Limited Stage Small Cell Lung Cancer: Treatment and Therapy

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Current Treatment Options in Oncology 2003, **4:**61–64
Current Science Inc. ISSN 1527-2729
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Opinion statement

Chemotherapy remains the key treatment for small cell lung cancer; today, that chemotherapy remains cisplatin and etoposide in a variety of acceptable schedules. Attempts to use new drugs in extensive disease have not been as successful as hoped; however, a recent trial from Japan supports the use of irinotecan and cisplatin over the standard cisplatin and etoposide, but these facts need to be verified in western countries. For limited disease, the addition of thoracic radiotherapy for all patients and prophylactic cranial irradiation (PCI) in complete, or near complete, responders have resulted in improved survival. The best results occur with early, intensive thoracic radiotherapy concurrent with chemotherapy and PCI after completion of systemic and local therapy. The use of PCI and thoracic radiotherapy in extensive disease is more controversial and less evidence based. PCI and thoracic radiotherapy may be considered only in patients who have achieved a "systemic" complete response and excellent response in the chest. However, both prospects should be supported if there is complete response systemically and near complete response locally. The role of surgery is of limited value in the unusual cases of mediastinal negative disease, but it is a good treatment for patients with peripheral nodules and sufficient pulmonary function to withstand thoracotomy.

Introduction

Small cell lung cancer seems to be decreasing in frequency and now constitutes only 15% of lung cancers [1]. Practically and operationally, small cell lung cancer is staged as "limited" or "extensive." The American Joint Commission ardently wants it staged by the customary tumor, node, metastasis system; however, no one performs this in practice, especially in the United States. Although the limited category technically includes pleural effusion, pleural nodules, bilateral supraclavicular involvement, and multiple ipsilateral lung nodules, in practice and in studies, these have been treated as extensive disease. The operational definition of "encompassed within a reasonable radiotherapy portal" holds sway and is prudent and reasonable.

The distinction between limited and extensive disease remains important in terms of treatment and prognosis, but there is not uniformity in what constitutes adequate staging to determine the category or stage. Although assessment of the brain remains mandatory, there are some clinicians who think that magnetic resonance imaging (MRI) needs to be used instead of head computed tomography (CT) with contrast. As one reassesses the patient before prophylactic cranial irradiation (PCI), the argument is that some patients may already have occult brain disease that can be found on MRI but missed with routine CTs. Currently, assessment of the brain is important and there is not sufficient evidence to mandate MRI over head CT, but one of the modalities is required. Bone scans remain an integral part of staging. The use of positron emission tomography scans seems logical, but is not adequately supported to be covered by Medicare. Bone marrow aspirates and biopsies are no longer routine.

Most analyses find performance status, gender, and weight loss greater than 10% prognostic. Elderly patients (> 65 years) with good performance status and no other comorbidities can be treated like younger patients; however, those with less than obvious comorbidities may manifest problems tolerating therapy.

Treatment

Pharmacologic treatment

- Extensive disease and limited disease are treated with chemotherapy. The benchmark chemotherapy continues to be cisplatin and etoposide. There is no evidence that adding a third drug produces anything more than toxicity in limited [2] or extensive disease [3].
- Based on their experience and practice and the randomized phase II study of Kosmidis *et al.* [4••], many physicians substitute carboplatinum for cisplatin. (Although the title of the reference calls this a phase III study, it was underpowered to show equivalence, thus can be viewed only as a randomized phase II study.) There is no defined optimal schedule of cisplatin and etoposide. Higher-dose cisplatin is not warranted and causes more toxicity. Etoposide requires at least three doses; many use more, but the higher dose of 120 mg/m^2 may lead to more toxicity, as may 100 mg/m^2. For limited disease small cell lung cancer, four cycles of therapy is adequate. There is no convincing evidence that more than four to six cycles is necessary in extensive disease.
- The concepts of "high-dose therapy" (with or without bone marrow transplant), "dose intensity," and "alternating non–cross-resistant regimens" may continue to have adherents; however, these ideas have never been established and their trail of credibility and promise has grown cold.

Cisplatin

Standard dosage 60 to 80 mg/m^2 intravenously (IV) on day 1 or 50 mg/m^2 on days 1 and 8.
Contraindications Poor renal or hearing function; hypersensitivity.
Mechanism of action DNA cross-links.
Main drug interactions Synergistic with etoposide.

Etoposide

Standard dosage 120 mg or 100 mg/m^2 IV on days 1 to 3 or 50 mg/m^2 IV on days 1 to 5.
Contraindications Hypersensitivity; inadequate bone marrow reserve.
Mechanism of action Topoisomerase-2 inhibitor.
Main drug interactions Bone marrow suppression.

Carboplatinum

Standard dosage 300 mg/m^2 IV on day 1.
Contraindications Some use AUC (area under the curve) formulation without data; this is the reported dose of Kosmidis *et al.* [4••].

Extensive disease

- The standard dosage for extensive disease is cisplatin, 60 mg/m^2 IV on day 1; irinotecan, 60 mg/m^2 IV on days 1, 8, and 15.
- Contraindications include sensitivity and diarrhea potential.

Radiation therapy

Thoracic radiotherapy

Thoracic radiotherapy is mandatory for all patients with limited disease. Early therapy, concurrent with cycle one or cycle two, has the bulk of evidence in its favor. Sequential therapy, with radiotherapy before or after chemotherapy,

produces inferior survival and local control [5,6]. The dose of 45 Gy given in 30 fractions (twice daily) in 15 treatment days, concurrently with cycle-one cisplatin and etoposide, is the standard dosage [7••]. Many have substituted other timing and other single doses in practice; however, there is no established alternate that is justified by data. A proposal to compare the standard to a higher once-daily dose of 63 Gy was rejected by the Concept Evaluation Panel managed by the Cancer Therapy Evaluation Program of the National Cancer Institute. However, a revised proposal along the same theme is being resubmitted substituting 70 Gy total dose thoracic radiotherapy as the goal of once-daily dose scheme.

Standard regimen 45 Gy given in 30 fractions in 3 weeks.

Contraindications None.

Complications Esophagitis.

Special points Concurrent with chemotherapy cycle one or two, or perhaps cycle three.

Cost effectiveness No cost-effectiveness studies were performed.

Prophylactic cranial irradiation

PCI is supported in all complete responders by a meta-analysis suggesting a 5% benefit in survival [8••]. Because the studies composing that meta-analysis are dated (from the 1980s and earlier), none of the studies use the currently accepted standard of cisplatin and etoposide as initial therapy. Current studies have a larger proportion of patients surviving than in the era of cyclophosphamide- and doxorubicin-based initial therapy; therefore, the potential for therapeutic benefit may be larger than from the studies that the meta-analysis estimated effect. The role of thoracic and brain radiotherapy in extensive disease generally has less evidence. One trial suggests that thoracic radiotherapy and PCI in patients with extensive disease improves survival [9]. Controversies about the use of thoracic radiotherapy and PCI for the elderly and those patients with extensive disease require additional trials.

Standard regimen 30 to 36 Gy given in 2-Gy fractions in 3 to 4 weeks, 25 Gy given in 2.5-Gy fractions in 2 to 3 weeks, or 24 Gy given in 3-Gy fractions in 1 to 2 weeks.

Contraindications None.

Complications Decreased neurocognitive functions; however, there are no series or anecdotal reports because cisplatin and etoposide have been used as a primary chemotherapy.

Main side effects Hair loss.

Special points Adds 5% to chance of survival.

Cost effectiveness No cost analyses were done.

Surgery

- The role of surgery is more intuitive than supported by hard fact. Patients with peripheral T1 or T2 tumors with negative mediastinum have had reasonable survival rates after surgery, followed by chemotherapy [10]. There is no established role for surgery in patients with N2 nodal disease. Investigators in Germany continue to pursue the potential for surgery in patients with limited disease after chemoradiotherapy induction [11].

Emerging therapies

- None of the new drugs have earned a place in the treatment of limited disease; however, one randomized trial from Japan supports a benefit of irinotecan plus cisplatin over cisplatin and etoposide [12••]. These observations require confirmatory trials in western countries to verify these results.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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Kosmidis *et al*. report that 300 mg/m^2 of carboplatinum is an equivalent to cisplatin given 50 mg/m^2 on days 1 and 2. However, this trial is not powered to establish equivalence.

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The US intergroup study provides proof of principle that intensive radiotherapy improves survival of patients with limited disease. Once-daily schedules of higher dose are used widely, but are not supported by evidence.

8. •• Auperin A, Arriagada R, Pignon JP, *et al.*: **Prophylactic cranial irradiation for patients with small cell lung cancer in complete remission.** *N Engl J Med* 1999, **341:**476–484.

This is the meta-analysis that proves a survival benefit of approximately 5% for patients treated with prophylactic cranial irradiation. Most of the studies predated current chemotherapy and radiotherapy schedules.

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12. •• Noda K, Nishiwaki Y, Kawahara M, *et al.*: **Irinotecan plus cisplatin for extensive small-cell lung cancer.** *N Engl J Med* 2002, **346:**85–91.

This is the Japanese report touting a survival advantage for patients treated with the every-4-week irinotecan/platinum regimen over the every-3-week platinum etoposide regimen.