SMALL CELL LUNG CANCER
Current Controversies & Update in Management
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Introduction

- Small cell lung cancer (SCLC) was initially recognized as an entity distinct from other types of lung cancer by pathologic examination 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 cell
  - Intermediate cell type
    - less regular shape
    - more cytoplasm
    - some large cell
    - more resistant to chemo
  - Combined subp: <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%
- Bronchoscopy: histological confirmation and extent of disease

**Staging**

Initially proposed by VA

- **Limited disease**
  - 30%
  - Corresponds to I-IIIB
  - Confined to one hemithorax & regional lymph nodes (including mediastinal, CL, hilar & ipsilateral supraclavicular)
  - Depends on, whether known tumor can be encompassed within one radiotherapy port
  - Ipsilateral pleural effusion
  - CL supraclavicular, rec laryngeal n and SVC can all be part of it

- **Extensive disease**
  - 70%
  - Exceeding beyond boundaries of limited disease
  - Cardiac tamponade, malignant pleural effusion and B/L parenchymal involvement

**Recommendation**

- Medical history and physical examination, complete blood counts, comprehensive chemistry panel, 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 extensive
- **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 with 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/L significantly 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/m² IV q 3wk
  Ifosfamide 5000 mg/m² IV day 1 q 3wk
  Hexamethylmelamine
  Lomustine
- Vinca alkaloids: Vincristine 2 mg IV q 3 wk
  Vindesine
- Epipodophyllotoxin: Etoposide 80 mg/m² IV d1-3 q 3 wk
  Teniposide
- Platinum analogues: Cisplatin 80 mg/m² IV q 3wk, day 1
  Carboplatin 300 mg/m² day 1 q 3 wk
- Miscellaneous: Doxorubicin 40 mg/m² IV q 3 wk
  Methotrexate
- 3rd generation drugs: irinotecan, 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

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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

**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 maintenance 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 treatment 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)
Role of surgery in node positive lung cancer study. May be followed by postoperative CT. Mediastinoscopy is best for T1-2N0. Subsequent reports published in the 1970s and early 1980s were abandoned after the British Medical Council (1973) and later studies published in the mid-1970s, and early 1980s were 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 + RT is superior to sequential TRT, where RT 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).

PCI may be recommended if CR is achieved required in all patients undergoing surgical resection. The data are divergent as to whether early TRT (ie, in week 1) is better than delayed TRT (ie, week 6 or week 13).

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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.

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 0996 compared doses of 45 Gy administered in 25 fractions for > 6 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.

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.
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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): the relative risk of death, absolute 3yr survival by 5.4%, absolute 1yr 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

MAINTENANCE TREATMENT

- 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

TREATMENT OF RELAPSED OR REFRACTORY SCLC

- Despite high initial response rates to chemotherapy (i.e., 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 progress, and the prognosis of this group of relapsed patients is poor. Patients who relapse < 3 months after frontline 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.
Elderly patients with poor performance status or with age did not appear to impact the delivery, tolerance, or performance status and the physiologic status of the elderly counterparts. Approximately 25% of patients with SCLC are > 70 years of age. One approach has been to maintain dose intensity but decrease toxicity by using a low-dose high-frequency regimen.

Identification of patients with poor prognosis: anatomic, physiological, and hematologic factors should be included. At present, a standard therapy for patients with poor-prognosis small cell lung cancer is a combination of carboplatin plus etoposide or carboplatin-gemcitabine. 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.

**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, and vincristine and carboplatin 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 poor prognosis (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/significant 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 laminectomy role of steroids? Steroids are recommended during RT for cord compression
- **Paraneoplastic syndromes:** hypoproteinemia at the time of diagnosis poor prognostic factor treatment is fluid restriction
Pentoxifylline reduces the production of pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α), in response to harmful stimuli and may protect against the cellular damage mediated by cytokines and produced by irradiation.

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 GM-CSF treatment 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 roxithromycin during chemotherapy reduced the incidence of neutropenic fever, neutropenic fever, fever, and the number of infections 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.).

The use of cisplatin and etoposide, currently the base of SCLC, 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 GM-CSF treatment 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.

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 to 10 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 amifostine. In a recent phase III study in 94 patients with SCLC treated with amifostine and with the aforementioned combined treatment, no benefits were observed in the control of esophagitis 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.

Neuropathy of Cisplatin: tricyclic antidepressants.

Ischemic coronary artery disease secondary to radiation may be present.

Neuropathy of Cisplatin: tricyclic antidepressants and vitamin E.

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 pro-inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α), 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 APPROACHES...**

Signal induction pathway:

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**CELL SURVIVAL PATHWAY MODULATORS**

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<td>Polysialic acid</td>
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**Angiogenesis Inhibitors**

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Is small cell lung cancer diagnosis a sentence of death?

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

thank you!