Extensive stage – small cell lung cancer(SCLC)

SCLC

- Common type of lung cancer
  - Generally comes under spectrum of neuroendocrine lung neoplasms
- Also known as oat cell carcinoma
- Highly aggressive type of cancer
- Has distinctive clinical manifestations that include
  - Frequent and widespread metastases
  - High sensitivity to chemotherapy (60%)

Anbazhagan R. Classification of Small Cell Lung Cancer and Pulmonary Carcinoid by Gene Expression Profiles. *Cancer research* .1999; 59:5119 –5122

Epidemiology

Constitutes ~20% of all lung cancers

>100,000 new cases occur world wide

Most common in 60-80 years old

There was recent decline in the number of cases

Anbazhagan R. Classification of Small Cell Lung Cancer and Pulmonary Carcinoid by Gene Expression Profiles. *Cancer research* .1999; 59:5119 –5122

Limited vs. extensive stage

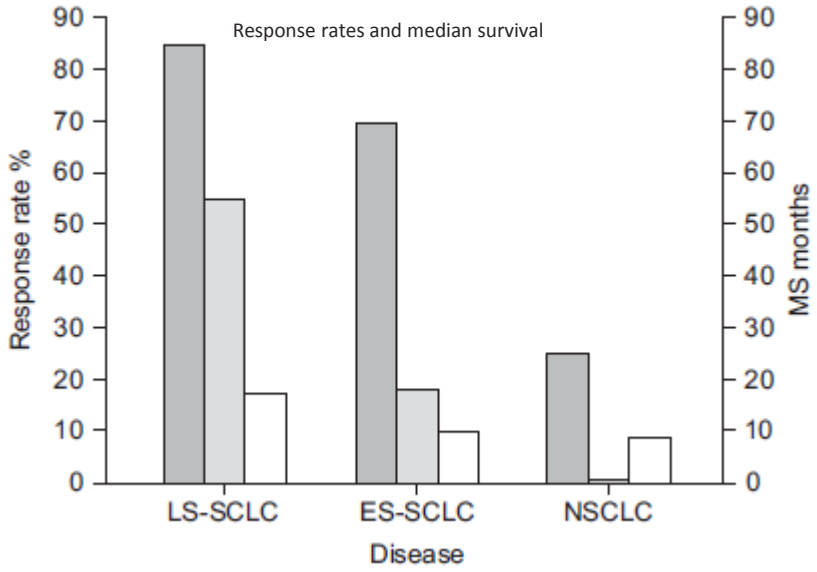
	Limited stage	Extensive stage
Incidence	1 out of 3 people with SCLC	2 out of 3 people with SCLC
Spread	Only in one lung and perhaps in lymph nodes on the same side of the chest	To other lung, to lymph nodes on the other side of the chest, or to distant organs
Area	confined to an area	Wide spread
Treatment	chemo-radiation ± PCI	Chemotherapy ± PCI

Lung Cancer (small cell) Overview. American cancer society. http://www.cancer.org/cancer/lungcancer-smallcell/overviewguide/lung-cancer-small-cell-overview-staging Accesed july 9,2014

Management of Extensive-stage SCLC (ES-SCLC)

Response to Chemotherapy

- In untreated, rarely survives a few months
- In treated, average survival 8-13 months
- SLCC on chemotherapy
  - Very chemosensitive tumour, rapid responses,
  - Response 60-80%
  - Complete remission 15-20%



I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

1st line chemotherapy in ES-SCLC

CDDP + VP-16 : main backbone of chemotherapy	Max 4-6 cycles
Carboplatin + VP-16	
CDDP + Irinotecan	
Carboplatin + Irinotecan	
Cyclophosphamide + doxorubicin + vincristine	

Marvaretta M Stevenson. Small Cell Lung Cancer Treatment Protocols. Medscape. 2013. http://emedicine.medscape.com/article/2007031-overview. Accessed July 9, 2014

Outcomes of 1st line platinum-based combination

	Response %		Survival		Toxicity CTC 3/4 %			
	OR	CR	Median months	At 1 yr %	NP	Anaemia	TP	Other
Cisplatin–etoposide	88	29	9.1	30	18			
Cisplatin–etoposide	61	10	8.6	30	70	35	13	6*
Cisplatin–irinotecan (JCOG 9511)	84	3	12.8	58	65	27	5	16¶
Cisplatin–irinotecan	48		9.3	35	36	5	4	21¶
Carboplatin–irinotecan		17	8.5	34	33	5	15	11¶
Cisplatin–irinotecan (S0124)	59	4	9.7	39	33	6	4	19¶
Cisplatin–epirubicin	74		10.9		42			
Cisplatin–topotecan (oral)	63	6	10.0	31	59	38	38	
Cisplatin–topotecan (intravenous)	55	10	10.3	40	36	12	19	
Carboplatin–pemetrexed	25		7.3		9	10	10	
Cisplatin–etoposide–paclitaxel	75	16	10.6	38	44	19	22	
Cisplatin–etoposide–ifosfamide	73	21	9.0	36	52	52	35	
Cisplatin–etoposide–cyclophosphamide–epirubicin	76	21	10.5	40	99	51	78	22+

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Platinum derivative + etoposide

- First-line treatment of ES-SCLC
- Superiority confirmed by 2 meta-analyses
- PUJOL et al.
  - Platinum-containing regimen yields a higher response rate & reduction of risk of death at 1 yr
  - without increase in toxic deaths

I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

Platinum derivative + etoposide

- European Lung Cancer Working Party (ELCWP)
  <u>Etoposide + cisplatin (EP)</u>
  - With etoposide, demonstrated a survival benefit
  - With cisplatin, significantly better than regimens using neither drug

In contrast

- Cochrane Collaboration

  <u>Platinum-based Vs nonplatinum-based regimens</u>
  - Suggested no significant Benefit
  - No significant difference in survival at 6, 12, 24 months
  - No significant difference in overall tumour response
  - Higher rates of nausea and vomiting, anaemia & thrombocytopenia

I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

PlatinumVs Non-Platinum

Etoposide and cisplatin (EP) Vs cyclophosphamide, epirubicin & vincristine

- In LS-SCLC, Significantly higher 2- and 5-yr survival rates in EP
- ES-SCLC, a trend in survival benefit
  - 8.4 months in EP group
  - 6.5 months in cyclophosphamide, epirubicin, vincristine

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Chemo-Controversy

Cisplatin

- Important side-effect nephrotoxicity,
  - Thus prevention is hyperhydration, maybe problematic in elderly
- Alternative is Etoposide + Carboplatin
- Hellenic Cooperative Oncology Group

  Etoposide + Cisplatin < Etoposide + Carboplatin
  - Demonstrated to be as effective & less toxic

Etoposide

- Intravenously or orally?
- Studies demonstrated that oral was
  - Less effective
  - Sometimes more toxic
  - Inferior survival

I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

ALTERNATIVES TO PLATIN/ETOPOSIDE

Despite high response rates, relapse rates are high and the overall prognosis remains poor rapid development of drug resistance

- Doxorubicin-containing regimens
  - Used for a long time in SCLC treatment
  - Phase III trials failed to demonstrate better overall survival
  - Haematological toxicity was significantly higher

I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

Alternatives To Platin/Etoposide - Epirubicin

- Modified anthracycline that is less cardiotoxic
- Demonstrated significant activity as a single agent in phase II
- Cisplatin/epirubicin Vs Etoposide + cisplatin (EP)
  - Similar overall objective response rates, median time to progression and median survival
  - Haematological toxicity was lower
- Practical advantage is administration in 1 day

I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

Alternatives To Platin/Etoposide - Irinotecan

- Camptothecin that acts as a topoisomerase I inhibitor
- In Japanese phase III trial

<u>Cisplatin + irinotecan > Etoposide + cisplatin (EP)</u>

  - Significantly more effective
  - Higher response rate (84 Vs 68%)
  - Longer median survival (12.8 Vs 9.4 months)
  - Higher 2-yr survival rate (19 Vs 5%)
  - Haematological toxicity less pronounced

In Contrast

- Southwest Oncology Group (SWOG)
  - Found no significant differences
- Study from Norway
  - Reporting a moderate benefit

Conflicting results have been obtained with platinum and irinotecan

I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

Alternatives To Platin/Etoposide – Topotecan & Belotecan

Topotecan

- Member of the camptothecin family
- Cisplatin/topotecan > etoposide + cisplatin (EP)
  - Demonstrated similarly tolerable
  - Increased haematological toxicity

Belotecan

- New camptothecin analogue
- Shown activity in SCLC in phase II trials
- Phase III trial currently running

I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

Alternatives To Platin/Etoposide – Pemetrexed & Paclitaxel

Pemetrexed

- Folic acid metabolism antagonist
- Anti-tumor activity comparable to standard regimens

Paclitaxel

- Member of the taxane family
- 29% response rate in refractory ES-SCLC
- Haematological toxicity lower
- Addition of paclitaxel to etoposide + cisplatin (EP)
- Did not improve time to progression or survival
- Associated with unacceptable toxicity

I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

2nd line chemotherapy in ES-SCLC

- Oral etoposide
- Oral topotecan
- IV topotecan
- Carboplatin + irinotecan
- Cisplatin + irinotecan
- Paclitaxel

Min 4-6 cycles

Marvaretta M Stevenson. Small Cell Lung Cancer Treatment Protocols. Medscape. 2013. http://emedicine.medscape.com/article/2007031-overview. Accessed July 9, 2014

Chemotherapy in Relapse

- High relapse rates are typical for SCLC
- Different patterns of relapse

I. Sensitive patients
   - Response to first-line therapy & treatment free interval of >90 days

II. Resistant patients
   - Relapse within 90 days

III. Refractory patients
   - Do not respond at all to first-line treatment

I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

Topotecan

- Only approved drug for SCLC which failed or relapsed after first-line chemotherapy
- Available in both IV & oral form

IV topotecan > cyclophosphamide, doxorubicin + vincristine

- Response rates 24 and 18%,
- Median survival was 25.0 and 24.7 weeks

Oral topotecan

- Shown to exhibit similar activity & tolerability as IV
- Greater symptom improvement
- Improved survival and quality of life

I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

Other possible 2nd line

- Paclitaxel + irinotecan
- Shown some activity in phase II trials

- Amrubicin
  - Shown some impressive results

<u>USA phase II trial</u>
- Myelosuppression observed
- No anthracycline-induced cardiotoxicity noted

<u>Japanese phase II trial</u>
- 37–60% response rates reported
- Response rate & median survival similar in sensitive and resistant patients

<u>Amrubicin Vs Topotecan Study</u>
- Supports amrubicin in both sensitive & resistant patients
- A higher response rate was achieved

I.K. Demedts, K.Y. Vermaelen, J.P. van Meerbeeck. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010; 35: 202–215

New drugs

Picoplatin	• Platinum analogue to overcome platinum resistance • Useful in relapsed SCLC • Less nephro-, neuro-and ototoxicity in phase I and II trials
Obatoclax	• Bcl-2 inhibitor • Evaluated in phase I/II trials including patients with SCLC
Temozolamide	• Oral alkylating agent • Evaluated in a phase II trial for relapsed SCLC

Demedts I K et al. Treatment of extensive-stage small cell lung carcinoma: current status and futureprospects. Eur Respir J 2010; 35: 202–215

Guidelines

International guidelines for ES-SCLC

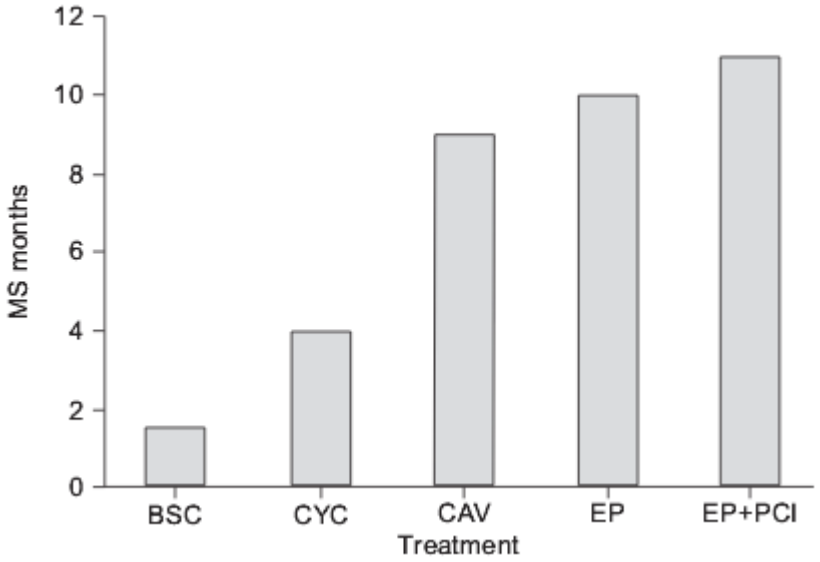
	ACCP	ESMO	NICE	NCCN
Publication year	2007	2008	2005	2009
First-line treatment	4–6 cycles of platinum-based chemotherapy Platin with etoposide or irinotecan	4–6 cycles of platinum-based chemotherapy Platin with etoposide	4–6 cycles of platinum-based chemotherapy Preferred combination not specified	4–6 cycles of EP, EC, IP, IC or CAV
PCI	Patients with CR	Patients with major response after chemotherapy	To be evaluated in clinical trials	Patients with CR or near-CR Not when multiple comorbid conditions, poor PS or impaired mental function
Thoracic radiotherapy	Patients with CR outside chest and CR or PR in chest	Not discussed	Patients with CR outside chest and CR or PR in chest	Patients with low-bulk metastatic disease and CR or near-CR
Second-line treatment	No drug regimen specified	No drug regimen specified	No drug regimen specified	Preferably in clinical trials Topotecan for relapse at 2–6 months Original regimen for relapse after >6 months

PCI- prophylactic cranial irradiation

Demedts I K et al. Treatment of extensive-stage small cell lung carcinoma: current status and futureprospects. Eur Respir J 2010; 35: 202–215

Median survival in ES-SCLC with various treatments

Median survival rate was high with **EP+ PCI** **(EP**: etoposide and platin; PCI: prophylactic cranial irradiation)



- BSC: best supportive care;
- CYC: cyclophosphamide;
- CAV: cyclophosphamide, doxorubicin and vincristine;
- EP: etoposide and platin;
- PCI: prophylactic cranial irradiation.

Demedts I K et al. Treatment of extensive-stage small cell lung carcinoma: current status and futureprospects. Eur Respir J 2010; 35: 202–215

Prognosis

- Median survival of 6 to 12 months with existing therapy
- Long-term disease-free survival is rare.
- Prophylactic cranial radiation improve survival
  - Prevents central nervous system recurrence
- Patients who had a complete response to chemotherapy shows improvement in survival rates

General Information About Small Cell Lung Cancer. National cancer institute. http://www.cancer.gov/cancertopics/pdq/treatment/small-cell-lung/healthprofessional/page1 Accesed 2014 july 9,2014

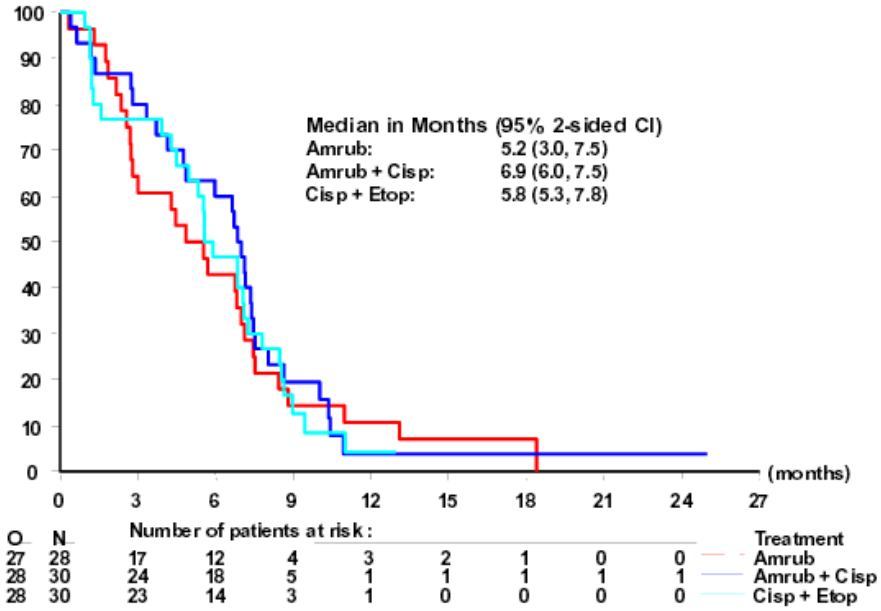
Study design

EORTC 08062 phase II randomized trial done on 41 patients with SCLC in japan

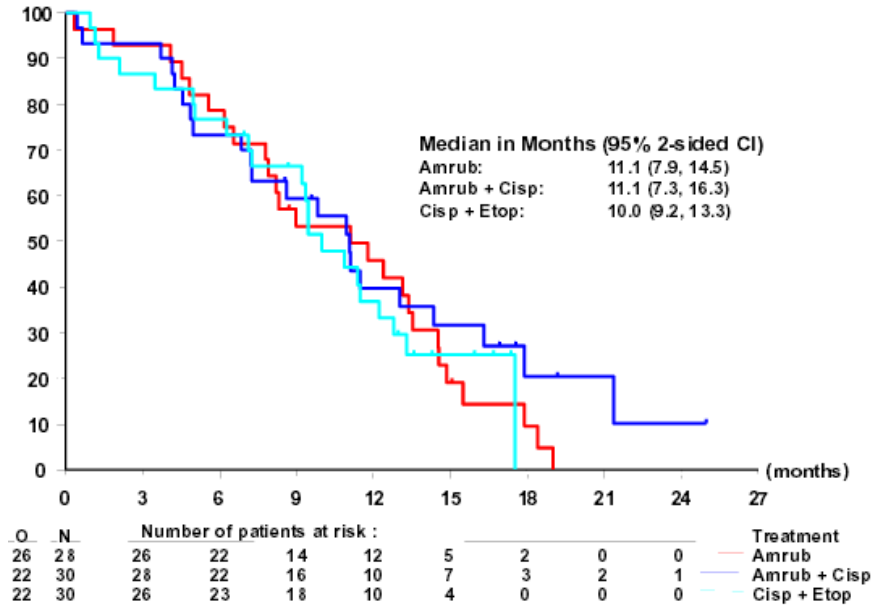
- Aim: Activity and safety of single agent amrubicin, cisplatin combined with amrubicin, and cisplatin combined with etoposide as first line treatment in extensive disease (ED) small cell lung cancer (SCLC)
- Patients were randomized to 3 weekly cycles of either
  - Amrubicin alone 45 mg/m ^{2} i.v. day(A)
  - Cisplatin 60 mg/m ^{2} i.v. d1 and amrubicin 40 mg/m ^{2} i.v. d1–3 (PA)
  - Cisplatin 75 mg/m ^{2} i.v. d1 and etoposide 100 mg/m ^{2} d1, d2–3 i.v./po(PE)

Mary E R. Randomised phase II study of amrubicin as single agent or in combination with cisplatin versus cisplatin etoposide as first-line treatment in patients with extensive stage small cell lung cancer – EORTC 08062. European journal of cancer. 2011;47: 2322-2330

Results



Progression free survival



Overall survival

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Conclusion

- ES-SCLC constitutes ~20% of all lung cancers
- Chemotherapy is the main modality of treatment
- Standard treatment with platin/etoposide has been unbeaten for >20 yrs
- Introduction of PCI, resulted in a 14% survival gain at 1 yr.
- EP+PCI (EP:etoposide and platin; PCI: prophylactic cranial irradiation) has more median survival rate compared to chemotherapy alone

Thank you