Small Cell Lung Cancer

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DISCLOSURES

Off-Label Usage
• Temozolomide

Financial Relationships with Relevant Commercial Interests
• Consultant AstraZeneca, Bristol-Myers Squibb, Chugai, Genentech BioOncology, Pfizer, Sanofi-Aventis, Ariad, GE Health care, Millenium
• Stockholder/Ownership Interest: KEW

Resolution
• Reviewed and found to be unbiased.
SMALL CELL LUNG CANCER

- Pathology and molecular pathogenesis
- Presentation
- Staging
- Treatment
- Prophylactic cranial irradiation
- Relapsed small cell lung cancer
The Recalcitrant Cancer Research Act of 2012 (H.R. 733) requires the National Cancer Institute (NCI) to “develop scientific frameworks” that will assist in making “progress against recalcitrant or deadly cancers.” Small cell lung cancer (SCLC) is a recalcitrant cancer as defined by its five-year relative survival rate of less than 7 percent and the loss of approximately 30,000 lives per year. While it is true that the outcomes for the other common forms of lung cancer (squamous cell and adenocarcinoma) need to be greatly improved, each of the three major types of cancer that originate in the lung present very different problems, requiring different solutions.

http://deainfo.nci.nih.gov/advisory/ctac/workgroup/SCLC/SCLCCongressionalResponse
• The Median Prevalence of Cigarette Smoking across the United States is 18.1% (20.5% for men and 15.8% for women)
• The Prevalence Ranged from 10.6% in Utah to 28.3% in Kentucky in 2012.
• Massachusetts has 18.2% of Adults Smoking Cigarettes in 2011 (9th)

http://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm#state
Cancer Death Rates* Among Men, US, 1930 - 2010

Cancer Death Rates* Among Women, US, 1930 - 2010

*Age-adjusted to the 2000 US standard population.
National Cancer Center for Health Statistics, Centers for Disease Control and Prevention.

American Cancer Society Statistics 2014
EPIDEMIOLOGY

- 224,210 men and women (116,000 men and 108,210 women) will be diagnosed at a median age of 70
- 159,260 men and women will die of cancer of the lung and bronchus in 2014
- The overall 5-year relative survival for 2002-2008 from 18 SEER geographic areas was 15.9%
- The percentage with localized disease at time of presentation is 15%, regional is 22%, and distant is 56% (6% is unstaged)

http://seer.cancer.gov/statfacts/html/lungb.html#survival
PATHOLOGY AND MOLECULAR PATHOGENESIS

- Non-Small Cell Lung Cancer 87%
- Small Cell Carcinoma 13%
  - Small Cell Carcinoma > 90%
  - Variant (Combined Small Cell Carcinoma) < 10%

Small cell lung cancer is the most closely linked with cigarette smoking.
  ▪ > 97% of patients have a history of cigarette smoking.
Squamous cell carcinoma and large cell carcinoma are
intermediately linked with cigarette smoking.
  ▪ Approximately 80% of patients have a history of cigarette smoking.
Adenocarcinoma is least closely linked to cigarette smoking.
  ▪ 70% of patients have a history of cigarette smoking.
Pulmonary carcinoid tumors are not associated with cigarette
smoking.
Markers of neuroendocrine differentiation

- Chromogranin A
- Synaptophysin
- CD56 or Neural Cell Adhesion Molecule (NCAM)

GENOMIC ANALYSES OF 152 SMALL-CELL LUNG CANCERS

UPDATE ON SMALL CELL LUNG CANCER

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- Staging
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## Presentation

<table>
<thead>
<tr>
<th>Local</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>50%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>40%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>35%</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>20%</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>50%</td>
</tr>
<tr>
<td>Weakness</td>
<td>40%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>30%</td>
</tr>
<tr>
<td>Paraneoplastic syndrome</td>
<td>15%</td>
</tr>
<tr>
<td>Fever</td>
<td>10%</td>
</tr>
</tbody>
</table>
### PRESENTATION OF PARANEOPLASTIC SYNDROMES

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Protein</th>
<th>Pts with SCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatremia of Malignancy</td>
<td>Arginine Vasopressin and Atrial Natriuretic Peptide</td>
<td>15%</td>
</tr>
<tr>
<td>Hypercalcemia of Malignancy</td>
<td>Parathyroid Hormone Related Peptide</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ectopic ACTH Syndrome</td>
<td>Adrenocorticotropic Hormone</td>
<td>3%</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>Growth Hormone Releasing Hormone</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>
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The staging classification for these patients is a simple two-stage Veterans Administration Lung Study Group System, updated in 1989 by International Association for the Study of Lung Cancer.

- **Limited stage:** Disease confined to 1 hemithorax with regional lymph nodes including either ipsilateral or bilateral hilar, mediastinal, and supraclavicular lymph node metastases and without ipsilateral pleural effusion that fit within a tolerable chest radiation field.

- **IASLC now recommends staging them using TNM; stage I-III and IV is roughly equivalent to limited or extensive stage disease.**

- **Extensive stage:** Disease beyond these boundaries.

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SMALL CELL LUNG CANCER: METASTATIC SITES

- Bone-35%
- Liver-25%
- Bone marrow-20%
- Brain-20%
- Extrathoracic lymph nodes-5%
- Subcutaneous masses-5%
# Small Cell Lung Cancer: Prognostic Factors

<table>
<thead>
<tr>
<th>Factors Consistently Reported</th>
<th>Factors Inconsistently Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good performance status</td>
<td>Normal serum sodium</td>
</tr>
<tr>
<td>Limited stage disease</td>
<td>Younger age</td>
</tr>
<tr>
<td>Female gender</td>
<td>Absence of liver or brain mets</td>
</tr>
<tr>
<td>Caucasian</td>
<td>Normal liver function tests</td>
</tr>
</tbody>
</table>
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SMALL CELL LUNG CANCER:
LIMITED STAGE SMALL CELL LUNG CANCER

Pre-treatment

12/13/2000

2 Years after Treatment
Cisplatin - 80; Etoposide - 100 / Q 21 days in sequential, Q 28 days in concurrent. PCI: 24 Gy 1.5 Gy BID to 45 Gy

SMALL CELL LUNG CANCER: LIMITED STAGE SMALL CELL LUNG CANCER

SMALL CELL LUNG CANCER: LIMITED STAGE SMALL CELL LUNG CANCER

Platinum - 60; Etoposide - 120 / Cycle Q 21 days PCI: 25 Gy

SMALL CELL LUNG CANCER:
LIMITED STAGE SMALL CELL LUNG CANCER

Patients with limited stage SCLC should be treated with concurrent chest radiotherapy with etoposide plus cisplatin. These patients lived longer than patients treated with chemotherapy alone.

- The chest radiotherapy should start with cycle 1 or 2.

- The chest radiotherapy should be given twice daily over 3 weeks.

- An ongoing trial comparing etoposide cisplatin plus 45 Gy given twice daily over 3 weeks versus 70 Gy once daily in 2 Gy fractions (NCT00632853).
Patients with a solitary pulmonary nodule and a diagnosis of SCLC should undergo evaluation for resection (2-3%).

Patients should have mediastinoscopy because 20% will have positive lymph nodes.

Patients should be treated with adjuvant chemotherapy following resection.

Surgery vs. no surgery for NO disease

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651 patients with extensive stage SCLC

Randomized to 4 cycles of irinotecan 60 mg/m2 IV on days 1, 8, and 15 plus cisplatin 60 mg/m2 on day 1 on 28 day cycle versus etoposide 100 mg/m2 on days 1, 2, and 3 plus cisplatin 80 mg/m2 on day 1 every 3 weeks

Followed for response, time to progression, and survival

SMALL CELL LUNG CANCER: IRINOTECAN FOR EXTENSIVE STAGE SMALL CELL LUNG CANCER


Overall Survival (%)

Time Since Enrollment (months)

CDDP/CPT-11 288/324 9.9 (9.2 to 11.1)
CDDP/VP16 285/327 9.1 (8.4 to 9.9)
282 patients with extensive stage SCLC

Randomized to 4 cycles of irinotecan 60 mg/m² IV on days 1, 8, and 15 plus cisplatin 60 mg/m² on day 1 on 28 day cycle versus amrubicin 40 mg/m² on days 1, 2, and 3 plus cisplatin 60 mg/m² on day 1 every 3 weeks

Followed for response, time to progression, and survival

AMRUBICIN FOR EXTENSIVE STAGE SCLC

SMALL CELL LUNG CANCER: STRATEGIES FOR EXTENSIVE STAGE SMALL CELL LUNG CANCER

- 140 limited and extensive stage patients treated with transplant doses of ifosfamide, carboplatin and etoposide (Tx) versus standard doses of the same drugs\(^1\)
- 724 patients with limited and extensive stage treated with etoposide and cisplatin +/- thalidomide\(^2\)
- 795 patients given topotecan 1.0 mg/m^2 IV days 1-5 plus cisplatin 75 mg/m^2 IV day 1 versus etoposide 100 mg/m^2 IV days 1-3 plus cisplatin\(^3\)

Patients with extensive stage SCLC should be treated with 2 drugs which produce moderate myelosuppression. Etoposide / cisplatin remains the standard treatment.

Patients with SCLC treated with intensive chemotherapy (adding paclitaxel or autologous transplant doses) do not live longer than patients treated with standard doses.
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SMALL CELL LUNG CANCER: PROPHYLACTIC CRANIAL IRRADIATION FOR LIMITED AND EXTENSIVE STAGE

Survival for Limited and Extensive Stage
N = 987


Survival for Extensive Stage
N = 286

Patient with ES SCLC with response to first-line platinum doublet chemotherapy were randomized to either PCI (25Gy/10 fractions) or observation (Obs) alone.

The patients were required to prove the absence of BM by MRI prior to enrollment.

The study was terminated because of futility when 163 were entered and there were 111 death.

The median OS was 10.1 and 15.1 months for PCI (n=84) and Obs (n=79), respectively (HR=1.38, 95%CI= 0.95-2.01; stratified log-rank test, $P=0.091$).

Seto et al. ASCO 2014 #7503
SMALL CELL LUNG CANCER: DOSE OF PROPHYLACTIC CRANIAL IRRADIATION

Patients with SCLC have a 60-80% actuarial risk of developing brain metastases within 2 years after the start of treatment.

PCI has been shown to prolong survival for patients with both limited and extensive SCLC with a response to chemotherapy.

PCI (2500 cGy) administered at the time of complete remission can reduce the chance of developing brain metastases by 50-67%.

51 Pts with SCLC Rx with PCI (16) or WBRT (35)
Median 18 Gy (range 10-24)
SMALL CELL LUNG CANCER: LONG-TERM OUTCOME OF PATIENT WITH LIMITED STAGE SCLC


SMALL CELL LUNG CANCER: LONG-TERM OUTCOME OF PATIENTS WITH EXTENSIVE STAGE SCLC


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SMALL CELL LUNG CANCER: TOPOTECAN FOR RELAPSED DISEASE

71 Rx 2.3 mg/m2/day PO Topotecan days 1-5 vs 70 Placebo

211 Rx 1.5 mg/m Topotecan IV on days 1-5 vs CAV


TOPOTECAN VERSUS AMRUBICIN FOR RELAPSED SCLC

Eligibility Criteria
- Small Cell Lung Cancer (SCLC)
- Extensive or Limited Disease
- Sensitive or refractory disease (Progression ≥ 90 or <90 days after completion of 1st line chemotherapy, Response to 1st line chemo)
- 1 prior chemotherapy regimen
- ECOG performance status 0-1
- Stratified: Sensitive/Refractory; Extensive/Limited

Primary endpoint: Overall Survival
Secondary endpoints: ORR, PFS, TTP, LCSS, quality of life, safety, sparse PK
Analyses: Interim (deaths = 294), Final (deaths = 490)
[97.5% power: 6.0 vs. 8.7 months (HR: 0.69)]
TOPOTECAN VERSUS AMRUBICIN FOR RELAPSED SCLC

* Unstratified log-rank test

Survival Probability

Time (months)

Amrubicin
Topotecan

# at risk
Amrubicin 343 250 109 94 50 32 17 7 3 1 0
Topotecan 164 122 77 43 22 8 4 1 1 0 0

HR=0.880
95% CI [0.733, 1.057]
P-value*=0.1701

N/Events Median OS 95% CI
Amrubicin 424/336 7.5 months 6.8 – 8.5
Topotecan 213/175 7.8 months 6.6 – 8.5

• Third-line therapy was comparable
  (46.5% topotecan vs. 47.4% amrubicin)
TOPOTECAN VERSUS AMRUBICIN FOR RELAPSED SCLC

Survival Probability

Time (months)

Sensitive Patients

N/Events Median OS 95% CI
Amrubicin 225/168 9.2 months 8.5-10.6
Topotecan 117/89 9.9 months 8.5-11.5

HR=0.936
95% CI [0.724, 1.211]
P-value*=0.6164

Refractory Patients

N/Events Median OS 95% CI
Amrubicin 199/168 6.2 months 5.5-6.7
Topotecan 96/86 5.7 months 4.1-7.0

HR=0.766
95% CI [0.589, 0.997]
P-value*=0.0469

* Unstratified log-rank test

Von Pawel WCLC 2011 #O01.02
Previously treated patients with sensitive relapse SCLC (48) or refractory SCLC (16).

24 had brain metastases including 13 with target lesions assessable by RECIST.

Treated with 21/28 days of 75 mg/m² of temozolomide.

Followed for toxicity, response, time to progression, and survival.

Pietanza et al. *Clin Cancer Res* 2012; 18:1138
4 of 13 Brain Mets had CR and 1 had a PR (38%RR)
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