SCLC: Developments in systemic treatment

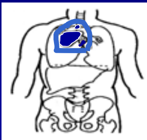
Egbert F. Smit, Dept. Pulmonary Diseases, Vrije Universiteit Medisch Centrum, Amsterdam, The Netherlands

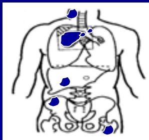
Outline

- Staging
- First line treatment
- Second line treatment

Staging of SCLC

- **1950: Veterans' Administration Lung Study Group (VALSG):**
  - **Limited Disease (LD): characterized by tumors confined to one hemi-thorax, although local extension and ipsilateral, supra-clavicular nodes could also be present if they could be encompassed in the same radiation portal as the primary tumor. No extra-thoracic metastases.**
  - **All other patients were classified as extensive disease (ED).**



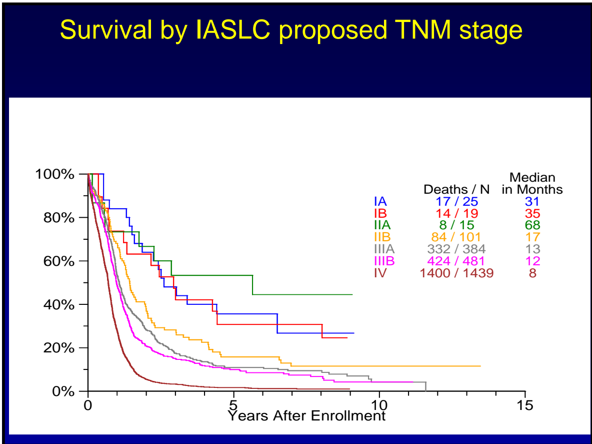


Available TNM Staging

Summary of small cell lung cancer cases from the IASLC international staging project database

	Clinical TNM	Pathological TNM	Clinical and Pathological TNM	cM1	Extensive or Limited Only	
Not Classified	1819	127	193	1532	0	3671
Extensive	88	0	4	2998	2038	5128
Limited	1308	1	18	0	2494	3821
Total	3215	128	215	4530	4532	12620

Survival by IASLC proposed TNM stage



Recommendations

- TNM staging should be applied in SCLC
- stratification by TNM stage be incorporated into clinical trials in Stage I-III SCLC.
- for prospective staging validation studies, more information must be collected to define N staging more clearly

Which staging procedures are needed?

Staging procedures should include medical history, physical examination, chest X-ray, complete blood count including differential count, liver and renal function tests, lactate dehydrogenase and sodium levels, and a CT scan of the chest and upper abdomen including the liver and adrenal glands.

In patients with symptoms or abnormal physical examination suggesting metastasis additional tests may include bone scintigraphy, CT scan or MRI of the brain, and bone marrow aspiration and biopsy. In the presence of a pleural and/or pericardial effusion two aspirations are needed in order to consider cytology negative. If extensive disease is detected by one test, further staging can be omitted [V, D].

ESMO guidelines. Ann. Oncol. 19, suppl 2,41,2008.

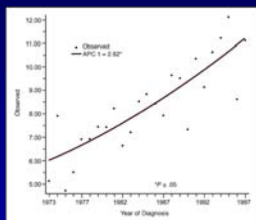
How about ^{18}FDG-PET scanning?

- 3 prospective studies
- Sensitivity for staging limited vs extensive stage 89% - 100%
- Specificity 78% - 95%
- "These data suggest that total body PET may be useful in staging of SCLC"

Ung et al. J. Natl. Cancer Inst. 99,1753,2007

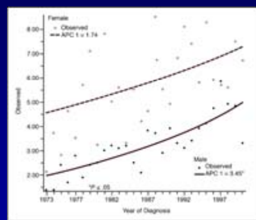
Survival in SCLC

Limited



5 year survival 1973 5%, 1998 10%

Extensive



2 year survival 1973 1.5%, 2000 4.6%

Govindan et al. J. Clin. Oncol. 24,4539,2006.

How has this "improvement" been achieved?

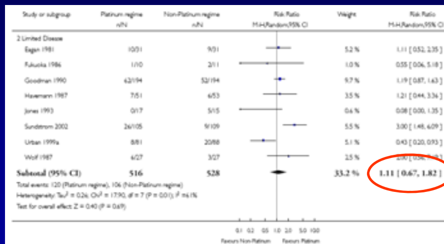
- ***No progress*** **in systemic treatment**
- ***Progress***
  - **Limited disease:**
    - **Use of early (accelerated) thoracic radiotherapy**
    - **Use of PCI**
  - **Extensive disease:**
    - **Use of PCI**

Front-line Chemo in SCLC Evolution

Author	Treatment	Survival (months)	
Green	BSC	1.5	BSC
Green	CTX	4.0	mono-CT
Sandler	CTX+ CCNU+ MTX	7.2	1st -generation poly-CT
Roth } Eckardt	CAV	8.3	2nd-generation poly-CT
Hanna	PE	9.4-10.2	platinum-based poly-CT

Ardizzoni, ASCO 2007

Platinum *vs* Non-Platinum Limited Disease



Cochrane Database review 2009

Platinum *vs* Non-Platinum Extensive Disease

Subtotal (95% CI) 1326 1312 41.6 % 1.06 [0.93, 1.21]

Cochrane Database Review 2009

How to improve treatment results in SCLC ED?

Dose intensification

ACE Dose intensification in limited disease does not improve survival; it may improve survival in extensive disease (Thatcher et al., JCO, 2000).

A 70% increase of CDE actual dose intensity does not translate into improved outcome (Ardizzoni et al. JCO, 20;3947;2002)

A 99% increase of ICE actual dose intensity does not translate into improved outcome (Lorigan et al, JNCI 97,666,2005)

Dose intensive chemotherapy does not improve survival

High-ICE Std-ICE

Proportion event-free

0.00 0.20 0.40 0.60 0.80 1.00

0 1 2 3 4 5 6 7 8

Years since randomization

High-ICE	69	35	8	7	5	3	2	2	0
Std-ICE	71	23	14	7	6	5	3	2	0

Leyvraz et al. J. Natl. Cancer Inst. 100,553,2008

Any New Treatment Options?

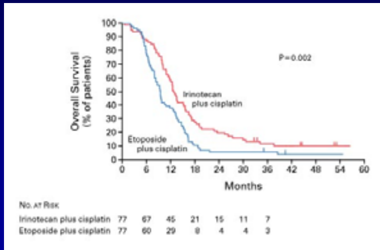
Chemotherapy

- Topo I Inhibitors
  - Irinotecan
  - Topotecan
  - Belotecan
- Pemetrexed

Targeted Agents

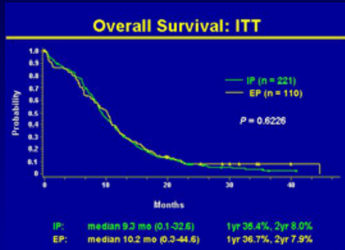
- Antiangiogenics
  - Thalidomide
  - Bevacizumab
- Anti C-Kit, EGFR…

IP vs EP in SCLC ED – Japanese experience

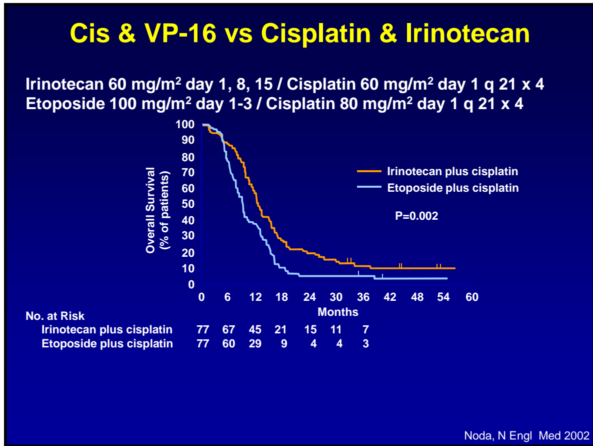


Noda et al. New Eng. J. Med. 346,2002,85

IP vs EP in SCLC ED – US experience

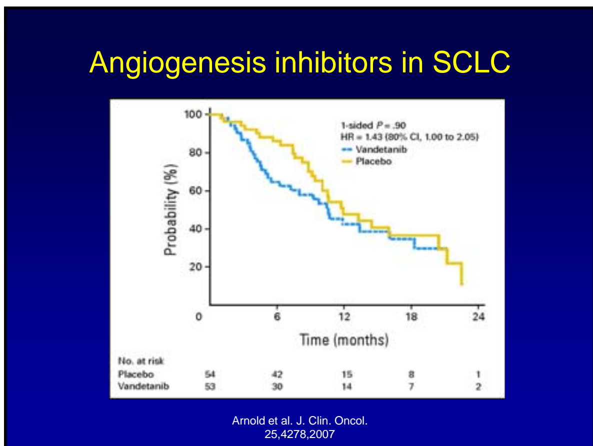


Hanna et al. Proc. ASCO 2005, #1094

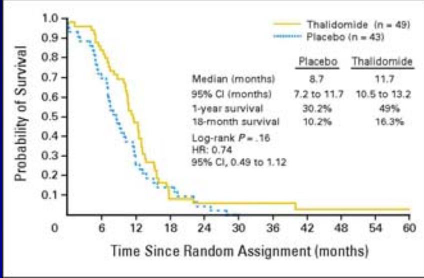


"ASCO 2008" negative phase III studies of

- irinotecan
- topotecan
- pemetrexed



Angiogenesis inhibitors in SCLC



Pujol et al. J. Clin. Oncol.
25,3945,2007

Targeted Therapies - Ongoing

- Pro-apoptotic agents
  - Oblimersen
  - ABT-263
  - AT-101
- C-Met inhibitors
  - AMG 102
- Neuropeptide receptor antagonists
  - Meclinertant
- Various
  - AZD0530
  - M-TOR inhibitors

Second line therapies

- **response to first-line therapy > 60%**
- **> 95 % relapse after first-line treatment**
- **second-line treatment often considered as indicated as part of palliation**

Chemotherapy for Relapsed Small Cell Lung Cancer: A Systematic Review and Practice Guideline

J Thor Oncol 2007; 2: 348

- The evidence for the clinical benefit of second-line chemotherapy in the treatment of patients with relapsed SCLC is limited. The selection of patients for treatment with second-line therapy should be dependent on the treatment-free interval, the extent of response to first-line therapy, residual toxicity from first-line therapy, and the PS of the patient.
- There is currently no standard second-line chemotherapy regimen for patients who fail to respond to or who relapse shortly after first-line therapy. Clinical trials are needed to determine the optimal treatment regimen.

Chemotherapy for Relapsed Small Cell Lung Cancer: A Systematic Review and Practice Guideline

- There is insufficient evidence to recommend a specific chemotherapy regimen. Nevertheless, in the opinion of the lung cancer disease site group, patients who relapse three or more months after having completed first-line chemotherapy may benefit from re-treatment with the same regimen that induced their initial response. This would generally mean re-treatment with EP. Alternative regimens may include CAV or Cb and etoposide.

Phase III 2nd line Topotecan SCLC

1. SCLC
2. 1 prior Cx regimen
3. >45 days off Cx
4. Nl organ function
5. No CNS involvement

RANDOMIZE

→ Topotecan 2.3 mg/m^2 x5 q 3wk

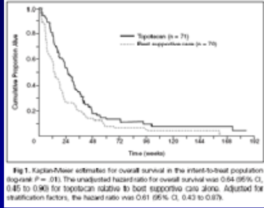
→ Best supportive care

Primary endpoint: OS

Secondary Endpoints: ORR, TTP, symptom assessment

O'Brian et al. J. Clin. Oncol. 24,5441,2006.

Overall Survival and Symptomatic Response



Detoriation QoL at 3 mo. Interval:

Topotecan -0.05 (-0.11 – 0.02)

BSC -0.20 (-0.27 – -0.12)

P < .05 for some symptoms.

Median OS Topotecan 25.9 wks vs 13.9 wks BSC, HR 0.64 (0.45 – 0.90) p = .01

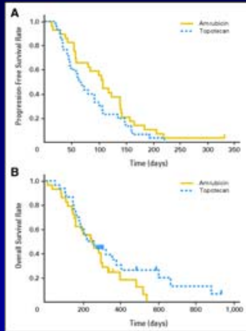
2nd Line Topotecan in SCLC

- **Superior to BSC**
- **Compared to CAV**
  - **Similar ORR, OS, Toxicity**
  - **Superior symptom improvement**
- **IV compared to Oral Topotecan**
  - **Similar ORR, OS, Toxicity, QoL**

Amrubicin

- 1990's Active agent in second line in Japan (ORR 65%)
- Phase II studies US & Europe in resistant relapse SCLC:
  - ORR 33%
  - Tox "manageable"
    - (Ettinger et al. Proc ASCO 2008)
- Currently phase III testing 1st and 2nd line

Amrubicin vs Topotecan in relapsed SCLC

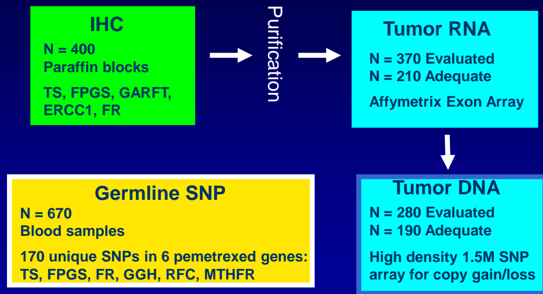


Inoue et al. J. Clin. Oncol. 26,5401,2008

CONCLUSION

- Survival Improvements achieved through RT
- Few developments in systemic therapy
  - Topotecan and Amrubicin 2nd line
- Better understanding of SCLC biology and bench to beside approaches are needed to improve clinical outcome.

Status of ED-SCLC Blood and Tumor Samples for Correlative Studies



Projected completion: Q3 – Q4 2008