SMALL CELL LUNG CANCER

Current Controversies & Update in Management

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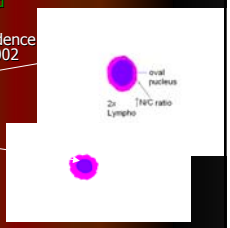
October 29,2004

Introduction

- Small cell lung cancer (SCLC) was initially recognized as an entity distinct from other types of lung cancer by pathologic examination in 1926 by Dr. Barnard
- Most malignant tumors of lung
- 20-25% of cases. Recent data suggests that incidence of SCLC is falling 14%(Proc Am Soc Clin Oncol 2002
- WHO classification: 3 types
  - Small/oat cell
  - Intermediate cell type
    - less regular shape
    - more cytoplasm
    - some large cell +
    - more resistant to chemo
  - Combined subgp: <1%
    - managed as small cell
    - same prognosis



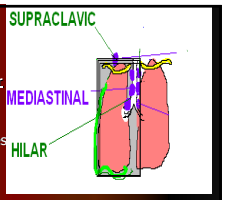
Photomicrograph of SCLC

- Usually arise from central bronchi
- At presentation 2/3rd have evidence of extensive disease (rapid growth; early metastasis)
- Frequent sites: Liver, CNS and bone
- Other sites: abdominal lymph nodes, adrenals

Approach

- Any new onset cough that persists for more than 2 wks in smoker more than 40 yrs old
- Hemoptysis
- Clubbing
- On CXR cavitation is not a feature
- Sputum cytology has a role because SCLC are central
  - yield from one sample 40%
  - repeated samples 80%
  - false +ve <1%
- Brochoscopy: histological confirmation and extent of disease

Staging



Initially proposed by VA gp
Presently International Association for study of Lung Cancer (IASLC) recommends

Limited disease: 30%

Corresponds to I-IIIB

- confined to one hemithorax & regional lymph nodes (including mediastinal, C/L hilar & ipsilateral supraclavicular)
- depends on, whether known tumor can be encompassed within one radiotherapy port
- ipsilateral pleural effusion
- C/L supraclavicular, rec laryngeal nv and SVC can all be part of it

Extensive disease: 70%

- exceeding beyond boundaries of limited ds
- cardiac tamponade, malignant pleural effusion and B/L parenchymal involvemaent

Recommendation

- medical history and physical examination, complete blood counts, comprehensive chemistry panels, CT scans of the chest and abdomen, a CT scan or MRI of the brain, and a bone scan.
- PET scanning is not recommended; grade of recommendation, D

PROGNOSTIC FACTORS

- Stage: limited vs exensive
- Histologic subclassification: poor if large cells are involved
- Metastasis

- Tumors with *c-myc:* more aggressive course
- N-*myc:* poor response to chemo
- p-53 Ab no correlation ?↑survival ! (cf NSCLC)
- Serum NSE: inversely related to survival algorithm: PI = zNSE + z(stage) + 2zPS, where PI represents the prognostic index, and z represents the regression coefficient. This algorithm segregated the patients into four groups with clearly different prognoses.
- **Cyfra 21-1** level over 3.6 ng/mL or a **tissue polypeptide-specific antigen** level over 140 U/Lsignificantly indicated a poor survival rate.
- **Serum chromogranin level:** poor prognosis

Host related prognostic factors

- **CERTAIN**: performance status
  - wt loss
  - LDH
- **Probable**: QOL and depressed mood
  - sex: females do better
  - alkaline phosphatase
  - Hb
  - serum albumin
- Possible: age, socioeconomic status, TLC, bicarbonate level, platelet count, soluble IL-2 R

TREATMENT

- Before 1970 surgery & RT were the most common form of treatment
- Appreciation of frequency & extent of metastases coupled with the sensitivity of SCLC to CT has led to the CENTRAL ROLE OF CT
- 5X ↑survival
- Long term disease free survival of more than 3 yrs in 5-10% as a whole and 15-20% of limited stage ds

Cytotoxic agents for SCLC

- Alkylating agents: **Cyclophosphamide** 1500 mg/m^2 IV q 3wk
  Ifosfamide 5000 mg/m^2 IV day 1 q 3wk
  hexamethylmelamine
  Lomustine
- Vinca alkaloids: **Vincristine** 2 mg IV q 3 wk
  Vindesine
- Epipodophyllotoxin: **Etoposide** 80 mg/m^2 IV d1-3 q 3wk
  Teniposide
- Platinum analogues: **Cisplatin** 80 mg/m^2 IV q 3wk, day 1
  Carboplatin 300 mg/m^2 day 1 q 3 wk
- Miscellaneous: **Doxorubicin** 40 mg/m^2 IV q 3 wk
  Methotrexate
- **3rd generation drugs: ironotecan, topotecan, paclitaxel**

- Earliest drug used was cyclophosphamide
  survival without any drug 2 mo
  cyclophosphamide prolonged it to 5 mo (1960)
- Single drug or combination ?

Combination therapy was introduced in 1970 and survival touched 5 yrs

CAV was earliest; still the SCLC was fatal in 95% cases

Which combination

- CAV was earliest; still the SCLC was fatal in 95% cases

- Cisplatin+etoposide(PE):

Less toxicity to lung and heart

When combined with RT: 2-year survival rates of 40%

- Cp was sometimes used instead of P in combination with E (CpE), having a similar response and survival as PE but with less nephro- and ototoxicity

- **For how long?** In the past, one of the frequently practiced approaches was to treat patients for the duration of their life
- only one study demonstrated a survival advantage for LD patients (in sharp contrast to numerous studies that showed no advantage at all/detrimental)
- no survival benefit was seen for eight cycles of CEV compared with four cycles
- Intergroup 0096 study produced convincing results with only four cycles of PE and local TRT
- **The current standard treatment protocol is four (to six) cycles of a platinum-based regimen + TRT.**

Other improvement efforts

- The dismal fate of a high recurrence rate was the impetus for investigating other approaches such as
  rapid alternation,
  dose intensification, and
  testing the Introduction of "third-generation" drugs such as irinotecan, topotecan, and paclitaxel
- The mathematic model of Goldie and Coldman indicated that rapid alteration of non–cross-resistant CHT should improve survival in SCLC. Tested and confirmed in practice this approach demonstrated an improvement in survival by adding CAV and PE in a sequential protocol (Fukoka 1991).
- Dose intensification: slight increase in survival
  much more↑in toxicity
  idea dropped

Third generation drugs

- **Irinotecan** was combined with P and compared with PE. A significant survival advantage for the irinotecan/P arm was observed

Disadvantage: high grade diarrhea

- **Topotecan** was initially shown to be effective in relapsed SCLC. So used for maintainence after PE

With the addition of topotecan, progression-free survival was improved but no impact on survival

- **Taxanes**: only modest benefit
  some studies showing increased no of treament related deaths and toxicities
  not a part of usual practice

Why combination with RT

- With chemotherapy alone intrathoracic failure occurs in 80% (median survival 10-14 mo)
- Addition of TRT resulted in an increase in the 3-year survival rate from 8.9 to 14.3%, an absolute improvement of 5%, and a relative improvement of nearly 50% (*Meta-analyses by Warde and Payne;& Pignon et al*)

Sequencing and Timing of Thoracic Radiation and Chemotherapy

- Murray and Coldman meta-analysis: best results were seen with TRT beginning 3 to 5 weeks from the start of chemotherapy. As radiation was further delayed, the benefit decreased and survival approached that seen with chemotherapy alone.
- Trials with alkylating agents: no improvement with RT
- Trials with platinum-etoposide: concurrent chemotherapy-TRT is superior to sequential TRT, where TRT is administered after chemotherapy
- the data are divergent as to whether early TRT (*ie*, in week 1) is better than delayed TRT (*ie*, week 6 or week 13).

- **Radiation dose**: retrospective analysis of patients treated at the Massachusetts General Hospital: improvement in local control as radiation doses were increased from 30 to 50 Gy
- **Fractionation**: The North American Intergroup trial 0096 compared doses of 45 Gy administered in 25 fractions for > 5 weeks to the investigational arm of doses of **45 Gy administered in 30 fractions for > 3 weeks**. Chemotherapy consisted of four cycles of cisplatin-etoposide. **The accelerated regimen resulted in improved local control** (intrathoracic failure: accelerated therapy arm, 36%; standard therapy arm, 52%) and long-term survival, which was 26% for the twice-daily regimen and 16% for the standard regimen. There was an increased rate of grade 3 esophagitis (26% vs 11%, respectively), but there were no other significant differences in toxicity

ROLE OF SURGERY

- abandoned after the British Medical Counsel(1973) published the results of their study comparing primary radiation therapy with surgery in patients with resectable SCLC with a 10-year follow-up
- subsequent reports published in the 1970s and early 1980s showed long-term survival in patients who had been treated with surgery alone who had very early-stage disease
- Best for T1-2N0
- May be followed by postop CT. Medistinoscopy is required in all patients undergoing surgical resection. PCI may be recommended if CR is achieved
- Role of surgery in node positive? Lung Cancer Study Group: 5 cycles of CAV+ RT± surgery: no difference in survival

EXTENSIVE DISEASE

- Meta-analysis by Pujol et al in Br J Cancer: patients randomized to a regimen containing cisplatin had a significant increase in the probability of response and survival with no significant increase in toxicity
- use of cisplatin and/or etoposide offered a significant survival advantage to patients with SCLC Berghmans et al
- In a meta-analysis by Chute et al: 2-month prolongation in median survival was demonstrated in patients with extensive-stage SCLC independently associated with both cisplatin-based therapy and in the improvement of best supportive care
- Carboplatin vs cisplatin: carboplatin plus etoposide is as effective as cisplatin plus etoposide but is less toxic (except for increased myelosuppression) *Brahmer and Ettinger*
- *The Hellenic Oncology Group phase III trial* :patients with both limited-stage and extensive-stage disease, the median survival time was 11.8 months for cisplatin plus etoposide and 12.5 months for carboplatin plus etoposide. The difference was not statistically significant, although the study was not powered to show equivalence

- recent Japanese trial compared cisplatin and irinotecan with cisplatin and etoposide. Patients randomized to the cisplatin/irinotecan arm did (statistically) significantly better than the group that was randomized to the cisplatin/etoposide arm (median survival time, 420 vs 300 days, respectively).
- **3rd drug** ? Hoosier Oncology Group evaluated the addition of ifosfamide to cisplatin and etoposide in a phase III trial of 171 patients with extensive-stage disease. At the expense of increased toxicity, the 2-year survival rate increased from 5 to 13% with the addition of ifosfamide
- Mavroudis et al compared the use of paclitaxel, etoposide, and platinum (TEP) with the use of etoposide and platinum. The study was terminated early, secondary to a higher number of toxic deaths in the TEP arm. Despite a statistically significant improvement in the time to progression for TEP, there was no difference in overall survival.
- phase III intergroup trial (**Cancer** and Leukemia Group B 9732) was reported comparing cisplatin and etoposide with or without paclitaxel in patients with extensive-stage SCLC. No significant survival advantage was seen with the addition of paclitaxel to cisplatin and etoposide in this study. On the other hand, there was an increased incidence of deaths from toxicities in the paclitaxel arm.

MAINTENANCE TREATMAENT

- Several randomized trials have demonstrated that 4 to 6 months of treatment is equal to prolonged treatment when survival is considered as the end point.
- In the meta-analysis reported by Sculier et al, 13 published randomized trials were included. One showed a statistically significant difference in survival in favor of maintenance therapy, 5 studies showed survival advantage in subgroups of patients, 1 study showed significantly shorter survival times with maintenance therapy, and 6 studies showed no difference.
- The Eastern Cooperative Oncology Group (ECOG) conducted a phase III trial in which patients showing a response to therapy or patients whose disease stabilized after receiving four cycles of cisplatin and etoposide were randomized to observation alone or to four cycles of topotecan therapy. Despite an improvement in progression-free survival, there was no difference in overall survival between the two groups.
- anti-GD3 immunization as maintenance treatment. Metalloproteinase inhibitors and inhibitors of angiogenesis also are being investigated in this fashion

Role of PCI

- It was frequently practiced in complete response (CR) and occasionally in good partial response (PR) patients, it was not unequivocally proved to produce superior survival
- Fear of toxicity: decline in neurocognitive function
- The issue was taken by meta-analysis by Perez et al(1981):
  - ↓ relative risk of death
  - absolute↑in 3yr survival by 5.4%
  - absolute ↑in ds free survival by 8.8%
  - ↓cumulative risk for CNS metastasis
  - issue of toxicity was clearly discarded
- The current approach is to administer PCI at the time of achieving CR, but its timing becomes important to avoid administration concurrently with CHT, and thus more CNS toxicity

TREATMENT OF RELAPSED OR REFRACTORY SCLL

- Despite high initial response rates to chemotherapy (*ie*, 45 to 75% CRs) reported in patients with limited-stage disease and 20 to 30% CRs in patients with extensive-stage disease, the response duration is usually short with a progression-free survival time of approximately 4 months for patients with extensive-stage disease and 12 months for patients with limited-stage disease. Most patients are destined to relapse, and the prognosis of this group of relapsed patients is poor. Patients who relapse < 3 months after first-line therapy are commonly called *refractory*, and patients who relapse 3 months after therapy are called *sensitive*. **Patients with late relapses after receiving initial therapy may be retreated with the same induction regimen used initially.**
- von Pawel et al compared cyclophosphamide, adriamycin, and vincristine (CAV) with topotecan as a single agent in patients who relapsed at least 60 days after the completion of initial therapy. that **topotecan was at least as effective as CAV** in the treatment of patients with recurrent SCLC and resulted in improved control of several symptoms. However, toxicity rates were high in both arms of the study, and alternative dose schedules of topotecan are currently being evaluated

TREATMENT OF ELDERLY

- Approximately 25% of patients with SCLC are > 70 years of age
- performance status and the physiologic status of the patient should guide treatment decisions rather than the patient's chronologic age
- good performance status (ECOG level 0 or 1) and normal organ function should be treated with optimal chemotherapy (and with radiotherapy, if indicated) as in their younger counterparts
- age did not appear to impact the delivery, tolerance, or efficacy of thoracic irradiation in the combined-modality management of patients with limited-stage SCLC. Greater myelosuppression is to be expected since equivalent exposure to a drug will lead to more myelosuppression in the elderly compared to their younger counterparts
- Elderly patients with poor performance status or with compromised organ function may be offered single-agent chemotherapy or polychemotherapy in attenuated doses

TREATMENT OF ELDERLY

- such "gentler" chemotherapy is inferior to optimal combination chemotherapy oral etoposide for 14 days combined with carboplatin on day 1 every 28 days ; abbreviated chemotherapy with CAV in full doses followed 3 weeks later by chemotherapy with cisplatin and etoposide in optimal doses ; or chemotherapy with platinum, adriamycin, vincristine, and etoposide in reduced doses
- A recently reported phase III trial compared carboplatin-gemcitabine therapy with cisplatin-etoposide therapy in patients with SCLC who had poor prognoses, with carboplatin-gemcitabine therapy exhibiting a more favorable overall toxicity profile at the expense of increased myelotoxicity.
- Another phase III trial compared the use of single-agent carboplatin with CAV, with carboplatin producing response rates, relief of tumor-related symptoms, and survival similar to that seen with CAV. There was a lower risk of life-threatening sepsis and less need for hospitalization in the group that received carboplatin.

Palliative treatment

- Identification of patients with poor prognosis: anatomic, performance status
- The Manchester Prognostic Score: (tumor stage,performance status, serum sodium, alkaline phosphatase, and serum lactate dehydrogenase
- One approach has been to maintain dose intensity but decrease toxicity by using a low-dose high-frequency regimen.
- In one study, the high-frequency arm showed similar response rates but significantly more myelosuppression compared with the standard regimen of alternating cyclophosphamide, doxorubicin, plus vincristine and cisplatin plus etoposide. The quality-of-life assessment in a subset of patients in the high frequency treatment arm, however, showed an improvement in general wellbeing,activity, and anorexia.
- At present, a standard therapy for patients with poor-prognosis small cell lung cancer is a combination of carboplatin plus etoposide; for those with very poorprognosis (eg, 20% survival at 1 year), a standard therapy is single-agent carboplatin. A number of newer drugs that may play a role in the management of these patients are currently being investigated, including taxanes, gemcitabine, topotecan, and vinorelbine
- RT may be used when there is poor response to chemo/sigificant toxicity

SPECIAL TREATMENT

- **CNS metastasis**: concurrent RT must as cytotoxic drugs have poor penetration in CNS
- **Leptomeningeal metastasis**: I/T MTX or high dose I/V Etoposide
- **Spinal cord compression**: ~3% Acute therapy required either RT or laminecomy
  role of steroids ? Steroids are recommended during RT for cord compression
- **SVC obstruction**: systemic chemotherapy alone produces sufficient relief. If the effect of CT is not observed in few days palliative RT is advocated 10 Gy in one fr or 30 Gy in 3-10 fr
- **Paraneoplastic syndromes**: hyponatremia at the time of diagnosis
  poor prognostic factor treatment is fluid restriction

TOXICITY OF TREATMENT

Haematologic toxicity

- The use of cisplatin and etoposide, currently the base of SCLC treatment, normally shows a medium level of myelosuppression, with a nadir of 7 to 14 days and an approximate recovery of 21 days.
- **GM-CSF ?**The systematic review of 12 randomized studies that included 2107 patients to evaluate the effectiveness of granulocyte and granulocyte macrophage colony-stimulating factors in the treatment of SCLC concerning survival, the rate of response, toxicity, and frequency of infection or neutropenic fever concluded that **their effectiveness was not demonstrated** in terms of a better rate of response or survival. Moreover, a harmful effect of the use of this cytokine before chemotherapy was observed in patients with LD who had received concomitant treatment with chemotherapy and radiotherapy
- prophylactic use of **ciprofloxacin plus roxitromycin during chemotherapy reduced the incidence of leukopenic fever, number of infections, the use ofantibiotics, and hospitalizations due to this fever by 50%, in addition to reducing infection-related mortality**
- **r-HuEPO** decreases the degree of anemia and the need for blood transfusion in patients with SCLC (de Campos et al)

Esophageal toxicity

- Rapid cell replacement of the mucosa cells in a normal esophagus makes this organ particularly sensitive to radiation-induced damage that at first appears to be an inflammatory response.
- On administration of isolated fractionated radiotherapy, a certain degree of acute esophagitis may be observed with symptoms that resolve easily within 7 to10 days and that are rarely severe with less than 50 Gy. Depending on the size of esophagus irradiated, severe esophagitis may appear after 60 Gy, which may evolve occasionally to stenosis.
- prophylaxis against esophagitis in SCLC may be the use of **amiphostine**. in a recent phase II study in 34 patients with SCLC treated with amiphostine and with the aforementioned combined treatment, no benefits were observed in the control of esophageal toxicity contrary to the positive results reported in NSCLC
- transdermic fentanyl (Durogesic) at a dose of 25 mg/72 hours in patients with grade 2 and 3 esophagitis

Pulmonary Toxicity

- radiotherapy particularly affects endothelial capillary cells and type I epithelial cells so that acute histologic changes are characterized by alterations in small vessels, with the subsequent development of vascular congestion and an increase in permeability. An exudate rich in fibrin is produced in the alveolar spaces, leading to **hyaline membranes**. In the chronic phase of fibrosis, an increase in the thickness of the alveolar walls is found as fibrosis of the subintimal layer of the vessels, with their consequent stenosis.
- Pentoxifylline reduces the production of proinflammatory cytokines, particularly tumor necrosis factor–alpha (TNF-a), in response to harmful stimuli and may, protect against the cellular damage mediated by cytokines and produced by irradiation.

- CARDIAC TOXICITY
- Light pericardial effusion post irradiation has been reported which is of little clinical significance
- On rare occasion large pericarditis may appear requiring pericardiocentesis
- Ischemic coronary artery disease secondary to radiation may be present
- Neuropathy of Cisplatin: tricyclic antidepressants and vitamin E

NOVEL APPOACHES…

Signal induction pathway:

Target	Agent	No. of pts	Response
GRP	2A11	12	CR 1 SD 4
CD117kit-tk	Imatinib	19	No response
Retinoid	ATRA, cisplatin, etoposide	22	CR 1 PR 9
Retinoid	Fenretinide	19	SD 5

CELL SURVIVAL PATHWAY MODULTORS

Agent	Target	No of pts	Response
Oblimersan + Paclitaxel	bcl-2	12	SD 2
Oblimersan +carboplatin/etoposide	bcl-2	16	PR 12/14
CCI-779	mTOR	16	SD 1

Immunotherapy

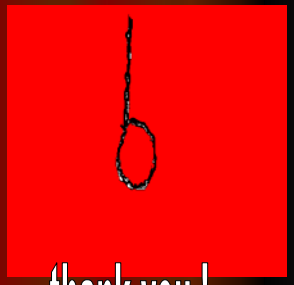
Agent	Target	No of pts	Phase	response
BEC2-BCG	GD3	15	I-SCLC	RFS>11 mo
Fucosyl GM1 vaccine	Fucosyl GM1	13	I-SCLC	
Polysialic acid	NCAM	13	I-SCLC	

Angiogenesis Inhibitors

agent	target	No of pts	phase	response
Marimastat	Matrix metalloprotease	555	III	
BAY 12-9566	Matrix metalloprotease	700	III	TTP↓
Thalidomide+ carboplatin /cisplatin	angiogenesis	26	II	CR 2/23 PR13/23 SD5/23

- *Is small cell lung cancer diagnosis a sentence of death ?*

.....answer is probably "no"
but still we have ***miles to go***.....



thank you !