

LUNG CANCER

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Learning Objectives

1. Construct an appropriate chemotherapy treatment plan for a patient with non–small cell lung cancer (NSCLC) given the stage and treatment history.
2. Devise an appropriate treatment plan for a given patient with NSCLC who has progressed after initial treatment.
3. Design a treatment plan for a patient with small cell lung cancer (SCLC) given the stage and treatment history.
4. Devise an appropriate treatment plan for a given patient with SCLC who has progressed after initial treatment.
5. Assess the impact of age, performance status, and comorbidities on patient prognosis and treatment outcomes.
6. Educate patients on current options for the prevention, early detection, and treatment of lung cancer, including potential complications associated with chemotherapy and targeted therapies.

Introduction

The estimated number of newly diagnosed cases of lung cancer in the United States in 2008 is 215,020 (114,690 in men and 100,330 in women), accounting for about 15% of cancer diagnoses. In men, the incidence rate is declining, from 102 cases per 100,000 in 1984 to 73.6 in 2004. In women, the rate is reaching a plateau of about 40 cases per 100,000. The 5-year survival rate for all stages of lung cancer combined is 15%. Lung cancer is the leading cause of cancer-related deaths in both men and women, accounting for around 29% of all cancer deaths. In 2008, an estimated 161,840 deaths were expected to occur in the United States from lung cancer.

Prevention

More than 85% of lung cancer cases are caused by voluntary and secondhand cigarette smoking. Smoking prevention and cessation are essential strategies to help reduce the incidence of lung cancer. In those who smoke,

smoking cessation programs should combine pharmacologic intervention with behavioral counseling. Former smokers continue to have an elevated risk of lung cancer, even years after quitting. For those who have quit smoking for 10 years, the risk is about 30% to 50% less than for current smokers.

Chemoprevention is defined as the use of specific pharmacologic agents to reverse, suppress, or prevent carcinogenesis. Chemoprevention for lung cancer among current and former smokers was investigated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, the Carotene and Retinol Efficacy Trial, and the Physicians' Health Study. Supplementation with α -tocopherol, retinyl palmitate, or aspirin had no effect on lung cancer incidence. The administration of beta-carotene, however, was associated with a higher incidence of lung cancer and increased mortality. Currently, no pharmacologic agents are recommended for lung cancer chemoprevention. Patients with a high risk of developing lung cancer or with a history of lung cancer are strongly encouraged to participate in chemoprevention trials. Chemoprevention agents currently being investigated for lung cancer include celecoxib, sulindac, iloprost, isotretinoin, oltipraz, phenethyl isothiocyanate, zileuton, and budesonide. Dietary supplements or complimentary medicines under investigation for this purpose include selenium, green tea extract, broccoli sprout extract, and inositol.

Early Detection

A screening technique that can detect lung cancer at an early stage, before it has spread, may be useful in decreasing lung cancer morbidity and mortality. Early studies using chest radiography or sputum cytology showed that screening did detect more early-stage lung cancers; however, screening had no impact on the prevalence of advanced cancer diagnoses or deaths from lung cancer. More recently, spiral computed tomography (CT) scans show promise in detecting lung cancers at an earlier stage in high-risk patients. In the International Early Lung Cancer Action Program, annual spiral CT scan screening detected lung cancer at an early stage and yielded a 92% survival rate at 10 years for patients undergoing surgical resection within 1 month of diagnosis. The impact of such a tool on lung

Abbreviations in This Chapter

AUC	Area under the curve
CAV	Cyclophosphamide plus doxorubicin plus vincristine
CT	Computed tomography
EGFR	Epidermal growth factor receptor
EP	Etoposide plus cisplatin
IP	Irinotecan plus cisplatin
LDH	Lactic dehydrogenase
NCCN	National Comprehensive Cancer Network
NSCLC	Non–small cell lung cancer
PCI	Prophylactic cranial irradiation
SCLC	Small cell lung cancer

cancer mortality should be further assessed before CT scan screening can be adopted into clinical practice.

The National Lung Screening Trial is an ongoing randomized, controlled study that compares spiral CT scans with chest radiographs for detecting lung cancer in high-risk individuals. Although this study is currently closed to enrollment, data collection is expected to continue through 2009. At present, the National Comprehensive Cancer Network (NCCN) does not recommend the routine use of spiral CT scans as a screening tool for the early detection of lung cancer.

Clinical Presentation and Diagnosis

Common signs and symptoms associated with lung cancer include cough, dyspnea, hemoptysis, wheezing, stridor, decreased appetite, weight loss, and chest pain. Extrapulmonary symptoms often encountered with advanced-stage disease include bone pain (with or without pathologic fractures), neurologic deficits, spinal cord compression, and hepatic dysfunction. In some cases, an associated paraneoplastic syndrome may occur at presentation, leading to further diagnostic work-up. Common paraneoplastic syndromes include cachexia, characterized by extreme muscle wasting and malnutrition; hyponatremia of malignancy; hypercalcemia, often presenting with mental confusion and nausea and vomiting; and Cushing syndrome. Other less-common paraneoplastic syndromes include Eaton-Lambert myasthenic syndrome, characterized by upper extremity weakness and diminished reflexes, and pulmonary hypertrophic osteoarthropathy, a clinical syndrome associated with clubbing of the fingers and toes, enlargement of the extremities, and painful swollen joints.

Initial diagnostic evaluation for a patient with suspected signs and symptoms of lung cancer includes a thorough history and physical examination, chest radiography, CT scan of the chest, and positron emission tomography. If clinical and radiologic evidence of a tumor is present, pathologic evaluation is performed to classify the lung cancer. Pathologic evaluation may include examination of bronchial brushings or washings and biopsy. Histopathologic type is determined for tumor classification, and immunohistochemical staining

is performed to differentiate between different subtypes of lung cancer and the presence or absence of epidermal growth factor receptor (EGFR) expression. Further molecular studies may be carried out to determine whether EGFR or KRAS mutations are present. KRAS is an oncogene associated with a poor prognosis in a variety of cancers, including lung. The extent of lymph node involvement can be determined by mediastinoscopy, bronchoscopy, and endobronchial ultrasound-guided transbronchial needle aspiration. Other diagnostic tests may include magnetic resonance imaging, bone scan, and bone marrow aspiration and biopsy.

Classification

The World Health Organization classifies lung cancer as two major histologic types: non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). About 80% to 85% of lung cancers are NSCLC, and 15% are SCLC. There are three major histologic subtypes included within NSCLC: adenocarcinoma, squamous cell (epidermoid) carcinoma, and large cell carcinoma. Treatment options and prognosis for these three subtypes are similar. Small cell lung cancer is more commonly associated with paraneoplastic syndromes at diagnosis, a more rapid rate of tumor growth, and more advanced disease at initial presentation.

Non–Small Cell Lung Cancer

Staging

Staging for NSCLC is based on clinical (history and physical examination, CT scans, positron emission tomography scans, and other laboratory tests) and pathologic evaluation. The tumor, node, and metastasis system established by the American Joint Committee on Cancer (Table 1-1) is used for staging NSCLC. Staging is used to select treatment options and predict survival. The 5-year survival rates for stages I, II, III, and IV NSCLC are 47%, 26%, 8.4%, and 1.6%, respectively. Common metastatic sites associated with stage IV NSCLC include lymph nodes (e.g., bronchopulmonary, mediastinal, supraclavicular) and distant sites (e.g., bone, liver, brain, bone marrow, adrenal glands).

Prognostic Factors

A variety of clinical, anatomic, and biologic factors have been associated with effects on patient prognosis (disease recurrence and survival). Favorable prognostic factors include early stage at diagnosis, good performance status, no significant weight loss (i.e., not more than 5% of body weight), and female sex. Performance status is based on the Eastern Cooperative Oncology Group performance scale (Table 1-2). This scale, commonly used in the NCCN guidelines, is a tool used to measure a patient's general performance ability. In general, patients with a good performance status (0 or 1) will most likely be able to tolerate aggressive treatment and achieve more optimal treatment outcomes. Those with an intermediate performance status of 2 are generally at a higher risk of treatment-related toxicities, and patients with a poor performance status (3 or 4) should receive best supportive care only. Factors associated with a poor prognosis include

Table 1-1. Tumor, Node and Metastasis Staging System for Lung Cancer

Primary tumor (T)			
TX	Primary tumor cannot be assessed, or tumor is proved by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ		
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus ^a (i.e., not in the main bronchus)		
T2	Tumor with any of the following features of size or extent: more than 3 cm in greatest dimension; involves main bronchus, 2 cm or more distal to the carina; invades the visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung		
T3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung		
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with malignant pleural effusion ^b		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor		
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)		
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene, or supraclavicular lymph node(s)		
Distant metastasis (M)			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis present		
Stage grouping			
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

^aThe uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

^bMost pleural effusions associated with lung cancer are because of a tumor. However, in a few patients, multiple cytopathologic examinations of pleural fluid are negative for a tumor. In these cases, fluid is nonbloody and is not an exudate. Such patients may be further evaluated by videothoracoscopy (VATS) and direct pleural biopsies. When these elements and clinical judgment dictate that the effusion is unrelated to the tumor, the effusion should be excluded as a staging element, and the patient should be staged T1, T2, or T3.

Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Ill. Original source for this material is the AJCC Cancer Staging Manual, 6th ed. (2002) published by Springer Science and Business Media LLC, www.springerlink.com.

Table 1-2. Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active; able to carry on all predisease performances without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light or sedentary work (e.g., light housework, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; incapable of self-care; totally confined to bed or chair
5	Dead

Reproduced from Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group (Robert Comis, M.D., Group Chair). *Am J Clin Oncol* 1982;5:649–55. Available at www.ecog.org/general/perf_stat.html. Accessed February 13, 2009.

advanced disease at diagnosis, involvement of multiple distant metastatic sites, presence of regional lymph node metastases, mutations of the tumor suppressor gene (p53), and activation of KRAS oncogenes. Histologic subtype and age have little or no prognostic significance in NSCLC.

Treatment

Surgery, radiation therapy, and chemotherapy are common modalities used to treat NSCLC. There are a variety of surgical options available; ideally, these should be discussed with and performed by a thoracic surgical oncologist. Surgery provides the best chance of cure for patients with stage I and II disease. Some, but not all, stage III tumors are resectable; however, there is no role for surgery in stage IV disease unless it is for palliation of symptoms. Radiation therapy is often used as an alternative to surgery for patients with stage I or II disease who have inoperable disease. Indications also include the combination of radiation therapy with chemotherapy as neoadjuvant or adjuvant therapy for stage II and III disease or as palliation of symptoms for stage IV disease. Depending on the stage, chemotherapy may be used alone or in combination with radiation therapy. Combined treatment may be administered either sequentially (i.e., chemotherapy followed by radiation therapy) or concurrently (i.e., chemotherapy given at the same time as radiation therapy, often referred to as concurrent chemoradiation).

The primary treatment goal for patients with early-stage disease (i.e., stage I, stage II, or resectable stage III) is cure. It is important in early-stage disease that the tumor is fully resected or irradiated to provide the best chance of cure. For those with more advanced disease (i.e., unresectable stages III and IV), prolongation of survival and palliation of symptoms is the optimal treatment outcome.

Stages I, IIA, and IIB (T2, N1)

For the optimal chance for cure, patients with stage I or II NSCLC should undergo surgical resection. After surgery, observation or adjuvant chemotherapy is indicated depending on the absence or presence of residual tumor. If the surgical margins are positive, further treatment such as concurrent chemoradiation may be indicated versus observation alone. Several recently published studies (e.g., the International Adjuvant Lung Cancer Trial, the National Cancer Institute of Canada Clinical Trials Group trial, and the Adjuvant Navelbine International Trialist Association) have all shown a statistically significant survival benefit with cisplatin-containing adjuvant chemotherapy regimens in patients with completely resected stage II NSCLC. Cisplatin combined with vinorelbine is considered one of the preferred regimens based on these studies.

Other cisplatin-containing regimens with significant activity in early-stage disease include cisplatin combined with etoposide or vinblastine. The dose-limiting toxicity associated with vinorelbine and etoposide is myelosuppression; both of these agents have a lower frequency of peripheral neuropathy compared with vinblastine. The combination of paclitaxel and carboplatin in the recently updated Cancer and Leukemia Group B 9633 trial did not show an overall survival advantage compared with observation alone at 5 years for patients with stage IB NSCLC. However, based on subset analysis, this regimen may be considered for patients with larger tumors. The regimen may also be appropriate for patients unable to tolerate cisplatin because of severe nausea and vomiting, nephrotoxicity, or neurotoxicity.

Stages IIB (T3, N0), IIIA, and IIIB

Treatment of stage IIB (T3, N0) NSCLC depends on tumor location. It is suggested that patients with resectable tumors located in the superior sulcus receive preoperative (neoadjuvant) concurrent chemoradiation, followed by surgical resection and adjuvant chemotherapy. Patients with tumors located in the chest wall, proximal airway, or mediastinum should undergo surgical resection as initial treatment. Adjuvant treatment options include chemotherapy, if surgical margins are negative; or, if surgical margins are positive, resection plus chemotherapy or concurrent chemoradiation followed by further consolidation chemotherapy. For any tumors previously discussed that are unresectable, treatment consists of concurrent chemoradiation.

Patients with suspected mediastinal lymph node involvement (stage IIIA or B, N2 disease) should first undergo further evaluation (magnetic resonance imaging and positron emission tomography scan) to rule out metastatic disease. For patients with metastatic disease, treatment options are followed for stage IV disease. If metastatic disease is ruled out and pathologic evaluation of the mediastinal lymph nodes is negative or contains minimal, nonbulky disease, treatment options are as above for stage IIA or IIB disease. For patients with bulky N2 disease (stage IIIA), surgical resection is usually not an option. For these IIIA patients, concurrent chemoradiation therapy appears to be superior to sequential therapy.

Concurrent chemoradiation regimens used for stage IIB (T3, N0) and IIIA NSCLC include the following two-drug regimens: etoposide plus cisplatin (EP), cisplatin

plus vinblastine, and paclitaxel plus carboplatin. Cisplatin plus vinblastine and paclitaxel plus carboplatin are also used for sequential therapy. Cisplatin-based regimens are preferred because carboplatin-based regimens have not been adequately assessed for equivalent outcomes.

Most stage IIIB tumors are unresectable. Concurrent chemoradiation therapy (regimens as in stage IIB) is recommended with or without consolidation chemotherapy. There is no consensus regarding the benefit of consolidation chemotherapy. Initial data evaluating concurrent chemoradiation with EP, followed by docetaxel, showed a 5-year survival rate of 29%; however, a more recent Phase III study did not show an improved survival benefit for consolidation therapy with docetaxel. Higher rates of hospitalizations and premature deaths were reported in those randomized to the docetaxel study arm. Choice of therapy mainly depends on patient tolerability and concomitant medical conditions.

Stage IV

Chemotherapy is the primary treatment modality for patients with advanced NSCLC and good performance status. Two-drug chemotherapy regimens provide responses superior to single-agent therapy. The expected overall response rates range from 25% to 35%. Time to disease progression is about 4–6 months, and median survival is 8–10 months. Rates of 1-year, 2-year, and 5-year survival are around 30% to 40%, 10% to 15%, and 1%, respectively. Platinum-based (i.e., cisplatin or carboplatin) chemotherapy regimens are preferred and may be combined with any one of the following: paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, or vinblastine. According to a recent meta-analysis, cisplatin-containing regimens (when combined with the newer agents such as paclitaxel, docetaxel, or gemcitabine) showed an 11% survival advantage compared with carboplatin combined with the same agent. In the palliative setting of advanced disease, however, it is controversial whether this small survival advantage justifies the routine use of cisplatin-based regimens. Carboplatin is easier to administer and has a more favorable toxicity profile. For those unable to tolerate a platinum-based regimen, reasonable alternatives include gemcitabine combined with paclitaxel or docetaxel. Clinical trials have not shown any one chemotherapy regimen to be superior; therefore, treatment choices should be individualized considering drug toxicities and patient comorbidities. Convenience and cost are other considerations for choice of regimen. Four to six cycles of chemotherapy are administered as long as the patient remains responsive to treatment or has stable disease. Adding a third chemotherapy agent does not confer additional improvement in overall outcome.

Bevacizumab is a monoclonal antibody targeted against vascular endothelial growth factor. When added to chemotherapy (carboplatin and paclitaxel), bevacizumab has shown a significant benefit over chemotherapy alone, demonstrating a 2-month median gain in both progression-free survival and overall survival in a Phase III trial of previously untreated stage IV patients with NSCLC. In a preceding Phase II study using the above combination, life-threatening pulmonary hemorrhage occurred in 6 of 66

patients who received the bevacizumab combination, 4 of which were fatal. This serious toxicity was more common among patients with squamous cell carcinoma; therefore, this histologic subtype was subsequently excluded from future clinical trials and U.S. Food and Drug Administration (FDA)-approved labeling. The NCCN recommends the combination of bevacizumab, carboplatin, and paclitaxel as a first-line treatment option for patients with advanced NSCLC with nonsquamous histology. For those who are not candidates for bevacizumab, a platinum-based chemotherapy regimen is recommended as first-line treatment as discussed previously.

When considering adding bevacizumab to chemotherapy, the benefits (additional 2-month median survival benefit), adverse effects and related monitoring, and additional cost of therapy should be assessed and individualized. Careful evaluation of bleeding risk should be performed before therapy with any bevacizumab-containing regimen. Patients who should not receive bevacizumab include those with squamous histology, history of hemoptysis, central nervous system metastases, concurrent anticoagulation, or concurrent chemotherapy with carboplatin plus gemcitabine (or any other chemotherapy regimen with a high risk of thrombocytopenia). The dose of bevacizumab for NSCLC is 15 mg/kg once every 3 weeks given as a short intravenous infusion. The first infusion is administered over 90 minutes, and subsequent infusions may be administered over 60 minutes and eventually over 30 minutes, depending on patient tolerability.

Gefitinib and erlotinib, small-molecule inhibitors of the EGFR tyrosine kinase, show significant anti-tumor activity as single agents in patients with relapsed NSCLC. It is currently not recommended, however, to combine a tyrosine kinase inhibitor with chemotherapy for treatment of relapsed disease. In Phase III studies, the addition of either of these tyrosine kinase inhibitors to chemotherapy (carboplatin plus paclitaxel) did not improve outcomes over chemotherapy alone in previously untreated patients with advanced disease.

It was recently reported that most patients who exhibit objective clinical responses to gefitinib or erlotinib have associated EGFR mutations. The NCCN guidelines suggest that erlotinib, with or without chemotherapy, may be considered for previously untreated patients with advanced NSCLC and known EGFR mutations. Of interest, patients whose tumors express EGFR mutations had never smoked or had remote smoking histories. The effects of EGFR and KRAS mutations were clinically correlated retrospectively in a previous study comparing first-line chemotherapy with carboplatin and paclitaxel with or without erlotinib. All patients with EGFR-mutant tumors showed improved objective response rates and time to disease progression. Patients with EGFR mutations who were treated with chemotherapy plus erlotinib (vs. chemotherapy alone) showed improved response rates and a trend toward improved time to disease progression, but there was no impact on survival. Patients treated with chemotherapy plus erlotinib who exhibited KRAS mutations showed less favorable clinical outcomes compared with chemotherapy alone. Preliminary data suggest that mutations associated with EGFR have a

positive impact on clinical outcomes in patients who receive chemotherapy plus erlotinib, whereas KRAS mutations are associated with a poor prognosis. Currently, data on EGFR and KRAS mutations are based on retrospective reviews and small population trials. Larger prospective trials are needed to further determine the impact of EGFR mutations, smoking history, and clinical outcomes in association with tyrosine kinase inhibitors.

Patients with a performance status of 2 may be candidates for chemotherapy; however, a less aggressive treatment regimen using single-agent therapy may be preferred to decrease the risk of developing significant toxicities. Any one of the chemotherapy agents with activity in NSCLC may be an acceptable choice. Platinum-based combination chemotherapy may be offered based on a careful evaluation of patient comorbidities and expected tolerability. For patients with a poor performance status (3 or 4), best supportive care is recommended. A limited number of patients may present with a solitary metastatic nodule in the brain, adrenal gland, or contralateral/ipsilateral lung. In these patients, surgical resection of the primary site and solitary nodule may be indicated, followed by chemotherapy.

Recurrent Disease

Established second-line treatment options for patients who experience disease progression during or after first-line therapy include docetaxel, pemetrexed, and erlotinib. In a Phase III study, improved survival outcomes were associated with erlotinib therapy. When docetaxel and pemetrexed were compared in a Phase III study for second-line treatment of advanced NSCLC, no significant differences were detected in clinical outcomes; however, docetaxel was associated with significantly more adverse events (e.g., neutropenia, febrile neutropenia, infection associated with neutropenia, hospitalizations, alopecia). Although the dose-limiting toxicity associated with pemetrexed is myelosuppression, the severity and frequency of anemia, thrombocytopenia, neutropenia, and febrile neutropenia (with or without associated infection) are reduced when supplemental folic acid and vitamin B₁₂ are given. The folic acid dosage most commonly given is 400 mcg/day orally, starting at least 7 days before the first dose of pemetrexed and continuing during treatment and for 21 days after the last dose of pemetrexed. Vitamin B₁₂ supplementation (1000 mcg by intramuscular injection) should be initiated 1 week before the first dose of pemetrexed and every three cycles thereafter. Dexamethasone (4 mg orally twice daily) for 3 days should also be initiated 1 day before the initiation of pemetrexed to reduce the risk of cutaneous reactions. Docetaxel also requires premedication with dexamethasone (8 mg orally twice daily) to reduce the incidence and severity of fluid retention and hypersensitivity reactions. Initiation of dexamethasone should start 1 day before docetaxel and continue for 3 days. Docetaxel and pemetrexed are administered by intravenous infusion (75 mg/m² over 1 hour and 500 mg/m² over 10 minutes, respectively) every 3 weeks.

Results of a Phase III study comparing erlotinib with best supportive care after failure of first- or second-line chemotherapy showed a 2-month survival advantage for

erlotinib. Common toxicities include dry skin, acneiform rash, and diarrhea.

In general, expected response rates to second-line chemotherapy are below 10%. The median response duration for docetaxel, pemetrexed, and erlotinib is 5.3 months, 4.6 months, and 7.9 months, respectively. Currently, there is no consensus regarding the optimal second-line treatment of patients with NSCLC. Choice of therapy is determined by patient performance status, expected toxicity profile, and cost. Treatment options for patients who progress after second-line therapy include erlotinib (if not previously prescribed), best supportive care, or enrollment in a clinical trial.

Small Cell Lung Cancer

Staging

The staging system used for SCLC is based on the Veterans Administration Lung Group two-stage classification. Limited-stage disease includes disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field. About 33% of patients with SCLC receive a diagnosis at this stage. Extensive-stage disease includes disease beyond the ipsilateral hemithorax, which may include malignant pleural or pericardial effusion or hematogenous metastases. Most patients with a diagnosis of SCLC present with metastases involving the contralateral lung, liver, adrenal glands, brain, bone, or bone marrow.

Prognostic Factors

Adverse prognostic factors associated with SCLC include a poor performance status (3 or 4), extensive-stage disease, weight loss, and bulky disease. Favorable prognostic factors for patients with limited-stage disease include a good performance status (0–2), female sex, age younger than 70 years, and normal lactic dehydrogenase (LDH). For those with extensive-stage disease, normal LDH and a single metastatic site are favorable prognostic factors.

Treatment

Treatment options for SCLC include surgery, radiation therapy, chemotherapy, and prophylactic cranial irradiation (PCI). Surgery has a limited role in SCLC. Small cell lung cancer is highly sensitive to radiation therapy and chemotherapy. The primary treatment goal for those with limited-stage disease (clinical stage I) is cure; the goal for those with clinical stage II disease and extensive-stage SCLC is prolongation of survival.

Limited Stage

Less than 5% of patients with SCLC have tumors of 3 cm or less with no lymph node involvement or metastases. Surgical resection followed by adjuvant chemotherapy may be offered to these patients. If nodal metastases are present, postoperative radiation therapy combined with chemotherapy is indicated. Patients with clinical stage II or higher cancer do not benefit from surgery.

Most patients with limited-stage SCLC and a good performance status benefit from concurrent chemoradiation. Adding thoracic radiation therapy to chemotherapy reduces

the local failure rate by 25% to 30% and increases the 2-year survival by 5% to 7% compared with chemotherapy alone. For optimal outcomes, it is preferable to initiate radiation therapy concurrently with the first or second chemotherapy cycle versus sequentially. The most commonly used chemotherapy regimen for SCLC is EP. For limited-stage disease, NCCN guidelines recommend EP plus concurrent thoracic radiation therapy as first-line treatment of those with a good performance status. The expected response rate is 70% to 90% with a median survival of 14–20 months. The 2-year and 5-year survival rates are 40% and 20%, respectively. It is suggested that carboplatin not routinely be substituted for cisplatin because of the lack of adequate clinical data in this setting; however, carboplatin may be considered for those unable to tolerate cisplatin.

Extensive Stage

Chemotherapy is the mainstay of treatment of extensive-stage SCLC in patients with a good performance status. Expected clinical response rates are between 60% and 70%, median survival is 9–11 months, and 2-year survival is less than 5%. Etoposide plus cisplatin is considered the standard first-line chemotherapy regimen for extensive-stage SCLC. Etoposide plus cisplatin combined with ifosfamide, cyclophosphamide plus an anthracycline, paclitaxel plus a colony-stimulating factor, or topotecan given after EP has only demonstrated a 1-month survival advantage compared with EP alone. A significant number of patients in these studies experienced a higher rate of hematologic toxicities.

Irinotecan plus etoposide offers an alternative to EP, demonstrating similar response rates, time to disease progression, and median survival (9.3 months vs. 10.2 months, respectively) in a Phase III study conducted in North America. A similar Phase III trial conducted by the Japanese Clinical Oncology Group, however, demonstrated a survival advantage for irinotecan plus etoposide compared with EP. The median survival was reported as 12.8 months for the irinotecan-containing regimen versus 9.4 months for EP. As a result, the trial was terminated early. It has been hypothesized that the differences in study results between the North American and Japanese trials are related to pharmacogenomic differences between these patient populations. Patients of Asian descent show a decreased level of gene transcription of uridine diphosphate (UDP)-glucuronosyltransferase, an enzyme that metabolizes irinotecan, which may account for differences in chemosensitivity and toxicities. Ongoing studies will further evaluate the differences in polymorphisms of UDP-glucuronosyltransferase and the effects on response rates, survival, and toxicities. In the above studies, the incidence of gastrointestinal adverse effects (diarrhea) was much higher in those who received irinotecan; however, hematologic toxicity (severe myelosuppression) was greater in those who received EP. Irinotecan combined with etoposide may therefore be an alternative for patients in whom severe hematologic toxicity is demonstrated or likely.

Carboplatin may be substituted for cisplatin in extensive-stage SCLC because it is easier to administer and has a more favorable toxicity profile. The FDA currently labels etoposide phosphate for combination therapy in SCLC.

This agent is a more water-soluble ester of etoposide. This increased water solubility lessens the potential for precipitation after dilution and intravenous administration, offering an alternative for patients with fluid restrictions who require solutions that are more concentrated and more stable. Clinically, etoposide phosphate and etoposide are considered equivalent in bioavailability, response to treatment, and toxicity profile. The doses of etoposide phosphate and etoposide are equivalent and range from 80 mg/m²/day to 100 mg/m²/day on days 1, 2, and 3, repeated every 3 weeks. The major difference is cost. Other strategies to improve overall response rates or survival, such as the use of alternating non-cross-resistant or dose-intense chemotherapy regimens, have not shown superiority to the EP regimen.

Prophylactic Cranial Irradiation

The risk of developing central nervous system metastases after achieving a complete response to SCLC treatment is about 35% to 60%. Prophylactic cranial irradiation is effective in decreasing the incidence of brain metastases by 25% at 3 years and increasing overall survival by 5.4%. Initially, it was thought that only patients with limited-stage SCLC would benefit from PCI; however, similar benefits have recently been demonstrated for extensive-stage disease. The NCCN currently recommends PCI for patients with either limited- or extensive-stage SCLC who achieve a complete response after initial treatment with chemotherapy. The risk of neurotoxicity is reduced if PCI is given after chemotherapy when the lowest fractionated doses are used. Patients with a poor performance status (3 or 4), impaired mental function, and significant comorbidities (e.g., end-organ dysfunction, pulmonary compromise, myelosuppression) should not receive PCI.

Recurrent Disease

Most patients with SCLC eventually relapse after treatment or develop disease progression during treatment. Subsequent treatment largely depends on the time to recurrence. If relapse occurs more than 6 months after initial treatment, the original chemotherapy regimen may be readministered. If relapse occurs between 3 months and 6 months after initial treatment, the patient may receive subsequent chemotherapy, which has an expected response rate of about 25%. Chemotherapy treatment options include topotecan, cyclophosphamide plus doxorubicin plus vincristine (CAV), gemcitabine, paclitaxel, docetaxel, oral etoposide, and vinorelbine. Topotecan is widely accepted as a second-line agent of choice, demonstrating response rates and survival similar to CAV. Fewer toxicities and greater symptom improvement were reported with topotecan compared with the CAV regimen. Patients who relapse during therapy or within 3 months after completion of therapy are considered refractory to treatment. Response to further chemotherapy, in general, is less than 10%. For patients with good performance status, single-agent chemotherapy with ifosfamide, paclitaxel, docetaxel, gemcitabine, or topotecan may be considered. Agent choice depends on the expected toxicity profile of the antineoplastic agent and patient comorbidities. Dose-limiting toxicity for ifosfamide includes hemorrhagic cystitis and myelosuppression, whereas the

taxanes (paclitaxel and docetaxel) are associated with neurotoxicity and myelosuppression. Myelosuppression is also a dose-limiting toxicity associated with gemcitabine and topotecan. Second-line chemotherapy is generally given until maximal benefit is achieved, until relapse, or until unacceptable toxicities occur.

Complications and Supportive Care

Patients with lung cancer often experience many medical complications. These complications may be associated with the primary tumor site and extent of metastases, treatment-related adverse effects, and concomitant medical conditions. The overall treatment plan for an individual patient is often determined by patient performance status and comorbidities, toxicity profile of the chemotherapeutic agents or targeted therapies, physician preference or experience, and cost or reimbursement factors. Individual patient and family goals and wishes must also be assessed and considered. Patients with a poor performance status (3 or 4) may experience more treatment-related complications than those having a more favorable performance status (0, 1, or 2).

Most chemotherapy regimens used in the management of lung cancer cause multiple, severe toxicities. In general, expected toxicities associated with chemotherapy include myelosuppression, nausea and vomiting, and alopecia. Cisplatin, one of the most active agents used for the treatment of NSCLC and SCLC, is commonly associated with severe nausea and vomiting (acute and delayed) and is considered one of the most emetogenic antineoplastic agents. Prevention of nausea and vomiting requires aggressive antiemetic therapy (see the chapter on supportive care). Other dose-limiting toxicities associated with cisplatin include neurotoxicity (manifested by peripheral neuropathy, auditory impairment, and visual disturbances) and nephrotoxicity. Aggressive pre- and posthydration promoting enhanced diuresis is required with cisplatin therapy to reduce the risk of nephrotoxicity. Supplementation with magnesium and potassium may also be warranted to prevent hypomagnesemia and hypokalemia. Patients considered poor candidates for cisplatin therapy include those with a history of severe nausea and vomiting, ongoing or history of kidney dysfunction, concurrent use of nephrotoxic drugs, auditory impairment, and peripheral neuropathy (attributable to any cause, including diabetic neuropathy), as well as patients with fluid restrictions. Although these toxicities may be reported for carboplatin, they generally occur less often and with less severity. Carboplatin may be substituted for cisplatin, depending on patient tolerability and comorbidities. The curative or palliative intent of treatment, however, should first be assessed before making this substitution.

Thrombocytopenia is the major dose-limiting toxicity associated with carboplatin. Early studies with carboplatin determined that pretreatment kidney function affects the severity of carboplatin-induced thrombocytopenia. A formula was derived (the Calvert equation) in which a dose of carboplatin necessary to induce a predetermined nadir could

be calculated. This formula is based on pretreatment kidney function and prior treatment status with chemotherapy:

$$\text{carboplatin dose (mg)} = \text{target area under the curve (AUC) (mg} \times \text{minute/mL)} \times [\text{glomerular filtration rate (mL/minute)} + 25]$$

The target AUC refers to the AUC of unbound carboplatin targeted for optimal efficacy and reduced toxicities. The physician must specify the desired AUC value (usually 6–8 mg/mL/minute is used for previously untreated patients, and a value of 4–5 mg/mL/minute is used for previously treated patients). Glomerular filtration rate or creatinine clearance and the value 25 adjust for kidney and nonkidney clearance of carboplatin.

Clinical controversies exist surrounding the use of the Calvert equation. These controversies include which method to use to determine creatinine clearance, which serum creatinine concentration to use if serum creatinine concentration is less than 1 mg/dL, and which weight to use for obese patients. Rounding a serum creatinine concentration up to 1 mg/dL may result in an underestimation of creatinine clearance (especially for concentrations less than 0.7 mg/dL) and a lower carboplatin dose. This may not achieve the target AUC value. The use of ideal body weight may severely underestimate the carboplatin dose needed to achieve the target AUC. The use of actual body weight has not resulted in undue toxicity; therefore, this may be most appropriate to use for patients who are not morbidly obese. It has been suggested to adjust the body weight for patients with body mass index greater than 25. In light of these controversies, the pharmacist must become familiar with these issues, know the limitations of the formulas used, and be able to discuss the optimal calculation method with the oncologist or practice group. Appropriate monitoring for platelet toxicity should be performed.

Complications associated with neutropenia and anemia may be avoided with the appropriate use of hematopoietic growth factors. In most situations in which patients experience a neutropenic complication from a prior cycle of chemotherapy, dosage reduction or treatment delay is warranted. If a dosage reduction or delay might compromise disease-free or overall survival (in which curative intent is the treatment goal), using a hematopoietic growth factor might be appropriate to maintain chemotherapy treatment at optimal doses and on schedule.

One of the classic adverse effects associated with erlotinib is rash, varying in description from dry skin to a severe acneiform rash or eruption. Because EGFR is expressed in the skin (by normal keratinocytes, skin fibroblasts, and the outer root of the hair follicle), it has been postulated that the associated rash is caused by receptor inhibition in the skin. Other mechanisms might include changes in the skin's microflora caused by EGFR inhibition, resulting in an inflammatory reaction (either localized or systemic).

Typically, this rash is dose-dependent, appears a few days after therapy initiation, and reaches a maximal effect after 2–3 weeks. Clinically, the rash appears as an itchy, acneiform, papulopustular eruption; telangiectasia (dilated superficial blood vessels); and xerosis (dry skin). Sometimes,

spontaneous improvement in the rash is observed; however, flare-ups may also be common. The rash or eruption usually disappears a few weeks after treatment is discontinued, but it may leave hyperpigmentation and xerosis. Multiple studies with EGFR inhibitors (including erlotinib) have reported a positive correlation between rash and clinical response, including survival. This suggests that rash could be a surrogate marker of effective target inhibition for patients receiving EGFR inhibitors and may be a tool for monitoring response to treatment. These observations should be further validated in prospective clinical trials.

Pharmacists should inform patients about these skin toxicities as well as how to treat symptoms when they appear. Treatment needs to be individualized according to the type and extent of the skin lesions. General measures to manage dry skin include the use of bath or shower oils (vs. gels or soaps) and emollient creams; sun exposure should be avoided. Telangiectasia will gradually disappear after several months. Mild grade 1 reactions (those with macular or papular eruptions or erythema that is asymptomatic) may not require treatment, or they may be treated with topical anti-acne treatments such as metronidazole, erythromycin, clindamycin, or benzoyl peroxide. If xerosis is present, these agents should be avoided because of their drying properties. Topical or systemic corticosteroids and retinoids should be avoided because they may further aggravate acne and other associated symptoms. Grade 2 reactions (grade 1 reaction plus pruritus or other associated symptoms) may be managed with an oral tetracycline (minocycline or doxycycline). Itching may be managed with an oral antihistamine. Grade 3 reactions (generalized symptomatic macular, papular, or vesicular eruptions) may necessitate discontinuation of therapy and delays in treatment. If necessary, maximal doses of oral antihistamines and oral tetracyclines may be tried and then tapered as the inflammation fades. Although extremely rare, grade 4 reactions (exfoliative or ulcerating dermatitis) necessitate permanent therapy discontinuation and possibly treatment in a burn unit.

The incidences of hypertension and proteinuria are increased in patients with NSCLC receiving bevacizumab in combination with chemotherapy versus chemotherapy alone (hypertension: 7% vs. 0.7%, respectively; proteinuria: 3.1% vs. 0%, respectively). Medical management with an antihypertensive agent such as an angiotensin-converting enzyme inhibitor, β -blocker, diuretic, or calcium channel blocker is often required. Blood pressure monitoring and urine dipstick monitoring for protein are recommended every 2–3 weeks (or more often for patients with preexisting conditions). In patients with medically uncontrolled hypertension or moderate to severe proteinuria (i.e., greater than 3.5 g of protein in 24 hours), temporary suspension of bevacizumab is recommended. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy, nephrotic syndrome, gastrointestinal perforation, or serious bleeding or thromboembolic events.

Many other complications specific to lung cancer and the associated paraneoplastic syndromes may require additional supportive care. Megestrol acetate (800 mg/day) has demonstrated improvement in appetite, weight gain,

and overall well-being in patients with cancer-associated cachexia. Cushing syndrome may respond to ketoconazole therapy, and those with hyponatremia of malignancy are treated with fluid restriction, hypertonic saline infusions (if symptomatic), or demeclocycline. Hypercalcemia of malignancy requires aggressive hydration with sodium chloride, calcitonin, and bisphosphonate therapy (either pamidronate disodium or zoledronic acid). Patients should continually be assessed and treated for pain, especially as the disease process advances (see the chapter on supportive care).

Elderly Patients

Treatment of lung cancer in the elderly patient can be challenging, but age alone should not be used to determine whether a patient is a candidate for treatment. Before treatment decisions are made, a comprehensive geriatric assessment should be performed to determine the optimal treatment plan. This assessment includes patient functional and nutritional status, comorbidities, polypharmacy, cognitive function, and emotional and socioeconomic issues. In general, older patients with a good performance status are able to tolerate chemotherapy as well as younger patients. Elderly patients dependent on assistance for activities of daily living are at increased risk of treatment complications, especially fatigue, neutropenia, anemia, mucositis, cardiac toxicity, and neurotoxicity. For palliative treatment, dosage adjustments of chemotherapy may be necessary to avoid undue toxicities. For curative treatment, hematopoietic growth factors may be used to maximize doses.

A limited number of studies have specifically addressed treatment of the elderly patient. Vinorelbine combined with gemcitabine in patients older than 70 years with advanced NSCLC and a good performance status (0, 1, or 2) was not shown to be any more effective than either agent alone, and the combination therapy was associated with more toxicity. A retrospective analysis of the combination of bevacizumab, carboplatin, and paclitaxel for NSCLC suggested that patients older than 70 may not have the survival advantage observed in the combined study population. In this analysis, elderly patients experienced substantially more toxicities than younger patients; therefore, caution should be used with this regimen in patients older than 70 who are candidates for bevacizumab. In the management of SCLC, combination chemotherapy is superior to single-agent chemotherapy in elderly patients with a good performance status (0, 1, or 2). For NSCLC or SCLC, carboplatin may often be substituted for cisplatin in the elderly population, especially for palliative treatment. Prospective evaluation in elderly patients is needed to further define optimal treatment regimens and dosing strategies.

Patient Education

On receiving a diagnosis of lung cancer, patients should be informed about their disease and associated outcomes (cure or palliation), treatment options, and the availability of clinical trials in their area. In addition, the risks and benefits

of all treatment modalities should be fully explained, especially the overall impact on quality of life. Appropriate palliative care should be initiated from the time of lung cancer diagnosis and should be intensified as the disease progresses and response to treatment diminishes. The patient and family are the most important members of the health care team and are the ultimate decision-makers in all aspects of therapy.

A diagnosis of lung cancer is very stressful; patients often may be anxious and depressed. Patients and families should be aware that there are many resources available in the community to help support people living with cancer (e.g., local branches of the American Cancer Society, disease-specific support groups affiliated with local or regional cancer centers). Patients often benefit from joining cancer support groups, where they can share experiences and gain the support of others. There are many Web-based resources available to patients as well. Cancer-specific information, supportive care, community resources, and other valuable information is available from the American Cancer Society, the American Society of Clinical Oncology, the NCCN, and many other organizations.

Counseling a patient about chemotherapy can be very complex because of the nature of the disease, the multiple drugs used in the chemotherapy regimen, the severe toxicities that may be encountered, and the multiple supportive care drugs that an individual may receive. Providing written information for the patient and family to take home should supplement patient counseling. In addition, keeping a diary of appointments, treatments, drug names, and complications should be encouraged. It is imperative that patients know when to call their doctor, nurse, or pharmacist regarding adverse effects, especially in the event of any signs or symptoms of life-threatening infection or bleeding.

Role of the Pharmacist

The pharmacist is an integral member of the health care team for the patient with lung cancer. It is important for pharmacists to stay informed about new treatment options, supportive care measures, and evidence-based guidelines as they emerge. Pharmacists provide multiple aspects of care beyond dose verification and calculations, chemotherapy preparation, and drug information. There are many opportunities for pharmacists to become actively engaged in patient counseling. Patient education and counseling may include discussions about smoking cessation therapies and avoidance of dietary supplements (especially the harmful effects of antioxidants and beta-carotene in smokers). Drug interactions and the management of skin-related toxicities should be thoroughly reviewed with patients receiving erlotinib. General and drug-specific adverse effects should routinely be discussed and monitored in all patients. Guidelines on how to prevent and manage these adverse effects can be shared with patients by providing literature that highlights the most serious aspects of these treatment-related adverse effects. It is also imperative to emphasize when the patient needs to contact his or her health care professional if a serious toxicity occurs.

Pharmacists routinely monitor laboratory parameters to ensure an adequate absolute neutrophil count and platelet

count before administering chemotherapy. Kidney and hepatic function are continually assessed to ensure adequate organ function. Guidance for dose modifications or change in therapy may be necessary for those with kidney or hepatic impairment. Maintaining patient profiles for patients receiving carboplatin will assist in monitoring changes in kidney function and platelet toxicity.

Apart from the chemotherapeutic agents prescribed, supportive care regimens should routinely be assessed for appropriateness, doses, and therapy duration. Examples include appropriate antiemetic prophylaxis based on the chemotherapy regimen, appropriate indications for hematopoietic growth factors, prophylaxis for reducing the incidence of hypersensitivity reactions, and any other preventive measures to prevent undue toxicity from a specific chemotherapeutic agent (e.g., dexamethasone and folic acid and vitamin B₁₂ supplementation with pemetrexed).

Conclusion

Lung cancer is the leading cause of cancer death worldwide. Continued efforts to improve smoking cessation strategies and the development and assessment of early detection methods are imperative to make an impact on morbidity and mortality associated with this disease. Diagnosis of lung cancer at an early stage offers the optimal opportunity for cure; however, most patients receive a diagnosis at more advanced stages. A plateau has been reached in responses achieved by double chemotherapy regimens for the treatment of advanced-stage NSCLC; however, newly developed targeted therapies may offer opportunities for improving response rates and survival. The treatment of SCLC remains a challenge, especially for extensive-stage disease, requiring further advancements in treatment modalities. Whenever possible, participation in clinical trials should be encouraged for all stages of lung cancer, from prevention and early detection to treatment.

Annotated Bibliography

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-small-cell lung cancer, v.2.2009. Available at www.nccn.org/professionals/physician_gls/PDF/nscl.pdf. Accessed February 23, 2009.
2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: small cell lung cancer, v.2.2009. Available at www.nccn.org/professionals/physician_gls/PDF/scl.pdf. Accessed February 23, 2009.

The NCCN is a not-for-profit alliance of leading cancer centers across the United States and worldwide. One of the most valuable resources provided by this organization is the NCCN Clinical Practice Guidelines in Oncology, providing evidence-based consensus recommendations on cancer treatment and supportive care. The NSCLC guidelines provide a comprehensive review of lung cancer prevention and screening, staging, evaluation, initial treatment of all stages, and treatment of recurrence. Also discussed are general principles of surgery, radiation therapy, and chemotherapy. The SCLC guidelines provide a comprehensive review on staging, treatment of limited- and extensive-stage disease,

and management of recurrence. General principles of surgery, radiation therapy, PCI, and chemotherapy are also discussed. Both of these guidelines are often updated, and most of the recommendations are category 2A, indicating a uniform consensus based on lower-level evidence (incorporation of clinical experience).

3. The International Early Lung Cancer Action Program Investigators. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;355:1763–71.

The investigators of this collaborative study evaluated the impact of spiral CT scans as a detection method for lung cancer. Participants included in this study were 40 years and older, physically able to undergo thoracic surgery, and at risk of lung cancer as determined by a history of smoking; occupational exposure to asbestos, beryllium, uranium, or radon; or exposure to secondhand smoke. Of the 31,567 asymptomatic men and women who underwent baseline screening with spiral CT scan, 405 participants received a diagnosis of lung cancer. This corresponds to a detection rate of 1.3%. A total of 27,456 participants did not have a positive finding on initial baseline screening and therefore underwent further annual CT scan screening. Of these participants, 74 received a diagnosis of lung cancer, resulting in a detection rate of 0.3%. Five additional participants developed lung cancer within 12 months after the baseline screening. For all 484 participants who developed lung cancer, the estimated 10-year survival rate was 80%. Clinical stage I lung cancer was detected in 85% of the cases (412 participants). Of these, 302 participants underwent surgical resection within 1 month of diagnosis, with an estimated 10-year survival of 92%. Controversies remain whether these study results alone can justify routine screening in high-risk individuals and whether CT scan screening reduces lung cancer mortality. As more diagnoses occur at an earlier stage, more surgical resections will be performed. The authors of this study conclude that CT scan screening is cost-effective.

4. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzales-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomized controlled trial. *Lancet Oncol* 2006;7:719–27.

The primary purpose of this study was to assess the survival benefit of adjuvant chemotherapy (vinorelbine plus cisplatin) compared with observation in patients with stage I, II, or IIIa NSCLC. The 5-year survival rates for chemotherapy compared with observation are as follows: stage I 62% (95% confidence interval [CI], 54–70) versus 64% (95% CI, 56–71; hazard ratio [HR] 1.1 [0.76–1.57]); stage II 52% (95% CI, 41–63) versus 39% (95% CI, 30–49; HR 0.71 [0.49–1.03]); and stage IIIa 42% (95% CI, 34–50) versus 26% (95% CI, 18–33; HR 0.69 [0.53–0.9]). The results of this study are consistent with several other large trials indicating that patients with stage IA and IB NSCLC do not benefit from adjuvant chemotherapy.

5. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–50.

Because of this key study, the combination of bevacizumab with paclitaxel and carboplatin is recommended as first-

line therapy for the treatment of stage IIIB and IV NSCLC. Candidates for treatment included those with nonsquamous cell NSCLC and a good performance status (0 or 1). Patients with the following were excluded: squamous cell histology; hemoptysis; central nervous system metastases; pregnancy or lactation; coagulation disorders; therapeutic anticoagulation; use of aspirin, nonsteroidal anti-inflammatory agents, or other platelet inhibitors; radiation therapy within 21 days of enrollment; surgery within 28 days of enrollment; significant cardiovascular disease; and uncontrolled hypertension. The primary purpose of this study was to determine if the addition of bevacizumab to paclitaxel and carboplatin (treatment group) improves survival. A statistically significant benefit in progression-free survival and response rate was described for the treatment group. Median overall survival was 12.3 months in the treatment group versus 10.3 months in the paclitaxel and carboplatin (control) group (HR for death 0.79; 95% CI, 0.67–0.92; $p=0.003$). Two-year survival rates were 23% in the treatment group compared with 15% in the control group. There were significantly more adverse events reported in the treatment group compared with the control group. These adverse events included hypertension, proteinuria, bleeding, neutropenia, febrile neutropenia, thrombocytopenia, hyponatremia, rash, and headache. Fifteen deaths occurred in the bevacizumab treatment group versus two deaths in the paclitaxel and carboplatin control group. Although adding bevacizumab improves survival in this limited subset of patients with NSCLC, a significant number of toxicities are associated with this regimen. Candidates for bevacizumab therapy include the youngest and most fit patients.

6. Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2004;22:3852–9.

This meta-analysis included eight clinical trials in which carboplatin was substituted for cisplatin for the treatment of advanced NSCLC to determine any differences in overall response rates or survival. Three of the clinical trials included older chemotherapy agents including etoposide, vindesine, mitomycin, and vinblastine. Five of the clinical trials included newer agents including paclitaxel, gemcitabine, and docetaxel. Overall response rates were higher for cisplatin-containing regimens compared with carboplatin. Cisplatin-based chemotherapy did not show a statistically significant improvement compared with carboplatin regimens in overall survival (HR 1.05; 95% CI, 0.907–1.216; $p=0.515$). Subset analysis of the five clinical trials that included one of the newer agents demonstrated an 11% improvement for the cisplatin-containing regimens (HR 1.106; 95% CI, 1.005–1.218; $p=0.039$). There was significantly more nausea and vomiting in the trials containing cisplatin compared with carboplatin; however, thrombocytopenia rates were significantly higher in trials containing carboplatin. The incidence of nephrotoxicity was similar for both agents. Conclusions from this meta-analysis do not overwhelmingly support the premise that cisplatin-based chemotherapy regimens in advanced NSCLC are superior to carboplatin-based regimens, especially in overall survival. There is a suggestion that cisplatin combined with one of the newer agents may confer a survival benefit. Some limitations are associated with this meta-analysis: several patients were excluded from the overall survival analysis in four of the trials, analysis of the end points was based on abstracted data versus individual patient data, and only eight studies were analyzed. For palliative treatment, choice of therapy may

still be dictated by expected patient tolerability until further prospective analysis can be performed.

7. Shepherd FA, Pereira JR, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–32.

The primary purpose of this randomized, Phase III, placebo-controlled trial was to determine whether erlotinib prolongs survival after the failure of first- or second-line therapy for NSCLC. Patients eligible for participation were 18 years or older with a performance status between 0 and 3. Patients had received one or two prior regimens of combination chemotherapy; they were no longer eligible for more chemotherapy. A total of 488 patients received erlotinib, and 243 patients received placebo. About half of the patients received one prior chemotherapy regimen, and the remaining half had received two or more prior chemotherapy regimens. Median overall survival was 6.7 months in the erlotinib group compared with 4.7 months in the placebo group (adjusted HR 0.70; 95% CI, 0.58–0.85; $p < 0.001$). Dose reductions in the erlotinib group were required in 12% and 5% of patients because of rash and diarrhea, respectively. Discontinuation of erlotinib occurred in 5% of patients versus 2% receiving placebo. Overall, this study demonstrates a survival benefit for erlotinib and, therefore, gained acceptance as a treatment option for second- and third-line therapy for advanced NSCLC. In second-line treatment, docetaxel has demonstrated a similar 2-month survival benefit. Erlotinib may have a more favorable toxicity profile compared with chemotherapy and is not associated with myelosuppression. About one-third of the patients in each treatment group had a performance status of 2 or 3, indicating that erlotinib may be offered and tolerated well in this subgroup of patients.

8. Eberhard D, Johnson BE, Amler LC, Goddard AD, Heldens SL, Herbst RS, et al. Mutations in the epidermal growth factor receptor and KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005;23:5900–9.

As previously discussed, patients with NSCLC and EGFR mutations are those without a smoking history and subsequently may be more responsive to EGFR inhibitors. The clinical outcomes of the EGFR and KRAS mutations are evaluated in this study based on a retrospective analysis of DNA sequencing from a previous study that combined erlotinib with carboplatin and paclitaxel. This study demonstrated that patients with EGFR mutations who received treatment with erlotinib (with or without chemotherapy) had significantly better responses to treatment. In patients with KRAS mutations, a negative impact on response and survival was demonstrated in patients receiving erlotinib-based combination therapy. Although this article is a clinical study, it provides a good review and explanation for the basis of EGFR and KRAS mutations.

8. Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007;357:664–72.

This is the first study to demonstrate the benefit of PCI in extensive-stage SCLC. Patients with extensive-stage SCLC who had achieved a response to systemic chemotherapy were randomized to receive PCI versus no further therapy (control group). This study included patients aged from 18 years to 75 years with a performance status of 0–2. Prophylactic cranial irradiation was initiated 4–6 weeks after chemotherapy

completion. At 1 year, the PCI group had significantly fewer symptomatic brain metastases compared with the control group (14.6% vs. 40.4%; HR 0.27 [95% CI, 0.16–0.44]). At 1 year, the overall survival rate was 27.1% (95% CI, 19.4–35.5) in the PCI group versus 13.3% (95% CI, 8.1–19.9) in the control group. Toxicities associated with PCI include headache, nausea and vomiting, fatigue or lethargy, and skin reactions. No significant differences were reported in role functioning, cognitive functioning, or emotional functioning between the two groups. The authors of this study conclude that PCI should be part of the standard of care for all patients with SCLC who have a response to initial chemotherapy. The NCCN has incorporated this recommendation into the SCLC treatment guidelines as well.

10. Hanna N, Bunn PA Jr, Langer C, Einhorn L, Guthrie T Jr, Beck T, et al. Randomized Phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006;24:2038–43.

This randomized, open-label, Phase III study demonstrated that irinotecan plus cisplatin (IP) is an equally effective regimen compared with the gold standard of EP in previously untreated patients with extensive-stage SCLC and a performance status of 0–2. There was no significant difference between the two groups in response rates, stable disease rates, or time to disease progression. There was also no difference detected in median survival between the two groups (9.3 months vs. 10.2 months for the IP and EP regimens, respectively; $p = 0.68$). Compared with the IP group, patients in the EP group experienced a significantly higher rate of hematologic toxicities including neutropenia, febrile neutropenia, anemia, and thrombocytopenia. However, patients who received IP developed a significantly higher rate of gastrointestinal toxicities including vomiting, diarrhea, and dehydration compared with the EP group. Although IP does not represent a major advance in the treatment of extensive-stage SCLC in improved responses or survival, it does offer an additional treatment option with less hematologic toxicity.

SELF-ASSESSMENT QUESTIONS

- B.A.'s father recently received a diagnosis of lung cancer. She comes to the clinic today with her father to discuss his treatment options with his oncologist. While in the clinic, B.A. expresses concerns about her own health and asks what she can do to minimize her risk of developing lung cancer. On further questioning, you learn that B.A. is 56 years old, smokes 1–2 packs of cigarettes per day, and has no significant history of alcohol or drug abuse. She currently takes vitamin supplements consisting of a “general” multivitamin as well as beta-carotene regularly. Apart from suggesting smoking cessation strategies, which one of the following is the best advice to offer B.A.?

 - Ask her to discuss obtaining baseline chest radiography with her physician to rule out any suspicious abnormalities and to follow up yearly thereafter.
 - Inform her that there is a new cancer detection test for lung cancer that may decrease her risk of dying of lung cancer.
 - Ask her to consider enrolling in a clinical trial for either cancer detection or cancer prevention.
 - Suggest she continue her present vitamin supplements and beta-carotene but also increase dietary intake of fruits and vegetables.
- J.S., a 62-year-old man, has been treated for bronchitis with multiple courses of antibiotics without resolution of symptoms. On further work-up, chest radiography showed a mass in the right upper lobe. Subsequently, a computed tomography (CT) scan detected a 4-cm by 2.5-cm mass. Bronchoscopy was performed, detecting no involved lymph nodes; however, the biopsy of the mass indicated squamous cell carcinoma. Further diagnostic work-up was negative, and J.S. is otherwise healthy. J.S. underwent surgical resection of the primary mass without complication. Surgical margins were negative. Which one of the following adjuvant therapies is best for J.S. at this time?

 - Observation alone.
 - Chemotherapy with paclitaxel and carboplatin.
 - Chemotherapy with vinorelbine and cisplatin.
 - Radiation therapy given concurrently with etoposide plus cisplatin (EP).
- T.A., a 68-year-old man, recently received a diagnosis of unresectable stage IIIB non–small cell lung cancer (NSCLC). He would like the “best treatment available” and would like to start therapy immediately. His medical history is noncontributory, and he leads an active lifestyle. T.A. states that he used to smoke 1 pack of cigarettes per day from the age of 25 but that he quit about 2 years ago. In addition to concurrent radiation therapy, which one of the following treatment options is best for T.A.?

 - EP followed by consolidation therapy with docetaxel.
 - EP.
 - Carboplatin plus paclitaxel.
 - Carboplatin plus etoposide.
- V.S. is a 57-year-old woman recently given a diagnosis of adenocarcinoma of the lung. Symptoms on presentation include nonproductive cough, 6.8-kg (15 lb) weight loss, and confusion. Further work-up indicates the presence of brain metastases. V.S. is a smoker (20 pack-year history) and has no other medical problems. She has been leading a very active lifestyle. Which one of the following chemotherapy regimens would be best for V.S.?

 - Docetaxel.
 - Carboplatin plus paclitaxel.
 - Carboplatin, paclitaxel, and bevacizumab.
 - Carboplatin, gemcitabine, and bevacizumab.
- Which one of the following patients has the best prognosis?

 - An 83-year-old man with adenocarcinoma (T2, N0, M0), capable of walking to the neighbor's house across the street daily; family visits often to clean the house and provide precooked meals.
 - A 67-year-old man with adenocarcinoma (T3, N3, M0), capable of brushing teeth, combing hair, and watching television.
 - A 56-year-old man with squamous cell carcinoma (T2, N2, M1), capable of taking daily walks around the subdivision with the neighbors; regularly works in his garden.
 - A 72-year-old man with large cell carcinoma (T2, N1, M0), capable of golfing several times weekly.
- One of the nurses in the clinic asks you to review the adverse effects of bevacizumab with a patient coming in for chemotherapy teaching. Currently, the patient's laboratory values are noncontributory and vital signs are stable. Current drugs include a multivitamin and atenolol. Which one of the following provides the best monitoring and follow-up teaching for this patient's bevacizumab therapy?

 - Be sure you have your blood pressure monitored and your urine checked every week when you come for a follow-up or treatment.
 - This medicine may cause your platelet count to go down significantly; your platelet count will be monitored at least monthly together with your white and red blood cell counts.
 - This medicine may cause significant nausea and vomiting; if it persists at home, be sure to contact us.

- D. This medicine may cause an allergic reaction; you will receive some drugs to help prevent this.
7. S.L. has stage IV NSCLC that progressed during therapy with carboplatin, paclitaxel, and bevacizumab. Although she feels fatigued, she is able to carry out most light chores around the house. After discussing her options with the oncologist, S.L. would like to pursue additional therapeutic options. Which one of the following represents the best treatment option for S.L.?
- Best supportive care.
 - Erlotinib.
 - Erlotinib, carboplatin, and paclitaxel.
 - Docetaxel.
8. A.S. is a 75-year-old man who completed chemotherapy several months ago with carboplatin and paclitaxel for stage IV NSCLC, tolerating the regimen fairly well. He states that he feels “pretty good” currently. However, his disease has progressed, and his oncologist would like to discuss further treatment options. His serum creatinine concentration is 1.1 mg/dL, and liver function tests are within normal limits. Performance status is 1. Which one of the following treatment options is best to offer A.S.?
- Vinorelbine.
 - Vinorelbine plus gemcitabine.
 - Carboplatin, paclitaxel, and bevacizumab.
 - Enrollment in a clinical trial.
9. A.B. is a 60-year-old woman with a diagnosis of limited-stage small cell lung cancer (SCLC). She has a 30 pack-year smoking history, performance status of 0, and no other medical conditions. All of her laboratory parameters are within normal limits. A.B. recently underwent a successful complete resection of her right upper lobe. Subsequently, her staging indicates T2, N1, M0 disease. Which one of the following is the best treatment plan for A.B.?
- EP.
 - EP plus concurrent thoracic radiotherapy.
 - EP plus concurrent thoracic radiotherapy, followed by prophylactic cranial irradiation (PCI).
 - EP plus sequential thoracic radiotherapy.
10. Which one of the following patients has the best prognosis?
- A 62-year-old woman with limited-stage SCLC, performance status of 0, and lactic dehydrogenase (LDH) 412 IU/L.
 - A 65-year-old woman with limited-stage SCLC, performance status of 1, and LDH 150 IU/L.
 - A 68-year-old woman with extensive-stage SCLC, performance status of 0, and LDH 200 IU/L.
 - A 70-year-old woman with extensive-stage SCLC, performance status of 0, and LDH 359 IU/L.
11. C.D., a 77-year-old man, recently received a diagnosis of extensive-stage SCLC. He has a history of chronic obstructive pulmonary disease and acute myocardial infarction. His serum creatinine concentration is 1.8 mg/dL. His wife states that during the day, C.D. is able to navigate around the house but needs assistance with bathing and with walking to the mailbox. Which one of the following is the best treatment course for C.D.?
- Etoposide.
 - EP.
 - Etoposide plus carboplatin.
 - Best supportive care.
12. T.Z. is a 60-year-old woman with extensive-stage SCLC who completed treatment with EP 8 months ago. She has just learned that more treatment will be necessary because new liver nodules have appeared on a follow-up CT scan. T.Z.’s performance status is 0 at this time. Which one of the following treatment regimens is best for T.Z.?
- Topotecan.
 - Ifosfamide.
 - EP.
 - Cyclophosphamide, doxorubicin, and vincristine (CAV).
13. R.H., a 68-year-old man with extensive-stage SCLC, is receiving treatment with EP, cycle 3. He complains of increasing shortness of breath, cough, fatigue, nausea, and a bothersome tingling sensation in the fingers and toes. His performance status is 1. His oncologist discusses the possibility that R.H. is not responding to treatment as expected and orders some follow-up tests 1 month earlier than planned. R.H. states that he would still like to pursue treatment even if his disease is not responding. Assuming his disease has progressed, which one of the following chemotherapy regimens is best for R.H.?
- Paclitaxel.
 - Docetaxel.
 - EP.
 - Gemcitabine.
14. T.J. is a 61-year-old man with extensive-stage SCLC who has received one course of chemotherapy with carboplatin and etoposide. He developed a significant amount of nausea and vomiting during his first course of chemotherapy, together with febrile neutropenia and alopecia. Which one of the following is the best option for T.J.’s next cycle of chemotherapy?
- Continue carboplatin and etoposide with dose reductions.
 - Continue carboplatin and etoposide at full dose; add a hematopoietic growth factor.
 - Change the regimen to EP.
 - Change to the CAV regimen.
15. A patient from the cancer clinic calls the pharmacy with a concern. She describes a new-onset rash and “bad case of acne” all over her face and upper chest. On further interview, you discover that she has been taking erlotinib for 1 month and is not experiencing any other

- complications. Which one of the following is the best course of action and advice to offer this patient?
- Initiate diphenhydramine as soon as possible. Most likely, this localized allergic reaction will resolve with a short course of an antihistamine.
 - Inquire if she has any itching or shortness of breath. If not, reassure her that this rash and acne-like skin condition is a common adverse effect associated with erlotinib.
 - Discontinue the erlotinib immediately. Advise her to schedule an appointment with the oncologist to discuss different treatment options.
 - Tell her to go to the emergency department for treatment. This may be the first sign of an allergic reaction that may dramatically worsen.
16. You receive the following chemotherapy order (cycle 1): pemetrexed 500 mg/m² given intravenously over 10 minutes on day 1. Repeat every 21 days. There are no other supportive care drugs ordered with this regimen. Which one of the following represents the best intervention before proceeding with this order?
- Check the patient's serum creatinine concentration.
 - Recommend an aggressive antiemetic regimen.
 - Suggest supplementation with magnesium and potassium.
 - Check with the nurse to ensure that the patient received a vitamin B₁₂ injection and prescription for folic acid.
17. F.A. is an 82-year-old woman who just received a diagnosis of advanced-stage NSCLC. The following findings were noted: current diabetes mellitus and hyperlipidemia, serum creatinine concentration 1.5 mg/dL, and performance status of 2. F.A. would like to proceed with treatment. Her first great-grandchild will be born in 2 months, and she wants to be there. Which one of the following is the most important consideration in making treatment decisions for F.A.?
- Age.
 - Performance status.
 - Serum creatinine value.
 - Patient goals.
18. G.K. will be receiving carboplatin plus paclitaxel. The nurse has requested that you spend some time reviewing the serious adverse effects of this regimen with G.K. and her family. Which one of the following counseling points is best to give G.K. regarding carboplatin?
- During the infusion of carboplatin, there is a high risk of an allergic reaction.
 - If any tingling in the fingers or toes occurs, you must contact your physician immediately.
 - If you experience any abnormal bruising or bleeding, contact your physician immediately.
 - Monitor your blood pressure at least once weekly; contact your physician if your blood pressure starts to rise.
19. D.J. has just completed his last course of chemotherapy for his extensive-stage SCLC. Before D.J. leaves the clinic today, the nurse wants to make sure he schedules an appointment for radiation therapy in 4 weeks to start his PCI. The patient is somewhat confused because he thought he was completely done with all of his treatments. Which one of the following statements is the best explanation to give D.J.?
- Schedule your appointment; you will meet with the oncologist before starting cranial irradiation for the prevention of CNS metastases.
 - All patients should receive cranial irradiation after chemotherapy; this is standard therapy for every patient with SCLC.
 - The patient is correct; the only treatment he should receive after today is more chemotherapy if his disease relapses.
 - The patient is correct; PCI is a treatment used only for patients with limited-stage SCLC.
20. S.T. is a 59-year-old woman about to receive her first course of chemotherapy with carboplatin and paclitaxel for advanced-stage NSCLC. Which one of the following laboratory parameters is most important in monitoring S.T. before administering carboplatin?
- Absolute neutrophil count.
 - Hemoglobin.
 - Platelet count.
 - Serum creatinine concentration.