin and 9.6 months for the other regimen. In another trial, the combination of cisplatin and gemcitabine again achieved a significantly higher response rate (41%) than cisplatin–etoposide (22%), but there was no difference in median survival time. Preliminary results of a Phase III comparison of gemcitabine plus paclitaxel versus carboplatin plus paclitaxel indicate no difference in response. Gemcitabine was associated with a significantly higher response rate of 38% versus 26% (p ≤ 0.029); however, there was no difference in median survival time: 8.6 months for gemcitabine–cisplatin and 9.6 months for the other regimen. In another trial, the combination of cisplatin and gemcitabine again achieved a significantly higher response rate (41%) than cisplatin–etoposide (22%), but there was no difference in median survival time.¹³¹ Preliminary results of a Phase III comparison of gemcitabine plus paclitaxel versus carboplatin plus paclitaxel indicate no difference in response.¹³² Gemcitabine was compared with cisplatin plus etoposide in two separate trials. Mane gold et al.¹²⁹ administered gemcitabine 1 g/m² on days 1, 8, and 15 of a 28-day cycle or cisplatin 100 mg/m² on day 1 and etoposide 100 mg/m² on days 1–3. Response rates were 18% for gemcitabine and 15% for cisplatin plus etoposide. Gemcitabine was associated with a median survival time of 5.7 months, versus 6.7 months for cisplatin–etoposide; one-year survival rates were 26% and 24%, respectively. In the other trial, patients received gemcitabine 1 g/m² on days 1, 8, and 15 or cisplatin 80 mg/m² on day 1 with etoposide 80 mg/m² for three days.¹³¹ Nineteen percent of the patients given gemcitabine had an 8.5-month median survival time, and the one-year survival rate was 40%. Patients who received cisplatin and etoposide had a 21% response rate, a median

Table 9.
Activity of Gemcitabine against Non-Small-Cell Lung Cancer

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. Patients</th>
<th>Regimen (mg/m²)</th>
<th>Response Rate (%)</th>
<th>Median Survival Time (mo)</th>
<th>One-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>113</td>
<td>44</td>
<td>GEM 1000</td>
<td>22</td>
<td>6.8</td>
<td>27</td>
</tr>
<tr>
<td>114</td>
<td>27</td>
<td>GEM 1000 days 0, 7, and 14</td>
<td>27</td>
<td>7¹</td>
<td>NR</td>
</tr>
<tr>
<td>115</td>
<td>76</td>
<td>GEM 1000–1250</td>
<td>20</td>
<td>9.2</td>
<td>35</td>
</tr>
<tr>
<td>116</td>
<td>37</td>
<td>GEM 1250</td>
<td>19</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>117</td>
<td>29</td>
<td>GEM 1250</td>
<td>21</td>
<td>7.5</td>
<td>NR</td>
</tr>
<tr>
<td>118</td>
<td>151</td>
<td>GEM 1250</td>
<td>22</td>
<td>9.4</td>
<td>42</td>
</tr>
<tr>
<td>119</td>
<td>42</td>
<td>GEM 800–1000</td>
<td>17</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>73</td>
<td>GEM 1000–1250</td>
<td>26</td>
<td>11</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>67</td>
<td>GEM 1000–1250</td>
<td>21</td>
<td>9.8</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>120</td>
<td>66</td>
<td>GEM 1000 days 1, 8, and 15</td>
<td>18</td>
<td>5.7</td>
<td>26</td>
</tr>
<tr>
<td>121</td>
<td>26</td>
<td>CIS 100 day 1, ETOP 100 days 1–3</td>
<td>15</td>
<td>6.7</td>
<td>24</td>
</tr>
<tr>
<td>24</td>
<td>CIS 80 day 1, ETOP 80 days 1–3 per 4-wk cycle</td>
<td>19</td>
<td>8.5</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>690</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean</td>
<td>...</td>
<td>20</td>
<td>8</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

¹⁰NR = not reported, GEM = gemcitabine, CIS = cisplatin, ETOP = etoposide.
¹¹Gemcitabine administered weekly for three weeks per four-week cycle.
¹²Overall median survival time.

Table 10.
Activity of Cisplatin Plus Gemcitabine against Non-Small-Cell Lung Cancer

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. Patients</th>
<th>Regimen (mg/m²)</th>
<th>Response Rate (%)</th>
<th>Median Survival Time (mo)</th>
<th>One-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>122</td>
<td>50</td>
<td>CIS 100 day 15, GEM 1000 days 1, 8, and 15</td>
<td>52</td>
<td>13</td>
<td>61</td>
</tr>
<tr>
<td>123</td>
<td>27</td>
<td>CIS 100 day 1, GEM 1000 days 1, 8, and 15</td>
<td>37</td>
<td>8.4</td>
<td>37</td>
</tr>
<tr>
<td>124</td>
<td>48</td>
<td>CIS 100 day 2, GEM 1000 days 1, 8, and 15</td>
<td>54</td>
<td>14.3</td>
<td>58</td>
</tr>
<tr>
<td>125</td>
<td>43</td>
<td>CIS 100 day 1, GEM 1000 days 1, 8, and 15</td>
<td>42</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>126</td>
<td>40</td>
<td>CIS 100 day 15, GEM 1200 days 1, 8, and 15</td>
<td>47.5</td>
<td>10.4</td>
<td>35</td>
</tr>
<tr>
<td>127</td>
<td>39</td>
<td>CIS 30/day × 3, GEM 1500 days 1, 8, and 15</td>
<td>26</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

¹³⁰CIS = cisplatin, GEM = gemcitabine, NR = not reported.
¹³¹Regimens administered every four weeks.

patients received the combination and 262 the single agent. Thirty percent of the patients who received the combination had a median survival time of 9.1 months. The cisplatin-only group had a response rate of 11% and a median survival time of 7.6 months. Both response (p < 0.0001) and survival (p = 0.004) were significantly in favor of the combination regimen. The one-year survival rates were 28% for cisplatin alone and 39% for the combination.

In a Phase III trial, gemcitabine plus cisplatin was compared with mitomycin, ifosfamide, and cisplatin.¹³⁰ There were 152 evaluable patients in the mitomycin–ifosfamide–cisplatin group and 155 in the gemcitabine–cisplatin group. The latter group had
survival time of 11 months, and a one-year survival rate of 31%. These studies indicate that single-agent gemcitabine is comparable to cisplatin plus etoposide with respect to response and survival. In these studies, gemcitabine was less toxic than cisplatin–etoposide. Myelosuppression was more severe with cisplatin–etoposide, as were nausea and vomiting.

An analysis of the hematologic toxicity associated with gemcitabine plus cisplatin reveals more thrombocytopenia when the drugs are administered as part of a 28-day cycle. Sandler et al.129 and Crino et al.130 each used a 28-day cycle in which gemcitabine 1000 mg/m2 was given on days 1, 8, and 15. Grade 3 and grade 4 thrombocytopenia occurred in 25% and 25% of the Sandler et al. patients, respectively, and in 26% and 38% of the Crino et al. patients. Platelet transfusions were required by 20% of the patients in the study by Sandler et al. and by 15% of the patients in the other study. In contrast, Cardenal et al.131 administered only two gemcitabine doses, one on day 1 and the other on day 8, per 21-day cycle. They reported a 39% rate of grade 3 thrombocytopenia and a 16% rate of grade 4 thrombocytopenia, and only 3% of the patients needed platelet transfusions. Response rates were comparable, suggesting that a 21-day cycle involving two gemcitabine doses produces less thrombocytopenia without sacrificing efficacy.

Phase II studies of carboplatin and gemcitabine have involved schedules similar to those used for cisplatin and gemcitabine (Table 11).133–139 Sederholm133 used a two-dose, three-week schedule and reported grade 4 thrombocytopenia in 7% of patients. When gemcitabine was administered in a three-dose, 28-day schedule, thrombocytopenia was reported to be dose limiting in 56% of patients and was grade 3 or 4 in 27–86%.136,138,139 Carrato et al.134 administered gemcitabine 1000 mg/m2 on days 1, 8, and 15 of a 28-day regimen and observed grade 4 thrombocytopenia in 61% of the first 32 patients enrolled, which led to omission of the third gemcitabine dose for the remaining 43 patients. The frequency of grade 4 thrombocytopenia was 17% in these patients. When a 28-day schedule was used, grade 4 thrombocytopenia was seen in 24–56% of patients. There were no significant differences in response rates or median survival times. Apparently the combination of gemcitabine and carboplatin, like that of cisplatin and gemcitabine, results in less thrombocytopenia without loss of efficacy when administered on a 21-day schedule (two doses of gemcitabine).

Gemcitabine carries FDA-approved labeling for use in combination with cisplatin for patients with inoperable, locally advanced non-small-cell lung cancer (stages IIIa and IIIb), as well as for patients with stage IV disease.140 The combination may be administered on a three- or four-week cycle. The manufacturer recommends that gemcitabine 1250 mg/m2 be administered on days 1 and 8 of a 21-day cycle, with cisplatin 100 mg/m2 given on day 1 after the gemcitabine infusion, or that gemcitabine 1000 mg/m2 be given on days 1, 8, and 15 of a 28-day cycle, with cisplatin 100 mg/m2 given on day 1.

Vinorelbine. Vinorelbine is a structural analogue of vinblastine. Clinical trials have found response rates of 6–33% and median survival times of 5–12 months (Table 12).141–152 The one-year survival rate, although infrequently reported, ranged from 13% to 53%.

Gridelli et al.152 performed a randomized clinical trial comparing vinorelbine plus BSC with BSC alone in elderly patients (≥70 years of age) with stage IIIb or IV disease. Although the investigators planned to enroll 350 patients, the study was discontinued after 161 patients were randomized because a significant survival advantage was found for vinorelbine on interim analysis. Patients who received vinorelbine had a median survival time of 6.7 months, versus 5 months for BSC alone. The one-year survival rates were 32% for vinorelbine and 14% for BSC alone (p = 0.03).

Vinorelbine has been combined with cisplatin.151,153–163 Table 13 summarizes nine trials involving 562 patients. The usual vinorelbine dose was 25–30 mg/m2 administered on days 1 and 8 of a 21-day cycle; 80–120 mg of cisplatin per square meter was administered on day 1. Response rates were 25–57%, median survival times were 8–15.7 months, and one-year survival rates were 33–56%.

LeChevalier et al.151 compared vinorelbine alone with vinorelbine plus cisplatin and cisplatin plus vindesine. The response rate was 14% for vinorelbine alone, 30% for vinorelbine plus cisplatin, and 19% for cisplatin plus vindesine. Vinorelbine–cisplatin was significantly more active than the other regimens. Median survival time was significantly longer for vinorelbine plus cisplatin (40 weeks) than for vinorelbine alone (31 weeks) or cisplatin plus vindesine (32 weeks). However, myelosuppression was significantly more common with vinorelbine–cisplatin than with the other two treatments. Grade 3 or 4 neutropenia was seen in 78.7% of the patients who received vinorelbine plus cisplatin, compared with 47.6% for vindesine plus cisplatin and 53% for vinorelbine alone.

Wozniak et al.152 compared vinorelbine plus cisplatin with cisplatin alone. Cisplatin 100 mg/m2 was administered every four weeks alone or with vinorelbine 25 mg/m2 weekly. There were 209 patients in the cisplatin group and 206 in the combination group. Twelve percent of patients who received cisplatin alone had an objective response, versus 26% of those given the combination (p = 0.002). Median survival times were eight months for the combination group...
Table 11.
Activity of Carboplatin Plus Gemcitabine against Non-Small-Cell Lung Cancer

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. Patients</th>
<th>Regimen (mg/m²)</th>
<th>Response Rate (%)</th>
<th>Median Survival Time (mo)</th>
<th>One-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>133</td>
<td>20</td>
<td>1250 days 1 and 8 q 3 wk</td>
<td>45</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>134</td>
<td>32</td>
<td>1000 days 1, 8, and 15</td>
<td>46</td>
<td>8.8</td>
<td>NR</td>
</tr>
<tr>
<td>135</td>
<td>43</td>
<td>1000 days 1 and 8 q 3 wk</td>
<td>37</td>
<td>8.8</td>
<td>NR</td>
</tr>
<tr>
<td>136</td>
<td>26</td>
<td>800–1200 days 1 and 8</td>
<td>50</td>
<td>16</td>
<td>62</td>
</tr>
<tr>
<td>137</td>
<td>28</td>
<td>1000 days 1, 8, and 15</td>
<td>50</td>
<td>7.2</td>
<td>30</td>
</tr>
<tr>
<td>138</td>
<td>33</td>
<td>1000 days 1, 8, and 15</td>
<td>48</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>139</td>
<td>50</td>
<td>1000 days 1, 8, and 15</td>
<td>51</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

<sup>a</sup>Doses indicated for gemcitabine. Carboplatin was administered to achieve an area under the concentration-versus-time curve (AUC) of 5 mg/mL - min unless noted otherwise. Regimens were administered every four weeks unless noted otherwise.

<sup>b</sup>Carboplatin was administered to achieve an AUC of 6 mg/mL - min.

<sup>c</sup>NR = not reported.

<sup>d</sup>Median survival time for responders only.

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Table 12.
Activity of Vinorelbine against Non-Small-Cell Lung Cancer<sup>+</sup>

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. Patients</th>
<th>Regimen (mg/m²)</th>
<th>Response Rate (%)</th>
<th>Median Survival Time (mo)</th>
<th>One-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>141</td>
<td>25</td>
<td>25 q wk</td>
<td>16</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>142</td>
<td>97</td>
<td>20–25 q wk</td>
<td>32</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>143</td>
<td>76</td>
<td>25–30 q wk</td>
<td>30</td>
<td>9</td>
<td>NR</td>
</tr>
<tr>
<td>144</td>
<td>43</td>
<td>30 q wk</td>
<td>23</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>145</td>
<td>70</td>
<td>30 q wk</td>
<td>33</td>
<td>8.3</td>
<td>NR</td>
</tr>
<tr>
<td>146</td>
<td>42</td>
<td>30 q wk</td>
<td>12</td>
<td>6.5</td>
<td>NR</td>
</tr>
<tr>
<td>147</td>
<td>25</td>
<td>25 q 1–2 wk</td>
<td>12</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>148</td>
<td>48</td>
<td>30 days 1 and 8 q 3 wk</td>
<td>6</td>
<td>6.8</td>
<td>NR</td>
</tr>
<tr>
<td>149</td>
<td>104</td>
<td>30 q wk</td>
<td>16</td>
<td>8</td>
<td>53&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>150</td>
<td>103</td>
<td>25 q wk</td>
<td>31&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>151</td>
<td>101</td>
<td>VIND 3 times/wk</td>
<td>9</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>Total</td>
<td>633</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean</td>
<td>...</td>
<td>21</td>
<td>...</td>
<td>9</td>
<td>34</td>
</tr>
</tbody>
</table>

<sup>a</sup>NR = not reported, CIS = cisplatin, VIND = vindesine.

<sup>b</sup>One-year survival rate for responders only.

<sup>c</sup>Vinorelbine produced a significantly higher response rate than vindesine (p = 0.0002).

<sup>d</sup>Includes only patients receiving vinorelbine alone.

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Table 13.
Activity of Vinorelbine Plus Cisplatin against Non-Small-Cell Lung Cancer<sup>+</sup>

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. Patients</th>
<th>Regimen (mg/m²)&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Response Rate (%)</th>
<th>Median Survival Time (mo)</th>
<th>One-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>153</td>
<td>60</td>
<td>VIN 30 q wk, CIS 120 days 1 and 29</td>
<td>25</td>
<td>8.8</td>
<td>34</td>
</tr>
<tr>
<td>154</td>
<td>50</td>
<td>VIN 30 days 1 and 5, CIS 100–80 day 1</td>
<td>50</td>
<td>13</td>
<td>54</td>
</tr>
<tr>
<td>155</td>
<td>35</td>
<td>VIN 30 days 1 and 8, CIS 100 day 1</td>
<td>40</td>
<td>15.7</td>
<td>56</td>
</tr>
<tr>
<td>156</td>
<td>30</td>
<td>VIN 20–30 q wk, CIS 120 days 1 and 29, then q 6 wk</td>
<td>33</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>157</td>
<td>30</td>
<td>VIN 25–30 days 1 and 8, CIS 80 day 1</td>
<td>46</td>
<td>10.6&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NR</td>
</tr>
<tr>
<td>158</td>
<td>126</td>
<td>VIN 30 days 1 and 8, CIS 80 day 1</td>
<td>37</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>159</td>
<td>74</td>
<td>VIN 25 days 1 and 8, CIS 80 day 1</td>
<td>57</td>
<td>10</td>
<td>45</td>
</tr>
<tr>
<td>160</td>
<td>83</td>
<td>VIN 25 days 1 and 8, CIS 80 day 1</td>
<td>34</td>
<td>9.2</td>
<td>33</td>
</tr>
<tr>
<td>161</td>
<td>74</td>
<td>VIN 30 days 1, 8, and 15; CIS 100 day 1</td>
<td>42</td>
<td>10.3</td>
<td>NR</td>
</tr>
<tr>
<td>72</td>
<td>VIN 30 q wk</td>
<td>42</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Total</td>
<td>562</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Mean</td>
<td>...</td>
<td>40</td>
<td>11</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>VIN = vinorelbine, CIS = cisplatin, NR = not reported.

<sup>b</sup>Regimens administered every three weeks unless noted otherwise.

<sup>c</sup>Mean survival time.

<sup>d</sup>Total includes only patients receiving vinorelbine and cisplatin.
and six months for the cisplatin group ($p = 0.0018$); one-year survival rates were 36% and 20%, respectively, and two-year survival rates were 12% and 6%. Of patients receiving the combination, 22% had grade 3 granulocytopenia and 59% had grade 4 granulocytopenia. The cisplatin-treated patients had a 5.5% rate of grade 4 granulocytopenia and 59% had grade 3 granulocytopenia. The cisplatin–epirubicin regimen had a 20% rate of grade 3 granulocytopenia and the same rate of grade 4 granulocytopenia.

Vinorelbine–cisplatin has been compared with cisplatin–epirubicin. Vinorelbine was administered at a dose of 25 mg/m$^2$ on days 1 and 8 of a three-week schedule, and cisplatin 60 mg/m$^2$ was given on day 1. In the cisplatin–epirubicin regimen, cisplatin was administered at 60 mg/m$^2$ and epirubicin at 120 mg/m$^2$ on day 1 of a three-week cycle. There was no significant difference in response rates between vinorelbine–cisplatin (27%) and cisplatin–epirubicin (33%), nor was there a significant difference in survival. The doses of cisplatin and epirubicin were lower than those usually used.

Kelly et al. compared vinorelbine plus cisplatin with paclitaxel plus carboplatin. Although there were no differences in response rates (27% for each group), median survival times (eight months each), or one-year survival rates (36% and 33%), the paclitaxel–carboplatin regimen was more tolerable.

Vinorelbine has been administered in many other two-drug regimens. The results of some of these trials are presented in Table 14. The response rates for these combinations with vinorelbine were, for carboplatin, 31–40%; ifosfamide, 30–33%; docetaxel, 23–51%; and gemcitabine, 19–72.5%. Median survival times ranged from 5 to 14 months, and one-year survival rates were 24–60%. The most common adverse effect associated with these regimens was myelosuppression. Phase II studies indicate no clearly superior two-drug combination with vinorelbine.

Frasci et al. compared gemcitabine plus vinorelbine with vinorelbine alone. Thirteen (31%) of 42 evaluable patients responded to the combination, while 9 (29%) of 31 responded to vinorelbine. The median survival time for the combination was 29 weeks, versus 18 weeks for vinorelbine. A one-year survival rate of 30% was projected for the combination, compared with 13% for vinorelbine ($p < 0.01$). Vinorelbine has approved labeling for use in combination with cisplatin in patients with stage III disease. Patients with stage IV disease may receive the combination or vinorelbine alone. The manufacturer recommends a dose of 30 mg/m$^2$ administered i.v. over 6–10 minutes.

Camptothecins. Topotecan and irinotecan have shown some activity against non-small-cell lung cancer. Irinotecan 100 mg/m$^2$ weekly was evaluated in three separate trials. The response rates were 32%, 34%, and 15%. Median survival times of 6.2 and 10.5 months were reported. There were no one-year survival data.

Topotecan appears less promising. Only one trial has been reported; the response rate was about 15%, the median survival time was 9.5 months, and the one-year survival rate was 30%. Irinotecan has been used in two-drug regimens with cisplatin or etoposide. Only two trials found activity superior to that of irinotecan alone. Masuda et al. administered irinotecan 60 mg/m$^2$ every three weeks plus cisplatin 80 mg/m$^2$ on day 1 to 64 patients and reported a 52% response rate, 10-month median survival time, and 33% one-year survival rate. Mori et al. administered irinotecan 160 mg/m$^2$ on day 1 and cisplatin 20 mg/m$^2$ per day by continuous i.v. infusion for five consecutive days to 41 patients. The response rate was 58.5%, the median survival time was 10 months, and the one-year survival rate was 44%.

Many three-drug regimens have been tried. Three of the most commonly investigated regimens are summarized in Table 15. The combination of gemcitabine, ifosfamide, and cisplatin has been used in over 130 patients. Response rates ranged from 43% to 59% (mean, 51%). Most of the trials are too recent for median or one-year survival data to be reported. Over 300 patients have received the combination of gemcitabine, vinorelbine, and cisplatin. Response rates ranged from 33% to 65% (mean, 52%). The median survival time was 11.5–13 months, and the one-year survival rate was 45–65% (mean, 52%). The most frequently used combination has been vinorelbine, ifosfamide, and cisplatin, given to over 450 patients. The average response rate was 45% (range, 17–67%), median survival times ranged from 7 to 14 months, and one-year survival rates ranged from 20% to 60% (mean, 42%), on the basis of seven trials providing median survival times and only three providing one-year survival rates.

There is scant literature on the duration of chemotherapy for patients with stage IV disease. In many trials of cisplatin-containing regimens, therapy was stopped after six cycles because of cumulative toxicity. Some clinicians have advocated treating the disease until one is forced to stop by toxicity or disease progression. Some of the newer combinations that do not contain cisplatin may allow for longer treatment periods. Only time will tell if prolonged therapy provides a significant benefit. One recent trial suggested that short-term therapy may be equivalent to longer treatment regimens. Smith et al. compared three cycles of mitomycin, vinblastine, and cisplatin with six cycles of the same regimen. One hundred fifty-five patients were randomized to receive three cycles and 153 to receive six cycles. Overall response rates were 31% after three cycles and 38% after six cycles; median survival...
Activity of Selected Two-Drug Vinorelbine-Containing Regimens against Non-Small-Cell Lung Cancer

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. Patients</th>
<th>Regimen (mg/m²)</th>
<th>Response Rate (%)</th>
<th>Median Survival Time (mo)</th>
<th>One-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>165</td>
<td>49</td>
<td>VIN 25 days 1, 8, and 15; GEM 1000 days 1, 8, and 15 q 4 wk</td>
<td>26</td>
<td>NR</td>
<td>33</td>
</tr>
<tr>
<td>166</td>
<td>28</td>
<td>VIN 35 days 1 and 15, GEM 1200 days 1 and 15 q 4 wk</td>
<td>46</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>167</td>
<td>32</td>
<td>VIN 25 days 1 and 8, GEM 1250 days 1 and 8 q 3 wk</td>
<td>25</td>
<td>8.3</td>
<td>38</td>
</tr>
<tr>
<td>168</td>
<td>51</td>
<td>VIN 15 days 1 and 8, GEM 1250 days 1 and 8 q 3 wk</td>
<td>30</td>
<td>12</td>
<td>49</td>
</tr>
<tr>
<td>172</td>
<td>50</td>
<td>VIN 30 days 1, 8, and 15; GEM 1000 days 1, 8, and 15 q 4 wk</td>
<td>46</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>173</td>
<td>60</td>
<td>VIN 25 days 1, 8, and 15; GEM 1200 days 1, 8, and 15 q 4 wk</td>
<td>19</td>
<td>9</td>
<td>NR</td>
</tr>
<tr>
<td>174</td>
<td>40</td>
<td>VIN 20 days 1, 8, and 15; GEM 800 days 1, 8, and 15 q 4 wk</td>
<td>72.5</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>175</td>
<td>40</td>
<td>VIN 35 days 1 and 15, IFOS 2000 days 1–3 q 4 wk</td>
<td>33</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>176</td>
<td>34</td>
<td>VIN 25 days 1 and 8, IFOS 2000 days 1–3 q 3 wk</td>
<td>30</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>177</td>
<td>41</td>
<td>VIN 25 day 1, DOC 100 day 2 q 3 wk</td>
<td>37</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>178</td>
<td>35</td>
<td>VIN 45 day 1, DOC 60 day 1 q 3 wk</td>
<td>51</td>
<td>14</td>
<td>60</td>
</tr>
<tr>
<td>179</td>
<td>39</td>
<td>VIN 20 days 1 and 5, DOC 75 day 1 q 3 wk</td>
<td>23</td>
<td>9.3</td>
<td>31</td>
</tr>
<tr>
<td>180</td>
<td>55</td>
<td>VIN 25 day 1, CAR 300 q 4 wk</td>
<td>40</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>181</td>
<td>77</td>
<td>VIN 25 days 1 and 8, CAR 350 day 1 q 4 wk</td>
<td>31</td>
<td>9.5</td>
<td>38</td>
</tr>
</tbody>
</table>

*VIN = vinorelbine, GEM = gemcitabine, NR = not reported, IFOS = ifosfamide, DOC = docetaxel, CAR = carboplatin.*

A number of drugs have demonstrated activity against small-cell lung cancer. Since small-cell lung cancer is often metastatic at diagnosis, surgery plays little if any role in its management. Most patients require systemic chemotherapy. About a third of patients with small-cell lung cancer have limited disease at diagnosis. Local irradiation is usually added to the treatment of patients with limited disease and may be used for prophylaxis of cranial lesions and for palliation of individual lesions. Small-cell lung cancer is much more likely than non-small-cell lung cancer to respond to chemotherapy, even when the disease is extensive. Responses are not durable, however, and most patients die in less than two years.

A number of drugs have demonstrated activity against small-cell lung cancer. In comparative studies, cisplatin plus gemcitabine demonstrated greater activity than cisplatin alone, and the combination of cisplatin and vinorelbine was more active than vinorelbine monotherapy. Cisplatin–paclitaxel and cisplatin–gemcitabine achieved higher response rates in head-to-head trials than the standard cisplatin–etoposide combination. Gemcitabine achieved a higher response than cisplatin plus etoposide in two trials. Response rates were higher with three-drug regimens. Gemcitabine, ifosfamide, and cisplatin produced response rates of 43–59%, while the combination of gemcitabine, vinorelbine, and cisplatin produced response rates of 33–65%. Most of the trials of vinorelbine, ifosfamide, and cisplatin found response rates exceeding 40%.

To be considered a new standard of therapy, a chemotherapy regimen should produce higher response rates than the previous standard or the same response with significantly less toxicity. However, a good response rate is not enough if there is no survival advantage as well. Although the newer agents have demonstrated significant activity with respect to tumor response, many are associated with median survival times of less than one year and one-year survival rates of just 30–40%. A hopeful note is that many of the double- and triple-drug combinations are so new that median and one-year survival results have yet to be determined. A survival advantage would set a new standard in the management of advanced non-small-cell lung cancer.

Management of small-cell lung cancer

Since small-cell lung cancer is often metastatic at diagnosis, surgery plays little if any role in its management. Most patients require systemic chemotherapy. About a third of patients with small-cell lung cancer have limited disease at diagnosis. Local irradiation is usually added to the treatment of patients with limited disease and may be used for prophylaxis of cranial lesions and for palliation of individual lesions. Small-cell lung cancer is much more likely than non-small-cell lung cancer to respond to chemotherapy, even when the disease is extensive. Responses are not durable, however, and most patients die in less than two years.

A number of drugs have demonstrated activity against small-cell
The most active agents are listed in Table 16. Combination chemotherapy is more effective than single agents with respect to both response and survival. The most commonly used combination is etoposide with either cisplatin or carboplatin. Additional combinations are shown in Table 17. The response rate for patients with limited disease is 80–95%, with up to 60% achieving a complete remission. Response rates of 60–80% have been noted in patients with extensive disease, with complete remission occurring in 15–20% of patients. Median survival times range from 12 to 20 months in patients with limited disease and from 7 to 11 months in those with extensive disease.

Over a dozen trials have compared chemotherapy alone with chemotherapy plus thoracic irradiation. Most of the trials were conducted in the 1980s and early 1990s, and a variety of antineoplastic agents, many not commonly used today, were administered. None of the newer agents, such as carboplatin, the taxanes, gemcitabine, vinorelbine, and the camptothecin derivatives (irinotecan, topotecan), were used. A direct comparison of these trials is impossible because of the differences in the drugs, administration schedules, and radiation doses. There was no consistency in the timing of radiation therapy. Radiation therapy was administered during or after chemotherapy or on an alternating schedule. Despite these differences, some of these trials found that chemotherapy...
therapy plus radiation therapy significantly improved local control, and several trials found an improvement in response rates and survival time in patients with limited disease.\textsuperscript{231-235} Two meta-analyses of these trials were conducted to evaluate the role of chemotherapy plus radiation therapy versus chemotherapy alone in patients with limited disease.

Warde and Payne\textsuperscript{236} analyzed 11 randomized trials published between 1984 and 1991. Their endpoints were the effect of the addition of radiation therapy on two-year survival, the toxicity of the combination, and the effect of irradiation on local disease control. Adding radiation therapy to chemotherapy resulted in a small but significant two-year survival benefit of 5.4%. However, adding irradiation also increased the risk of death from therapy by 1.2%. Local control was improved by 25.3% with the addition of radiation therapy. The second meta-analysis, by Pignon et al.,\textsuperscript{237} looked at 13 randomized trials published from 1976 to 1988 and involving 2140 patients with limited disease. The analysis included nine of the trials that had been reviewed by Warde and Payne, plus four others. The addition of radiation therapy reduced the death rate by 14%, resulting in a three-year survival advantage of 5.4%. The effects of therapy on local disease control were not assessed.

These analyses indicate that, for patients with limited small-cell lung cancer, the addition of radiation therapy to combination chemotherapy results in a moderate improvement in both local control and survival. Both ASCO and NCCN recommend combination chemotherapy and radiation therapy for patients with limited disease.\textsuperscript{43,44}

Radiation therapy can be administered sequentially, concurrently, or on an alternating schedule. No randomized trials have addressed these different schedules. The meta-analysis by Pignon et al.\textsuperscript{237} found no significant differences in outcomes on the basis of the irradiation schedule.

A few trials have been conducted to study the effect of the timing of radiation therapy. Murray et al.\textsuperscript{238} administered alternating cyclophosphamide–doxorubicin–vincristine and etoposide–cisplatin to 308 patients with limited disease. The patients were randomized to receive thoracic irradiation early (beginning in week 3) or late (beginning in week 15). There was no significant difference between the two groups in the rate of complete remission: 84.5% for early irradiation and 81.1% for late irradiation. However, the patients who received early irradiation had a significantly longer median relapse-free survival period (15.4 versus 11.8 months), longer median overall survival period (21.2 versus 16 months), and higher five-year survival rate (20% versus 11%).

Jeremic et al.\textsuperscript{239} administered carboplatin and etoposide followed by four sequential cycles of cisplatin and etoposide plus radiation administered in a hyperfractionated schedule of 1.5 Gy twice daily to a total dose of 54 Gy. Patients were randomized to receive the radiation therapy during weeks 1–4 or 6–9 of the protocol. The median survival time for patients who received early irradiation was 34 months, compared with 26 months after late irradiation ($p = 0.052$ with univariate analysis and $p = 0.027$ with multivariate analysis); five-year survival rates were 30% and 15%, respectively. Patients who received early irradiation had significantly better control of local disease, but there

Table 16. Activity of Single Agents against Small-Cell Lung Cancer\textsuperscript{a}

<table>
<thead>
<tr>
<th>Agent</th>
<th>With Prior Therapy</th>
<th>Without Prior Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>13</td>
<td>63</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>14</td>
<td>...</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>Etoposide</td>
<td>5</td>
<td>82</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>43</td>
<td>57</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>29</td>
<td>45</td>
</tr>
<tr>
<td>Teniposide</td>
<td>22</td>
<td>55</td>
</tr>
<tr>
<td>Topotecan</td>
<td>17</td>
<td>39</td>
</tr>
<tr>
<td>Vincristine</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>14</td>
<td>26</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Adapted in part from reference 230.

Table 17. Activity of Combination Chemotherapy against Non-Small-Cell Lung Cancer\textsuperscript{209-229}

<table>
<thead>
<tr>
<th>Combination</th>
<th>Response Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide and cisplatin</td>
<td>71–94</td>
</tr>
<tr>
<td>Carboplatin and etoposide</td>
<td>59–87</td>
</tr>
<tr>
<td>Cyclophosphamide, doxorubicin, and vincristine</td>
<td>80–90</td>
</tr>
<tr>
<td>Carboplatin, etoposide, and vincristine</td>
<td>82</td>
</tr>
<tr>
<td>Cyclophosphamide, doxorubicin, and etoposide</td>
<td>72–80</td>
</tr>
<tr>
<td>Cyclophosphamide, doxorubicin, vincristine, and etoposide</td>
<td>56–84</td>
</tr>
<tr>
<td>Cyclophosphamide, vincristine, doxorubicin, and etoposide</td>
<td>77–95</td>
</tr>
<tr>
<td>Ifosfamide, carboplatin, and etoposide</td>
<td>53–86</td>
</tr>
<tr>
<td>Etoposide, ifosfamide, and cisplatin</td>
<td>67–73</td>
</tr>
<tr>
<td>Etoposide–cisplatin alternating with cyclophosphamide–doxorubicin–vincristine</td>
<td>82–85</td>
</tr>
</tbody>
</table>
were no differences with respect to distant metastases. This indicates that the survival advantage of early irradiation is most likely due to its effect on local disease. Murray and Coldman\textsuperscript{243} reviewed published reports on the timing of irradiation in 2440 patients and concluded that early irradiation is associated with a long-term survival benefit.

**Chemotherapy.** In the 1970s and 1980s, one of the most active chemotherapy regimens used was cyclophosphamide, doxorubicin, and vincristine (CDV). This combination was reported to induce overall response rates of 80% or higher with limited disease and 65–70% with extensive disease.\textsuperscript{244} However, median survival times were only 12–15 months in patients with limited disease and 8–12 months in patients with extensive disease. In the mid-1980s, the combination of cisplatin and etoposide was found to be an effective regimen for patients who relapsed after CDV treatment. Cisplatin–etoposide produced response rates of around 50% in patients who were refractory to CDV or had relapsed.\textsuperscript{209} This finding led to trials of cisplatin–etoposide as a first-line regimen, and response rates of 71–94% and complete response rates of 30–53% were observed.\textsuperscript{209} Median survival times were 12–16 months (limited disease) and 9–10 months (extensive disease).

Evans et al.\textsuperscript{227} studied CDV versus CDV alternating with cisplatin–etoposide in patients with extensive disease. One hundred forty-four patients received CDV, while 145 received the other regimen. Objective response rates were seen in 47% of patients who received CDV alone and in 65% of those on the alternating schedule (p < 0.003); complete responses were seen in 10% and 13% of the two groups, respectively. Patients who received the alternating regimen had significantly longer progression-free survival time and overall survival time.

Fukuoka et al.\textsuperscript{228} compared CDV with cisplatin–etoposide and with CDV alternating with cisplatin–etoposide. The overall response rates for cisplatin–etoposide (78%) and for the alternating regimen (76%) were significantly higher than the rate for CDV (55%). Patients who received the alternating regimen lived for a median of 11.8 months, versus 9.9 months for both of the other two regimens. The authors projected that 10.4% of the CDV group, 11.5% of the cisplatin–etoposide group, and 21.4% of the alternating group would survive two years. Survival was significantly longer for the alternating regimen versus CDV (p = 0.059) but not versus cisplatin–etoposide. There were no survival differences among patients with extensive disease, but among patients with limited disease, survival was significantly longer after the alternating regimen than after CDV (p = 0.014) or cisplatin–etoposide (p = 0.023).

Carboplatin is associated with an overall response rate of 52–56% in chemotherapy-naive patients with small-cell lung cancer.\textsuperscript{243,244} Since carboplatin is less toxic than cisplatin, trials of etoposide combined with carboplatin were conducted to determine the activity of the regimen. Among patients with limited disease, response rates ranged from 77% to 82%, complete response rates were 3–40%, and median survival times were 9.5 to 15.3 months. Among patients with extensive disease, response rates were 56–87.5%, complete response rates were 9–16%, and median survival times were 8.1–9.5 months.\textsuperscript{197–200} The response and survival results were comparable to those achieved with cisplatin–etoposide. In a Phase III trial, Kosmidis et al.\textsuperscript{243} randomized patients to receive six cycles of either cisplatin–etoposide or etoposide–carboplatin. Patients with limited disease after three cycles received thoracic irradiation, and those with extensive disease who achieved a complete remission also received radiation therapy. Response rates for cisplatin–etoposide were 73% for limited disease and 50% for extensive disease. After etoposide–carboplatin therapy, response rates were 86% for limited disease and 64% for extensive disease. There was no difference in response or survival between the two groups, but etoposide–carboplatin was associated with significantly less toxicity. Etoposide–carboplatin became the preferred regimen for small-cell lung cancer.

**Newer agents.** Docetaxel has been evaluated in two studies. Smyth et al.\textsuperscript{244} reported a 25% response rate among 28 evaluable patients who received docetaxel as a second-line treatment at a dose of 100 mg/m\textsuperscript{2} every three weeks. This dose was associated with considerable myelosuppression; 71% of patients had grade 4 neutropenia. Hesketh et al.\textsuperscript{245} treated 43 chemotherapy-naive patients with docetaxel at the same dose and schedule. Ten patients (23%) achieved an objective response and a median survival time of nine months. Myelosuppression was much less in these patients, with only 8% having grade 4 neutropenia.

Paclitaxel has been used in three trials. Smit et al.\textsuperscript{246} administered a dose of 175 mg/m\textsuperscript{2} every three weeks and reported a 29% response rate and a 3.3-month median survival time among 24 patients with previously treated disease. Ettinger et al.\textsuperscript{247} and Kirschling et al.\textsuperscript{248} administered paclitaxel 250 mg/m\textsuperscript{2} every three weeks to chemotherapy-naive patients. Ettinger and colleagues restricted patients to only four cycles of therapy, and those who achieved a partial response were switched to cisplatin–etoposide. The rate of response to paclitaxel alone was 34%. The Kirschling group did not limit the number of cycles and reported a response rate of 53%. Median survival time in the study by Ettinger et al. was influenced by cisplatin–etoposide and was reported to be 10 months. Kirschling et al. found a 9.3-month median survival time.
Irinotecan has been evaluated in three trials, the first two involving previously treated patients. Two trials used 100 mg/m² weekly and found response rates of 33% and 47%.249,250 In the third trial, irinotecan was administered at 350 mg/m² every three weeks to chemotherapy-naive patients. Only 6 patients (16%) responded. Topotecan has been the most extensively studied of the newer agents. At least nine trials have been conducted, mostly in patients with prior chemotherapy.252-260 In two trials, the regimen consisted of 1.25 mg/m² per day for five days every three weeks.253,254 Response rates were 11% and 15%, and median survival times were 20 and 22 weeks. In five trials, conducted in a total of 456 patients, topotecan was administered at 1.5 mg/m² per day for five days every three weeks.255-259 In four of these five studies, patients were classified as chemotherapy sensitive, defined as disease progressing more than 90 days after first-line treatment, and chemotherapy refractory, defined as disease progressing during first-line therapy or less than 90 days later. There were 195 chemotherapy-sensitive patients and 261 chemotherapy-refractory patients. Thirty-five chemotherapy-sensitive patients responded, for an overall response rate of 18% (range, 6–38%), and 32 (12%) of the patients with refractory disease responded. In the only trial conducted in newly diagnosed patients, topotecan 2 mg/m² per day was administered for five days every three weeks to 48 patients.252 There were 19 responses (39%) and a 10-month median survival time.

Topotecan was compared with CDV in a Phase III trial involving patients who had responded to initial chemotherapy and relapsed less than 60 days later.260 Twenty-six (24%) of 107 patients responded to topotecan, while 19 (18%) of 104 responded to CDV. There was no difference in median survival time—25 weeks with each treatment. Topotecan was associated with significantly more anemia and thrombocytopenia than CDV, but there was no difference in the frequency of neutropenia or febrile neutropenia between the treatments. CDV was associated with a 17% rate of decreased left ventricular ejection fraction, versus 8% for topotecan. Topotecan-treated patients had better symptom control.

Topotecan was approved as a second-line agent for use in patients with chemotherapy-sensitive small-cell lung cancer. The currently approved dosage regimen is 1.5 mg/m² per day for five days every three weeks.261 Gemcitabine has undergone very limited evaluation in patients with small-cell lung cancer. Cormier et al.262 performed a Phase II trial of gemcitabine 1000–1250 mg/m² per week for three weeks, repeated every four weeks, in 26 newly diagnosed patients. An overall response rate of 27% and a 12-month median survival time were reported.

Vinorelbine has been evaluated in at least four trials.263-266 In three trials, it was administered at 30 mg/m² per week.263-265 Vinorelbine was administered as a first-line agent to 30 patients, 8 of whom (27%) achieved a partial response. There were 24 partial responses (23%) among 106 patients with prior therapy. These trials indicate that vinorelbine has activity against small-cell lung cancer, but its usefulness as a single agent appears to be limited.

Vinorelbine was combined with carboplatin in a Phase II trial in patients with extensive disease.267 The regimen consisted of carboplatin 300 mg/m² on day 1 and vinorelbine 25 mg/m² on days 1 and 8, repeated every four weeks. Seventy-four percent of the patients responded, 23% of them with complete remissions. It appears that vinorelbine merits further assessment in combination regimens.

Several newer agents have demonstrated activity against small-cell lung cancer. Their true role needs to be determined through trials of combination therapy, especially with such agents as cisplatin, carboplatin, and etoposide. Few such trials have been completed. Groen et al.268 reported a 73.5% rate of response to paclitaxel and carboplatin among 34 patients who had had previous chemotherapy. Median survival time, however, was only 7.2 months. In another trial, paclitaxel was administered in two doses, 135 and 175 mg/m², in combination with cisplatin 75 mg/m² in chemotherapy-naive patients.269 A 71% response rate was seen with the lower paclitaxel dose, versus 89% at the higher dose. Survival times were similar: 7.9 and 8.8 months, respectively. A Phase II trial of irinotecan plus carboplatin found a response rate of 83% among 40 patients with limited disease and 86% among 35 patients with extensive disease.270 Median survival times were 14.3 months (limited disease) and 13 months (extensive disease). A disappointing response rate of only 29% was seen in a trial of 28 chemotherapy-sensitive patients who received topotecan and cisplatin.271 Only 17% of chemotherapy-refractory patients responded to the same regimen.272

A variety of two- and three-drug combinations have been evaluated (Table 18).267-274 One regimen combined carboplatin, etoposide, and paclitaxel. In two trials, carboplatin was administered at a dose based on an AUC of 5 mg/mL·min while the other trial used a dose based on an AUC of 6 mg/mL·min.272,273 Etoposide was administered orally at 100 mg/m² per day for 7 days in one trial272 and at alternating doses of 50 and 100 mg every day for 10 days in the other.273 Paclitaxel doses ranged from 135 to 200 mg/m². There were 132 responses among 151 evaluable patients (87%), including 48 complete responses (36%). A median survival time of 17 months was reported for patients with limited disease in one of the trials. Median
survival times were not yet reached in patients with limited disease in the other trial. Patients with extensive disease had median survival times of 7–10 months. One trial that used cisplatin instead of carboplatin found a 90% response rate (16% complete) and a median survival time of 10.8 months. These trials indicate activity comparable to that achieved with other regimens, including standards such as cisplatin–etoposide and etoposide–carboplatin. Randomized studies need to be completed to assess the true role of these newer combinations.

**Dose intensification.** Other avenues used in an attempt to increase survival include high-dose therapy, weekly therapy, high-dose therapy with stem-cell or bone marrow support, and maintenance chemotherapy. Administration of high doses or administration of standard doses in a compressed time period is often referred to as dose intensification.

The intensity of a drug’s activity can be increased by increasing the size of the dose, shortening the dosing interval, or prolonging the therapy. A number of clinical trials have been conducted with high doses of standard combinations. Although the dose-intensive regimens have been able to increase the response rate, there has been no significant impact on survival. At least four randomized studies have compared a standard-dose regimen with a high-dose regimen of the same drugs (Table 19). Two of the trials compared standard-dose CDV with high-dose CDV. In one trial, 103 patients were randomized to standard-dose cyclophosphamide 1000 mg/m², doxorubicin 50 mg/m², and vincristine 2 mg or to cyclophosphamide 1500 mg/m², doxorubicin 60 mg/m², and vincristine 2 mg. There was no significant difference in response rates (61% versus 71%) or survival (8 versus 9 months) between standard-dose and high-dose therapy, respectively. In the other trial, Johnson et al. reported similar response rates (53% versus 63%) and survival times (8.1 versus 6.8 months). Ihde et al. compared standard-dose cisplatin–etoposide with a high-dose regimen and found no differences in response or survival. The fourth randomized trial compared two dosage levels of a four-drug combination consisting of cyclophosphamide, etoposide, cisplatin, and epirubicin. There were no differences in response or survival.

With standard regimens, the agents are usually given on a three- to four-week schedule. Intensified regimens may involve administration every week. At least six randomized trials have compared standard schedules with weekly therapy. There was no response or survival advantage in any trial.

Two trials employed a modified dose-intensification approach by reducing the dosage interval by one week. Thatcher et al. randomized patients to receive cyclophosphamide, doxorubicin, and etoposide every three weeks or every two weeks. A significantly higher complete remission rate was reported for the more intensive regimen (40% versus 28%) (p = 0.02). However, there was no difference in overall response (79% versus 78%). Dose intensification did have a significant impact on survival. Patients receiving the more

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**Table 18. Activity of Selected Combination Regimens against Small-Cell Lung Cancer**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. Patients</th>
<th>Regimen (mg/m²)</th>
<th>Response Rate (%)</th>
<th>Median Survival Time (mo)</th>
<th>One-Year Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>267</td>
<td>43, ED</td>
<td>VIN 25 days 1 and 8, CAR 300 day 1 q 4 wk</td>
<td>74</td>
<td>8.5</td>
<td>44</td>
</tr>
<tr>
<td>268*</td>
<td>15, LD</td>
<td>PAC 175/3 hr day 1, CAR AUC = 7</td>
<td>83</td>
<td>7.2</td>
<td>9</td>
</tr>
<tr>
<td>269</td>
<td>19, ED</td>
<td>PAC 135 day 1, CIS 75 day 1</td>
<td>62</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>270</td>
<td>21, ED</td>
<td>PAC 175 day 1, CIS 75 day 1</td>
<td>71</td>
<td>7.9</td>
<td>24</td>
</tr>
<tr>
<td>271*</td>
<td>44, ED</td>
<td>PAC 175 day 1, CIS 75 day 1</td>
<td>89</td>
<td>8.8</td>
<td>38</td>
</tr>
<tr>
<td>272</td>
<td>40 LD</td>
<td>IRIN 60/wk × 3, CIS 60 day 1 q 4 wk</td>
<td>83</td>
<td>14.3</td>
<td>18*</td>
</tr>
<tr>
<td>273</td>
<td>35, ED</td>
<td>CIS 60 day 1 q 4 wk</td>
<td>86</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>274*</td>
<td>28, sensitive</td>
<td>TOP 0.75/day × 5, CIS 60 day 1</td>
<td>29</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>275</td>
<td>24, refractory</td>
<td>TOP 0.75/day × 5, CIS 60 day 1</td>
<td>17</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>276</td>
<td>15, ED</td>
<td>CAR AUC = 5 day 1, ETOP 50 or 100/day p.o. (alternating days 1–10), PAC 135 day 1</td>
<td>93</td>
<td>17</td>
<td>68</td>
</tr>
<tr>
<td>277</td>
<td>38, ED</td>
<td>CAR AUC = 6 day 1, ETOP 50 or 100/day (alternating days 1–10), PAC 200 day 1</td>
<td>65</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>278</td>
<td>41, LD</td>
<td>CAR AUC = 6 day 1, ETOP 50 or 100/day (alternating days 1–10), PAC 175/1 hr day 1</td>
<td>98</td>
<td>&gt;16*</td>
<td>68</td>
</tr>
<tr>
<td>279</td>
<td>38, LD</td>
<td>CAR AUC = 5 day 1, ETOP 100 p.o. days 2–8, PAC 175/1 hr day 1</td>
<td>84</td>
<td>10</td>
<td>38</td>
</tr>
<tr>
<td>280</td>
<td>38, ED</td>
<td>CIS 75 day 2, ETOP 80 i.v. days 2–4, PAC 130 day 1</td>
<td>88.5</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*ED = extensive disease, VIN = vinorelbine, CAR = carboplatin, LD = limited disease, PAC = paclitaxel, AUC = area under the concentration-versus-time curve (mg/mL · min), CIS = cisplatin, IRIN = irinotecan, TOP = topotecan, NR = not reported, ETOP = etoposide.

*Regimens administered every three weeks unless noted otherwise.

*Therapy was second line.

*Two-year survival rate.

*Significantly different from corresponding value for ED patients (p < 0.008).
intensive regimen had one- and two-year survival rates of 47% and 13%, compared with 39% and 8% for standard therapy (p = 0.04). There were no differences in nonhematologic toxicities between the two groups, nor did quality-of-life assessments differ.

Steward et al. randomized patients to receive vincristine, ifosfamide, carboplatin, and etoposide every four weeks or every three weeks. Although there were no differences in response rates between the regimens, the every-three-week schedule was associated with a significant survival advantage: a median survival time of 11.7 months versus 14.8 months for the more intensive regimen. The two-year survival rate was 18% for standard therapy and 33% for dose-intensified therapy.

The data on weekly administration of chemotherapy indicate that such intensification does not improve response or survival over conventional schedules. Myelosuppression is considerable and may result in treatment delays. Dose intensification achieved by reducing the interval by one week appears to have some promise, but additional trials are needed.

Many clinicians advocate four to six cycles of therapy; however, the optimum duration of therapy remains controversial. Sandler reviewed the data for 11 randomized trials comparing induction chemotherapy (four to six cycles) with induction chemotherapy plus maintenance therapy. The number of patients in these trials ranged from 66 to 687. Most trials compared 4–6 cycles with as many as 12 cycles. Only two studies found a survival advantage for maintenance therapy. Maurer et al. randomized 57 patients who had achieved a complete remission to six more cycles of therapy (various regimens) or observation. Only patients with limited disease had a survival advantage—16.8 months with maintenance therapy versus 6.8 months without it. Cullen et al. randomized 93 patients who had achieved a complete response after CDV to eight more cycles or no additional treatment. Patients with extensive disease lived for 372 days with maintenance therapy and 259 days without it. Byrne et al. reported the opposite results: a survival advantage for patients who did not receive maintenance therapy over those who did. The increased hematologic toxicity with maintenance therapy and the fact that maintenance therapy had no survival impact in 9 of 11 trials led to the conclusion that there was no role for maintenance therapy in these patients.

In some trials, high-dose chemotherapy was followed by autologous bone marrow transplantation.
such studies were reviewed by Krug et al.\textsuperscript{290} There was no standardization among these trials. Patients received one to three antineoplastic agents before the transplantation procedure. Radiation therapy was administered to the chest alone, to the chest and head, to the head alone, or not at all. Patients with limited or extensive disease were enrolled in six trials, patients with limited disease only in three, and patients with extensive disease only in one. A total of 293 of 387 patients treated with induction chemotherapy achieved a complete or partial response. One hundred seventy of these patients (58\%) received a bone marrow transplant. Forty patients (24\%) of the 170 achieved a complete remission after transplantation. Median survival times ranged from 8 to 15+ months, and there were 15 transplantation-related deaths (8.8\%). These survival figures are no better than those achieved with standard chemotherapy alone.

**Therapy in the elderly.** Many physicians are hesitant to treat older patients with small-cell lung cancer with the same regimens used in younger patients. A popular treatment for elderly patients has been etoposide given orally as a single agent. Etoposide was chosen because it is active against small-cell lung cancer, is fairly well tolerated, and can be administered orally in an outpatient setting. One of the first trials was conducted by Smit et al.\textsuperscript{292} They administered etoposide 160 mg/m\textsuperscript{2} per day orally for five consecutive days every four weeks to 35 patients age 70 years or over. Most of the patients had extensive disease and poor performance status. The response rate was 71\%, and the median survival time was 16 months among those with limited disease and 9 months among those with extensive disease.

Etoposide was compared with combination chemotherapy in two trials. Clark\textsuperscript{290} compared etoposide 50 mg twice daily for 10 days with CDV or etoposide plus vincristine. Etoposide was administered to 171 patients and was associated with a response rate of 61\%, a median survival time of 130 days, and a one-year survival rate of 11\%. The 168 patients who received combination therapy had a 73\% response rate, a 183-day median survival time, and a one-year survival rate of 13\%. Patients who received combination therapy had less life-threatening myelosuppression and a significantly longer median survival time.

Souhami et al.\textsuperscript{294} compared oral etoposide (\(n = 75\)) with CDV alternating with etoposide–cisplatin (\(n = 80\)) in patients who were elderly or had a poor performance status. Responses were seen in 33\% of those who received etoposide, versus 46\% of those given combination therapy \((p < 0.01)\). Median survival times were 4.8 months with etoposide and 5.9 months with the combination. One-year survival rates were 9.8\% and 19.3\%, respectively \((p < 0.05)\). There were no differences in serious toxicities. Patients who received the combination also reported a higher quality of life. These trials indicate that elderly patients not only can tolerate combination regimens but that they may also have a better outcome than with etoposide monotherapy. Elderly patients who can tolerate standard combination regimens should receive them.

**Prophylactic cranial irradiation.**

One of the most common sites for metastatic spread of small-cell lung cancer is the brain. Many patients have clinically unapparent brain involvement when they begin receiving chemotherapy. However, 50\% or more of those who survive two years have disease relapse in the brain because of the drugs’ inability to cross the blood–brain barrier.\textsuperscript{295} Irradiation can reduce the relapse rate in the brain to 6\%.\textsuperscript{296} Irradiation of patients who have clinically undetectable disease in the brain is known as prophylactic cranial irradiation (PCI).

PCI is associated with several problems. First, few patients live long enough to develop brain tumors; thus, many patients receiving PCI are unnecessarily exposed. Second, PCI is associated with significant toxicities. The adverse effects may be acute or delayed. Acute toxicity is usually limited and transient and may consist of headaches, alopecia, and problems with hearing, taste, and appetite. Delayed effects may be more serious and include memory loss, cognitive dysfunction, personality changes, motor difficulties, and fatigue. In some patients, cerebral atrophy and abnormalities in the white matter occur, and 10–25\% develop dementia.\textsuperscript{296} The third problem with PCI involves survival. Glantz et al.\textsuperscript{295} reviewed 11 randomized trials of PCI published between 1977 and 1995. PCI was administered to 518 patients, and 540 were observed. PCI significantly reduced the frequency of subsequent brain metastases in 9 of the 11 studies. However, there was no difference in median or two-year survival figures between patients who received PCI and those who did not. To further complicate the issue, a recent meta-analysis of seven randomized trials found that PCI was associated with a 5.4\% survival advantage at three years in people who achieved a complete response with chemotherapy (20.7\% with PCI versus 15.3\% without it).\textsuperscript{297} Glantz and colleagues\textsuperscript{295} concluded that PCI should be offered only to patients with limited disease who achieve a complete response with initial therapy and have a good performance status. The NCCN guidelines on the management of small-cell lung cancer state that PCI may be considered in patients who achieve a complete response after initial therapy but indicate that further analysis is needed.

**Summary.** Standard chemotherapy regimens, such as cisplatin and etoposide, can induce remissions in 70–90\% of patients with small-cell lung cancer. Regimens pairing cis-
platin or carboplatin with agents such as paclitaxel, topotecan, irinotecan, and vinorelbine can achieve response rates comparable to those for standard regimens. Since remission rates are so high, it is unlikely that new combinations will improve the overall response in this disease. The main way such agents could affect response rates would be to increase the number of patients who achieve a complete remission. An improvement in rates of complete remission, while desirable, would represent a minimal gain if there were no increase in survival time.

Attempts to increase survival time, including dose intensification, dose intensification with bone marrow or stem-cell support, and maintenance therapy, have failed. The addition of radiation therapy has resulted in a survival advantage, but only for patients with limited disease. Although there are many new drug combinations, the median survival data indicate no advantage over standard regimens. Additional trials—perhaps combining the newer agents with each other—need to be conducted in an attempt to improve survival in patients with this disease.

Economic considerations
Lung cancer accounts for 20% of all cancer care costs in the United States, or a total annual expenditure of $8 billion.308 The cost of therapy relative to the poor outcomes has led to many cost-effectiveness trials.

Evans309 used a computer model developed in Canada to compare the cost of gemcitabine with that of BSC in patients with advanced non-small-cell lung cancer. It was assumed that all patients received the same number of cycles of gemcitabine, that all cycles were uncomplicated, and that tests were not duplicated over time. BSC cost $20,914 per patient from diagnosis through terminal care in 1993 Canadian dollars. Gemcitabine therapy cost an average of $22,172 per patient on the basis of an assumed cost of $1,000 per cycle for the drug. An average survival gain of 0.42 year was assumed for patients who received gemcitabine. This translated into an average cost of $3,193 per year of life gained, which is extremely cost-effective in Canada, where the cost-effectiveness threshold is $50,000 per year of life gained.

Two retrospective analyses of the cost-effectiveness of vinorelbine, several combination regimens, and BSC have been performed.300,301 These studies used clinical outcomes data from a trial by LeChevalier et al.151 and other sources. Evans300 using data from the Canadian health care system, compared the cost associated with vinorelbine alone (inpatient), vinorelbine plus cisplatin (both inpatient and outpatient), vindesine plus cisplatin (inpatient), etoposide plus cisplatin (outpatient), and vindesine plus cisplatin (outpatient) versus the cost of BSC. The model simulated the management of patients with stage IV non-small-cell lung cancer in Canada in 1993. Data included in the analysis were costs of diagnosis, hospitalization, antineoplastic agents, antiemetics, and terminal care. Overall costs of each of the drug regimens and BSC were very close. Inpatient costs ranged from $136,000 per patient for vinorelbine alone to $141,000 for BSC and reached a high of $159,000 for vindesine plus cisplatin. Outpatient costs ranged from $127,000 for vinblastine plus cisplatin to $141,000 for vinorelbine plus cisplatin. Vinorelbine–cisplatin had the best survival advantage over BSC, 0.45 versus 0.27–0.29 year of life saved with the other regimens. The cost per year of life saved ranged from $7,450 to $30,770, depending on the regimen and the site of care (inpatient or outpatient). Although vinblastine–cisplatin and etoposide–cisplatin were the most cost-effective regimens, vinorelbine–cisplatin provided a larger survival advantage over BSC.

Smith et al301 compared the cost in 1994 U.S. dollars of vinorelbine, vinorelbine plus cisplatin, and vindesine plus cisplatin in patients with advanced non-small-cell lung cancer. Costs included those of laboratory work, professional services, antineoplastic drugs, antiemetics, and therapy for toxicity. Most hospitalization costs were excluded, as were terminal care costs. Both vinorelbine–cisplatin and vindesine–cisplatin were more cost-effective than vinorelbine alone. Vinorelbine–cisplatin was the most cost-effective treatment at $15,500 per year of life saved. A review of both trials concluded that vinorelbine alone or with cisplatin was more cost-effective than BSC and that vindesine plus cisplatin was the most cost-effective regimen evaluated.302

Decision analysis was used to compare the cost of seven antineoplastic regimens (vinorelbine alone, gemcitabine alone, and cisplatin in combination with vindesine, etoposide, vinblastine, vinorelbine, or paclitaxel) with that of BSC in patients with metastatic non-small-cell lung cancer in Canada.303 A computer model simulated the cases of patients with advanced disease and reported the findings in 1995 Canadian dollars. Costs for diagnosis, treatment, follow-up, relapse, and terminal care were included. All the chemotherapy regimens increased survival over BSC, but only vinorelbine–cisplatin resulted in lower direct costs. The average total cost for BSC was $25,904 per patient, compared with $24,828 for vinorelbine plus cisplatin. Vinorelbine–cisplatin was the most cost-effective regimen per year of life gained, while BSC was the least cost-effective. The authors concluded that their results add economic support to the idea that BSC should be abandoned as a standard of care for patients with metastatic lung cancer.

All of these cost analyses were retrospective and relied on efficacy data from other trials. All comparisons were based on models and assumed procedures that would be performed on each patient. Hospitalization
costs were included in some analyses and excluded from others. A definition of hospitalization costs was not included in any study. Toxicity costs were not always included or defined. Despite these limitations, chemotherapy appears to be cost-effective compared with BSC. Which drug regimen is most cost-effective is unknown. There are no data on some of the more common regimens used to treat lung cancer. The cost of the newer agents has not been evaluated either. Since some of the newer agents may be associated with higher response rates, longer survival times, and less toxicity, cost comparisons of new combinations with standard regimens and BSC would be desirable.

Conclusion
Lung cancer, although highly preventable, is usually diagnosed at an incurable stage. Chemotherapy is playing an increasingly important role alongside surgery and radiation therapy in the management of this disease.

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