REVIEW ARTICLE

DRUG THERAPY

Alastair J.J. Wood, M.D., *Editor*

Multidisciplinary Management of Lung Cancer

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N Engl J Med 2004;350:379-92.

In 2004, an estimated 173,700 Americans will receive a diagnosis of lung cancer, and 164,440 of them will die of the disease. Despite years of research, the prognosis for patients with lung cancer remains dismal, with a five-year survival rate of 14 percent. Nevertheless, lung cancer may be curable in its early stages, and most patients derive some benefit from treatment such as longer survival or amelioration of symptoms. The topic was last reviewed in the *Journal* in 1992.[1] This review will focus on the multidisciplinary management and treatment of lung cancer, with particular emphasis on phase 3 studies.

Figure 1 shows a model of the pathogenesis of lung cancer, with its progression from normal tissue to frankly malignant tissue. Lung cancer is divided into two types: non–small cell and small cell. Non–small-cell lung cancer consists of several subtypes, predominantly adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma, which are all treated in the same manner. Small-cell lung cancer is a very aggressive neuroendocrine lung carcinoma, treated primarily with chemotherapy and, occasionally, radiotherapy. Treatments and their adverse effects are managed by multiple physicians, with different subspecialty expertise; careful coordination of the patient's care is essential.

PRINCIPLES OF RADIOTHERAPY IN LUNG CANCER

Radiotherapy is usually delivered by an external beam from a linear accelerator. Standard therapy for unresectable disease consists of approximately 60 Gy, with the dose divided among 30 sessions over a period of six weeks, although higher doses have been used.[3] In normal organs, the toxic effects of radiation include pneumonitis, esophagitis, skin desquamation, myelopathies, and cardiac abnormalities.[4] These effects may be minimized by using three-dimensional computed tomography (CT) to guide therapy or by modulating the intensity of radiotherapy in order to spare normal tissue. Concurrent chemotherapy may increase the effectiveness of radiation by sensitizing the tumor to radiation, but it can also increase the adverse effects (particularly esophagitis).

GENERAL APPROACH TO CHEMOTHERAPY

Many chemotherapeutic agents are effective against both small-cell and non–small-cell lung cancer (Table 1). Among the most active are those of the platinum family: cisplatin, which cross-links DNA, and carboplatin, a cisplatin analogue. Most studies suggest that carboplatin is as efficacious as cisplatin but less toxic. However, published data do not support the frank substitution of carboplatin for cisplatin in patients with curable disease.[5,6] The adverse effects of chemotherapy can be severe but are generally manageable and reversible. Major effects include nausea, vomiting, alopecia, myelosuppression, nephrotoxicity, neuropathies, high-pitch hearing loss, and electrolyte depletion. Eto-

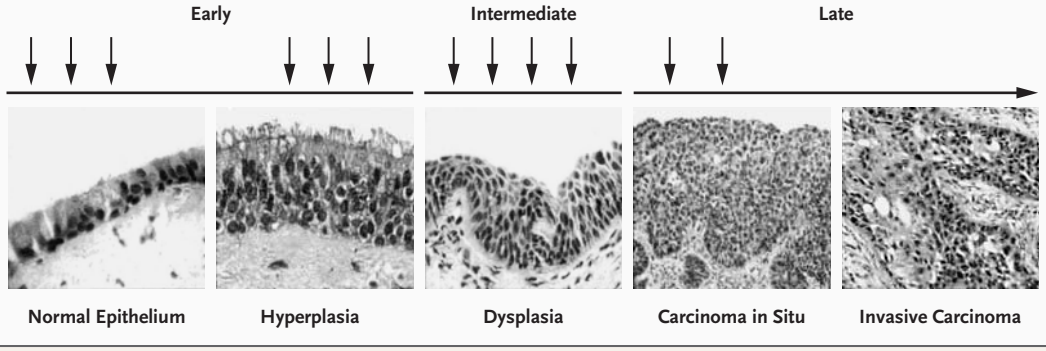

Figure 1. Sequential Pathogenetic Changes Involved in Lung Cancer.
Although multiple genetic markers (indicated by the arrows) are abnormal in lung cancers, the timing of their appearance during the lengthy preneoplastic process varies. Several alterations have been described in histologically normal specimens of bronchial epithelium from smokers. Other changes (such as hyperplasia and metaplasia) have been detected in slightly abnormal epithelium and are regarded as early changes. Molecular changes detected frequently in dysplasia are regarded as intermediate in timing, whereas those usually detected in carcinoma in situ or invasive stages are regarded as late changes. Modified from Hirsch et al.[2]

poside, docetaxel, paclitaxel, gemcitabine, vinorelbine, and irinotecan are often used in combination with a platinum agent.

NON–SMALL-CELL LUNG CANCER

STAGING AND EVALUATION

The tumor, node, and metastasis (TNM) staging system for lung cancer, developed by the American Joint Committee on Cancer, is shown in Table 2.[7,8] Before treatment recommendations can be made for a given patient, the size of the tumor, lymph-node status, and possible presence of metastases must be ascertained. Lung cancer often spreads to the draining nodes in the hilum and mediastinum. Mediastinal involvement (N2) places the patient in a higher stage and may render the tumor unresectable, if it is close to vital mediastinal structures. Accurate noninvasive assessment of hilar and mediastinal nodes is difficult. Clinical staging is based on the size of the lymph node as determined by CT. Until fairly recently, the use of a cutoff for normal nodes of 10 to 15 mm provided sensitivities and specificities for detecting nodal metastases of only 40 to 70 percent, but this approach was the only noninvasive option.[9,10] Even small, peripheral, T1 lesions (Table 2), often considered to be associated with a low risk of mediastinal spread, frequently involve these nodes.[11]

Positron-emission tomography (PET) has emerged as an important noninvasive test for mediastinal assessment. This approach operates on the principle that tumors cause increased uptake of radiolabeled glucose that can be imaged. Retrospective data from several trials suggest a sensitivity and specificity of 85 percent and 88 percent, respectively, for the mediastinal staging of non–small-cell lung cancer with the use of PET, and the results of a prospective study support these findings.[12] The combination of PET and CT appears to have an even greater sensitivity and specificity than the use of either method alone,[13] and the use of both should be strongly considered as part of the preoperative evaluation. The gold standard for mediastinal evaluation is lymph-node biopsy by means of bronchoscopy or, if needed, the more invasive mediastinoscopy. To distinguish potentially curable from incurable disease, radiologic studies that indicate the presence of mediastinal disease should be followed by biopsy of identified nodes before a tumor is deemed to be unresectable. Brain magnetic resonance imaging[14] and bone scanning[15] should be performed in all patients who have N2 disease or other clinical indications before aggressive local therapy is considered.

SURGERY

Surgery is the mainstay of treatment for patients with non–small-cell lung cancer, particularly for those with early disease. Surgery should include resection (pneumonectomy or lobectomy) and mediastinal-node mapping. Complete lymph-node

Table 1. Chemotherapy for Lung Cancer.*

Drug	Type of Agent	Major Adverse Effects	Comments
Platinum agents			
Cisplatin (Platinol)	Atypical alkylator	Nausea and vomiting (common),† nephrotoxicity, ototoxicity, neuropathy, myelosuppression (mild), electrolyte wasting (potassium and magnesium)	Hydration required before and after administration
Carboplatin (Paraplatin)	Atypical alkylator	Myelosuppression,† nausea and vomiting (mild), neurotoxicity (rare), nephrotoxicity (rare)	Dose usually determined by area under the curve, taking renal function into account with use of the Calvert formula
Nonplatinum agents			
Etoposide (VePesid)	Topoisomerase II inhibitor	Myelosuppression,† nausea and vomiting, stomatitis, diarrhea	Stomatitis and diarrhea rare with normal dose
Topotecan (Hycamptin)	Topoisomerase I inhibitor	Myelosuppression,† nausea and vomiting, diarrhea, headache	Increased monitoring of liver function necessary
Irinotecan (Camptosar)	Topoisomerase I inhibitor	Myelosuppression,† diarrhea, nausea and vomiting	
Gemcitabine (Gemzar)	Antimetabolite	Myelosuppression,† nausea and vomiting, diarrhea, edema, influenza-like syndrome	Increased monitoring of liver function necessary
Paclitaxel (Taxol)	Microtubule inhibitor	Myelosuppression,† mucositis, peripheral neuropathy, hypersensitivity reaction, nausea and vomiting	Requires pretreatment with dexamethasone, diphenhydramine hydrochloride, ranitidine
Docetaxel (Taxotere)	Microtubule inhibitor	Myelosuppression,† edema and fluid retention, mucositis, diarrhea, nausea and vomiting	Requires treatment with dexamethasone before, during, and after infusion
Vinorelbine (Navelbine)	Microtubule inhibitor	Myelosuppression,† nausea and vomiting	Mild vesicant
Vincristine (Oncovin)	Microtubule inhibitor	Neuropathy,† constipation	Vesicant
Doxorubicin (Adriamycin)	Anthracycline antibiotic	Myelosuppression,† cardiomyopathy, nausea and vomiting, diarrhea, stomatitis	Cardiotoxic effects occur with cumulative doses of more than 375 mg/m^2 of body-surface area; potent vesicant; precautions against extravasation necessary
Cyclophosphamide (Cytoxan)	Alkylating agent	Myelosuppression,† nausea and vomiting, hemorrhagic cystitis	Hemorrhagic cystitis rare with standard doses
Ifosfamide (Ifex)	Alkylating agent	Myelosuppression,† nausea and vomiting, hemorrhagic cystitis, nephrotoxicity, neurotoxicity	Mesna given to prevent hemorrhagic cystitis

* The following are principles of combination chemotherapy: use drugs active against the cancer to be treated, use drugs with different mechanisms of action, use drugs with different toxicity profiles, and use each drug at the maximal effective dose. Regimens for non–small-cell lung cancer typically combine a platinum drug with a nonplatinum drug. Regimens for small-cell lung cancer usually consist of etoposide and cisplatin, etoposide and carboplatin, irinotecan and cisplatin, cyclophosphamide, doxorubicin, and vincristine, or ifosfamide, carboplatin, and etoposide.

† This is a major, usually dose-limiting, adverse effect.

dissection should be performed if the tumor is resectable and mediastinal nodes are involved.

ADJUVANT THERAPY

Adjuvant therapy refers to the use of radiation or chemotherapy to improve survival after a tumor has been treated surgically.

Radiotherapy

Adjuvant radiotherapy has been considered a means to eliminate small deposits of tumor cells adjacent to or draining from the primary tumor site. Unfortunately, the results of adjuvant radiotherapy have been quite variable; some trials show a benefit,[16] whereas most show none (Table 3; additional information has been deposited with the National Auxiliary Publications Service [NAPS]*).[21,32,33] A large meta-analysis published in 1998 suggested that postoperative radiotherapy was detrimental, with a

*See NAPS document no. 05612 for 16 pages of supplementary material. To order, contact NAPS, c/o Microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.

Table 2. Staging of Lung Cancer.*

Stage	Tumor	Node	Metastasis	General Description	Survival Rate	
					1 Yr	5 Yr
Non–small-cell lung cancer						
Local						
IA	T1	N0	M0	T1 tumor: ≤3 cm, surrounded by lung or pleura; no tumor more proximal than lobe bronchus	94	67
IB	T2	N0	M0	T2 tumor: >3 cm, involving main bronchus ≥2 cm distal to carina, invading pleura; atelectasis or pneumonitis extending to hilum but not entire lung	87	57
IIA	T1	N1	M0	N1: involvement of ipsilateral peribronchial or hilar nodes and intrapulmonary nodes by direct extension	89	55
Locally advanced						
IIB	T2	N1	M0		73	39
	T3	N0	M0	T3 tumor: invasion of chest wall, diaphragm, mediastinal pleura, pericardium, main bronchus <2 cm distal to carina; atelectasis or pneumonitis of entire lung		
IIIA	T1	N2	M0		64	23
	T2	N2	M0			
	T3	N1	M0			
	T3	N2	M0	N2: involvement of ipsilateral mediastinal or subcarinal nodes		
IIIB	Any T	N3	M0	N3: involvement of contralateral (lung) nodes or any supraclavicular node	32	3
Advanced						
IIIB	T4	Any N	M0	T4 tumor: invasion of mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; separate tumor nodules; malignant pleural effusion	37	7
IV	Any T	Any N	M1	Distant metastasis	20	1
Small-cell lung cancer						
Limited disease				Evidence of tumor confined to ipsilateral hemithorax; can be encompassed by a single radiation port		
Extensive disease				All other diseases, including metastatic disease		

* Data are adapted from Mountain and Dresler.[7] The staging system was developed by the American Joint Commission on Cancer. T denotes tumor, N node, and M metastasis.

21 percent increase in the relative risk of death, and was particularly harmful for patients with stage I disease.[34] However, this analysis included data that are very dated, given the availability of modern radiotherapy and staging techniques. One important exception must be mentioned: in 1986, a trial from the Lung Cancer Study Group demonstrated that adjuvant radiotherapy prevented local recurrence in patients with N2 disease but did not improve overall survival.[16] These limited data have become the rationale for the use of postoperative radiation in otherwise healthy patients with N2 disease. Postoperative radiotherapy should not be used outside of a clinical trial for any other type of patients, unless the surgical margins are positive and repeated resection is not feasible.

Chemotherapy

Given the poor prognosis for patients with early non–small-cell lung cancer, even with adequate surgical resection, many patients probably have undetectable microscopic metastasis at diagnosis. In theory, chemotherapy with a cytotoxic agent may eliminate micrometastases, improving survival. Although this concept is appealing, the results of trials are mixed (Table 3 and NAPS document 05612). Most trials evaluating chemotherapy have combined patients with different stages of disease (usually

Table 3. Results of Selected Studies of Non–Small-Cell Lung Cancer.

Type of Study and Group	Regimens	Conclusions or Results
Adjuvant chemotherapy and radiotherapy after surgery		
Holmes and Gail[17]	Cyclophosphamide, doxorubicin, and cisplatin vs. immunotherapy	Increased survival with adjuvant chemotherapy
Lung Cancer Study Group[18]	Cyclophosphamide, doxorubicin, cisplatin, and radiotherapy vs. radiotherapy alone	14% Increase in 1-yr survival rate with chemotherapy
Keller et al.[19]	Etoposide, cisplatin, and radiotherapy vs. radiotherapy alone	No advantage of chemotherapy
International Adjuvant Lung Cancer Trial Collaborative Group[20]	Cisplatin-based adjuvant chemotherapy vs. observation	4% Absolute increase in overall survival with adjuvant chemotherapy at 5 yr (P<0.003)
Lafitte et al.[21]	Radiotherapy vs. no therapy	No survival advantage; decreased rate of local recurrence only among patients with N2 disease (P=0.03)
Addition of chemotherapy to radiotherapy in inoperable cancer		
Dillman et al.[22,23]	Cisplatin, vinblastine, and radiotherapy vs. radiotherapy alone	Increased survival rates at 1, 2, 3, and 7 yr with chemotherapy (13% vs. 6%)
Curran et al.[24]	Cisplatin, vinblastine, and concurrent radiotherapy vs. cisplatin, vinblastine, and sequential radiotherapy	Increased survival with concurrent radiotherapy (P=0.046), but increased incidence of esophagitis as well (25% vs. 4%)
Neoadjuvant chemotherapy in stage IIIA disease		
Roth et al.[25,26]	Etoposide and cisplatin before and after surgery vs. surgery and radiotherapy	Increased survival with chemotherapy (56% vs. 15% at 3 yr)
Rosell et al.[27,28]	Mitomycin, ifosfamide, and cisplatin before surgery and radiotherapy vs. surgery and radiotherapy	Increased median survival with chemotherapy (26 mo vs. 8 mo)
Neoadjuvant chemotherapy in stage I, II, or IIIA disease		
Depierre et al.[29]	Mitomycin, ifosfamide, and cisplatin before surgery and radiotherapy vs. surgery and radiotherapy	No benefit for patients with N2 disease; small survival advantage for patients with N0 or N1 disease at 1 and 4 yr
Chemotherapy for advanced disease		
Schiller et al.[30]	Cisplatin and paclitaxel vs. cisplatin and gemcitabine, cisplatin and docetaxel, and carboplatin and paclitaxel	Results approximately equivalent for all regimens; most adverse effects with cisplatin plus gemcitabine but also slightly higher survival rate; least adverse effects with carboplatin plus paclitaxel
Johnson et al.[31]	Carboplatin, paclitaxel, and gefitinib vs. carboplatin and paclitaxel	No advantage for gefitinib when given with standard chemotherapy

stage II and III). Modern trials usually use platinum-based regimens, since this class is the most active against non–small-cell lung cancer. Most individual trials have not shown a statistically significant benefit of adjuvant chemotherapy,[19,35-37] and the few that did[18,38] suggested that there was only a small (10 to 15 percent) survival advantage several years after diagnosis in patients with incompletely resected tumors[17] or stage III tumors.[39]

A large meta-analysis reported in 1995[40] evaluated data on adjuvant chemotherapy from all trials that took place between 1965 and 1991. The use of adjuvant therapy based on alkylating agents (mainly cyclophosphamide and nitrosourea) proved detrimental. Treatment with cisplatin-based therapy resulted in a moderate (13 percent) reduction in the risk of death that did not reach statistical significance (P=0.08). Trials that used a combination of chemotherapy and radiation had similar results.[40] A subsequent study from the Eastern Cooperative

Oncology Group[19] similarly did not show a benefit of multimodal postoperative adjuvant therapy (cisplatin, etoposide, and radiotherapy). The results of the International Adjuvant Lung Cancer Trial are reported elsewhere in this issue of the *Journal*.[20] In this study of 1867 patients randomly assigned to either cisplatin-based adjuvant chemotherapy or no adjuvant therapy, adjuvant chemotherapy provided an absolute advantage of 5 percent for disease-free survival at five years and of 4 percent for overall survival.[20] Adjuvant chemotherapy, as currently administered, may provide a small benefit in certain patients, but this particular subgroup is very difficult to define with the use of current techniques. On the basis of the results of the International Adjuvant Lung Cancer Trial[20] and the aforementioned meta-analysis,[40] one should strongly consider the use of adjuvant platinum-based chemotherapy in patients with stage I, II, or IIIA non–small-cell lung cancer.

NEOADJUVANT THERAPY

Neoadjuvant therapy refers to the use of nonsurgical therapy as initial treatment (chemotherapy or radiotherapy) for cases in which surgery is a suboptimal initial approach. Ideally, neoadjuvant radiotherapy results in shrinkage of the tumor, allowing for a complete surgical resection. Neoadjuvant chemotherapy might result both in tumor shrinkage and early eradication of systemic micrometastases.

Nonresectable Tumors

Stage III tumors or those invading vital structures are often described as either nonresectable or marginally resectable. For many years, the mainstay of treatment for these tumors was radiotherapy (total dose, 60 Gy). The risk of local recurrence was diminished, but the rate of long-term survival was still poor (5 percent).[41] The results of several phase 2 studies provided preliminary support for the addition of chemotherapy to radiotherapy, and a landmark trial of this combined approach, reported in 1990 by Dillman et al.[22] (Table 3 and NAPS document 05612), demonstrated increased rates of three-year survival (23 percent as compared with 11 percent) and long-term survival.[23] Subsequent randomized trials (NAPS document 05612) reported a variable benefit for combined therapy — some findings were positive,[42,43] and others were not.[44-46] Two large meta-analyses (Table 3 and NAPS document 05612) have provided support for the benefits of combined chemotherapy and radiotherapy. A meta-analysis by Pritchard and Anthony showed that combined therapy for unresectable disease resulted in a significant decrease in the relative risk of death at both one and three years.[47] Similarly, Marino et al. reported a 24 percent reduction in the risk of death at one year and a 30 percent reduction at two years for combined cisplatin-based chemotherapy and radiotherapy.[48]

The optimal sequence of combined therapy has yet to be determined, although concurrent therapy appears to be superior to sequential (segregated) therapy.[24,49] Furuse et al. demonstrated that the use of concurrent chemotherapy and radiotherapy rather than sequential therapy improved survival.[49] Curran and colleagues obtained similar results in a large study: concurrent therapy resulted in a survival rate of 25 percent, as compared with 4 percent for sequential therapy (P=0.046).[24] The concurrent approach appears to increase the rate of adverse events, mainly esophagitis (21 percent, as compared with 4 percent, in the study by Curran et al.).[24] Given its apparent superiority, we believe that concurrent chemotherapy and radiotherapy should be used in all patients, if possible.

Additional approaches are being explored. For example, in multicenter,[50] single-center,[51] and phase 2 trials,[52] the combination of carboplatin, paclitaxel, and concurrent radiotherapy improved survival (median, 20.5 months), with acceptable rates of adverse effects. This apparently promising approach must be examined in phase 3 trials.

Resectable Tumors

In patients with non–small-cell lung cancer, resectable tumors can range from stage I to stage IIIA. Although surgery is the mainstay of therapy for such tumors, survival after surgery alone remains suboptimal. For tumors involving the chest wall, diaphragm, or pleura (T3) without visible mediastinal involvement, en bloc resection of the entire tumor should be performed. T3 tumors involving the superior sulcus of the lung (Pancoast's tumor) have a propensity to invade surrounding thoracic inlet structures and are associated with a high incidence of local recurrence, because tumor-free margins cannot be achieved. Several retrospective, single-institution studies have shown improved survival and decreased rates of local recurrence with combined neoadjuvant chemotherapy and radiotherapy.[53-55] Studies using combined neoadjuvant chemotherapy and radiotherapy followed by surgical resection[56,57] have demonstrated two-year survival rates in the range of 50 to 70 percent, which is

higher than the historical rate of approximately 20 percent among patients receiving postoperative radiotherapy alone.[53] Even patients with vertebral invasion may have a significant survival advantage with aggressive multimodality therapy.[58] Neoadjuvant chemoradiotherapy followed by complete surgical excision is thus the preferred approach to these tumors.

Tumors with ipsilateral mediastinal spread (N2) may be resectable but fall into the category of locally advanced tumors (stage IIIA), which are associated with poor survival[8] (Table 2). Because of its success in patients with nonresectable (N2) tumors, combined neoadjuvant chemotherapy and radiotherapy have been used in patients with resectable N2 tumors. In theory, neoadjuvant therapy facilitates early systemic therapy for micrometastases, as well as tumor shrinkage, which can lead to a more complete resection. In 1989, Skarin et al. reported the results of neoadjuvant cisplatin-based chemotherapy followed by surgery and radiotherapy in patients with resectable stage III disease.[59] Median survival was 32 months, and the 1-year survival rate was 75 percent, both of which were higher than previously reported rates.[59]

Two randomized, controlled trials evaluating the efficacy of combined neoadjuvant therapy for resectable non–small-cell lung cancer were reported in 1994 (Table 3 and NAPS document 05612).[25,27] Roth et al. studied 60 patients who were randomly assigned to receive either six cycles of preoperative cisplatin-based therapy or surgery alone.[25] Patients receiving neoadjuvant chemotherapy had a median survival of 64 months, as compared with 11 months for those undergoing surgery alone; the 3-year survival rates were 56 percent and 15 percent, respectively. Rosell et al. studied 60 patients who were randomly assigned to either surgery alone or induction cisplatin-based chemotherapy followed by surgery and radiotherapy.[27] Median survival was 26 months in the combined-treatment group, as compared with 8 months in the surgery-only group. Long-term follow-up in both these studies supported the findings that this combined-treatment approach was beneficial.[26,28] A third, smaller study had similar findings.[60]

The studies by both Roth et al.[25] and Rosell et al.[27] have been criticized for several reasons, including their small size (60 patients in each), imbalances between groups, and poorer-than-expected outcomes in the control groups. Depierre and colleagues performed a much larger study that explored the uses of neoadjuvant chemotherapy in 355 patients with early non–small-cell lung cancer who were randomly assigned to receive either preoperative chemotherapy with two cycles of chemotherapy followed by surgery or surgery alone.[29] Patients with chemotherapy-responsive disease underwent two additional cycles of postoperative chemotherapy, and radiotherapy was used for patients who had T3N2 disease or an incomplete resection of tumor. There was a nonsignificant trend toward a survival advantage for those who received combined therapy (P=0.15). Subgroup analysis showed that combined therapy did not benefit patients with N2 disease (relative risk of death, 1.04). Further analysis demonstrated that the risk of distant recurrence was lower in the chemotherapy group, but there was no significant difference in the risk of locoregional relapse, raising the possibility that chemotherapy eradicated microscopic metastases. Thus, the results of this larger study contrast with those of Roth et al.[25] and Rosell et al.[27]

The use of a neoadjuvant approach to all stages of non–small-cell lung cancer is currently being assessed. Pisters and colleagues reported the results of a phase 2 trial, the Bimodality Lung Oncology Team (BLOT) study, in which neoadjuvant carboplatin and paclitaxel followed by surgery were used in patients with early disease and appeared to be highly successful (a survival rate of 85 percent at one year).[61] A second phase 2 study, which used a combination of gemcitabine and cisplatin, had a similar outcome.[62] In our opinion, otherwise healthy patients with locally advanced (N2) disease should receive neoadjuvant chemotherapy, although this approach is controversial. For patients with earlier-stage disease, data concerning neoadjuvant therapy are too premature to recommend such treatment outside of a clinical trial. Future studies of operable tumors will probably address the potential benefit of additional postoperative (adjuvant) chemotherapy in patients whose tumors have responded to neoadjuvant chemotherapy.

Advanced Disease

Currently, virtually no patient with disease as advanced as stage IIIB or IV will be cured. Although chemotherapy is the backbone of treatment for metastatic disease, response rates are low, and survival times poor. In the past, many patients with advanced non–small-cell lung cancer received no therapy, since the toxicity of therapy was thought to outweigh the benefits. It is now clear, however, that treatment

can be beneficial. Several meta-analyses have reported moderate gains in survival when chemotherapy is used, as compared with the best supportive care. Increases in median survival appear to be in the range of two to four months, and increases in the one-year survival rate appear to range from 10 to 20 percent.[40,48,63] Studies have also suggested important gains in other therapeutic end points such as the time to disease progression and the quality of life.[64-66] The benefits of therapy are usually restricted to otherwise healthy patients with lung cancer — that is, those who maintain a good functional status.

Although many agents are active against non–small-cell lung cancer, single-agent platinum therapy remained the backbone of treatment until the 1990s. Phase 3 studies in the 1980s did not show that adding a second or third agent was beneficial.[67,68] With the development of additional cytotoxic drugs, such as gemcitabine, vinorelbine, paclitaxel, and docetaxel, combination therapy was reevaluated. Several randomized trials evaluating these newer agents in combination with cisplatin, as compared with cisplatin alone, showed response rates favoring combination therapy, with minimal additional toxicity (Table 3 and NAPS document 05612).[69-75]

In 2000, Bonomi et al. were the first to report a better response rate with the use of a modern combination — paclitaxel and cisplatin — than with an older regimen, etoposide and cisplatin.[76] In the 1990s, numerous two-drug regimens were in common use, although there were few data from direct comparisons of their efficacies. In 2002, Schiller et al. reported on a comparison of four commonly used two-drug regimens for advanced lung cancer[30] (Table 3 and NAPS document 05612). All four treatment groups had virtually identical rates of survival and adverse effects, and all response rates were higher than historical response rates with the use of a single agent. Other trials have had similar results.[77-79] Unless specific reasons dictate otherwise, patients with advanced lung cancer should, in our opinion, receive a two-drug regimen of chemotherapy.[79] Although some practitioners withhold chemotherapy solely on the basis of a patient's age (with the cutoff often arbitrarily set as 70 years), several trials have demonstrated that, as compared with younger patients, the elderly have similar rates of tolerance and receive similar benefits from chemotherapy and should therefore be treated similarly.[80,81] Several trials have examined three-drug combinations. Two have shown that this approach increases toxic effects without improving survival,[82,83] and such regimens should therefore not be used.

The optimal duration of therapy has long been debated. A randomized trial compared three cycles of cisplatin-based therapy with six cycles in patients with advanced disease and found only increased toxicity with prolonged administration of chemotherapy,[84] as have other trials.[85,86] Patients with advanced disease should therefore initially be limited to three or four cycles of two-agent chemotherapy.

Since in virtually all patients with advanced disease, initial therapy will ultimately fail, second-line therapy will often be necessary.[87] Most patients will have received first-line platinum-based therapy, and because of presumed tumor resistance and drug toxicity, second-line platinum therapy is not usually used. Several randomized studies suggest that docetaxel may offer some survival benefit in such a second-line setting, as compared with both the best supportive care[88] and other agents.[89] Other agents (e.g., gemcitabine) have activity in this setting as well and may be considered for otherwise healthy patients who can maintain good, independent function.

Patients with a single, solitary metastasis may benefit from resection of the metastatic lesion. The five-year survival rate among patients who undergo resection of a solitary brain metastasis[90] followed by whole-brain radiotherapy[91] can reach 10 to 20 percent; the use of subsequent chemotherapy should be considered but has not been well studied. Resection of a solitary adrenal metastasis can also increase long-term survival, although the data are less definitive.[92,93]

SMALL-CELL LUNG CANCER

In contrast to non–small-cell lung cancer, small-cell lung cancer is characterized by its propensity for early metastases and a rapid doubling time.[94] Rather than TNM staging, a more practical scheme divides small-cell lung cancer into limited and extensive disease. Limited disease is defined as a tumor that can be encompassed within a single, tolerable radiation port; all other tumors are characterized as extensive. Because of the tumor's propensity for early metastasis, all patients should undergo a staging workup consisting of a history taking and a physical examination, a basic laboratory evaluation, chest CT, bone scanning, and imaging of the

brain. With the use of this evaluation, only one third of patients who present with small-cell lung cancer will be classified as having limited disease. Bone marrow evaluation, although used in the past, adds little information and is not required.[95]

LIMITED DISEASE

Because small-cell lung cancer has a propensity for early spread yet is responsive to chemotherapy, surgical resection is usually not considered part of the treatment algorithm. Patients with a solitary lung nodule and no evidence of nodal involvement on mediastinal staging should still undergo mediastinal-node dissection at the time of surgery[96] and receive postoperative chemotherapy, with the addition of radiation if the mediastinum is involved on microscopical examination of lymph nodes.[97] In actuality, these patients are usually first identified at the time of surgery for an undiagnosed lung nodule, because pathological examination reveals small-cell lung cancer. For patients who receive a diagnosis on the basis of a biopsy, management should consist of combined chemotherapy and radiotherapy without surgery.

Studies in the 1970s and 1980s demonstrated that combination chemotherapy was clearly superior to single-agent therapy.[98,99] Several studies compared two commonly used regimens, etoposide and cisplatin with vincristine, doxorubicin, and cyclophosphamide. The outcomes among patients treated with etoposide and cisplatin were superior in one study[100] but not in the other[101] (Table 4 and NAPS document 05612). Two meta-analyses suggested a moderate benefit of combination chemotherapy and radiotherapy as compared with chemotherapy alone for patients with limited disease (on the order of a 15 percent decrease in the risk of death).[105,106]

Concurrent chemotherapy and radiotherapy appear to provide better five-year survival rates than sequential therapy.[103] Delivering radiotherapy earlier during chemotherapy is better than delivering it later.[107] One randomized trial demonstrated improved five-year survival with minimal additional toxicity when hyperfractionated radiotherapy (i.e., given twice instead of once daily) was used, with the same total dose of 45 Gy.[104] However, this approach has been slow to catch on as standard therapy, most likely because of the increased time involved on the part of both patients and physicians.

Lad et al. did not find that the resection of a residual mass after concurrent chemotherapy and radiotherapy was beneficial in patients with limited disease.[108] When combined therapy is used in patients with limited disease, the rates of thoracic recurrences are decreased, but the rates of distant recurrences, particularly in the brain, are increased. Some studies report up to a 50 percent incidence of brain metastasis two years after diagnosis.[109,110] Prophylactic cranial irradiation has long been

Table 4. Important Randomized Trials of Small-Cell Lung Cancer.

Group	Regimens	Conclusions or Results
Extensive disease		
Fukuoka et al.[100]	Etoposide and cisplatin Vincristine, doxorubicin, and cyclophosphamide Etoposide and cisplatin alternating with vincristine, doxorubicin, and cyclophosphamide	No advantage of alternating regimens; patients treated with etoposide and cisplatin more likely to have a response to therapy
Roth et al.[101]	Etoposide and cisplatin Vincristine, doxorubicin, and cyclophosphamide Etoposide and cisplatin alternating with vincristine, doxorubicin, and cyclophosphamide	No advantage of alternating regimens; no difference in survival among groups
Noda et al.[102]	Etoposide and cisplatin Irinotecan and cisplatin	Median survival better with cisplatin and irinotecan (12.8 mo vs. 9.4 mo) and 2-yr survival rate higher (19.5% vs. 5.2%), incidence of diarrhea higher, and incidence of neutropenia lower
Limited disease		
Takada et al.[103]	Etoposide and cisplatin plus concurrent radiotherapy Etoposide and cisplatin plus sequential radiotherapy	Increased 2- and 5-yr survival rates and higher incidence of myelosuppression with concurrent therapy
Turrisi et al.[104]	Chemotherapy plus once-daily radiotherapy Chemotherapy plus twice-daily radiotherapy	Increased 5-yr survival rate with twice-daily radiotherapy (26% vs. 16%)

thought to decrease the incidence of brain-only metastasis. A meta-analysis showed a 5.4 percent increase in the three-year rate of overall survival among patients with small-cell lung cancer in complete remission who underwent prophylactic cranial irradiation, as well as a large reduction in the incidence of brain metastasis (relative risk as compared with those who did not undergo prophylactic cranial irradiation, 0.46).[111] Once brain metastases appear, patients do not have a good response to treatment. Limited studies suggest that prophylactic cranial irradiation does not result in clinically significant neuropsychological sequelae, the most likely long-term effect,[109] particularly when patients are neurologically intact before radiotherapy and the doses are limited to 24 to 36 Gy. However, over time, the radiotherapy could contribute to cognitive abnormalities. Despite this possibility, most oncologists recommend prophylactic cranial irradiation to patients with small-cell lung cancer in complete remission,[112] mainly because of its potential to increase the quality of life, as well as its small survival benefit.

EXTENSIVE DISEASE

For extensive small-cell lung cancer, the treatment of choice has long been chemotherapy alone consisting of a combination of cisplatin and etoposide. Carboplatin is equivalent to cisplatin in this setting.[113] A recent randomized trial compared the use of cisplatin with either irinotecan or etoposide in patients with extensive disease.[102] Patients treated with irinotecan and cisplatin had an increase in both median survival (12.8 months vs. 9.4 months) and two-year survival rate (19.5 percent vs. 5.2 percent) and less severe hematologic toxic effects but a higher incidence of diarrhea.[102] The addition of paclitaxel to cisplatin plus etoposide for extensive small-cell lung cancer increased the toxic effects without adding a significant survival advantage.[114,115] Confirmatory trials of irinotecan are ongoing, but either

Table 5. General Approach to the Treatment of Lung Cancer According to Stage.*

Stage	Primary Treatment	Adjuvant Therapy	Outcome
Non–small-cell lung cancer			
I	Surgical resection	Chemotherapy†	5-Yr survival rate, >60–70%
II	Surgical resection	Chemotherapy, with or without radiotherapy†	5-Yr survival rate, >40–50%
IIIA (resectable)	Preoperative chemotherapy followed by surgical resection (preferable) or surgical resection	Radiotherapy with chemotherapy (if not given previously) or without chemotherapy	5-Yr survival rate, 15–30%
IIIA (unresectable) or IIIB (involvement of contralateral or supraclavicular lymph nodes)	Chemotherapy plus concurrent radiotherapy (preferable) or chemotherapy followed by radiotherapy	None	5-Yr survival rate, 10–20%
IIIB (pleural effusion) or IV	Chemotherapy with 2 agents for 3 or 4 cycles (preferable)	None	Median survival, 8–10 mo 1-Yr survival rate, 30–35% 2-Yr survival rate, 10–15%
	Surgical resection of solitary brain metastasis and surgical resection of primary (T1) lesion		5-Yr survival rate , 10–15%
Small-cell lung cancer			
Limited disease‡	Chemotherapy plus concurrent radiotherapy	None	5-Yr survival rate, 15–25%
Extensive disease‡	Chemotherapy	None	5-Yr survival rate, <5%

* All chemotherapy regimens include either cisplatin or carboplatin. A complete list of clinical trials is available at http://www.cancer.gov. Up-to-date approaches to the treatment of non–small-cell and small-cell lung cancer are available from the National Comprehensive Cancer Network at http://www.nccn.org.

† This regimen is based on data from the International Adjuvant Lung Cancer Trial, which demonstrated a small but significant survival advantage with cisplatin-based adjuvant therapy.[20] Physicians should strongly consider such therapy for appropriate patients.

‡ Prophylactic cranial irradiation is recommended for all patients with a complete response to initial therapy.

etoposide or irinotecan in conjunction with cisplatin is appropriate as first-line therapy. Other agents (e.g., topotecan) are active against small-cell lung cancer, are useful for relapsed disease, and are being evaluated for first-line use.[116]

SUMMARY AND FUTURE DIRECTIONS

Table 5 summarizes the management approaches to lung cancer. Future directions for treatment are heavily weighted toward targeted therapies — namely, those aimed at molecular abnormalities involved in the pathogenesis of lung cancer[117] — rather than traditional cytotoxic agents.[118] A recent review describes many of these therapies, some of which have had moderate activity in a phase 2 setting.[119] Cellular targets abound, with the epithelial growth factor receptor the best studied. The first compound against this receptor, gefitinib, has recently been approved for use on the basis of moderate tumor responses, as well as improvements in the quality of life.[120] Unfortunately, no additional benefit was seen when gefitinib was combined with standard therapy.[31] Other compounds, such as those that target protein kinase C, vascular endothelial growth factor, cyclooxygenase-2, and farnesyl transferase, are being tested. Many of the available data are suboptimal; meta-analyses are used frequently instead of adequately powered, randomized, controlled trials. Since little further progress is expected with the use of traditional cytotoxic agents,[121] new agents and approaches must be evaluated if we are to advance therapy for lung cancer.

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