Treatment of Lung Cancer

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KEYWORDS

• Lung cancer • Small cell • Non–small cell • Chemotherapy • Radiotherapy • Surgery • Molecular therapy

KEY POINTS

- Early-stage non–small cell lung cancer (NSCLC) is managed primarily by surgical resection, with adjuvant chemotherapy for selected patients.
- Stage III NSCLC is treated with combined modality therapy, usually concurrent chemotherapy plus radiotherapy, with curative intent.
- Advanced NSCLC remains an incurable disease treated primarily with chemotherapy and/or radiotherapy with palliative intent.
- Molecularly targeted therapy can greatly benefit selected patients with advanced NSCLC with specific genetic mutations.
- Limited-stage small cell lung cancer (SCLC) is treated with concurrent chemoradiotherapy with curative intent. Chemotherapy can prolong survival in patients with extensive-stage SCLC.

NON–SMALL CELL LUNG CANCER

Non–small cell lung cancer (NSCLC), which accounts for 85% of all cases of lung cancer, includes the histologic subtypes of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The goals of therapy for patients with NSCLC depend on the stage of disease: for patients with stage I to III disease, the goal is cure, whereas, for those with stage IV disease, the goals are palliation of symptoms and prolongation of life. Initial staging procedures need to answer 3 questions to adequately guide therapeutic decision making: (1) is the primary tumor confined to the lung with or without involvement of the hilar or peribronchial lymph nodes (stage I/II)? (2) Is the primary tumor invading the mediastinum or has the cancer spread to mediastinal lymph nodes (stage III)? (3) Are there distant metastases (stage IV)?

Stage I/II NSCLC

Surgery

About 25% of patients with NSCLC have stage I or II disease, with tumor confined to the lung (T1–T2) with (N1) or without (N0) metastases to hilar or peribronchial lymph nodes. The goal of therapy in these patients is cure, which is achievable in 60% to 80% and 40% to 50% with stage I and stage II disease, respectively. The primary curative modality is surgical resection with either lobectomy or pneumonectomy, depending on the extent of disease, along with mediastinal lymph node sampling or dissection (**Box 1**). When the chest wall or diaphragm is involved, an en bloc resection of these structures along with the lung may be required. An older randomized trial found that sublobar resections, such as wedge resection or segmentectomy, are inferior to lobectomy, with a higher rate of local/regional recurrence and lower

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Box 1
Treatment of stage I/II NSCLC

Local therapy

Lobectomy with mediastinal lymph node sampling (pneumonectomy if required to achieve negative margins)

Local therapy options in high-risk patients

Sublobar resection (wedge, segmentectomy)

Conventional external-beam radiation therapy

Stereotactic body radiation therapy

Radiofrequency ablation

Adjuvant chemotherapy

Stage IB (consider if tumor ≥4 cm)

Stage IIA/B (recommended)

Platinum-based, 2-drug regimen × 4 cycles

5-year survival rate.[1] However, because of improved imaging techniques and the trend toward the diagnosis of smaller, more peripheral tumors, lung-sparing procedures are currently being reevaluated. A retrospective analysis of 784 patients who underwent either sublobar resection or lobectomy for stage IA tumors (<3 cm) noted no differences in efficacy outcomes.[2] However, other retrospective analyses have shown that sublobar resections result in lower survival rates than lobectomy in patients with tumors greater than or equal to 3 cm. Prospective, nonrandomized trials have suggested that, for patients with small tumors, limited resections may provide the same outcomes as lobectomy, particularly in older patients and those with limited lung function.[3] Based on these observations, an ongoing, phase III, Cancer and Leukemia group B (CALGB) trial is randomizing patients with tumors less than or equal to 2 cm and no evidence of lymph node metastases to undergo either sublobar resection or lobectomy.

Thoracic surgical techniques have improved markedly in the past decade, with the major advance being video-assisted thoracoscopic surgery (VATS). VATS lobectomy is associated with reduced acute postoperative pain, less impairment in pulmonary function, and shorter hospital stays. A recent meta-analysis reported no difference in the locoregional recurrence, but a significant decrease in systemic recurrence and improvement in 5-year survival with VATS lobectomy compared with open lobectomy.[4] The lower rate of pulmonary morbidity with VATS has opened up the surgical option for patients who are not considered candidates for open thoracotomy.[5] However, a recent retrospective analysis found a higher intraoperative complication rate with VATS versus open lobectomy, and no differences in in-hospital mortality, length of stay, wound infection rate, or pulmonary and cardiovascular complication rates.[6] There are, as yet, no specific guidelines to assist in deciding between VATS versus open thoracotomy. Recent reports have shown the feasibility and safety of robotic lobectomy, but it remains to be determined whether this technology offers any significant advantages compared with conventional VATS or open approaches.[7]

Before surgery, patients need appropriate preoperative assessment to ensure that they can tolerate the predicted reduction in lung volume, especially because most patients with lung cancer are current or former smokers with impaired baseline pulmonary function. At a minimum, patients need full pulmonary function testing, including diffusion capacity (carbon monoxide diffusion in the lung [DLCO]), with further evaluations, such as quantitative V/Q scans or exercise capacity testing, conducted if pulmonary function is impaired. Cardiac status should also be assessed before surgery. All patients should be encouraged to stop smoking before surgery because complication rates and postoperative mortality are both substantially higher among patients who are active smokers.[8]

Nonsurgical therapy

Conventional radiotherapy Some patients with stage I/II NSCLC are not candidates for surgical resection, primarily because of impaired lung function. In such situations, the standard of care is radiation therapy (RT) to the primary tumor and any involved lymph nodes (see **Box 1**). Clinical trial RTOG 73-01, in which patients with inoperable NSCLC were randomized to various doses of RT, concluded that a total dose of 60 Gy administered in daily fractions of 2 Gy over 6 weeks resulted in the best local control and 2-year survival rates.[9] The 5-year survival rates for patients with medically inoperable stage I NSCLC treated with conventional RT range from 15% to 48%, with a local failure rate of about 50%.[10] Although these outcomes are clearly inferior to those of patients who undergo surgical resection, it is not clear whether these differences are caused by the inadequacy of conventional RT or patient selection.

A major limitation of RT is the occurrence of normal lung injury with higher radiation doses. The incorporation of specialized computed tomography (CT) scanners and software that allows three-dimensional delineation of the tumor and adjacent normal structures has greatly improved the safety of thoracic RT. Other advances, including

intensity-modulated radiotherapy, respiratory gating and control, and the use of positron emission tomography (PET) to guide target volume, have allowed radiation oncologists to maximize the delivery of radiation to the tumor and minimize damage to normal surrounding tissues.

Stereotactic body RT Stereotactic body RT (SBRT) incorporates multiple photon beams to deliver a high dose of radiation to a defined volume of tumor with a high level of precision in a small number of fractions. In addition to the potential for improved tumor kill caused by higher dose therapy, SBRT also allows a significant decrease in the dose received by surrounding normal tissue. SBRT is applicable to small (<5 cm) tumors and requires the minimization and/or tracking of tumor motion with radiation delivery at specific points in the respiratory cycle. The total dose and fractionation for SBRT varies between 30 Gy in 1 fraction to 60 Gy in 3 to 5 fractions. The biologic effective dose of these treatments is higher than the absolute value of the dose, with 60 Gy in 3 fractions being roughly equivalent to 150 Gy delivered in conventional 2 Gy daily fractions. For patients with medically inoperable stage I NSCLC, SBRT has achieved excellent local control rates of 85% to 96% and 5-year survival rates of more than 50%.[11] In addition, patients do not need to meet a minimum threshold of pulmonary function to undergo SBRT.

Toxicity associated with SBRT is generally limited, with severe adverse events reported in less than 5% of patients.[12] The major side effects are pulmonary injury, chest wall pain, and rib fractures. Toxicity rates are higher when SBRT is applied to tumors near the major bronchi, with an 11-fold increase in the risk of severe toxicity in patients with central tumors compared with those with peripheral tumors.[12]

Thus far, SBRT has been used primarily in patients with medically inoperable stage I NSCLC (see **Box 1**), although ongoing trials are comparing SBRT with sublobar resections in patients with marginal lung function (forced expiratory volume in 1 second or DLCO <50%), and even with lobectomy in patients who are deemed fit for optimal resection.

Radiofrequency ablation Radiofrequency ablation (RFA) involves imparting thermal injury through electromagnetic energy generated from a probe emitting high-frequency alternating current. The probe is placed with CT guidance, usually under conscious sedation. Pathologic studies have shown that a well-circumscribed region of coagulative necrosis develops around the RFA probe. An important limiting factor to the adequacy of tumor ablation by RFA is heat loss through convection by means of nearby blood circulation, the heat-sink effect. This effect is particularly problematic if the target tumor sits close to blood vessels larger than 3 mm in diameter. The major complications of RFA are pneumothorax requiring chest tube placement in 11% of patients, pleural effusion, and intrapulmonary hemorrhage. No significant decline in post-RFA lung function has been reported.

RFA can be used as primary treatment of stage I NSCLC in patients who are not surgical candidates, or as salvage therapy for recurrent lung tumors (see **Box 1**). A recent prospective study of RFA in patients with either primary lung cancer or lung metastases from other primary sites reported that the complete ablation rate by imaging was 80% for tumors less than or equal to 3.5 cm, with 1-year and 2-year survival rates of 70% and 48%, respectively, in patients with NSCLC.[13] Another study of 75 patients with stage I NSCLC reported a 27% 5-year survival rate.[14] Overall, these results seem to be comparable with those achieved with external-beam RT. All reports on RFA have shown that outcomes vary based on tumor size, with declining rates of complete response in tumors greater than 3 cm in diameter. A recent report on 64 patients with stage I NSCLC who were not candidates for lobectomy and were treated with either sublobar resection, cryotherapy, or RFA found that all outcomes, including overall and cancer-specific survival, were similar with each of these treatment modalities.[15] Although this was not a randomized study, these results suggest that RFA is a reasonable option for medically inoperable patients with stage I NSCLC. The value of nonsurgical treatments in patients with localized NSCLC remains to be determined in prospective clinical trials.

Adjuvant therapy

Distant relapse is the primary cause of death in patients with NSCLC who die within 5 years of a complete surgical resection. Thus, even when the cancer seems to be limited to the lung, undetected micrometastases remain a common problem. Randomized clinical trials have recently shown an absolute improvement of 5% to 15% in the 5-year survival rate for patients with stage II and III NSCLC who receive adjuvant platinum-based chemotherapy after complete surgical resection (see **Box 1**).[16] However, there is no clear benefit for adjuvant chemotherapy in patients with stage I disease. Secondary analyses have shown that patients with stage IB NSCLC who have tumors greater than or equal to 4 cm may derive a survival benefit from adjuvant chemotherapy.[17,18]

Any of the platinum-based, 2-drug chemotherapy regimens that are currently used in patients with advanced NSCLC are considered reasonable options for treatment in the adjuvant setting. Adjuvant chemotherapy should be started within 2 to 3 months of surgical resection, so only patients with good performance status who have an uncomplicated surgical recovery within that timeframe should be considered for adjuvant treatment. Although standard adjuvant therapy consists of 4 cycles of an appropriate regimen, the toxicity of chemotherapy after lung resection can be challenging and only 60% to 70% of patients are able to complete all 4 cycles of therapy. Toxicities vary based on the agents used, but common toxicities include neutropenia, anemia, nausea, vomiting, fatigue, and neuropathy.[19]

Stage III NSCLC

Up to 35% of patients with NSCLC present with stage III disease in which the primary tumor has directly invaded local structures outside the lung (T3–T4) and/or the cancer has spread to mediastinal lymph nodes (N2–N3). These locally advanced tumors are generally not amenable to primary surgical resection. In addition, they are usually associated with systemic micrometastases that frequently result in distant relapse. In the past, RT or surgical resection were used to treat patients with locally advanced NSCLC, yielding 5-year survival rates less than 5% because of frequent systemic recurrences. Patients with locally advanced disease are now most commonly treated with combined modality therapy incorporating chemotherapy and RT in an effort to control both local and distant disease (**Box 2**). Initial studies of sequential chemotherapy followed by RT reported improved 5-year survival rates of 10% to 15%.[20]Concurrent administration of chemotherapy and radiotherapy subsequently further increased long-term survival rates to 20% to 30%, with median survival times of 18 to 24 months.[21,22] Standard chemotherapy regimens used during chemoradiotherapy include cisplatin or carboplatin plus etoposide, paclitaxel or, more recently, pemetrexed. Definitive RT is given 5 d/wk for 6 to 7 weeks to a total dose of 60 to 70 Gy.[23–25] The increase in survival with concurrent therapy is mirrored by increased toxicity, primarily esophagitis and pneumonitis. Many patients with locally advanced NSCLC are not able to tolerate concurrent chemoradiotherapy because of poor performance status, substantial weight loss, or comorbid conditions. In such patients, the treatment plan needs to be individualized to optimize control of symptoms and the disease, without inducing excessive therapy-related complications (see **Box 2**).

Box 2
Treatment of stage III NSCLC

Standard therapy

Concurrent chemotherapy plus definitive radiotherapy

Induction chemoradiotherapy followed by surgical resection (selected patients with non-bulky mediastinal lymph nodes who do not require pneumonectomy for adequate resection)

Options in poor-risk patients

Sequential chemotherapy followed by radiotherapy

Radiotherapy alone

Pathologic stage III following surgical resection

Adjuvant chemotherapy: platinum-based, 2-drug regimen × 4 cycles

Consider adjuvant radiotherapy after completion of chemotherapy

Several trials have evaluated trimodality therapy, using induction chemotherapy or chemoradiotherapy before surgical resection with further chemotherapy or RT after surgery. Patients enrolled in such studies must be fit and have non-bulky mediastinal disease. Thus far, these trials have failed to show a clear survival benefit for trimodality therapy compared with standard, definitive chemoradiotherapy for patients with stage III NSCLC.[26] However, secondary analyses suggest that some patients may benefit from this approach. Therefore, induction chemoradiotherapy followed by surgery should be considered in a select subgroup of patients to maximize the possibility of cure (see **Box 2**).

Some patients who undergo surgery for clinical stage I or II NSCLC have microscopic involvement of mediastinal lymph nodes on pathologic review following apparent complete resection. These patients have a high risk of systemic relapse and should receive adjuvant chemotherapy. Although adjuvant RT does increase local control rates, it has not resulted in a clear survival benefit in patients with completely resected NSCLC. However, based on retrospective analyses suggesting an improvement in overall survival with adjuvant RT in patients with microscopic mediastinal lymph node involvement (N2), mediastinal RT, given after the completion of adjuvant chemotherapy, is a reasonable option in such patients.[19]

Stage IV NSCLC

NSCLC is diagnosed at an advanced stage in more than 40% of patients. The widespread use of PET has contributed to a recent increase in the proportion of patients being diagnosed with advanced, or metastatic, disease.[27] Common metastatic sites include the contralateral lung, brain, bone, liver, and adrenal glands. In patients with advanced disease, clinical and molecular differences between adenocarcinoma and squamous cell carcinoma are increasingly being used in therapeutic decision making. The outcome of patients with advanced NSCLC has steadily improved in the past 2 decades as a result of more effective therapeutic options, improved supportive care measures, and stage migration because of advanced imaging technology.[28]

First-line chemotherapy

Platinum-based chemotherapy is the cornerstone of treatment of patients with advanced NSCLC.[29] The superiority of platinum-based chemotherapy compared with best supportive care was conclusively established in randomized studies that noted improvements in both overall survival and quality of life.[30] Combination chemotherapy results in higher response rates and better overall survival than single-agent therapy.[31] Combination regimens consisting of cisplatin or carboplatin plus a third-generation chemotherapeutic agent, such as paclitaxel, docetaxel, vinorelbine, gemcitabine, or pemetrexed, have all shown similar efficacy, but varying toxicity, when used as first-line therapy, suggesting that an efficacy plateau had been reached with standard cytotoxic chemotherapy in patients with advanced NSCLC.[32,33] For patients with a good performance status (Eastern Cooperative Oncology Group [ECOG] scale 0–1), platinum-based chemotherapy remains the standard of care (**Box 3**). For patients with a marginal performance status (ECOG 2), single-agent therapy may be a more reasonable option based on the poor overall prognosis in these patients. Cytotoxic chemotherapy does not benefit patients with a poor performance status (ECOG 3–4).

Given that advanced NSCLC is an incurable disease in which the overall goal of care is palliation, carboplatin-based regimens have become a more popular alternative than cisplatin-based regimens in the United States because of their more favorable toxicity profile. Randomized studies have established that 4 cycles of combination chemotherapy is optimal for first-line therapy.[34] Continuation of chemotherapy beyond 4 cycles often leads to excessive toxicity without improvement in overall survival. Modern, platinum-based chemotherapy regimens result in objective response rates of 30% to 40%, median overall survival of 8 to 10 months, and 1-year and 2-year survival rates of 30% to 40% and 20% to 25%, respectively.

Box 3
Treatment of advanced-stage NSCLC

First-line therapy (combination chemotherapy)
Carboplatin/cisplatin + paclitaxel
Carboplatin/cisplatin + docetaxel
Carboplatin/cisplatin + pemetrexed (nonsquamous)
Carboplatin/cisplatin + gemcitabine
Bevacizumab (nonsquamous)[a]
Erlotinib (EGFR-mutant tumor)
Crizotinib (ALK-mutant tumor)

Second-line therapy (single-agent therapy)
Docetaxel
Pemetrexed (nonsquamous)
Erlotinib
Crizotinib (ALK-mutant tumor)

Third-line therapy (single-agent therapy)
Erlotinib

Maintenance therapy (single-agent therapy)
Pemetrexed (nonsquamous)
Erlotinib
Bevacizumab (nonsquamous)[b]

[a] In combination with platinum-based chemotherapy.
[b] Only in patients who received bevacizumab plus chemotherapy as first-line therapy.

Maintenance therapy

Maintenance therapy, or early second-line therapy, refers to the continued treatment of patients with an active therapeutic agent after achieving an objective response or stable disease with 4 cycles of first-line chemotherapy. The purpose of maintenance therapy is to delay disease progression, improve overall survival, and maintain the period of symptomatic benefits achieved with first-line therapy. The US Food and Drug Administration (FDA) has approved both pemetrexed and erlotinib as maintenance therapy in patients with advanced NSCLC.

In a randomized, phase III study, pemetrexed was compared with placebo in patients who had achieved disease control with a platinum-based first-line regimen.[35] Pemetrexed maintenance resulted in modest improvements in both progression-free and overall survival, particularly for

patients with adenocarcinoma who garnered a 5-month improvement in median survival. Another randomized study compared maintenance erlotinib with placebo.[36] In the overall study population, erlotinib led to a modest, but statistically significant, improvement in both progression-free and overall survival. Patients whose tumors had an activating EGFR mutation had a more robust benefit. However, both of these studies were flawed in that less than 20% of patients in the placebo arms received either pemetrexed or erlotinib, respectively, on disease progression, which likely exaggerated the observed clinical benefits of maintenance therapy.[35,36] In addition, patients in the maintenance therapy arms received more active therapy overall than those in the placebo arms. These issues are underscored by a study that randomized patients to receive docetaxel as either maintenance therapy or salvage therapy and reported similar overall survival in those patients who received docetaxel in both arms.[37] Proponents of maintenance therapy have argued that maintenance therapy may be beneficial precisely because it ensures that patients receive a greater number of active agents.[38] The use of maintenance therapy is currently considered an option for patients without progression of disease after the completion of first-line chemotherapy (see **Box 3**). The decision on whether or not to use maintenance therapy is based on multiple factors, including disease burden, patient preference, performance status, disease-related symptoms, treatment-related side effects, and cost.

Salvage chemotherapy

Most patients who receive first-line chemotherapy develop progression of disease within 4 to 6 months. Docetaxel and pemetrexed are both approved by the FDA as second-line chemotherapy in patients with advanced NSCLC (see **Box 3**). Docetaxel has shown superiority compared with best supportive care in relapsed NSCLC based on modest improvements in overall survival and symptom control.[39] Pemetrexed was directly compared with docetaxel in a large, randomized study of patients with relapsed, advanced NSCLC and had similar efficacy, but less toxicity.[40] The benefits of pemetrexed seem to be restricted to patients with nonsquamous histology.[41] Both docetaxel and pemetrexed yield a response rate of less than 10% and a median survival of approximately 8 months in the second-line setting.

Erlotinib, an EGFR inhibitor, is also approved for therapy for relapsed, advanced NSCLC. In a large phase III study, patients with progressive NSCLC following 1 or 2 prior chemotherapy regimens were randomized to receive either erlotinib or placebo.[42] Erlotinib resulted in a response rate of 9%, greater symptom relief, and a modest improvement in overall survival (6.7 months vs 4.7 months; $P<.001$). Although approved for use in unselected patients, erlotinib has been most effective in the subset of patients whose tumors harbor activating mutations of the EGFR gene.[43,44]

Targeted therapy

In the past decade, there has been a large increase in knowledge regarding critical cell-signaling pathways that affect carcinogenesis, cellular proliferation, evasion of apoptosis, and metastasis. As a result, numerous therapeutic agents that interact with specific molecular targets have been developed to improve outcomes for patients with many types of cancer, including NSCLC.

EGFR mutation EGFR is part of a critical cell-signaling pathway in NSCLC. Activation of EGFR results in phosphorylation of downstream proteins that then promote cancer proliferation and metastasis. EGFR tyrosine kinase inhibitors (TKI), such as erlotinib and gefitinib, were initially evaluated without molecular selection in patients with relapsed NSCLC.[42,45] In 2004, it was recognized that robust clinical responses to EGFR TKIs were linked to activating mutations in exons 19 or 21 of the EGFR gene and that these mutations are associated with certain clinical characteristics, such as female sex, adenocarcinoma histology, never smokers, and east Asian ethnicity.[43,44] In patients with tumors harboring EGFR-activating mutations, EGFR TKIs are superior to chemotherapy with response rates of 60% to 80% and median progression-free survivals of 9 to 11 months (see **Box 3**, **Table 1**).[46–50] In the white population, EGFR mutations are observed in 10% to 15% of patients with advanced NSCLC. These agents are associated with a favorable toxicity profile, with the main toxicities being rash and diarrhea. Molecular testing for EGFR mutations has now become a standard approach for patients with advanced lung adenocarcinoma.

ALK gene rearrangement Rearrangement of the ALK gene is observed in 4% to 5% of tumors from patients with advanced NSCLC, and is associated with never-smoking status and adenocarcinoma histology.[51] The resulting fusion protein acts as a dominant oncogenic signal.[52] Crizotinib, an inhibitor of the ALK kinase, has recently received accelerated approval by the FDA for the treatment of patients with ALK mutation–positive NSCLC. Crizotinib results in an objective response rate of nearly 60% and a median progression-free survival of 10 months in patients with relapsed NSCLC with an ALK gene rearrangement

Table 1
Randomized trials of EGFR inhibitors versus chemotherapy in EGFR-mutant NSCLC

			Response Rate		Progression-free Survival		Overall Survival	
Study	Regimens	N	%	*P*	Median	HR (*P*)	Median	HR (*P*)
IPASS[46]	Gefitinib	132	71	<.001	NR	0.48 (<.001)	21.6 mo	1.00 (.99)
	Carboplatin + paclitaxel	129	47		NR		21.9 mo	
NEJSG[47]	Gefitinib	114	74	<.001	10.8 mo	0.30 (<.001)	30.5 mo	(.31)
	Carboplatin + paclitaxel	114	31		5.4 mo		23.6 mo	
WJTOG[48]	Gefitinib	86	62	<.0001	9.2 mo	0.49 (<.0001)	Not reported	
	Cisplatin + docetaxel	86	32		6.3 mo			
OPTIMAL[49]	Erlotinib	82	83	<.0001	13.7 mo	0.16 (<.0001)	Not reported	
	Carboplatin + gemcitabine	72	36		4.6 mo			
CTONG[50]	Erlotinib	77	58	<.0001	9.7 mo	0.37 (<.0001)	22.9 mo	0.80 (.42)
	Platinum + docetaxel or Platinum + gemcitabine	76	15		5.2 mo		18.8 mo	

Abbreviations: CTONG, China thoracic oncology group; EURTAC, European Erlotinib Versus Chemotherapy; IPASS, Iressa Pan-Asia study; NEJSG, North-East Japan study group; WJTOG, West Japan thoracic oncology group.

(see **Box 3**, **Table 2**).[53–55] Daily oral administration of crizotinib is well tolerated, and is now being compared with standard chemotherapy in randomized studies of patients with ALK mutation–positive NSCLC.

Antiangiogenic therapy Angiogenesis is a critical event for tumor formation and metastasis. The vascular endothelial growth factor (VEGF) is an important regulator of angiogenesis and has been extensively evaluated as a target for anticancer therapy. Bevacizumab is a monoclonal antibody that binds to VEGF and inhibits new vessel formation. Bevacizumab is approved by the FDA for use in combination with chemotherapy as first-line treatment in patients with advanced NSCLC based on a randomized trial in which bevacizumab plus chemotherapy resulted in a higher response rate and improved overall survival (12.3 months vs 10.3 months, $P = .003$) compared with chemotherapy alone (see **Box 3**).[56] Common side effects of bevacizumab include hypertension, bleeding, arterial thrombosis, and proteinuria. The use of bevacizumab is not recommended for patients with squamous cell histology because of a high risk of pulmonary hemorrhage.[57] Several other antiangiogenic agents have been evaluated in patients with advanced NSCLC, with disappointing results. Thus far, efforts to identify biomarkers to aid patient selection for antiangiogenic therapy have been unsuccessful.

Future Directions

There are some novel targeted agents and predictive biomarkers for the treatment of advanced NSCLC. In a recent study analyzing NSCLCs for mutations in several relevant genes, including EGFR, HER2, KRAS, MET, BRAF, PI3K, and PTEN, a dominant, activating mutation

Table 2
ALK inhibition in ALK mutation–positive NSCLC

			Response		
Trial	Agent	N	Objective Response Rate (%)[a]	Disease Control Rate (%)[b]	Median Progression-Free Survival
Phase I[53,54]	Crizotinib 250 mg by mouth twice daily	119	61	88	10 mo
Phase II[55]	Crizotinib 250 mg by mouth twice daily	76	54	91	Not reported

[a] Objective response rate = complete response rate + partial response rate.
[b] Disease control rate = complete response rate + partial response rate + stable disease rate.

was found in tumors from 54% of patients with advanced lung adenocarcinoma.[58] Efforts are now underway to study specific targeted agents in these molecularly distinct patient subsets with the overall goal of selecting appropriate therapy based on the mutational profile of the individual patient's tumor. In patients with squamous cell histology, amplification of the fibroblast growth factor receptor was recently noted in nearly 25% of tumors.

Given the growing number of molecular targets and therapeutic agents available for specific subgroups of patients with NSCLC, it is important to obtain sufficient tissue specimens to allow an accurate diagnosis and molecular studies. Core biopsies are preferable to aspiration biopsies in patients with suspected lung cancer to maximize the diagnostic yield of the specimens. The shift toward individualized therapy for NSCLC has begun to yield significant improvements in patient outcomes during the past decade.

Box 4
Stage-specific treatment of SCLC

LS

Cisplatin + etoposide × 4 cycles (substitute carboplatin if cisplatin is contraindicated)

Early, concurrent thoracic radiotherapy

Prophylactic cranial irradiation for responders

Surgical resection followed by adjuvant chemotherapy (stage I only)

ES

Platinum-based chemotherapy (eg, carboplatin + etoposide) × 4 to 6 cycles

Prophylactic cranial irradiation for responders

Recurrent disease

Single-agent chemotherapy

Palliative radiotherapy, as indicated for symptoms

Clinical trials of investigational agents

SMALL CELL LUNG CANCER

Small cell lung cancer (SCLC) is an aggressive malignancy characterized by neuroendocrine differentiation, early metastases, and initial responsiveness to therapy. The overall incidence of SCLC peaked in the 1980s and has been declining since then, with SCLC now comprising about 15% of all cases of lung cancer.[59,60]

The Veterans' Administration Lung Group classification scheme is routinely used to stage SCLC.[61] Limited stage (LS) is defined as tumor confined to 1 hemithorax, with or without regional lymph node involvement, which can be safely encompassed in a single radiotherapy port. Extensive stage (ES) is defined as disease that has spread beyond this point, including malignant pleural effusion and hematogenous metastases. At presentation, two-thirds of patients have ES disease.[60] The tumor-node-metastasis (TNM) staging system for lung cancer can be applied to SCLC because the T and N descriptors, and the overall stage I to IV groupings, are discriminatory for survival in SCLC, as well as NSCLC.[62]

Treatment

Radiotherapy

The goal of therapy in patients with LS-SCLC is cure, which can be achieved through combined modality therapy with chemotherapy plus radiation (**Box 4**). Two meta-analyses have concluded that the addition of definitive thoracic RT to chemotherapy significantly improves 2-year to 3-year overall survival in patients with LS-SCLC by 5.4% ($P = .001$).[63,64] In addition, initiating thoracic RT early in the course of chemotherapy yields a 5% 2-year overall survival benefit compared with late RT ($P = .03$).[65] The optimal fractionation schedule of thoracic RT remains unclear, with discrepant findings in 2 large randomized trials. Turrisi and colleagues[66] randomized 417 patients with LS-SCLC to receive standard cisplatin plus etoposide with 45 Gy of early, concurrent RT given either once daily over 5 weeks or twice daily over 3 weeks. There was a significant improvement in overall survival in patients receiving twice-daily RT compared with those receiving once-daily RT (5-year survival, 26% vs 16%; $P = .04$). The primary criticism of this trial is a the lack of biologic equivalence between the radiation doses administered on the 2 arms caused by the low total dose given to patients receiving once-daily RT. A second trial randomized 262 patients with LS-SCLC to receive standard cisplatin plus etoposide with either once-daily RT to 50.4 Gy in 28 fractions or twice-daily RT to 48 Gy in a split course of 32 fractions.[67] This trial found no significant differences in overall survival between the 2 arms (3 years: once-daily arm, 34%, vs twice-daily arm, 29%; $P = .49$). However, late initiation of RT with the third cycle of chemotherapy and the use of split-course therapy in the twice-daily arm may have compromised the outcome of this study. It is hoped that the role of hyperfractionated RT in LS-SCLC will be more clearly defined in ongoing, well-designed trials.

Up to 60% of patients with SCLC develop brain metastases during the course of their illness. A meta-analysis of studies evaluating prophylactic cranial irradiation (PCI) reported a 25% decrease in the incidence of brain metastases (58.6% vs 33.3%, $P<.001$) and a 5.4% increase in 3-year overall survival (15.3% vs 20.7%, $P = .01$) with the addition of PCI after primary treatment.[68] Most patients included in this meta-analysis had LS-SCLC. To determine the role of PCI in patients with ES-SCLC, a European Organisation for Research and Treatment of Cancer (EORTC) trial randomized 286 patients with ES-SCLC to receive PCI or not to receive PCI after response to initial chemotherapy.[69] The investigators reported that PCI decreased the incidence of symptomatic brain metastases (14.6% vs 40.4%, $P<.001$) and increased the 1-year survival rate (27.1% vs 13.3%, $P = .003$) without a long-term decrement in global quality of life. Based on these trials, PCI is now recommended for patients with either LS-SCLC or ES-SCLC who have a good performance status after achieving a response to initial therapy (see **Box 4**).

Chemotherapy

Without treatment, patients with SCLC have a poor prognosis, with median survival times of 7 to 14 weeks depending on stage. Early trials with single agents revealed high rates of partial response of brief duration. Subsequent clinical trials of combination chemotherapy regimens, such as cyclophosphamide, doxorubicin, and vincristine (CAV) or etoposide and cisplatin (EP), yielded significant improvements with response rates of 60% to 80%, complete response rates of 15% to 25%, and median survival times of 7 to 10 months.[70,71] A recent phase III study comparing EP with cyclophosphamide, epirubicin, and vincristine (CEV) reported that overall survival was significantly better in patients receiving EP (10.2 vs 7.8 months, $P = .0004$).[72] In addition, 2 meta-analyses have shown a modest survival advantage for cisplatin-based therapy.[73,74] EP is now the preferred regimen in both ES-SCLC and LS-SCLC (see **Box 4**).

Several newer combinations of drugs have shown promising efficacy in early phase trials. Among these, the combination of irinotecan plus cisplatin (IP) has garnered the most interest, and 3 randomized trials comparing IP with EP in patients with ES-SCLC have been completed (**Table 3**). The first study, from Japan, reported that IP resulted in significantly better response rate, progression-free survival, and overall survival.[75] However, 2 randomized trials in Western patients have failed to confirm these findings, with both reporting no significant differences in response rate or survival between patients receiving IP or EP.[76,77] A large, phase III trial comparing EP with the combination of cisplatin plus topotecan, a drug related to irinotecan, also failed to show any significant differences in the efficacy of these 2 regimens (see **Table 3**).[78] Therefore, EP remains the standard of care for non-Japanese patients with SCLC.

A variety of chemotherapy-based strategies, including dose intensification, weekly administration, 3-drug regimens, high-dose consolidation with stem cell rescue, alternating or sequential non–cross-resistant regimens, and maintenance therapy, have failed to yield substantial improvements in survival, and many of these approaches have resulted in unacceptable toxicity.

Table 3
Randomized trials of cisplatin plus irinotecan or topotecan in ES-SCLC

			Response Rate		Overall Survival			
Trial	Arm	N	%	*P*	Median (mo)	1 y (%)	2 y (%)	*P*
Noda et al,[75] 2002	IP	77	84	.02	12.8	58.4	19.5	.002
	EP	77	68		9.4	37.7	5.2	
Hanna et al,[76] 2006	IP	221	48	NS	9.3	35	8	.74
	EP	110	44		10.2	35	8	
Lara et al,[77] 2009	IP	324	60	.56	9.9	41	NR	.71
	EP	327	57		9.1	34	NR	
Eckardt et al,[78] 2006	TP	389	63	NS	9.0	31	NR	.48
	EP	395	69		9.2	31	NR	

Abbreviations: EP, etoposide + cisplatin; IP, irinotecan + cisplatin; NR, not reported; NS, not significant; TP, oral topotecan + cisplatin.

Recurrent disease

Most patients with LS-SCLC, and nearly all with ES-SCLC, develop recurrence of disease. Recurrent SCLC is categorized as either resistant (primary progression or recurrence within 3 months of initial therapy) or sensitive (recurrence more than 3 months after initial therapy), with lower response rates to second-line therapy noted in those with resistant disease. For patients whose initial response lasts for more than 6 to 8 months, the reinitiation of the initial chemotherapy regimen may be the favored approach, with reported response rates of up to 60%.[79] For patients relapsing within 6 months of initial therapy, treatment with a second-line agent seems to be a more appropriate strategy.

The benefit of second-line therapy in patients with recurrent SCLC was shown in a randomized trial that compared oral topotecan with best supportive care and reported that overall survival was significantly better in patients receiving chemotherapy (median survival, 26 vs 14 weeks; 6-month survival, 49% vs 26%; $P = .01$).[80] Many single agents and combination regimens have been evaluated in noncomparative phase II trials of patients with relapsed SCLC. Although response rates seem to be higher with combination therapy, overall survival does not seem to be improved and the toxicity of combination regimens can be excessive. One randomized phase III trial compared single-agent topotecan with the combination of CAV in patients with relapsed SCLC and found no significant differences in response rate (24% vs 18%, $P = .29$), time to progression (13 vs 12 weeks, $P = .55$), or overall survival (median, 25 vs 25 weeks, $P = .79$).[81] However, hematologic toxicity was significantly greater with CAV. Based on these results, single-agent chemotherapy is the preferred approach for patients with recurrent SCLC who have maintained a good performance status (see **Box 4**).

Future Directions

The investigational drug amrubicin has shown promising activity in patients with SCLC. Single-agent amrubicin has yielded response rates of up to 79% in chemotherapy-naive patients with ES-SCLC and up to 52% in patients with recurrent disease.[82,83] However, a randomized, phase III trial comparing amrubicin with topotecan in patients with recurrent SCLC reported a significant improvement in response rate with amrubicin (31% vs 17%, $P = .0002$), but no significant differences in progression-free or overall survival.[84]

Numerous molecular pathways that drive the progression of cancer have been identified and many therapeutic agents that target these pathways have been developed. Many such molecularly targeted strategies have been evaluated in clinical trials in patients with SCLC. Thus far all of them, including antiangiogenic agents, metalloproteinase inhibitors, growth factor inhibitors, and proapoptotic agents, have failed to show promising clinical activity. Despite these setbacks, more molecular strategies are now being evaluated in preclinical and clinical studies in SCLC, including those targeting apoptotic pathways (small-molecule Bcl-2 inhibitors) and cancer stem cells (Notch and hedgehog inhibitors).[85]

From 1973 to 2002, the 2-year survival rate for patients with LS-SCLC improved incrementally from 15% to 22%, whereas little improvement was noted for patients with ES-SCLC (3.4%–5.6%).[56] It is clear that new, more effective therapeutic strategies are needed if there are going to be any further substantial gains in the treatment of patients with SCLC.

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