

Small-cell Lung Cancer Treatment – Present Status and Expectations

a report by

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Small-cell lung cancer (SCLC) comprises 15% to 20% of all lung cancers and is almost always smoking-related. Approximately 60% to 70% of patients diagnosed with SCLC have extensive-stage disease. The most common metastatic sites at diagnosis are bone, the liver, adrenal glands and the brain. One critical aspect for improving the treatment approach to SCLC may well be to perform a more accurate staging of the disease at diagnosis. The introduction of fluorodeoxyglucose positron emission tomography (FDG-PET) appears to be of value for the initial staging and treatment planning of patients with presumed limited-stage disease, and might well affect later patient management. The principal value of FDG-PET in limited-stage SCLC is the detection of additional sites of disease within the thorax.¹ In one study, PET-detected lymph nodes or primary prompted the enlargement of the radiation volume in 29% of the population.²

SCLC is extremely sensitive to both chemotherapy and radiotherapy. In limited-stage disease, the addition of thoracic radiotherapy improves survival over chemotherapy alone. When treated with combinations of chemotherapy and thoracic radiation, limited-stage SCLC represents a subset of lung cancer in which long-term survival can be achieved. Over the last 15 years, clinical trials have demonstrated that concurrent chemoradiotherapy is superior to sequential treatment and that early use of concurrent radiation is superior to later use. A small but significant improvement in two-year overall survival for early radiotherapy versus late radiotherapy was observed in a systematic review analysing randomised trials published after 1985, addressing the timing of radiotherapy in limited-stage disease.³ Essential questions related to the optimisation of thoracic radiotherapy remain unanswered. In particular, the optimal radiotherapy dose, fractionation and treatment volume have yet to be defined. In limited-stage disease, etoposide/cisplatin has become the standard regimen because of its ability to be administered concurrently at full dose with thoracic radiotherapy, as well as its putative superiority to other regimens. Prophylactic cranial irradiation reduces brain relapse rates, and modestly improves survival in patients in clinical remission.⁴ The role of surgery in limited

SCLC is still a matter of controversy. A randomised study addressing this issue seems to be justified.⁵

Chemotherapy remains the essential component for the treatment of all SCLC patients, regardless of age or performance status. Despite having more weight loss, poorer performance status, increased pulmonary toxicity and more deaths attributed to treatment, survival has not been significantly worse in older individuals. Fit elderly patients with limited-stage SCLC can receive combined-modality therapy with the expectation of relatively favourable long-term survival.⁶

Despite high response rates to initial chemotherapy, the majority of patients with SCLC subsequently relapse and die of the disease. Multiple trials have shown that maintenance and consolidation chemotherapy is not effective in improving survival and, at present, four to six cycles of chemotherapy is considered optimal.⁷ Improved systemic therapy is needed. The availability of several new agents in the 1990s with clear activity in this disease led to optimism that the cure rate could be improved. In chemotherapy-naïve SCLC patients, the contribution of new agents such as epirubicin, paclitaxel, irinotecan or topotecan in combination with cisplatin has been compared with the reference regimen etoposide/cisplatin in randomised trials.

The Spanish Lung Cancer Group (SLCG) performed a prospective phase 3 trial comparing etoposide/cisplatin versus high-dose epirubicin/cisplatin in 402 SCLC patients.⁸ The epirubicin/cisplatin regimen showed a similar activity with a slightly lower toxicity profile regimen than the reference regimen of etoposide/cisplatin. However, in limited-stage disease, epirubicin is not the optimal drug to combine with thoracic radiotherapy because of its potential cardiotoxicity.

The Cancer and Leukemia Group B (CALGB) analysed the role of paclitaxel in one study in which extensive-stage disease patients were randomised to receive paclitaxel/etoposide/cisplatin or etoposide/cisplatin.⁹ This phase 3 study failed to demonstrate any advantage in terms of survival for the addition of paclitaxel to standard

doses of etoposide/cisplatin and was furthermore associated with an unacceptable toxic death rate. A European study, randomly assigning SCLC patients to therapy with paclitaxel/etoposide/carboplatin or carboplatin/etoposide/vincristine, did demonstrate an advantage for the paclitaxel-containing arm.¹⁰

The Japanese Cooperative Oncology Group addressed the impact of irinotecan in the treatment of extensive-stage disease. In a phase 3 trial chemotherapy-naïve patients receiving irinotecan/cisplatin had a survival advantage (12.8 months) compared with those receiving etoposide/cisplatin (9.4 months; $p=0.002$).¹¹ However, in a recent study, also performed in extensive-stage disease, overall survival was similar for patients who received irinotecan/cisplatin (9.3 months) and for those who received etoposide/cisplatin (10.2 months; $p=0.6$).¹²

Several factors may be responsible for the difference in the results of these two trials analysing irinotecan/cisplatin combination, among them the differences in the administration schedule, patient characteristics or pharmacogenomics. The role of topotecan in extensive-stage SCLC has been analysed in a clinical trial in which 784 patients were randomised to receive either oral topotecan/cisplatin or intravenous (IV) etoposide/cisplatin.¹³ The two treatment regimens in the study showed comparable activity in terms of overall survival and one-year survival rate.

In SCLC, dose-intensity studies have yielded conflicting results. In a recent randomised phase 3 trial, 318 SCLC patients were randomly assigned to receive six cycles of ifosfamide/carboplatin/etoposide with a four-week (standard arm) or two-week (dose-dense arm) interval between cycles.¹⁴ Patients in the dose-dense arm received filgrastim and had autologous blood collected before cycles two to six, which was returned 24 hours after treatment. Dose-dense ifosfamide/carboplatin/etoposide chemotherapy for SCLC led to shorter treatment duration and less neutropenic sepsis than standard treatment, but did not improve survival.

In SCLC, a promising approach is the use of biological agents to maintain response. Unfortunately, recent randomised trials using metalloproteinase inhibitors such as marimastat and vaccination with BEC2/Bacillus of Calmette and Guerin (BCG) have been negative.^{15,16} Studies in SCLC cell-lines and human tissues suggest that the ganglioside fucosyl GM1 vaccine is an abundant yet specific target. In SCLC patients, synthetic fucosyl GM1 vaccine will be tested following chemotherapy.¹⁷ Improving the survival rate of patients with SCLC requires a better understanding of tumour biology and the subsequent development of novel therapeutic strategies.

Unfortunately, the biological processes that underlie SCLC are currently not well defined. Initial data showing Kit overexpression in SCLC tumours led investigators to analyse imatinib in SCLC treatment. However, in two phase 2 trials performed in patients with relapsed SCLC, imatinib failed to demonstrate any clinical activity.^{18,19} Despite frequent Kit protein expression in some tumour types, Kit and platelet-derived growth factor receptor- α polypeptide (PDGFRA) gene mutations are uncommon in most human cancers, including SCLC.²⁰

A crucial target in SCLC is bcl-2, a member of a large family of related genes, which encodes both positive and negative apoptotic regulators. SCLC shows baseline and inducible expression of bcl-2, which may contribute to therapy resistance. Oblimersen sodium is an antisense oligonucleotide compound designed to specifically bind to human bcl-2 messenger RNA (mRNA), resulting in catalytic degradation of bcl-2 mRNA, and subsequent decrease in bcl-2 protein translation. Enhancement of the efficacy of anticancer treatments with oblimersen bcl-2 antisense therapy represents a promising new apoptosis-modulating strategy. A dose-finding study was performed evaluating the combination of oblimersen/ carboplatin/etoposide in patients with previously untreated extensive-stage SCLC.²¹ Of 14 patients assessable for response, an encouraging 86% response rate was documented. Bortezomib, an inhibitor of the proteasome that plays a critical role in the degradation and regulation of many proteins involved in cell cycle regulation, is also being analysed in SCLC patients.²²

There are several tyrosine kinases receptors (TKRs) that are overexpressed in SCLC, including c-Met.^{23,24} C-Met contains an external semaphoring-like domain, a cytoplasmatic juxtamembrane domain, a TK domain and multiple tyrosines that bind to adapter molecules. The overexpression of c-Met and activated mutations can lead to carcinogenesis in multiple tumours. C-Met can associate with and activate multiple signal transducing intermediates such as Grb2, the p85 subunit of PI3-kinase (PI3-K), Stat-3 and Gab1, when activated by autophosphorylation. NCI-H69 SCLC cells show robust expression of c-Met. It would now be useful to study the inhibition of c-Met as a therapeutic target in SCLC treatment. PI3-K is an important part of c-Met downstream signalling. The PI3K pathway controls a number of cellular processes including cytoskeletal organisation, cell growth and survival. The constitutive PI3-K activity in SCLC regulates proliferation, anchorage-independent growth and apoptosis. The mammalian target of rapamycin (mTOR) kinase, a serine/threonine kinase, is structurally related to PI3-K. The inhibition of

mTOR blocks the activity of p70S6k, which mediates the phosphorylation and activation of the 40S ribosomal protein S6 kinase and the eukaryotic initiation factor 4E-binding protein-1, leading to growth arrest in the G1 phase of the cell cycle. Other cell-cycle regulatory functions mediated by p70S6k are Cdk activation and retinoblastoma protein phosphorylation, as well as the upregulation of cyclin D1. Inhibition of p70S6k could therefore abrogate the uncontrolled proliferation of malignant cells that exhibit increased constitutive PI3-K activity. CCI-779 (temsirolimus), an ester of rapamycin, inhibits mTOR. In an Eastern Cooperative Oncology (ECOG) trial, 87 extensive-stage SCLC patients with stable disease or response after induction chemotherapy received CCI-779 at two different doses (25mg or 250mg weekly).²⁵ Median survival for patients who received the 25mg dose was 6.5 months and for patients who received

the 250mg dose, median overall survival was nine months ($p=0.02$).

Sonic hedgehog (Shh), a mammalian hedgehog (Hh) pathway ligand, mediates epithelial-mesenchymal interactions in lung development by signalling to adjacent lung mesenchyme, as indicated by expression of the Hh receptor.²⁷ Analysis of SCLC tissue showed that five of 10 tumours expressed Shh. The vulnerability of SCLC to Hh pathway may represent a new therapeutic approach. Cyclopamine specifically inhibits the Hh pathway. Treatment of NCI-H249 SCLC cells with cyclopamine resulted in a significant growth inhibition.

In summary, in spite of moderate improvements in survival results for SCLC patients, the prognosis is still dismal and emphasises the urgent need for continued studies of new therapies in this population. ■

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