Update on Small Cell Lung Cancer, 1992

Rafal Wierzbicki, MD, FRCPI(C)

Small cell lung cancer (SCLC) accounts for approximately 20–25% of all lung cancers. Although it had been known for quite some time that SCLC was a disseminated disease, there was no truly comprehensive approach to the treatment of this disease until the advent of systemic chemotherapy. In the early 1970s it was found that combination chemotherapy was superior to the use of single agent therapy. This finding was followed by the discovery that different combination chemotherapy regimens, combined with radiation therapy resulted in an increase in median duration of survival of patients with limited disease SCLC. Still, even with the currently available comprehensive approaches only about 20% of patients with limited disease (LD) and less than 2% of patients with extensive disease (ED) experience long-term survival. The third workshop on SCLC arranged by the International Association for the Study of Lung Cancer summarized the current knowledge.
Staging Systems

Two systems are available for the staging of SCLC patients: the classical Veterans Administration (VA) Lung Cancer Study Group system of limited or extensive disease and the recently revised TNM system. The current recommendation is that LD category includes patients with disease restricted to one hemithorax with regional lymph node metastases including hilar, ipsilateral and contralateral mediastinal and/or supraclavicular nodes. In addition patients with ipsilateral pleural effusion are included, independent of whether the cytology is positive or negative. All patients with disease beyond the above description are defined as having ED. By this definition the ED is equivalent to stage IV of TNM staging, whereas limiting disease is equivalent to stages I–III. Stage IV should also be subdivided into stage IV-A with a single thoracic organ system afflicted and IV-B with disease in more than one extrathoracic organ.

Prognostic Factors

Multivariate analysis on large patient populations has demonstrated that in addition to stage and performance status as well as weight loss; alkaline phosphatase, plasma sodium and LDH are independent prognostic factors. The recently published analysis from the Canadian Group identified the four groups according to recursive partition and amalgamation (RECPAM) by the following eight attributes: disease extent, performance status, serum alkaline phosphatase, serum LDH, mediastinal spread, sex, white blood cell count (WBC) and liver metastases. The four resulting groups were distinguished by median survival times of 59, 49, 35 and 24 weeks respectively. Individualization of the treatment plan based on prognostic factors is encouraged.

Chemotherapy

In North America in the late 1970s, CAV (cyclophosphamide, Adriamycin® and vincristine) was the standard combination chemotherapy regimen used in the treatment of patients with SCLC. VP-16 and cisplatin combination have been reported to induce good responses in some patients relapsing after CAV. The overall response rate in this study was 55%. Given the encouraging results obtained with VP-cisplatin the National Cancer Institute of Canada (NCIC) Lung Group decided to investigate the use of this combination as a first line chemotherapy regimen.

The overall response rate was 86% with 43% of CRs and median duration of survival for responders with limited disease of 16 months. Since cisplatin + VP-16 appeared to be non cross-resistant with CAV the next step was to test the Goldie-Coldman hypothesis. Based on mathematic models, Goldie & Coldman suggested that since tumour cells rapidly develop resistance to chemotherapeutic agents, the best approach would be to administer concurrently full doses of as many active agents as possible with different mechanisms of action early in the treatment cycle. Since most of the effective agents are myelosuppressive, this strategy would probably be too toxic. The mathematic model suggested that the next best strategy might be to alternate non cross-resistant chemotherapy regimens. In the next NCI of Canada trial, 289 evaluable patients with extensive SCLC disease were randomized to six treatment cycles with either CAV or CAV alternating with VP-16/cisplatin. In this study the alternating arm was statistically superior to standard CAV therapy in overall response rate (80% compared with 63.2%), complete response rate, progression free survival and overall survival. Major toxicities were equally frequent in both treatment groups. This regimen of alternating CAV/VP-16, cisplatin can therefore be suggested as standard, particularly for patients with LD.

Role of Radiation Therapy

In the first trial of the Canadian Group patients with LD SCLC were randomized to receive three courses of CAV followed by three courses of VP-platinum vs six courses of alternating CAV and VP-platinum and responding patients were randomized to low or high dose locoregional radiotherapy (2500cGy vs 3750cGy). The median local progression free survival on high dose was 49 weeks vs 38 weeks on standard dose. It therefore appeared that high dose radiotherapy as administered in this study had a beneficial impact on local control although there was no improvement in the overall survival. The next study of the Canadian Group addressed the question of importance of the timing of thoracic irradiation in the combined modality therapy of this disease; 308 patients with LD SCLC were randomly assigned to receive the same alternating chemotherapy and early thoracic irradiation 4000cGy concurrent with the first cycle of etoposide-cisplatin (week 3) vs late thoracic irradiation receiving the same radiation concurrent with the last cycle of etoposide-cisplatin (week 15). After completion of all chemotherapy and
thoracic irradiation patients without progressive disease received prophylactic cranial irradiation (25cGy). Although complete remission rates were not significantly different between the two arms, progression free survival and overall survival were superior in the early thoracic irradiation arm. The median survival time for early radiotherapy was 22 months vs 16 months of late radiotherapy. Future research will include: optimizing volume, total dose and fractionation, as well as concurrent chemo/radiotherapy protocols.  

**Dose Intensity**

The concepts of dose–response relationship and dose intensity are distinguished via analysis of chemotherapeutic regimens. Using the database for CAV there was no consistent relation between cyclophosphamide dose intensity (DI) and outcome; however, Adriamycin\(^6\) DI in ED SCLC was highly significantly associated with both response rate and survival time. The same was subsequently proven to be true for cisplatin and VP-16. In the CODE trial\(^{14}\) the DI was increased by more frequent treatments rather than by increasing the dose size. The structure of this outpatient protocol includes weekly administration of chemotherapy with alternation of myelosuppressive and non-myelosuppressive treatments, supportive corticosteroids, gastro-protective agents and prophylactic antibiotics. Although the duration of chemotherapy was brief (9–12 weeks) the total cumulative doses of drugs delivered were similar to the standard regimens; 94% of patients responded to chemotherapy with 44% attaining complete remission (CR). Median time to progression was 43 weeks and median survival was 61 weeks, the 2-year survival rate was 30%. There is currently a National Cancer Institute of Canada phase 3 trial comparing CODE vs alternating CAV vs VP-16 chemotherapy.

**Maintenance Therapy**

In most recently published reports maintenance chemotherapy either as a continuation after achieving response or as a reinduction showed no survival benefit and perhaps a reduction in the quality of life of patients treated with longer chemotherapy.\(^{15,16}\)

**Future Studies and Recommendations**

**New agents**

Investigators at research institutes are urged to continue the search for new agents. However, the success of the commonly used combination chemotherapy regimens has made it increasingly difficult to evaluate those. If phase 2 studies are conducted only in previously treated patients, useful agents might be inappropriately discarded. The experience with etoposide (VP-16) serves to illustrate the reason for this concern. In phase 2 studies of patients relapsing after combination chemotherapy the response rates to VP-16 were less than 10% and of brief duration. This level of activity would not generally justify further evaluation. However, in previously untreated patients, VP-16 had a response rate of approximately 40% making it one of the three or four most active agents against SCLC. In an attempt to circumvent this problem the NCIC Lung Cancer Group decided to evaluate new agents as first line therapy in the non-curable subpopulation of patients with ED SCLC. If patients failed to show a response by two courses of treatment or demonstrated early progression after a single cycle of chemotherapy they were crossed over to a standard chemotherapy regimen to allow them the opportunity to receive an active regimen early in the course of treatment. Two such studies were published.\(^{17,18}\) In the first of the studies there were no responses seen to investigational agents; however, when the patients were crossed over to VP-16 cisplatin, the median survival time of the whole group was 31 weeks—comparable with standard treatments. In the second trial, epirubicin showed considerable activity with 50% objective responses and the median survival of all patients was 35 weeks.

**Chronic oral daily administration of etoposide**

Etoposide at a dose of 50 mg/m\(^2\) po × 21 days is a well-tolerated outpatient regimen particularly suitable for older or poor performance patients with ED SCLC\(^{19}\) with or without cisplatin.\(^{20}\) The logical step then is to substitute carboplatin\(^{21}\) in order to minimize toxicity.

**Biological response modifiers**

The clinical evaluation of biological response modifiers in SCLC is still in an early phase. Although interferons have been used for many years their place is likely to be in the micrometastatic disease in the adjuvant setting. There currently is a trial in the Mayo Clinic addressing that question with interferon-gamma. Growth factors have been shown to increase the dose
intensity of drugs delivered in various regimens with SCLC but as yet there is no data supporting their addition to standard treatments since no improvement in survival has been demonstrated. Anti-bombazine monoclonal antibodies might be used to block the autocrine function of this hormone.22,23

Surgery

Patients with very limited SCLC (TNM stages 1 and 2) have been effectively managed by initial surgery and postoperative chemotherapy. There is currently a Lung Cancer Study Group trial addressing the question of resection after chemotherapy for this group of patients but at the present, the question of surgery remains investigational.24

Strategies to overcome multi-drug resistance

The spontaneous occurrence of resistant tumour cell mutants is a significant obstacle to further improvement in the management of patients requiring chemotherapy. The multiple drug resistance (MDR) phenotype is of major importance since it leads to resistance to a group of chemically dissimilar but highly active drugs such as Adriamycin®, etoposide and the vinca-alkaloids. The MDR is associated with poor cellular uptake and retention of the cytotoxic drugs. This impairment appears to be related to the membrane alteration including over expression of the drug transport P-glycoprotein by amplification of the MDR-1 gene.25 Calcium channel blocking agents such as verapamil and treprodel derivative such as tamoxifen in laboratory investigations modify resistance and are capable of reversing MDR. A phase I/II study26 demonstrated the feasibility of combining the resistance modifiers and chemotherapy.

Elective cranial irradiation

The available information suggests that the fraction of patients in complete response who develop brain metastases as the sole site of recurrent disease when cranial irradiation is not given is 10%. Because of significant late neurological complications after prophylactic (elective) cranial irradiation (PCI)27 its clinical use in complete responders is considered optional since no individual randomized trial or collective data analysis has shown any survival benefit for PCI treated patients.28

Specific Clinical Situations

With respect to certain clinical situations in the management of SCLC, including central nervous system (CNS) metastases, superior vena cava syndrome and paraneoplastic syndromes, the recent literature has shed further light on the usefulness of chemotherapy.

CNS metastases

The management of primary CNS involvement at the start of systemic treatment is generally concomitant radiotherapy since most cytostatic agents were presumed not to penetrate sufficiently into brain metastases. Recent observations have questioned this concept.29 Patients treated with chemotherapy without radiotherapy have shown good responses with CT documented decrease in size of space occupying lesions in the brain. Treatment of leptomeningeal carcinomatosis is generally disappointing, intrathecal methotrexate remains the most widely used treatment.

Superior vena cava obstruction

Superior vena cava obstruction is a clinical complication caused by an obstruction of the venous return at the level of superior vena cava. Neoplastic diseases are now responsible for more than two-thirds of the adult cases, with SCLC being the commonest and non-Hodgkin's lymphoma next. In a recent review30 studies have shown that systemic chemotherapy alone in almost all cases produces sufficient relief from this condition with the effect usually observed within a few days and time to response is similar to radiotherapy.31

Paraneoplastic syndromes

Small cell lung cancer is unusual because of its frequent association with paraneoplastic syndromes which occur in approximately 20% of patients at presentation. The most frequent and best understood are those that result from ectopic hormone secretion by the tumour. Although a large variety of peptide hormones have been excreted by SCLC cells, ectopic production of anti-diuretic hormone (ADH) and corticotropin
(ACTH) are seen most frequently. The production of such hormones may or may not be associated with overt clinical syndromes depending on the functional activity and level of the ectopic hormone produced. When clinically overt the palliation of symptoms related to paraneoplastic syndromes almost exclusively still depends on the general responsiveness to the systemic therapy. It has recently been identified that the presence of Cushing's syndrome is associated with a low response to chemotherapy, short survival and a high rate of complications to therapy.

Early and late toxicity

All therapeutic actions directed against early adverse effects should be precisely recorded in protocols and study reports. Physicians can reduce acute and chronic toxic reactions today by limiting induction chemotherapy to four or six cycles, substituting less toxic agents for patients with underlying medical problems and avoiding doxorubicin and alkylating agents in simultaneous combination with radiotherapy. Second primary tumours including non-SCLC should be sought and histologically confirmed because they are potentially curable by surgery. According to available data, the frequency of acute leukemia is probably increased in SCLC patients who should be monitored for this complication during long-term follow-up.

Supportive care

Adequate antibiotic therapy during neutropenic episodes should include aminoglycosides or alternatively should consist of third generation cephalosporins as single agents or in combination with aminoglycosides. Further causative and clinical research into weight loss in SCLC patients is encouraged. At present no data supports any adjuvant nutritional manoeuvre directed at modifying weight loss. Overall quality of life of SCLC patients has been shown to improve on treatment paralleling high response rates obtained by modern chemotherapy/radiotherapy approaches.

Cost effectiveness

Since carcinoma of the lung is a leading cause of cancer death in the Western world and is increasing in Saudi Arabia, its treatment will become increasingly costly to the health care system. It is therefore important that new therapies for this disease be carefully evaluated. Until recently assessment of new therapies have usually included an evaluation of treatment efficacy and occasionally assessment of the impact of treatment on quality of life. While these factors are important in therapeutic decision making, it is becoming increasingly apparent that resources for the provision of health care are not unlimited and that clinicians must be cognizant of economic factors when making clinical decisions. In a recent NCIC study an economic evaluation of a randomized trial of CAV alone vs CAV alternating with VP-16/platinum was undertaken. A survival benefit of 1.6 months in favour of alternating chemotherapy was associated with an additional cost of 450 (1984) Canadian dollars per patient. This translated to a cost of 3,370 Canadian dollars per year of life gained. The cost-effectiveness of chemotherapy was comparable with that of treatments of common non-malignant diseases.

References


21. Current KFSH Study. (Principal investigator Dr Adnan Ezzat.)


