Small Cell Lung Cancer (SCLC): Update in Therapy

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March 1, 2010
Small Cell Lung Cancer (SCLC)

- 12% of lung cancer
- Strongest epi link with smoking
- Very high growth fraction
- Propensity for early dissemination
- Initially very chemo- and radiosensitive, but relapse virtually inevitable
Staging in SCLC

• “Limited disease” (LD) able to be included in one radiotherapy port
• “Extensive disease” (ED) beyond one port
• Modern definition of LD includes
  – ipsilateral pleural effusions
  – contralateral mediastinal and/or supraclav LN
  – Only pts with extrathoracic disease have ED

Fig. 1. Survival curves of patients with LD according to VALG (LD-VALG), patients with ED by IASLC (ED-IASLC) and patients with ED by VALG and still LD by IASLC (LD-ED).

Valg excluded pl eff in LD; IASLC included pl eff in LD.
Limited disease (LD) SCLC

- 15% - 25% of patients with SCLC
- Overall response rate 80% - 90% (CR 50+%)  
- Cure rate ~15%
- Median survival 18 months  
- Only pts obtaining a complete response are long-term survivors

Hanna NH and Einhorn LH. Clin Lung Cancer 2002;4:87
Increase in survival for patients with LD SCLC

- Median survival
  - 1972-81: 12 months
  - 1982-92: 17 months
- 5/30 trials were pos.
  - All 5 evaluated some aspect of thoracic radiotherapy (TRT)
- Survival improvement confirmed in SEER database

Role of surgery in LD SCLC

- Largely abandoned in the 1970’s with the development of multi-agent chemotherapy regimens
- Most data are from small, retrospective series
- The sequence of surgery before or after chemotherapy has never been studied prospectively
  - Pathologic complete response rates: (5 - 35)%
- Rationale for surgery after induction therapy: intrathoracic recurrence ~40% after chemo/TRT
LCSG 831: Randomized trial of chemotherapy followed by surgical resection vs. no surgery

Registration, N=328

Induction CAV x 5

Objective Response

Randomize, N=146

Thoracotomy

No Surgery

Thoracic and Brain Irradiation

Randomized trial of chemotherapy followed by surgical resection vs. no surgery

- Pathologic CR rate 19%
  - 10% residual NSCLC
- 40% rate of intrathoracic relapse (no difference)
- No difference in survival
  - Median survival 15.4 (S) and 18.6 months
  - No subset identified that improved with surgery
- Caveats
  - Central lesions only, 1/3 of responders not randomized, 23% incomplete resection rate, etc.

Surgery in SCLC
(ACOSOSG plans randomized trial)

• Clinical stage T1-T2 N0 disease, or SPN identified intraoperatively as SCLC
  – Perform MSLND and lobectomy
  – Post-op chemotherapy for N0 disease…PCI
  – Post-op chemoradiation for N1 or N2 disease…PCI
• Potentially resectable, clinical stage N2 disease
  – No role for surgery
• Post-initial treatment: persistence/growth in a residual mass
  – 10% lesions may have NSCLC component
• In surveillance following treatment for SCLC
  – Risk of second primary tumor

Shepherd FA. JTO 2010;5:14
PCI meta-analysis

• Individual pt data from 7 trials, 1977-95
• N=987, CR after treatment
  – 15% patients with extensive disease
• XRT: 8 – 40 Gy, over 1 - 20 fractions
• Absolute increase in survival at 3 years
  – 5.4% (15.3% versus 20.4%)
• Neurocognitive effects not addressed

Auperin A, et al. NEJM 1999;341:476
RTOG 0212: Phase II/III randomized trial of two doses and two schedules of PCI for LD SCLC (N=720)

Induction Therapy: Chemo+ TRT

Randomize

2.5 Gy/day, M-F, x 10 fractions = 25 Gy total

2.0 Gy/day, M-F, x 18 fractions = 36 Gy total

1.5 Gy/day, M-F, x 24 fractions (BID) = 36 Gy total

No difference in incidence of brain mets (~25% at 2y)

Worsened overall survival at 2 y in high dose PCI pts (42% vs 37%, p=0.05)

Limited disease SCLC: Thoracic radiotherapy (TRT)

- Meta-analyses (N=2140)
  - TRT: 40 – 50 Gy, usually sequential
  - Increase in 5 year survival 5.4%
  - HR death with TRT 0.86 (p=0.001)
    - HR death patients > 70 years 1.07 (NS)
  - No information on toxicity, local control

- Refinements
  - Radiotherapy dose, fractionation, toxicity, timing
  - Chemotherapeutic agents

Limited disease SCLC: Timing of Thoracic radiotherapy

Fried DB, et al. JCO 2004;22;4837
Limited disease SCLC: Timing of Thoracic radiotherapy

- Consider delaying the onset of TRT to cycle 3 of EP
  - With a malignant pleural effusion
  - In order to shrink the radiation port
- Consider sequential chemo, followed by TRT
  - Poor PS, co-morbidities, excessive risk of mortality if pneumonia developed, etc.
- GCSF worsens thrombocytopenia when given during XRT
Thoracic radiotherapy in LD SCLC: Fractionation – Intergroup trial 0096

<table>
<thead>
<tr>
<th></th>
<th>Once daily</th>
<th>Twice daily</th>
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<tbody>
<tr>
<td>N</td>
<td>206</td>
<td>211</td>
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<tr>
<td>TRT</td>
<td>1.8 Gy/25 Fx qD</td>
<td>1.5 Gy/30 Fx BID</td>
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<tr>
<td>Med survival</td>
<td>19 mo</td>
<td>23 mo</td>
</tr>
<tr>
<td>2 year OS</td>
<td>41%</td>
<td>47%</td>
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<tr>
<td>5 year OS</td>
<td>16%</td>
<td>26%*</td>
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<tr>
<td>Local failure</td>
<td>52%</td>
<td>36% (p=0.06)</td>
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<tr>
<td>Gr ¾ esophagitis</td>
<td>16%</td>
<td>32%*</td>
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<tr>
<td>TRM</td>
<td>N=5</td>
<td>N=6</td>
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</table>

* p<0.05

Thoracic radiotherapy in LD SCLC: Fractionation – Intergroup trial 0096

Figure 1. Kaplan–Meier Estimates of Overall Survival for All 417 Patients Assigned to Treatment Groups.

Thoracic radiotherapy in LD SCLC: Dose – RTOG 9712 and 0239

- Rationale: improve local control (persistent local failure > 40%), reduce esophagitis
- RTOG 9712: multicenter dose escalation
  - TRT during first two cycles of EP chemotherapy
  - 1.8 Gy once daily to 36 Gy followed by
  - Escalating boost dose (1.8Gy BID days 23 - 31)
- MTD: 61.2 Gy in 34 Fx of 1.8 Gy/Fx
- 3/8 patients had Gr 3 esophagitis
RTOG 0239
Phase II study of accelerated high dose TRT with concurrent EP for patients with LD SCLC

Radiation Therapy
Large field 28.8 Gy: 1.8 Gy per fraction, 5 days per week for 16 fractions;
On days 23-26, BID: use AP/PA fields in a.m. @ 1.8 Gy per fraction;
boost with 2nd treatment in p.m. @ 1.8 Gy per fraction;
Then off-cord boost, 1.8 Gy, BID, x last 5 days for a total dose of 61.2 Gy in 5 wks

Concurrent Chemotherapy
Chemotherapy will be started on day 1 of thoracic radiotherapy (+/-24 hours)
Cisplatin, 60 mg/m² i.v. day 1; Etoposide, 120 mg/m² i.v. day 1;
Etoposide, 240 mg/m² p.o. per day on days 2 and 3 or Etoposide 120 mg/m² i.v. per day on days 2 or 3 (see Section 7.1.4);
Repeat cycle every 3 weeks x 2 cycles, followed by adjuvant chemotherapy alone x 2 cycles

Adjuvant Chemotherapy
Cycle 3: Day 43 (Cisplatin; Etoposide) and days 44 and 45 (Etoposide, p.o. or i.v.)
Cycle 4: Day 64 (Cisplatin; Etoposide) and days 65 and 66 (Etoposide, p.o. or i.v.)

DOSE SCHEDULE

<table>
<thead>
<tr>
<th>Large Field (1.8 Gy/fx)</th>
<th>Boost (1.8 Gy BID) x (off cord)</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>Day 8</td>
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<tr>
<td>Day 1</td>
<td>Day 2</td>
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<tr>
<td>Day 15</td>
<td>Day 29</td>
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<tr>
<td>XRT a.m.</td>
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<td>L</td>
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<td>XRT p.m.</td>
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<td>B</td>
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<td>Cycles 1-2</td>
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<tr>
<td>C</td>
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<td>E</td>
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<td>E</td>
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<tr>
<td>E</td>
<td></td>
</tr>
<tr>
<td>KEY: L = Large Field; B = Boost Field; C = Cisplatin; E = Etoposide</td>
<td>Total Dose = 61.2 Gy</td>
</tr>
</tbody>
</table>
Thoracic radiotherapy in LD SCLC: RTOG 0239

- Preliminary results
- N = 72
- 2 yr overall survival 37%
- 2 yr locoregional control 80%
- Severe esophagitis 18%
RTOG 0538/CALGB 30610: Phase III trial of 3 doses and 3 schedules of TRT for LD SCLC: presently accruing

**LD SCLC** \(\rightarrow\) Randomize

- **2.0 Gy/day x 35 Fx = 70 Gy total (CALGB)**
- **1.8 Gy/day x 16 Fx, followed by 1.8 Gy BID x 18 Fx = 61.2 Gy total (RTOG 0239)**
- **1.5 Gy BID x 15 Fx = 45 Gy total (standard)**

LD SCLC: Refining chemotherapies

- No value in adding a 3rd cytotoxic agent
  - Coop group studies: taxol, topo, TPZ
- No value in adding vandetanib as targeted maintenance
- SWOG adding bevacizumab to EP and concurrent TRT
  - 3/29 pts died of tracheoesophageal fistulae
  - FDA monitoring toxicity very closely

LD SCLC: Elderly patients

- NEJM meta-analysis
  - No survival benefit TRT for pts > 70 yrs
- Retrospective subgroup analysis of Turrisi trial (N=50 pts > 70 yrs; 13%)
  - 10% vs. 1% mortality (older vs. younger)
  - BID vs. daily TRT: no impact on survival

Trend toward inferior overall survival in older patients (14 mo vs. 22 mo)

FIGURE 1. Overall survival rates comparing older to younger patients.

LD SCLC: Elderly patients

  - 55 elderly patients with limited stage SCLC
  - One cycle of CAV, followed by
  - One cycle of EP/concurrent TRT (20 – 30 Gy)
  - RR 79% (CR 51%)
  - Median survival 12 months
  - 5 year survival 18%
  - 3 treatment related deaths
Fig 1. (A) Standard regimen; (B) abbreviated regimen. TI, thoracic irradiation; PCI, prophylactic cranial irradiation.
Extensive disease (ED) SCLC

- Comprises 75% - 85% of SCLC pts
- Overall response rate ~50%
  - Complete response rate 10%
- Time to progression 4 – 5 months
- Median survival 8 – 10 months
- No long term survivors

Hanna NH and Einhorn LH. Clin Lung Cancer 2002;4:87
Increase in survival of patients with ED SCLC over 20 years

- Median survival
  - 1972 - 81: 7 months
  - 1982 - 90: 8.9 months
- 5/21 trials were pos.
- Improved survival correlated with
  - Year of treatment
  - Use of cisplatin
- Survival improvement confirmed in SEER database

Chute JP, et al. JCO 1999;17:1794
PCI in ED SCLC improves OS!

- N = 286 responders to 1st line chemo
- Half randomized PCI up to 30 Gy
- Primary endpoint: development of symptomatic brain mets
- PCI tolerated well
  - No difference in role, cognitive, or emotional functioning; increased fatigue and weight loss

Slotman B, et al. NEJM 2007;357:664
Cumulative incidence of symptomatic brain mets

Brain mets at 1 yr
PCI 15%
No PCI 40%
HR 0.27
Overall survival at 1 yr
PCI 27%
No PCI 13%
HR 0.68
Trying to improve upon EP: Replacing etoposide with irinotecan

Figure 1: Treatment Schema: JCOG 9511

Randomize

- Irinotecan 60 mg/m², days 1, 8, 15
- Cisplatin 60 mg/m², day 1
- q 4 weeks × 4 cycles

- Etoposide 100 mg/m², days 1-3
- Cisplatin 80 mg/m², day 1
- q 3 weeks × 4 cycles

(n = 154)

Noda K, et al. NEJM 2002;346:85
Trying to improve upon EP: Replacing etoposide with irinotecan

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Irinotecan/Cisplatin Versus Etoposide/Cisplatin: Response and Survival</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Irinotecan/ Cisplatin (n = 77)</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>84%</td>
</tr>
<tr>
<td>Complete Response</td>
<td>3%</td>
</tr>
<tr>
<td>Median Progression-Free Survival</td>
<td>6.9 months</td>
</tr>
<tr>
<td>Median Overall Survival</td>
<td>12.8 months</td>
</tr>
<tr>
<td>2-Year Survival</td>
<td>19.5%</td>
</tr>
</tbody>
</table>

Noda K, et al. NEJM 2002;346:85
Overall survival of 331 pts randomized to either EP or IP in US confirmatory trial


Trying to improve upon EP: Unsuccessful strategies

- Adding a 3rd cytotoxic agent to EP
- Increasing dose intensity or dose density of EP
- Adding maintenance chemo after EP
- Use of platinum + pemetrexed doublet

Socinski MA, et al. JCO 2009;27:4787
ED SCLC: First line research

- Amrubicin
  - Synthetic anthracycline
  - Potent topo II inhibitor
  - Approved in NSCLC and SCLC in Japan
  - Pending FDA approval in US (2nd line)
  - 40 mg/m² IV push over 5 min d 1-3 q 21d
  - When combined with carbo (AUC 5) in 1st line setting, dose is 35 mg/m²

ED SCLC: First line research

• Adding bevacizumab
  – ECOG 3501 (N=64)
    • Added to EP at 15 mg/kg d1 q 21d
    • ORR 69%
    • Phase III (ECOG 4506) development on hold
  – CALGB 30306 (N=72)
    • Added to IP (given d1 and 8) at 15 mg/kg d1 q 21d
    • ORR 62%; median OS 11.7 months
    • 1 yr OS 49%

• Both studies had no ≥ grade 3 hemorrhagic events

Sandler A, et al. PASCO 2007; #7564; Ready N, et al. PASCO 2007; #7563
Bcl-2 antisense therapy *worsened* overall survival in untreated ED SCLC: Randomized phase II study CALGB 30103

ED SCLC: First line open studies

- **UWCCC**: EP + AT101, oral *bcl-2* inhibitor
- **ECOG 1508**
  - EP + GDC0449 or IMC-A12
    - Evaluating role of hedgehog and IGFR signaling
- **CALGB 30504**
  - Phase II of sunitinib with etoposide and either platinum
- **Completed accrual, analysis pending**
  - ECOG 5501: sequencing of topo I inhibitor with EP or IP
Oral topotecan vs. BSC in relapsed SCLC

Fig 1. Kaplan-Meier estimates for overall survival in the intent-to-treat population (log-rank P = .01)


QoL improved with oral topotecan
3% FNP with topotecan
Relapsed ED SCLC: Research

• Amrubicin
  – Randomized phase II in sensitive relapse: ≥ 3 mo since EP or IP (N=76)
    • ORR superior to IV topo (44% vs. 11%)
    • Median survival superior (9.3 vs. 7.7 mo)
  – Resistant/refractory 2nd line (N=39)
    • ORR 33% (0% expected)
  – Toxicity: myelosuppression, anorexia, N/V

Jotte R, et al. PASCO 2009; #8028
Ettinger DS, et al. PASCO 2008; # 8041
Relapsed SCLC: Other treatments

• CAV equally efficacious compared to IV topotecan
  – 25 week median survival for both
  – Slightly increased neutropenia with CAV
    • But no difference in febrile neutropenia

• Gemcitabine
• Vinorelbine
• Irinotecan

JCO 1999;17:658; JCO 2003;21:1550
Relapsed SCLC: Compounds under investigation

• Open to accrual: topo +/- VEGF Trap
• Bortezomib
  – SWOG to combine with a cytotoxic
• Picoplatin
  – Active in CDDP resistant models
• Temozolomide
• Newer generation \textit{bcl-2} inhibitors
  – AT101, obatoclax, ABT-737

JTO 2006;1:996; ASOC Educational Book 2009
ED SCLC in the elderly

- Single agent oral etoposide yields inferior results
- Carbo/etoposide used frequently
  - Consider empiric wbc support, dose reduction
  - Small phase II studies: median survival 9 mo
- Carbo (AUC4) + Amrubicin (35 mg/m^2)
  - ORR 89%
  - Median survival 18.6 months
  - 17% incidence of febrile neutropenia
    - No treatment-related deaths

Molecular biology of SCLC: No single abnormality universally implicated in etiology of SCLC

- Chromosomal abnormalities
  - Loss of 3p (tumor suppressor genes)
- Oncogenes
  - c-myc: 80% SCLC RNA overexpression
  - Bcl-2: 75% SCLC
- p53 and Rb mutations common
- Receptor tyrosine kinase abnormalities
  - c-Kit
  - Insulin-like growth factor-1, VEGF, TGF-β
  - c-Met and hepatocyte growth factor
Thyroid cancer

- Please read (G->Team->Lung Cancer->Articles for Fellows)
  - 2008 JCO Pfister and Fagin editorial
  - 2010 JCO Wells SA: Medullary Thryoid Ca

- Differentiated: papillary, follicular (Hurthle variant)
- Undifferentiated: anaplastic
- Medullary: parafollicular C cells
Differentiated thyroid cancer

- Develop metastatic disease
  - Papillary 10%
  - Follicular 25%
  - Hurthle cell 35% (less RAI avid)
- Treatment: surgery->RAI->TSH suppression
- Surgery->whole body RAI scan (low dose)->therapeutic RAI (high dose)->repeat whole body RAI scan (low dose)
  - Often repeated 2 or 3 times as needed
  - Dedifferentiation seen in 1/3 of pts with persistent thyroid ca
  - Iodine refractory = FDG avid = PET positivity
Thyroid cancer: Targeted therapies

- **Mutations**
  - Papillary: BRAF, RET, RAS
  - Follicular: RAS, PAX8/PPARgamma
  - Medullary, familial: RET > 95%
    - Sporadic: RET > 50%

- VEGFR TKIs efficacy in both differentiated and medullary

- Clinical caveat: External beam radiation less efficacious in thyroid cancer
Thymoma and thymic carcinoma

- 4 good articles in the G drive folder
- Thymoma is relatively chemo-sensitive
  - CAP used often pre-resection (ORR>70%)
  - Carbo/Taxol less effective than cisplatin and doxorubicin-based regimens
- Resection of metastatic disease, followed by chemo, can be curative
- Pts with thymomas at risk for 2\textsuperscript{nd} malignancies: NHL, GI, sarcoma

Lemma GL, et al. PASCO 2008:#8018