

SMALL CELL LUNG CANCER AND PROGRESS OVER 20 YEARS

Effort: B Achievement: F

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Small cell lung cancer (SCLC) is characterized by a rapid doubling time, early development of metastatic disease and sensitivity to chemotherapy and radiation. Despite additions to treatment regimens over the past 20 years, including prophylactic cranial radiation, improvements in survival with this disease have been modest: the vast majority of patients with SCLC will die within 2 years.

INCIDENCE AND ETIOLOGY

The incidence of SCLC is declining, representing 13% of all lung cancers in 2002, compared with 17% in 1986.¹ Despite this, SCLC continues to account for approximately 4% of all cancer mortality.²

STAGING

The 2-stage Veterans Administration Lung Group staging system continues to be used in clinical practice. Limited-stage SCLC (LSCLC) refers to a volume of disease that can be encompassed within a tolerable radiation field, an area that may include hilar, mediastinal and supraclavicular adenopathy, while extensive-stage disease (ESCLC) is everything else. A recent study showed that survival of patients with LSCLC with an effusion is intermediate between those with limited-stage disease without effusion and those with extensive-stage disease, suggesting that the tumour, node, metastasis (TNM) staging systems can identify patients with distinct prognoses.³ In practice, most patients with a cytology proven malignant effusion are considered to have extensive-stage disease. The American Joint Committee on Cancer - L'Union Internationale Contre le Cancer (AJCC/UICC) TNM classification, 7th edition, is now the recommended staging system for SCLC, although the adoption into clinical practice is slow. At the time of diagnosis 60-70% of patients have extensive-stage disease.

THE ROLE FOR SURGERY

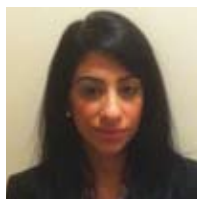
There is no role for surgery alone as the primary treatment for LSCLC. As part of multimodality therapy, initial surgery may improve survival in a limited set

of patients with Stage IA disease who have had appropriate preoperative nodal evaluation, although data is retrospective.⁴ Due to the presumed high likelihood of disseminated micro-metastases, most centres recommend adjuvant treatment with cisplatin and etoposide. Surgery after induction chemoradiotherapy may improve local control and survival in a carefully selected subset of patients with Stage I-IIIa disease if complete resection is achieved, as demonstrated by recent Phase II data.⁵

EVOLUTION OF CHEMOTHERAPY

In LSCLC, the relatively inexpensive combination of cisplatin + etoposide chemotherapy (EP) along with thoracic radiation remains the standard of care, as these modalities can be combined at full doses with tolerable toxicity profiles. EP regimens are superior to cyclophosphamide combination chemotherapy.⁶ Attempts to increase dose intensity or add other agents caused more hematologic and nonhematologic toxicities with lower survival rates when compared to full-dose EP and radiation.⁷ Paclitaxel + EP in a Phase II trial seemed to have comparable survival numbers, but significant esophagitis and mortality due to toxicity resulted.⁸

For ESCLC, combination chemotherapy with a platin and etoposide remains the standard of care in the first-line setting. Cisplatin-containing regimens are superior to cyclophosphamide-based therapies.⁹ Carboplatin can be used if cisplatin is contraindicated, although response rates are lower compared with EP.¹⁰ Adding other agents such as paclitaxel or ifosfamide to EP has not impacted survival enough to outweigh the added toxicities.¹¹ Irinotecan when combined with cisplatin initially had promising results in a Japanese study, with median survivals of 12.8 months vs 9.4 months. However, a Phase III North American study, of irinotecan and cisplatin with a different dosing regimen failed to show any benefit over standard EP.¹² Epirubicin combined with cisplatin compared to EP has similar outcomes but less hematologic toxicity and presents another viable alternative for treatment of ESCLC in the first-line setting.¹³ Four drug regimens



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have shown modest improvements in response rates and overall survival (OS), however the added toxicities have also limited their clinical application.¹⁴

For ESCLC, 4 to 6 cycles of induction treatment is optimal. A meta-analysis revealed small but statistically significant improvements in progression-free survival (PFS) and OS with maintenance chemotherapy.¹⁵ However, randomized trials have failed to prove superiority.

RADIATION THERAPY

Radiation therapy, when combined with chemotherapy, has improved intrathoracic tumour control rates and OS in patients with LSCLC.^{16,17} Modest survival improvements occur with early concurrent therapy, and if treatment is completed within 30 days of chemotherapy initiation.¹¹ Total dose and fractionation schedules remain an area of active research. One study demonstrated a 10% improvement in OS when 45 Gy of radiation therapy was delivered twice-daily over 3 weeks compared to 45 Gy daily over 5 weeks. Although rates of esophagitis were higher in the twice-daily treatment group, overall tolerability was comparable.¹⁸

PROPHYLACTIC CRANIAL IRRADIATION

At the time of diagnosis of ESCLC, 14-24% of patients will have brain metastases.¹¹ A meta-analysis of 7 randomized trials, with a predominantly LSCLC population with complete response to initial therapy, demonstrated a 50% reduction in the development of brain metastasis and a 5.4% improvement in 3-year OS with prophylactic cranial irradiation (PCI).¹⁹ A randomized Phase III trial evaluated the role of PCI in ESCLC after chemotherapy and demonstrated a reduction in the incidence of symptomatic brain metastases and improvement in survival.²⁰ PCI has thus been established as the standard of care for all patients with SCLC who respond to initial therapy.

SECOND-LINE THERAPY

Relapses are common despite high response rates to initial chemotherapy and recurrent disease is considered incurable. Chemosensitivity is inversely related to the rapidity of recurrence: SCLC that progresses through initial therapy or within 3 months of completion is considered "refractory." Disease recurring >3 months after completion of first-line therapy is considered sensitive, and disease that

occurs >6 months after initial treatment is often treated with the same regimen with a useful response.

Response rates of 8-28% are seen with CAV treatment after first-line EP.²¹ Single-agent topotecan, intravenous and oral, improves survival, quality of life and symptom control when compared to best supportive care in relapsed SCLC.²² Oral topotecan has emerged as one viable option in the second-line treatment of SCLC. Amrubicin has also shown activity in relapsed SCLC and, when compared in a Japanese Phase II study to oral topotecan, demonstrated higher response rates and PFS.²³ In a North American Phase II trial, the response rate was lower although still promising.²⁴ Many other drugs have been investigated in the second line, including irinotecan, gemcitabine, paclitaxel, docetaxel and vinorelbine, but none demonstrates significant improvements in efficacy.

CURRENT OUTCOMES

Survival of patients with LSCLC and ESCLC has modestly increased over the past 3 decades. Two-year survival of patients with ESCLC was 4.6% in 2000 compared with 1.5% in 1973. Median survival is now estimated at 8-13 months. Five-year survival is poor at 1-2%. Median survival of patients with LSCLC is 15-20 months, compared with 12-17 months in the 1980s; 20-40% of patients will survive to 2 years and 10-13% will survive to 5 years with limited-stage disease.¹

NEW DIRECTIONS AND CHALLENGES

Several new cytotoxic agents continue to be evaluated in SCLC. Amrubicin in the first-line setting in combination with cisplatin achieved a response rate of 88% and median OS of 14 months in a Japanese study.²⁵ North American and European trials are underway to determine the efficacy of amrubicin in other ethnic groups.

Immunotherapy and targeted agents have generally been unsuccessful in changing the outcome of SCLC. Interferon therapy has not show benefit but did increase toxicity. Thalidomide has failed to show any benefit when added to chemotherapy and caused thrombotic events.^{26,27} Oblimersen, a B-cell lymphoma-2 (Bcl-2) antisense oligonucleotide, demonstrated a trend towards a worse outcome as initial therapy for ESCLC.²⁸ In relapsed SCLC, imatinib and gefitinib have not been successful. Bevacizumab and sorafenib both seem to have some activity in

sensitive relapsed SCLC from Phase II data.

Although the incidence of SCLC is declining, survival outcomes remain dismal. Systemic chemotherapy for SCLC has not significantly advanced in the last 20 years. Unlike the case in several other tumour sites, the understanding of molecular pathways has not yet led to the use of targeted agents that provide a clear survival advantage. However, combinations of targeted agents with chemotherapy and the investigation of new targeted therapies is ongoing. It is to be hoped that the two decades of minimal progress merely herald an imminent explosion of new clinical breakthroughs to parallel the progress made in NSCLC.

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