LUNG CANCER

Incidence of major histologic types*

15-20% Small-cell carcinoma

20-25% Squamous cell carcinoma

40% Adenocarcinoma

15% Large-cell carcinoma

5% other

Anatomy
Anatomy - SCLC
Histology
Histology
Histology

“Oat Cell”
Histology
Causes

• Smoking
  – nicotine
  – nitrosamines
  – benz-a-pyrene

• + Uranium dust (radon)

• + bis (chloromethyl) ethyl ether

• + asbestos
Origin

- Neuroendocrine markers
  - Chromogranin
  - Synaptophysin
  - neuron-specific enolase
  - CD56
  - peptide hormones (calcitonin, AVP, oxytocin, gastrin-releasing peptide, POMC-ACTH, etc)
- Kulchitsky cells* vs. type II pneumocytes
- 5-15% of tumors contain both SCLC & NSCLC
Uniform Genetic Alterations in SCLC

- Loss of Rb tumor suppressor function
- Loss of p53 tumor suppressor function
- Conditional knockout of Rb and p53 in the lungs of transgenic mice results in SCLC with a latency of 10-12 months.
- What are the additional molecular alterations that are required beyond loss of Rb and p53 function?
NSCLC Transformation to SCLC

- EGFR mut Adenoca
- erlotinib 
- gefitinib
- EGFRi resistance
- 5%
- SCLC

-No 2° mutation
-No bypass
-activation of Ras-MAPK
NSCLC Transformation to SCLC

EGFR mut Adenoca

- erlotinib 
- gefitinib

EGFRi resistance

- No 2o mutation
- No bypass activation of Ras-MAPK

P53 mutation

????

?PIK3CA mut

Rb loss of function

SCLC

Niederst et al. Nature Communications 2015 DOI: 10.1038
Genome Sequencing

• Approximately 150 SCLC tumors sequenced
• About 200 protein-altering mutations, at least 10% of which appear to be drivers
• Numerous additional fusion proteins, deletions, and amplifications
• Additional pathways affected include DNA repair and histone modification (inactivation)
• Proteomics confirm Sox (stem cell transcription factor) and PARP overexpression
Genomic alterations in small cell lung cancer.

Signalling pathways recurrently affected in SCLC.

Staging Procedures

- Hx and PE
- chest CT with cuts through liver & adrenals
- bronchoscopy and/or FNA
- LFT’s, CPK, LDH
- head CT or MRI
- radionuclide bone scan or PET/CT
- bone marrow biopsy if otherwise limited with cytopenias
### SMALL CELL LUNG CANCER

**Extrathoracic disease sites at presentation**

<table>
<thead>
<tr>
<th>Finding</th>
<th>Percentage with Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>19%-38%</td>
</tr>
<tr>
<td>Liver</td>
<td>17%-34%</td>
</tr>
<tr>
<td>Adrenals</td>
<td>5%-31%</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>15%-30%</td>
</tr>
<tr>
<td>Brain</td>
<td>10%-15%</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>7%-25%</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>3%-11%</td>
</tr>
</tbody>
</table>

Small Cell Lung Cancer Treatment

• Limited: tolerable radiation port; 25-30%
  – Concurrent radiation (45 Gy BID or 66 Gy daily) combined with cisplatin/etoposide chemotherapy
  – median survival increases from 6 months to 15-16 months
  – 5 yr survival rate is approximately 20-25%
Limited Disease: Radiotherapy

- 5-10% 5 yr survival when used alone
- If pt not able to tolerate concomitant tx, sandwich therapy is second best
- few studies show a benefit to sequential therapy
- Surgery may replace XRT if mediastinum staged
Small Cell Lung Cancer Treatment

• Extensive: 70-75%
  – Platinum/etoposide chemotherapy, response rates >80%
  – median survival increases from 3 to 6 months with cytoxan & 9-10 months with combination chemo
  – 5 yr survival is approximately 1-3%, unchanged over the past 30 yrs
Small Cell Lung Cancer
Combination Chemotherapy

• Cisplatin/Etoposide
  – Overall, best tolerated regimen
  – 80 mg/M² D1/ 80 mg/M² D1-3 Q 3 wks; outcome no different than 135 mg/M² / 400 mg/M² (D1-5)
  – May substitute carboplatin (AUC 5) for cisplatin, but will be exchanging nephrotoxicity for myelotoxicity (esp. thrombocytopenia)
Overall survival

![Overall survival graph]


- **IP (n = 221)**
  - Median 9.3 months (0.1-32.6)
  - 1 year 35%, 2 years 8.0%

- **EP (n = 110)**
  - Median 10.2 months (0.3-44.6)
  - 1 year 35.2%, 2 years 7.9%

**P = .74**
Duration of therapy

• While study results are mixed, no evidence that more than 6 cycles in unselected patients is beneficial
• Some evidence that 4 cycles is as good as 6, but regimens tested did not include EP
• XRT to residual intra-thoracic disease may provide modest survival benefit in extensive disease.
PCI

• In a large meta-analysis, PCI improved survival for those limited stage patients who attained a complete response, in addition to the minority of extensive patients who also achieved a CR; analysis extended to “good” PR patients
• 2400 rads probably as good as higher doses
• No demonstrable effect on neuropsychiatric parameters.
Special Circumstances

- **SVC syndrome**
  - May proceed with combination chemotherapy (+ XRT if limited stage)
  - If pt will not tolerate immediate systemic tx, initiate palliative XRT, followed by chemo

- **Brain metastases at DX**
  - Asymptomatic, may proceed with systemic chemotherapy followed by XRT
  - Symptomatic, WBXRT vs SRS followed by systemic tx
Salvage therapy

- CAV for EP failures and visa versa
- topotecan (1-1.5 mg/M² x 5 Q 3 wk)
- oral topotecan (2.3 mg/m² D1-5 q 3 wk)
- Irinotecan (300-250 mg/m² q 3 wk)
- Temozolomide (75 mg/m² 21/28 d)
- consider XRT for localized symptomatic disease, esp. CNS
- Investigational protocol
Future (Promising?) Approaches

- Immunotherapy: Nivolumab ± ipilimumab
- Rova-T (+ Bcl-2 antagonists)
- Multi-targeted tyrosine kinase inhibitors that inhibit VEGFR (angiogenesis)
  - Maintenance sunitinib
- PARP inhibitors (+ temozolomide)
- Aurora kinase inhibitors (MYC-amplified)
- Genomically-targeted therapies:
  - imatinib/sunitinib in Kit mutant tumors
  - PI3K inhibitors in PI3K & PTEN mutant tumors
Phase II study of maintenance sunitinib following irinotecan and carboplatin as first-line treatment for patients with extensive-stage small-cell lung cancer

D.R. Spigel et al. / Lung Cancer 77 (2012) 359–364
Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial

Lancet Oncol 2016
Published Online
June 4, 2016
http://dx.doi.org/10.1016/S1470-2045(16)30098-5
Paraneoplastic Syndromes

• Endocrine
  – SIADH
  – Cushing’s
  – diarrhea (VIP)
  – hypoglycemia (insulin)

• Neurologic
  – Eaton-Lambert
  – Sensorimotor neuropathy
  – cerebellar degeneration
  – limbic encephalopathy
Extra-Pulmonary Small Cell

- Most frequent sites
  - GI (esophageal)
  - larynx
  - cervix
  - Bladder & Prostate
- Treat using same principles as SCLC
- Must distinguish from carcinoid and Merkel cell