Case Studies in Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations

Part 8 of 12: Limited-Stage Small-Cell Lung Cancer in a 65-Year-Old Woman

Dear Colleague:

Small-cell lung cancer (SCLC) is the most aggressive type of lung cancer and is almost always widely disseminated at patient presentation. It is, however, the most responsive to chemotherapy. Treatment decisions are based largely on the results of staging studies, which differentiate limited- from extensive-stage disease. Current first-line treatment protocols produce a complete response in 45% to 75% of patients with limited-stage disease, but the majority of patients who respond will ultimately develop recurrent disease. Upon recurrence, second-line therapy is selected based on consideration of likelihood of response, toxicity, and quality of life.

This Tx Reporter presents the case of a 65-year-old woman who has limited-stage SCLC. After achieving a complete response to first-line therapy, her disease recurs with multiple metastases to the bone. This case discusses staging and first-line therapy for limited-stage SCLC. It also describes treatment options for recurrence, including the option of a drug holiday during a time of stable disease.

We are pleased to offer you Limited-Stage Small-Cell Lung Cancer in a 65-Year-Old Woman, part 8 of the 12-part series, Case Studies in Recurrent Gynecologic and Lung Cancer: Chemotherapeutic Innovations. These case-based newsletters, designated for .25 CME credit each, will focus on gynecologic cancers and lung cancer. Presentations of patient cases and discussion of relevant treatment dilemmas and options by a distinguished faculty of oncologists are designed to update you on the latest clinical trial results and their implications for clinical practice.

We hope you find this series helpful and informative, and that the discussions will assist you in incorporating this information into your clinical practice.

Sincerely,

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Part 8 of a 12-Part Series

Patient Description

Ms. F is a 65-year-old homemaker with two adult children and a good health history. She sought initial medical attention due to the recent onset of shortness of breath, chest pain, and weight loss. She admitted to a smoking history of 40 pack-years. A physical examination showed decreased air entry to both lung bases, with decreased breath sound and dullness on percussion at left upper lobe. No clubbing of her fingers was observed. Laboratory testing showed normal chemistries, including liver and renal function tests, calcium, and magnesium, as well as normal complete blood cell count and differential. Pulmonary function tests revealed adequate functional reserve with mild small airway obstruction. Ms. F was otherwise healthy, having no significant co-morbidities.

Chest x-ray showed a large left upper lobe mass, located peripherally, with hilar lymphadenopathy. A bronchoscopy with brushing and biopsy was negative. A diagnosis of small-cell lung cancer (SCLC) was made following a transthoracic computed tomography (CT)-guided needle biopsy.

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Clinical Decision Point

Question 1: Which of the following tests for staging would you recommend?

a. CT scan or magnetic resonance imaging (MRI) of the brain, CT scan of the chest and abdomen, and bone scan
b. Positron emission tomography (PET) imaging
c. Bone marrow biopsy
d. a and b
e. a and c

Discussion

(a) The combination of CT scan or MRI of the brain, CT scan of the chest and abdomen, and bone scan is an appropriate and recommended staging strategy due to the early and aggressive spread of SCLC.4,5 During initial staging at presentation, approximately 67% of patients have evidence of metastases to the liver, adrenal glands, bone, bone marrow, or brain that are evident on routine staging.6 However, metastatic disease is probably present in almost all patients and is one of the major reasons for administering chemotherapy to patients with local disease. Staging is important for establishing prognosis and making informed treatment decisions, which may differ in patients with extensive and locally advanced disease, although guidelines suggest that staging should not delay the start of treatment by more than 7 to 10 days due to the rapid course of the disease.4

Limited-stage SCLC is defined as disease confined to the ipsilateral hemithorax within a single radiation port, while extensive-stage SCLC involves metastases.1 In patients with limited-stage disease, complete response rates to chemotherapy range from 45% to 75% compared with 20% to 30% in patients with extensive-stage disease.1,7 However, the response duration is usually short, with a progression-free survival of about 12 months in patients with limited-stage disease and 4 months in patients with extensive-stage disease.1

Although systemic chemotherapy is recommended in both limited- and extensive-stage SCLC, chest radiotherapy is recommended only in limited-stage SCLC, unless required for palliation of extensive-disease symptoms.1,8 Meta-analyses of more than 2000 patients with limited-stage disease have suggested that chest radiotherapy reduces local failure by 25% to 30% and improves 2-year survival by 5% to 7% in these patients.1,4

PET imaging may be useful in the staging of SCLC, although it has not yet been adequately studied, and therefore, is not considered a standard staging procedure.4 A preliminary study of 25 patients with SCLC found that PET detected all primary lesions, lymph node metastases, and distant metastases detected by other staging procedures.3 Similarly, another study of 30 patients with SCLC found that 23 of 36 PET exams were concordant with those of the other staging procedures.3 A third study of 36 patients with malignant lung nodules evaluated PET of the thorax at 70 and 123 minutes after injection of 18F-fluorodeoxyglucose.3 Dual time-point PET resulted in a high sensitivity and specificity for detection of malignant lung tumors. Based on these limited data, however, guidelines do not call for use of PET in routine staging of patients with SCLC outside of a clinical trial.3

The value of bone marrow biopsy in staging is not universally agreed upon. However, a unilateral bone marrow aspirate and biopsy may be useful for patients with limited- but not extensive-stage disease.1 Bone marrow involvement is uncommon as the sole manifestation of metastatic disease. Typically, therefore, biopsy is not performed unless the patient has signs or symptoms of bone marrow involvement (pain, cytopenia in the absence of chemotherapy or radiation, and elevated lactate dehydrogenase levels). Bone marrow involvement will advance the stage of SCLC and may increase the toxicity of chemotherapy due to decreased bone marrow reserve.

Clinical Decision Point

Question 2: Given that standard treatment for limited-stage SCLC is combination chemotherapy plus radiation, which of the following chemotherapy combinations would you advise?

a. Cisplatin/irinotecan
b. Cisplatin/etoposide
c. Carboplatin/etoposide
d. Cyclophosphamide, doxorubicin, and vincristine (CAV)

discussion

(b) The combination of cisplatin and etoposide is the most frequently used chemotherapy combination in limited-stage SCLC.12 Multiple clinical trials have demonstrated that cisplatin/etoposide plus concurrent radiation can achieve a median survival of 18 to 24 months and a 40% to 50% 2-year survival with <3% treatment-related mortality.8 When administered concurrently with radiotherapy, cisplatin/etoposide has a better toxicity profile than CAV.13 Unlike CAV, cisplatin/etoposide may be given concurrently with thoracic radiotherapy.15 In addition,
In addition to thoracic radiotherapy, prophyllactic cranial irradiation (PCI) may be warranted in patients with SCLC, about 40% of whom develop intracranial metastases. One trial evaluated the effects of PCI on brain metastasis and overall survival in 300 patients with SCLC in complete remission.14 Patients were randomized to receive PCI, 24 Gy in eight fractions during 12 days, or no PCI (control). The 2-year cumulative rate of brain metastasis as an isolated first site of relapse was 19% in the treatment group versus 45% in the control group (P < 10^-6). In addition, the total cumulative development of brain metastases was 67% versus 40%, respectively (P < 10^-11). Likewise, a meta-analysis of all randomized PCI trials has reported a decrease in symptomatic brain metastases from 25% to 5%.15 For patients in complete remission (predominantly limited-stage disease), PCI produced a 4% survival advantage. Thus, PCI is strongly recommended for patients with limited-stage disease in complete remission.1

Case Continues
Ms. F underwent radiotherapy 60 Gy for 30 days, concurrent with the start of cisplatin/etoposide (cisplatin 75 mg/m² IV on day 1 and etoposide 100 mg/m² IV on days 1 to 3 every 21 days for 5 months). Her response to therapy was tracked by a CT scan after the third cycle, and again after the last cycle. No evidence of disease was found, and she was determined to have achieved complete response. She also underwent prophylactic cranial radiation, which she tolerated well. She was followed with a routine physical every 3 months, with a chest x-ray scheduled at her 1-year anniversary of completion of therapy. Just prior to that date, however, she developed a new cough and bone pain. A chest x-ray and bone scan revealed a recurrence in her lung and multiple bony metastases.

Despite the recurrence, the patient’s performance status was good (ECOG = 0). Ms. F continued to have no co-morbidities and to enjoy as high a quality of life as possible.

Clinical Decision Point
Question 3: Given her clinical situation and desire for a high quality of life, what treatment would you select for this patient’s tumor recurrence?

a. CAV
b. Retreatment with cisplatin/etoposide
c. Topotecan alone
d. Experimental therapy

Discussion
(c) Topotecan, a semisynthetic derivative of camptothecin that inhibits topoisomerase I, is approved for the treatment of chemo-sensitive SCLC after failure of first-line chemotherapy. Approval was based on a pivotal phase 3 randomized trial that compared topotecan with CAV, a standard first-line chemotherapy regimen. The trial included 211 patients with SCLC who had relapsed at least 60 days after completion of first-line therapy. Response was seen in 24% (26/107) of patients who received topotecan compared with 18% (19/104) of patients who received CAV (P = .285). Greater relief of dyspnea, anorexia, hoarseness, and fatigue was reported among the topotecan group compared with the CAV group. Grade 4 neutropenia occurred less frequently in the topotecan group (38% versus 51%, P < .001), but grade 4 thrombocytopenia and grade 3/4 anemia occurred less frequently in the CAV group (10% versus 18% and 1% versus 7%, respectively; P < .001 for both).

The approved dose of topotecan is 1.5 mg/m² by IV over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day course. An alternative weekly topotecan dosing regimen is currently under investigation, however. Clinical studies of weekly topotecan in ovarian cancer19-21 and extensive-stage treatment-naïve SCLC have demonstrated that this regimen appears to be less toxic, yet offers equivalent efficacy, as well as greater patient convenience.

Some clinicians may consider cisplatin/etoposide to be another option in light of Ms. F’s sensitive relapse (relapse 3–6 months from time of last chemotherapy). However, with a treatment history of six cycles of cisplatin/etoposide, she has a higher likelihood of responding to topotecan than to retreatment with cisplatin/etoposide, since there is little cross-resistance among these drugs.

Experimental chemotherapies include single-agent regimens with gemcitabine or taxanes, combination regimens with doxorubicin, docetaxel, and cyclophosphamide. Biologic agents, such as angiogenesis inhibitors, are also under investigation. These therapies, however, have yet to be studied in phase 3 randomized trials.
Shortness of breath, chest pain, and weight loss

CT of the head, chest, and abdomen and bone scan all negative

Radiotherapy 60 Gy for 30 days, concurrent with the start of cisplatin 75 mg/m² IV on day 1 and etoposide 100 mg/m² IV on days 1 to 3 every 21 days for 5 months

Diagnosis: limited-stage SCLC

Prophylactic cranial radiation; routine physical every 3 months; chest x-ray scheduled at 1 year anniversary of completion of therapy

Four 3-week cycles of topotecan 1.5 mg/m² by IV; doxorubicin and etoposide for symptomatic bone metastases; zoledronic acid for grade 2 bone metastases

Three more cycles of topotecan 1.5 mg/m² by IV followed by a “drug holiday.”

Maintains option to restart chemotherapy should evidence of progression develop

Figure 1. Summary of treatment administered to case study patient

Case Continues

Ms. F was started on 3-week cycles of topotecan 1.5 mg/m² IV daily for 5 days. Radiotherapy was also restarted for palliation of symptomatic bone metastasis. In addition, Ms. F was started on zoledronic acid for the treatment of bone metastases.

After four cycles of topotecan at the approved dose, Ms. F achieved a partial response. An advantage of topotecan is that the cycles can be continued as long as the patient responds to and tolerates the treatment. Ms. F tolerated topotecan therapy well, experiencing only a grade 2 neutropenia. Therefore, she proceeded to receive three more cycles before opting for a “drug holiday.”

She continues to do well a few months postchemotherapy.

Summary

The standard treatment of limited-stage SCLC is combination chemotherapy and radiation, with the regimen of choice being cisplatin/etoposide. In cases of extensive-stage SCLC, carboplatin may replace cisplatin with equal efficacy and reduced toxicity. For complete responders, PCI is recommended. Although long-term survival is possible, many patients do develop relapsed disease. Topotecan has been approved for use in patients whose disease progresses after cisplatin treatment. The treatment goal for second-line therapy is palliation, with due consideration of toxicity and quality of life. For these reasons, many patients may choose a drug holiday during a period of disease stability. Temporary freedom from the demands of chemotherapy relieves treatment adverse effects and allows the patient to enjoy life without the restrictions of physician appointments and drug administration schedules.
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CME Instructions
To receive documentation of your participation in this 12-part CME activity (for which each newsletter equals .25 hour for a total of 3.0 hours of CME credit), please complete the following steps:

1. Read each newsletter carefully.
2. Complete the CME Posttest included at the end of each newsletter.
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Please select the most appropriate response to each question.
1. CT imaging of the head, chest, and abdomen is not considered part of an appropriate staging strategy for SCLC.
   ❑ True    ❑ False

2. Bone marrow toxicity of thoracic radiotherapy typically enhances the hematologic toxicity of cisplatin/etoposide.
   ❑ True    ❑ False

3. Topotecan is a topoisomerase I inhibitor that is approved for the treatment of chemosensitive SCLC after failure of first-line chemotherapy.
   ❑ True    ❑ False

4. Radiotherapy administered concurrent with beginning of chemotherapy has shown no advantage in terms of disease-free interval and survival compared with radiotherapy administered sequentially.
   ❑ True    ❑ False

5. Patients who choose to take a drug holiday at a time when disease is stable can choose to restart therapy should evidence of progression develop.
   ❑ True    ❑ False
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Instructions: Please complete this survey, along with the CME Posttest, and mail or fax (both sides) to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424; fax: 973-890-8822.

1. Please rate the extent to which you achieved the learning objectives:

   - Compare the efficacy and safety of available regimens for treating recurrent gynecologic and lung cancers.
   - Consider the risks and benefits of extending the platinum-free interval and its impact on future responses to additional treatment regimens.
   - Formulate a treatment strategy that maximizes outcomes and reduces toxicity through judicious sequencing of therapies and dosing schedules when treating patients with platinum-sensitive, recurrent gynecologic or lung cancer.
   - Discuss future clinical applications, including activity and toxicity profiles, of novel combinations and schedules of chemotherapies, including topoisomerase inhibitors, alone or in combination with platinum agents, in the treatment of gynecologic and lung cancer.

2. Please rate the overall value of this enduring material:

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Thank You for Your Participation