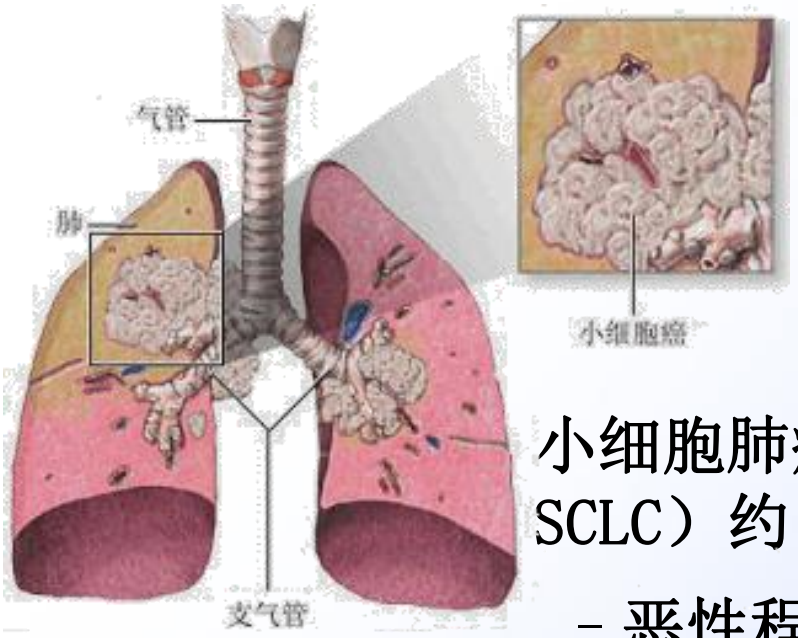
小 细 胞 肺 癌的一线化疗

First-line chemotherapy for small cell lung cancer (SCLC)

内容提要

- 概述
- 流行病学
- 发病机制
- 临床表现
- 分期
- 治疗

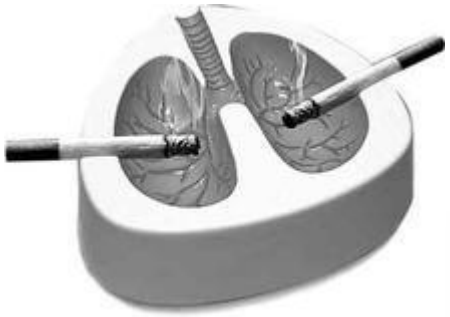
概述



小细胞肺癌（Small Cell Lung Cancer，SCLC）约占肺癌的15%

- 恶性程度高
- 倍增时间短
- 转移早且广泛
- 对化疗、放疗敏感且初治缓解率高
- 极易发生继发性耐药且容易复发

流行病学



SCLC发生率

1986年：17%

2002年：13%

2002年：50%

1973年：28%

女性SCLC发生率

The surveillance, epidemiologic, and end results database (United States, 1970 to 2006)

发病机制

- SCLC的分子发病机制研究剧多
  - 染色体异常
    - 多个染色体位点基因缺失，这些位点是一系列抑癌基因的基因座
    - 超过98%的SCLC存在端粒酶RNA亚基与端粒酶活性的上调
  - 抑癌基因异常
    - 约90%的SCLC中存在p53失活性突变，40%-70%的SCLC中存在异常p53蛋白表达
    - 在超过90%的SCLC患者可见Rb的完全缺失或者突变
  - 无受体癌基因
    - 75%-95%的SCLC中存在Bcl-2的上调
    - 18%-31%的SCLC中可见MYC的激活
  - 信号通路
    - 磷酸次黄嘌呤核苷酸3-激酶/AKT/mTOR途径
  - 受体酪氨酸激酶和生长因子
  - 细胞内分子伴侣
  - 细胞表面标志物
  - 进化通路

  ……

临床表现

- 小细胞肺癌早期可无症状，诊断时最常见的症状为乏力（80%）、咳嗽（70%）、气短（60%）、体重下降（55%）、疼痛（40-50%）、咯血（25%）。
  - 由原发肿瘤引起的症状和体征
    - 咳嗽、咯血、胸闷、气短
  - 肿瘤在胸腔内扩展所致的症状和体征
    - 胸痛、上腔静脉综合征、咽下困难、呛咳、声音嘶哑、霍纳综合征、肺部感染
  - 肿瘤肺外转移引起的症状体征
    - 转移至淋巴结、胸膜、骨、脑、心包、肾上腺及肝脏等
  - 肿瘤肺外表现及全身症状
    - 类癌综合征、癌肿伴肌无力综合征 、抗利尿激素分泌不当综合征、肥大性肺性骨关节病、库欣综合征

分期

- 美国退伍军人医院肺癌研究小组（Veterans' Affairs Lung Study Group，VALSG)制定的SCLC分期系统
- 国际肺癌研究协会（International Association for the Study of Lung Cancer，IASLC)制定的TNM分期系统(T: Primary Tumor, N: Regional Lymph Nodes, M: Distant Metastasis)

TNM staging system for lung cancer (7th edition)

Primary tumor (T)	
T1	Tumor ≤3 cm diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus
T1a	Tumor ≤2 cm in diameter
T1b	Tumor >2 cm but ≤3 cm in diameter
T2	Tumor >3 cm but ≤7 cm, or tumor with any of the following features:
	Involves main bronchus, ≥2 cm distal to carina
	Invades visceral pleura
	Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor >3 cm but ≤5 cm
T2b	Tumor >5 cm but ≤7 cm
T3	Tumor >7 cm or any of the following:
	Directly invades any of the following: chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus <2 cm from carina (without involvement of carina)
	Atelectasis or obstructive pneumonitis of the entire lung
	Separate tumor nodules in the same lobe
T4	Tumor of any size that invades the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe
Regional lymph nodes (N)	
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

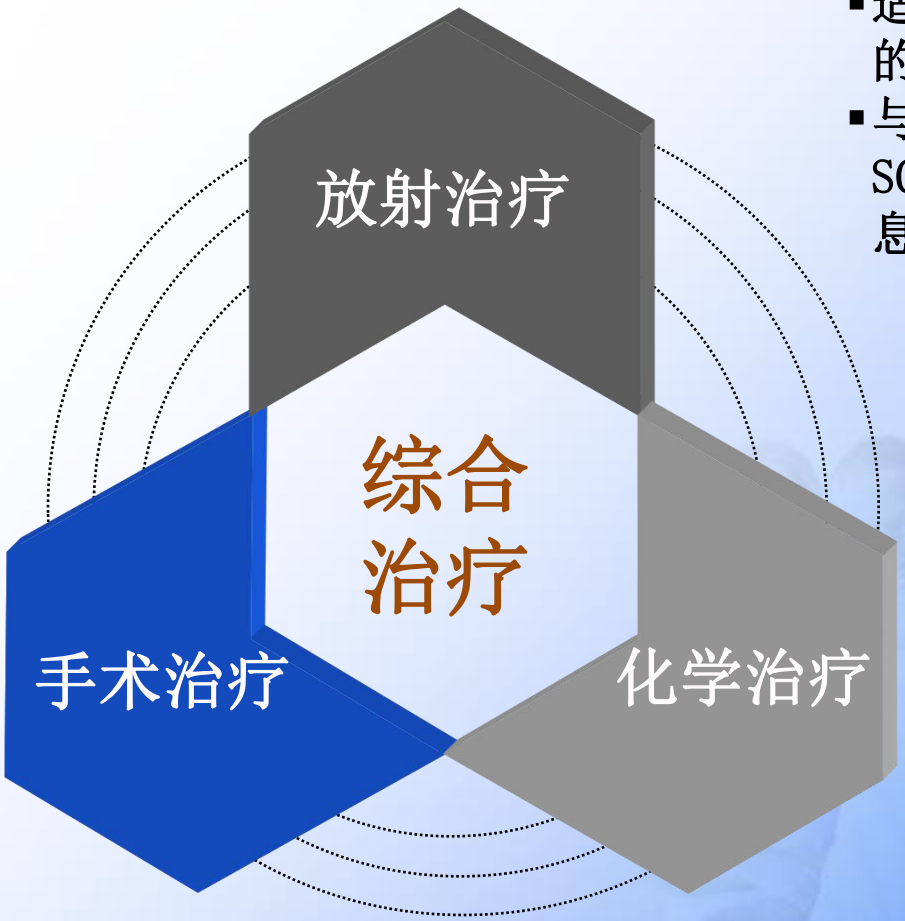
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion		
M1b	Distant metastasis (in extrathoracic organs)		
Stage groupings			
Stage IA	T1a-T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a,T1b,T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,T1b,T2a,T2b	N2	M0
	T3	N1,N2	M0
	T4	N0,N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a or M1b

Adapted from: Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groups in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007; 2:706.

治疗

放射治疗
- 适用于各期SCLC的治疗
- 与化疗联合用于SCLC根治性及姑息性治疗

手术治疗
- Stage Ⅰ（＜5%）标准分级评估后考虑 手术治疗
- **Stage**Ⅳ必要时手术，旨在缓解症状、支撑气道及减轻瘤负荷



化学治疗
- LS-SCLC --------
  RR:80%-90%;
  CR:50%-60%;
  MSD:14-20M.
- ES-SCLC --------
  RR:60%-80%;
  CR:15%-20%;
  MSD:8-13M.

RR: response rates; CR: complete responses ; MSD: median survival durations

活性化疗药物

以下化疗药物对于SCLC有很强的活性

铂化合物类	顺铂、卡铂
拓扑异构酶抑制剂	依托泊苷、替尼泊苷、伊立替康、拓扑替康
烷化剂类	异环磷酰胺、磷酰胺
抗生素类	多柔比星、表柔比星、氨柔比星
抗微管类	紫杉醇，多西他赛，长春新碱

Platinum-based combinations——Cisplatin plus Etoposide

Cycle length: Every 21 days for four cycles.

Drug	Dose and route	Administration	Given on days
Cisplatin	80 mg/m^2 IV	Dilute in 250 mL normal saline (NS) and administer over 60 minutes. Do not administer with aluminum needles or sets.	Day 1
Etoposide	100 mg/m^2 IV daily	Dilute in 500 mL NS* or 5% dextrose in water (D5W) to final concentration <0.4 mg/mL. Infuse over 30 to 60 minutes; if infused more rapidly, severe hypotension may occur.	Days 1, 2, and 3

Pretreatment considerations:

- **Hydration:** IV fluid to establish a urine flow of at least 100 mL/hour for at least two hours prior to and two hours after cisplatin administration. Refer to UpToDate topic on "Cisplatin nephrotoxicity", section on Prevention.
- **Emesis risk:** HIGH. Refer to UpToDate topic on "Prevention and treatment of chemotherapy-induced nausea and vomiting".
- **Prophylaxis for infusion reactions:** Routine prophylaxis not indicated. Refer to UpToDate topic on "Infusion reactions to systemic chemotherapy".
- **Vesicant/irritant properties:** Cisplatin is an irritant but can cause significant tissue damage; avoid extravasation. Refer to UpToDate topic on "Chemotherapy extravasation injury".
- **Infection prophylaxis:** Primary prophylaxis with hematopoietic growth factors is not recommended. Refer to UpToDate topic on "Use of granulocyte colony stimulating factors in patients with chemotherapy-induced neutropenia".
- **Dose adjustment for baseline liver or renal dysfunction:** The optimal approach to cisplatin therapy in patients with preexisting renal impairment is unknown. Such patients were excluded from the original trial[1]. A lower starting dose of etoposide may be needed for patients with renal or liver impairment[2]. Refer to UpToDate topics on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease" and "Chemotherapy-related nephrotoxicity and dose modification in patients with renal insufficiency".

Platinum-based combinations——Cisplatin plus Etoposide

Monitoring parameters:

- CBC with differential and platelet count weekly during treatment.
- Basic metabolic panel (creatinine and electrolytes) and liver function tests prior to each cycle.
- Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated.

Suggested dose alterations for toxicity:

- **Myelotoxicity:** Day 1 ANC should be >1500 cells/mm^3 and platelets should be >75,000/mm^3 for treatment during each cycle. Etoposide dose reductions should be based on the following table, taking into account the nadir ANC and platelet count along with day 1 ANC and platelet count for each cycle[1].

Etoposide dose	Nadir ANC, cells/mm	Nadir platelet count per mm^3	Day 1 ANC	Day 1 platelet
25 percent reduction	750 to 999	50,000 to 99,999	Greater than 2000	Greater than 100,000
50 percent reduction	Less than 750	Less than 50,000	Greater than 2000	
Hold	Less than 750	Less than 50,000	1500 to 2000	75,000 to 100,000

- **Neurotoxicity:** Neuropathy usually is seen with cumulative doses of cisplatin >400 mg/m^2, although there is marked interindividual variation. Refer to UpToDate topic on "Neurologic complications of platinum-based chemotherapy".
- **Nephrotoxicity:** Hold cisplatin until serum creatinine <1.5 mg/dL and/or blood urea nitrogen <25 mg/dL. For grade ≥2 nephrotoxicity during treatment (creatinine >1.5 times normal value despite adequate hydration), creatinine clearance should be determined prior to next cycle, and cisplatin dose reduced if <60 mL/min. Refer to UpToDate topic on "Cisplatin nephrotoxicity".
- **Other severe non-hematologic toxicity:** Etoposide and cisplatin should be withheld or doses decreased depending on clinical judgement.

If there is a change in body weight of at least 10 percent, dose should be recalculated for all drugs.

IV: intravenous; CBC: complete blood count; ANC: absolute neutrophil count; %: percent.
* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Platinum-based combinations——Carboplatin plus Etoposide

Cycle length: 21 days, for a maximum of six cycles.

Drug	Dose and route	Administration	Given on days
Carboplatin	AUC* = 5 mg/mL x min IV	Dilute in 250 mL normal saline (NS)[Δ] and administer over 30 minutes.	Day 1
Etoposide	100 mg/m^2 IV	Dilute in 500 mL NS[Δ] or 5 percent dextrose in water (D5W) to final concentration <0.4 mg/mL. Infuse over 30 to 60 minutes; if infused more rapidly, severe hypotension may occur.	Days 1, 2, and 3

Pretreatment considerations:

- **Emesis risk:** MODERATE on day 1 and LOW on days 2 and 3. Refer to UpToDate topic on "Prevention and treatment of chemotherapy-induced nausea and vomiting".
- **Vesicant/irritant properties:** Carboplatin and etoposide are irritants. Refer to UpToDate topic on "Chemotherapy extravasation injury".
- **Infection prophylaxis:** Routine primary prophylaxis with hematopoietic growth factors is not recommended (incidence of febrile neutropenia is about 5 percent[1]). Refer to UpToDate topic on "Use of granulocyte colony stimulating factors in patients with chemotherapy-induced neutropenia".
- **Dose adjustment for baseline liver or renal dysfunction:** Each carboplatin dose should be calculated based upon renal function by use of the Calvert formula*. A lower starting dose of etoposide may be needed for patients with renal or liver impairment[2]. Refer to UpToDate topics on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease" and "Chemotherapy-related nephrotoxicity and dose modification in patients with renal insufficiency".

Platinum-based combinations——Carboplatin plus Etoposide

Monitoring parameters:
• CBC with differential and platelet count weekly during treatment.
• Electrolytes and liver and renal function prior to each cycle of chemotherapy.
Suggested dose alterations for toxicity:
• **Myelotoxicity:** Dose adjustment based on myelotoxicity was not reported in the final publication. Per protocol, cycles were delayed for up to 42 days to allow neutrophils to return to ≥1500 cells/mm^3 and platelets to ≥100,000/mm^3[1]. However, the FDA-approved labeling recommends that the dose of carboplatin be reduced by 25 percent if platelets are <50,000 /mm^3 and/or ANC is <500 cells/mm^3.
• **Nonhematologic toxicity:** Chemotherapy should be held for grade 3 and 4 nonhematologic toxicities (except for neurotoxicity) and is only restarted after the toxicity has resolved to patient's baseline[1].
• **Hepatotoxicity:** No formal etoposide dosing recommendations were reported in this publication. However, accepted dose reductions per product information may be found in the literature. Refer to UpToDate topic on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease".
• **Nephrotoxicity:** Alterations in renal function during therapy may require a recalculation of the carboplatin dose. Refer to UpToDate topic on "Chemotherapy-related nephrotoxicity and dose modification in patients with renal insufficiency".
If there is a change in body weight of at least 10 percent, dose should be recalculated for all drugs.

IV: intravenous; CBC: complete blood count; ANC: absolute neutrophil count.
* AUC (area under the concentration X time curve) is converted to a patient-specific carboplatin dose (in mg) according to renal function by using the Calvert formula. The Calvert Formula is total dose (mg) = (target AUC) x (GFR + 25). If using measured serum creatinine, limit the maximal GFR for the calculation to 125 mL/min. Refer to UpToDate topic on "Chemotherapy-related nephrotoxicity and dose modification in patients with renal insufficiency".
Δ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

一线化疗

NCCN推荐SCLC一线化疗方案

From NCCN Guidelines
For SCLC
Version 2.2013

Platinum plus Etoposide

Cisplatin plus Etoposide	Carboplatin plus Etoposide
•LS-SCLC •ES-SCLC	•LS-SCLC •ES-SCLC

一线化疗

Cisplatin versus carboplatin

美国临床医师

LS-SCLC:
Cisplatin
plus
Etoposide

Higher
Response Rate

ES-SCLC :
Carboplatin
plus
Etoposide

Better
toxicity
profile

Overall Response Rate

Cisplatin v.s. carboplatin

随机临床研究(35样本，1项)： 64% v.s. 50%

随机临床研究(大样本，4项)： 67% v.s. 66%

Cisplatin versus carboplatin——Toxicity

Cisplatin

- 胃肠道副反应：恶心、呕吐
- 血液系统副反应：骨髓抑制
- 肾功能损伤
- 听力损伤10% to 30%
- 大剂量使用时需水化和利尿，病患顺应性低

Carboplatin

- 胃肠道副反应较轻
- 肾毒性较低
- 无需水化和利尿，病患顺应性高
- 血液副反应较多：贫血、白细胞减少、嗜中性白血球减少症、血小板减少，但出血及其并发症较少见

一线化疗

Platinum plus Camptothecin regimens for ES-SCLC

Etoposide versus Irenotecan

Drug	Dose	Route	Given on days	Cycles (days×cycles)	Median survival (months)
Cisplatin Etoposide	80mg/m² 100mg/m²	IV IV	1 1, 2, 3	21×4	9.4
Cisplatin Irenotecan	60mg/m² 60mg/m²	IV IV	1 1, 8, 15	28×4	12.8
Carboplatin Etoposide	AUC 4 120mg/m²	IV PO	1 1~5	21×4	7.1
Carboplatin Irenotecan	AUC 4 150mg/m²	IV IV	1 1	21×4	8.5

•三项大样本的随机临床研究(非日本)均没有得到Irenotecan疗效优于Etoposide的结果

•Carboplatin 剂量为AUC 5且Etoposide给药途径为IV的随机临床研究亦没有得到Irenotecan疗效优于Etoposide的结果

•3/4级嗜中性白血球减少症： Etoposide v.s. Irenotecan 92% v.s. 65%

•3/4级腹泻： Etoposide v.s. Irenotecan 0 v.s. 17%

一线化疗

Cisplatin plus Epirubicin regimen for LS-SCLC & ES-SCLC

Etoposide versus Epirubicin

Drug	Dose	Route	Given on days	Cycles (days×cycles)	Median survival (months)
Cisplatin Etoposide	100mg/m² 100mg/m²	IV IV	1 1, 2, 3	21×4	10.1
Cisplatin Epirubicin	100mg/m² 100mg/m²	IV IV	1 1	21×4	10.9

- 血液毒性(3~4级嗜中性白血球减少症）：Etoposide v.s. Epirubicin 57% v.s. 42%
- 每周期仅进行1天化疗，病人顺应性提高

一线化疗

Three or Four Drugs Combinations

Paclitaxel plus PE

- LS-SCLC：无直接比较Paclitaxel plus PE和PE的随机临床研究
- ES-SCLC：Paclitaxel plus PE和PE疗效无明显差异

Ifosfamide plus PE

- 一项随机临床研究（171样本）证明Ifosfamide plus PE疗效优于PE
- 另一项小样本研究未得到相同结论

Cyclophosphamide & Epirubicin plus PE

- Median survival(months)：PE v.s. four drugs 9.3 v.s. 10.5
- Response Rate: PE v.s. four drugs 61% v.s. 77%

PE: Platinum plus Etoposide Regimen

特殊人群（老年患者）用药

Subset analysis – overall survival

Subgroup	Number of patients (%)	MST (months) CE	MST (months) SPE
PS 0–1	162 (74)	10.9	10.1
PS 2–3	58 (26)	8.3	8.1
<70 years and PS 3	18 (8)	7.1	6.9
⩾70 years and PS 0–2	202 (92)	10.8	10.0

CE, carboplatin plus etoposide; MST, median survival time; PS, performance status; SPE, split doses of cisplatin plus etoposide.

Therapeutic response (WHO)

	CE	SPE	Total
CR	5	5	10
PR	75	75	150
NC	17	11	28
PD	11	16	27
NE	2	3	5
Total	110	110	220
Response rate	73%	73%	
95% CI	63–81%	63–81%	

CE, carboplatin plus etoposide; CI, confidence interval; CR, complete response; NC, no change; NE, not evaluable; PD, progressive disease; PR, partial response; SPE, split doses of cisplatin plus etoposide; WHO, World Health Organization.

特殊人群（老年患者）用药

Toxicities (JCOG Toxicity Criteria, Worst Grade of Any Course)

	CE					SPE					
	Grade					Grade					
Toxicity	1	2	3	4	3+4 (%)	1	2	3	4	3+4 (%)	P-value
Haematologic											
Leucopenia	5	45	46	13	(54)	8	43	49	7	(51)	0.79
Neutropenia	0	5	46	58	(95)	4	7	41	57	(90)	0.22
Anaemia	9	58	32	—	(29)	20	45	27	—	(25)	0.54
Thrombocytopenia	20	18	29	32	(56)	16	15	12	5	(16)	<.01
Non-haematologic											
Nausea/vomiting	40	24	2	—	(2)	46	28	3	—	(3)	0.68
Diarrhoea	8	9	1	0	(1)	11	3	1	0	(1)	1.0
Bilirubin	—	31	0	0	(0)	—	16	1	0	(1)	0.50
AST	47	9	3	0	(3)	30	8	6	0	(6)	0.33
ALT	40	9	2	0	(2)	38	8	4	0	(4)	0.45
Creatinine	10	2	0	0	(0)	27	3	1	0	(1)	0.50
Hyponatraemia	38	11	7	11	(16)	46	20	6	9	(14)	0.58
PaO2	39	21	7	1	(10)	44	23	2	1	(4)	0.22
Fever	15	15	0	0	(0)	21	16	0	0	(0)	—
Infection	12	15	5	3	(7)	16	7	5	1	(6)	0.78
Bleeding	8	1	0	0	(0)	4	0	0	0	(0)	—
Neurologic-sensory	2	1	0	—	(0)	3	2	0	—	(0)	—
Alopaecia	67	22	—	—		66	15	—	—		

CE, carboplatin plus etoposide; JCOG, Japan Clinical Oncology Group; PaO_2, partial pressure of oxygen; SPE, split doses of cisplatin plus etoposide.

主要参考文献

1. Anthony Elias. Pathobiology and staging of small cell carcinoma of the lung. *UpToDate* Oct 2012. Available at:
2. Karen Kelly. First-line chemotherapy for small cell lung cancer. *UpToDate* Oct 2012. Available at:
3. Okamoto H, Watanabe K, Kunikane H, et al. Randomized phase III trial of carboplatin(C) plus etoposide (E) vs. split doses of cisplatin (P) plus etoposide (E) in elderly or poor-risk patients with extensive disease small cell lung cancer (abstract #7010). J Clin Oncol 2005

感 谢 聆 听 ！

增进化疗疗效方法

- 交替或序贯使用互不交叉耐药之联合化疗方案
- 增加化疗剂量强度
- 化疗周期调整