

Chapter 62: Lung Cancer**INTRODUCTION**

- *Lung cancer* is a solid tumor originating from the bronchial epithelial cells. This chapter distinguishes between nonsmall cell lung cancer (NSCLC) and small cell lung cancer (SCLC) because they have different natural histories and responses to therapy.

PATHOPHYSIOLOGY

- Lung carcinomas arise from normal bronchial epithelial cells that have acquired multiple genetic lesions and are capable of expressing a variety of phenotypes.
- Activation of proto-oncogenes, inhibition or mutation of tumor suppressor genes, and production of autocrine (self-stimulatory) growth factors contribute to cellular proliferation and malignant transformation. Molecular changes, such as overexpression of c-KIT in SCLC and epidermal growth factor receptor (EGFR) in NSCLC, also affect disease prognosis and response to therapy.
- Smoking is responsible for approximately 80% of lung cancer cases. Other risk factors are exposure to environmental respiratory carcinogens (eg, asbestos, benzene, and arsenic), genetic risk factors, and history of other lung diseases (eg, chronic obstructive pulmonary disease [COPD] and asthma).
- The major cell types are SCLC (~15% of all lung cancers), adenocarcinoma (~50%), squamous cell carcinoma (<30%), and large cell carcinoma. The last three types are grouped together and referred to as NSCLC.

CLINICAL PRESENTATION

- The most common initial signs and symptoms are cough, dyspnea, chest pain, or discomfort, with or without hemoptysis. Many patients also exhibit systemic symptoms such as anorexia, weight loss, and fatigue.
- Disseminated disease can cause neurologic deficits from CNS metastases, bone pain, or pathologic fractures secondary to bone metastases, or liver dysfunction from hepatic involvement.
- Paraneoplastic syndromes are signs and symptoms that occur at sites away from the primary tumor or its metastases and are not associated with direct tumor involvement. They occur more frequently with lung cancer than any other tumor, and more frequently with SCLC than with NSCLC.

DIAGNOSIS

- Chest radiographs, endobronchial ultrasound, computed tomography (CT) scan, and positron emission tomography (PET) scan are the most valuable diagnostic tests. Integrated CT–PET technology appears to improve diagnostic accuracy in staging NSCLC over CT or PET alone.
- Pathologic confirmation is established by examination of sputum cytology and/or tumor biopsy by bronchoscopy, mediastinoscopy, percutaneous needle biopsy, or open-lung biopsy.
- All patients must have a thorough history and physical examination to detect signs and symptoms of the primary tumor, regional spread of the tumor, distant metastases, paraneoplastic syndromes, and ability to withstand aggressive surgery or chemotherapy.

STAGING

- The World Health Organization has established a TNM staging classification for NSCLC based on primary tumor size and extent (T), regional lymph node involvement (N), and presence or absence of distant metastases (M).
- A simpler system is commonly used to compare therapeutic modalities. Stage I includes tumors confined to the lung without lymphatic spread, stage II includes large tumors with ipsilateral peribronchial or hilar lymph node involvement, stage III includes other lymph node and regional involvement, and stage IV includes any tumor with distant metastases.
- A two-stage classification is widely used for SCLC. Limited disease is confined to one hemithorax and can be encompassed by a single radiation port. All other disease is classified as extensive.

TREATMENT**Nonsmall Cell Lung Cancer**

- **Goals of Treatment:** Definitive cure is the desired outcome with early-stage disease. Prolongation of survival is desired in patients with advanced-stage disease.
- The stage of NSCLC and the patient's comorbidities and performance status (ie, the ability to perform activities of daily living) determine which treatment modalities will be used. The intent of treatment—curative or palliative—influences the aggressiveness of therapy.

Recommendations for Chemotherapy, Radiation Therapy, and Surgery

- Genetic testing of tumors should be performed at the time of diagnosis in all patients, including those with localized disease.
- Local disease (stages IA and IB) is associated with a favorable prognosis. Surgery is the mainstay of treatment and may be used alone or in some situations with radiation therapy (RT) and/or chemotherapy.
- Stage IIA and IIB diseases are primarily treated with surgery followed by adjuvant chemotherapy (**Table 62-1**). Platinum-based regimens are preferred and should be given concurrently rather than sequentially with RT. Chemoradiotherapy is recommended for medically inoperable patients who can tolerate combined modality therapy.
- Optimal outcomes for stage III disease are achieved with multimodality therapy. Patients with operable disease should be considered for surgery preceded or followed by systemic chemotherapy. Current recommendations for patients with resectable stage IIIA disease include chemotherapy followed by surgery or radiation, depending on individual patient and tumor features.
- Patients with stage IIIA disease who are not surgical candidates or have a tumor that cannot be resected, and nearly all stage IIIB patients, are typically treated with both an active platinum-containing regimen and concurrent radiotherapy. Patients who respond to chemotherapy should then receive maintenance therapy with **durvalumab**, a programmed death ligand-1 (PD-L1) inhibitor that significantly improves 2-year survival and median progression-free survival (PFS).
- Patients with stage III disease who are not candidates for radiation are treated like those with stage IV disease. Chemotherapy is administered to palliate symptoms, improve quality of life, and increase duration of survival. Therapy depends on patient-specific factors (performance status is most important) and tumor characteristics.

- Three pathways have been identified for advanced NSCLC: (1) immune sensitive (PD-L1+), (2) targetable genetic mutation-driven, which is further divided based on the mutation (EGFR, ALK, BRAF, NTRK, and ROS1), and (3) nonbiomarker-driven therapy treatment, which is further classified as squamous histology or nonsquamous histology due to drug toxicity and efficacy. Select regimens for each group are outlined in **Table 62-2**.
- First-line therapy for patients with NSCLC with PD-L1+ tumors is **pembrolizumab**, an immune checkpoint inhibitor that binds to the programmed death-1 (PD-1) receptor on T cells. As compared with a platinum doublet chemotherapy regimen, **pembrolizumab** demonstrated increased median PFS. Use chemotherapy as second-line therapy after failing **pembrolizumab**.
- Treatment options for patients with advanced lung cancer and a targetable genetic driver mutation include:
 - (1) Patients with a tumor that harbors a *mutation in the EGFR receptor* should receive first-line EGFR tyrosine kinase inhibitor therapy with **osimertinib**. **Osimertinib**, a third-generation EGFR tyrosine kinase inhibitor, shows the most impressive activity in patients with EGFR-positive tumors. In addition to significantly longer PFS, **osimertinib** has improved CNS penetration resulting in improved CNS response rates and less CNS disease as the cause of progression. First- and second-generation EGFR tyrosine kinase inhibitors include **afatinib**, **erlotinib**, or **gefitinib**. A meta-analysis suggests that these three agents have similar PFS results and response rates about two times higher than chemotherapy. Subsequent therapy after progression during treatment with an EGFR inhibitor depends on initial treatment and further genetic evaluation of the tumor. Most patients will proceed to a platinum doublet chemotherapy with or without an immunotherapy agent.
 - (2) Patients with a tumor with an *ALK rearrangement* should receive initial treatment with an ALK inhibitor, with a preference for **alectinib**. Other ALK inhibitors approved for first-line therapy are **ceritinib** and **crizotinib**. **Lorlatinib** was recently approved as second-line therapy after failure on a first-line ALK inhibitor.
 - (3) Patients with a tumor with a *mutation in ROS1* should be treated with **crizotinib**. Patients should receive **lorlatinib** as second-line therapy.
 - (4) Patients with a tumor with the *BRAF V600E mutation* should receive combination therapy with two kinase inhibitors, **trametinib** and **dabrafenib**.
 - (5) Patients with a tumor with a *neurotrophic receptor kinases (NTRK) gene fusion* should receive **larotrectinib**.
- Combination chemotherapy is the preferred option for patients with metastatic NSCLC who are not candidates for targeted therapies or have progressed despite targeted therapies and are candidates for further therapy. Platinum-based chemotherapy doublets consisting of **cisplatin** or **carboplatin** combined with **paclitaxel** (or **nab-paclitaxel**), **docetaxel**, **gemcitabine**, **pemetrexed**, or **vinorelbine** are considered standard care and equally effective in nonsquamous NSCLC.
- Guidelines recommend adding **bevacizumab**, a recombinant, humanized monoclonal antibody that neutralizes vascular endothelial growth factor (VEGF) to chemotherapy for patients with advanced NSCLC of nonsquamous cell histology, no history of recent significant hemoptysis, no CNS metastasis, and not receiving therapeutic anticoagulation.
- The most recent treatment advance for metastatic NSCLC is the addition of PD-1 (**nivolumab**, **pembrolizumab**) or PD-L1 (**atezolizumab**) inhibitors, regardless of the level of PD-L1 expression. Clinical guidelines recommend the combination of PD-1 or PD-L1 directed therapy and chemotherapy as first-line therapy for patients with nonbiomarker-driven NSCLC.
- Maintenance therapy is the ongoing use of one or more agents after a positive tumor response to four to six cycles of an initial chemotherapy regimen until disease progression. Continuation or switch maintenance therapy improves survival of NSCLC patients with nonsquamous histology. In continuation maintenance therapy, patients receive ongoing treatment with at least one of the agents used in the initial chemotherapy regimen. Alternatively, switch maintenance therapy starts a new agent not included in the initial regimen. **Pemetrexed** is the most established maintenance chemotherapy option.
- Monotherapy with **nivolumab**, **pembrolizumab**, **atezolizumab**, **docetaxel**, or **pemetrexed** is the most commonly considered option for second-line therapy in patients with a good performance status who progress during or after first-line chemotherapy. **Nivolumab**, **pembrolizumab**, and **atezolizumab** are options in the second-line setting for patients who have not previously received one of the drugs in the class.
- The efficacy of **docetaxel** has recently been improved with the addition of **ramucirumab** which binds to VEGF. Guidelines list **nivolumab**, **pembrolizumab**, or **atezolizumab** as preferred second-line regimens but **docetaxel** with or without **ramucirumab** has emerged as a standard second-line option because immunotherapy and **pemetrexed** are commonly used as first-line and maintenance therapy.

TABLE 62-1

Common Chemotherapy Regimens Used in the Adjuvant Treatment of Nonsmall Cell Lung Cancer

Regimen	Drugs and Doses	Frequency and Number of Cycles
Cisplatin/Etoposide	Cisplatin 100 mg/m ² IV day 1 Etoposide 100 mg/m ² IV daily on days 1, 2, and 3	Every 28 days for 4 cycles
Cisplatin/Vinorelbine	Cisplatin 50 mg/m ² IV days 1 and 8 Vinorelbine 25 mg/m ² IV days 1, 8, 15, and 22	Every 28 days for 4 cycles
	Cisplatin 100 mg/m ² IV day 1 Vinorelbine 30 mg/m ² IV days 1, 8, 15, and 22	Every 28 days for 4 cycles
Carboplatin/Paclitaxel	Carboplatin AUC 6 IV day 1 Paclitaxel 200 mg/m ² IV day 1	Every 21 days for 4 cycles
Cisplatin/Pemetrexed	Cisplatin 75 mg/m ² IV day 1 Pemetrexed 500 mg/m ² IV day 1	Every 21 days for 4 cycles (for nonsquamous histology only)

TABLE 62-2

Selected Regimens Used to Treat Advanced-Stage Nonsmall cell Lung Cancer

Place in Therapy	Regimen	Nonbiomarker Driven				EGFR Mutation Positive	ALK Rearrangement Positive
		Nonsquamous		Squamous Cell			
		Drugs, Doses, Frequency	Regimen	Drugs, Doses, Frequency	Regimen		

								Frequency
First line	Carboplatin/Paclitaxel/Bevacizumab	Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m ² IV on day 1 Bevacizumab 15 mg/kg IV on day 1 Repeat cycle every 3 weeks × 6 cycles—bevacizumab maintenance until progression	Gemcitabine/Cisplatin	Gemcitabine 1250 mg/m ² IV on days 1 and 8 Cisplatin 75 mg/m ² IV on day 1 Repeat cycle every 21 days × 6 cycles	Erlotinib	Erlotinib 150 mg (one 150 mg capsule) daily on an empty stomach	Crizotinib	Crizotinib 250 mg (one 250 mg capsule) twice daily without regard to meals
	Carboplatin/Pemetrexed	Carboplatin AUC 5 IV on day 1 Pemetrexed 500 mg/m ² IV on day 1 Repeat cycle every 3 weeks	Carboplatin/Paclitaxel/Pembrolizumab	Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m ² IV on day 1 or nab-paclitaxel 100 mg/m ² IV on days 1, 8, 15 Pembrolizumab 200 mg IV on day 1	Afatinib	Afatinib 40 mg (one 40 mg tablet) daily on an empty stomach	Alectinib	Alectinib 600 mg (four 150 mg capsules) twice daily with food
				Repeat cycle every 3 weeks × 4 cycles—pembrolizumab maintenance up to 31 additional doses or until progression				
	Platinum/Pemetrexed/Pembrolizumab	Cisplatin 75 mg/m ² or carboplatin AUC 5 IV on day 1 Pemetrexed 500 mg/m ² IV on day 1 Pembrolizumab 200 mg IV on day 1 Repeat cycle every 3 weeks × 4 cycles—pembrolizumab maintenance up to 31 additional doses or until progression			Osimertinib	Osimertinib 80 mg (one 80 mg tablet) daily without regard to meals		
	Carboplatin/Paclitaxel/Bevacizumab/Atezolizumab	Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m ² IV on day 1 Bevacizumab 15 mg/kg IV on day 1 Atezolizumab 1200 mg IV on						

		day 1 Repeat cycle every 3 weeks × 4 or 6 cycles—atezolizumab and bevacizumab maintenance until progression						
Second line	Docetaxel/Ramucirumab	Docetaxel 75 mg/m ² IV day 1 Ramucirumab 10 mg/kg IV day 1 Repeat every 21 days	Docetaxel/Ramucirumab	Docetaxel 75 mg/m ² IV day 1 Ramucirumab 10 mg/kg IV day 1 Repeat every 21 days	Osimertinib (if patient has not previously received)	Osimertinib 80 mg (one 80 mg tablet) daily without regard to meals	Brigatinib	Brigatinib 90 mg (one 90 mg tablet) daily for 7 days, then 180 mg (one 180 mg tablet) daily. Take without regards to meals
	Nivolumab	Nivolumab 3 mg/kg IV day 1 Repeat every 2 weeks	Nivolumab	Nivolumab 3 mg/kg IV day 1 Repeat every 2 weeks				
	Pembrolizumab	Pembrolizumab 2 mg/kg IV day 1 Repeat every 3 weeks	Pembrolizumab	Pembrolizumab 2 mg/kg IV day 1 Repeat every 3 weeks				

Small Cell Lung Cancer

- **Goals of Treatment:** The goals include cure or prolonged survival, which requires aggressive combination chemotherapy.

Limited Disease

- Use of surgery in SCLC is limited to solitary nodules without evidence of metastasis to lymph nodes.
- SCLC is very radiosensitive; radiation is preferred for treatment of local disease over surgery. Radiation is given concurrently with chemotherapy, and the regimen of choice is **etoposide** and **cisplatin** (EP regimen; see **Table 62-3**).
- Radiotherapy is used to prevent and treat brain metastases, a frequent occurrence with SCLC. Prophylactic cranial irradiation (PCI) is used in patients with limited or extensive disease to reduce the risk of brain metastases.

TABLE 62-3

Chemotherapy Regimens Used in the Treatment of SCLC

	Regimen	Drugs and Doses
First line	Etoposide/Cisplatin (EP)	Cisplatin 75 mg/m ² IV on day 1 Etoposide 100 mg/m ² IV on days 1–3; repeat cycle every 3 weeks for 4–6 cycles or Cisplatin 60 mg/m ² IV on day 1 Etoposide 120 mg/m ² IV on days 1–3; repeat cycle every 3 weeks for 4–6 cycles
	Etoposide/Carboplatin (EC)	Carboplatin AUC 5–6 IV on day 1 Etoposide 120 mg/m ² IV on days 1–3; repeat cycle every 3 weeks for 4–6 cycles
	Cisplatin/Irinotecan (IP)	Cisplatin 60 mg/m ² IV on day 1 Irinotecan 60 mg/m ² IV on days 1, 8, 15; repeat cycle every 4 weeks for 4–6 cycles or Cisplatin 30 mg/m ² IV on day 1 Irinotecan 65 mg/m ² IV on days 1 and 8; repeat cycle every 3 weeks for 4–6 cycles
	EC + atezolizumab ^a	Carboplatin AUC 5 IV on day 1 Etoposide 100 mg/m ² IV on days 1–3 Atezolizumab 1200 mg IV on day 1; repeat cycle every 3 weeks for 4 cycles followed by Atezolizumab 1200 mg every 3 weeks as maintenance
Second line	Topotecan	Topotecan 1.5 mg/m ² /day IV days 1–5; repeat every 3 weeks
	Nivolumab	Nivolumab 3 mg/kg IV; repeat every 2 weeks

^aExtensive stage only.

Extensive Disease

- The EP regimen is the regimen of choice to treat extensive-stage SCLC, with **irinotecan** and **cisplatin** as an acceptable alternative. The addition of the PD-L1 inhibitor **atezolizumab** to **carboplatin/etoposide** improved median PFS and overall survival and is the first significant improvement over standard platinum plus **etoposide** chemotherapy.
- Concurrent radiotherapy is not routinely used in extensive disease.

Relapsed Disease

- Relapsed SCLC is usually less sensitive to chemotherapy. **Topotecan** (IV and oral) is considered the second-line treatment of choice, but other agents should be considered because of its modest efficacy. If relapse occurs more than 3 months after first-line chemotherapy, national guidelines recommend single-agent **topotecan**, **gemcitabine**, **irinotecan**, **paclitaxel**, **docetaxel**, oral **etoposide**, **temozolomide**, and **vinorelbine**; CAV regimen (**cyclophosphamide**, **doxorubicin**, and **vincristine**); and participation in a clinical trial.
- Nivolumab** was recently approved for relapsed SCLC.
- SCLC that recurs within 3 months of first-line chemotherapy is considered refractory to chemotherapy and unlikely to respond to a second-line regimen. Patients should receive best supportive care or be enrolled in a clinical trial.

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluate tumor response to chemotherapy for NSCLC at the end of the second or third cycle and at the end of every second cycle thereafter. Patients with stable disease, objective response, or measurable decrease in tumor size should continue treatment until four to six cycles have been administered. Consider maintenance therapy with **pemetrexed** in responding patients with nonsquamous histology.
- Evaluate efficacy of first-line therapy for SCLC after two or three cycles of chemotherapy. If there is no response or progressive disease, therapy can be discontinued or changed to a non-cross-resistant regimen. If responsive to chemotherapy, the induction regimen should be administered for four to six cycles. Responding patients benefit from the addition of PCI following initial therapy.
- Intensive therapeutic monitoring is required for all patients with lung cancer to avoid drug-related and radiotherapy-related toxicities. These patients frequently have numerous concurrent medical problems requiring close attention.
- References should be consulted for management of common toxicities associated with the aggressive chemotherapy regimens used for lung cancer.

See Chapter 146, Lung Cancer, authored by Val R. Adams and Keith A. Hecht, for a more detailed discussion of this topic.

