SURGERY FOR LIMITED-DISEASE SMALL-CELL LUNG CANCER

SCLC is a highly aggressive disease characterized by its rapid doubling time, high growth fraction, early development of disseminated disease, and dramatic response to first-line chemotherapy and radiation. In general, surgical resection is *not* routinely recommended for patients because even patients with LD-SCLC still have occult micrometastases. However, the most recent American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend surgical resection over nonsurgical treatment in SCLC patients with clinical stage I disease after a thorough evaluation for distant metastases and invasive mediastinal stage evaluation (grade 2C). After resection, these patients should receive platinum-based adjuvant chemotherapy (grade 1C). If the histologic diagnosis of SCLC is made in patients on review of a resected surgical specimen, such patients should receive standard SCLC chemotherapy as well.

CHEMOTHERAPY

Chemotherapy significantly prolongs survival in patients with SCLC. Four to six cycles of platinum-based chemotherapy with either cisplatin or carboplatin plus either etoposide or irinotecan has been the mainstay of treatment for nearly three decades and is recommended over other chemotherapy regimens irrespective of initial stage. Cyclophosphamide, doxorubicin (Adriamycin), and vincristine (CAV) may be an alternative for patients who are unable to tolerate a platinum-based regimen. Despite response rates to first-line therapy as high as 80%, the median survival ranges from 12 to 20 months for patients with LD and from 7 to 11 months for patients with ED. Regardless of disease extent, the majority of patients relapse and develop chemotherapy-resistant disease. Only 6–12% of patients with LD-SCLC and 2% of patients with ED-SCLC live beyond 5 years. The prognosis is especially poor for patients who relapse within the first 3 months of therapy; these patients are said to have *chemotherapy-resistant disease*. Patients are said to have *sensitive disease* if they relapse more than 3 months after their initial therapy and are thought to have a somewhat better overall survival. These patients also are thought to have the greatest potential benefit from second-line chemotherapy **(Fig. 107-7)**. Topotecan is the only FDA-approved agent for second-line therapy in patients with SCLC. Topotecan has only modest activity and can be given either intravenously or orally. In one randomized trial, 141 patients who were not considered candidates for further IV chemotherapy were randomized to receive either oral topotecan or best supportive care. Although the response rate to oral topotecan was only 7%, overall survival was significantly better in patients receiving chemotherapy (median survival time, 26 weeks vs 14 weeks; $p = .01$). Moreover, patients given topotecan had a slower decline in quality of life than did those not receiving chemotherapy. Other agents with similar low levels of activity in the second-line setting include irinotecan, paclitaxel, docetaxel, vinorelbine, oral etoposide, and gemcitabine. Clearly novel treatments for this all too common disease are desperately needed.

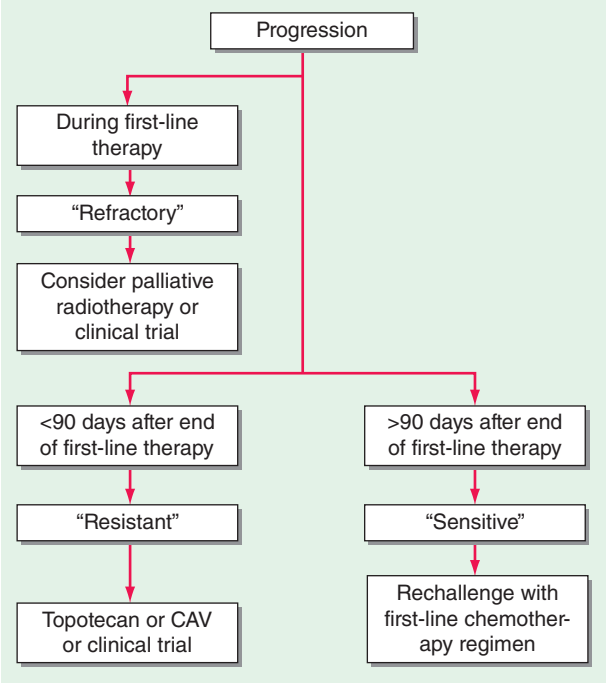

FIGURE 107-7 Management of recurrent small-cell lung cancer (SCLC). CAV, cyclophosphamide, doxorubicin, and vincristine. *(Adapted with permission from JP van Meerbeeck et al: Lancet 378:1741, 2011.)*

THORACIC RADIATION THERAPY

Thoracic radiation therapy (TRT) is a standard component of induction therapy for good performance status and limited-stage SCLC patients. Meta-analyses indicate that chemotherapy combined with chest irradiation improves 3-year survival by approximately 5% as compared with chemotherapy alone. The 5-year survival rate, however, remains disappointingly low at ~10–15%. Most commonly, TRT is combined with cisplatin and etoposide chemotherapy due to a superior toxicity profile as compared to anthracycline-containing chemotherapy regimens. As observed in locally advanced NSCLC, *concurrent* chemoradiotherapy is more effective than *sequential* chemoradiation but is associated with significantly more esophagitis and hematologic toxicity. Ideally TRT should be administered with the first two cycles of chemotherapy because later application appears slightly less effective. If for reasons of fitness or availability, this regimen cannot be offered, TRT should follow induction chemotherapy. With respect to fractionation of TRT, twice-daily 1.5-Gy fractioned radiation therapy has been shown to improve survival in LD-SCLC patients but is associated with higher rates of grade 3 esophagitis and pulmonary toxicity. Although it is feasible to deliver once-daily radiation therapy doses up to 70 Gy concurrently with cisplatin-based chemotherapy, there are no data to support equivalency of this approach compared with the 45-Gy twice-daily radiotherapy dose. Therefore, the current standard regimen of a 45-Gy dose administered in 1.5-Gy fractions twice daily for 30 days is being compared with higher-dose regimens in two phase III trials, one in the United States and one in Europe. Patients should be carefully selected for concurrent chemoradiation therapy based on good performance status and adequate pulmonary reserve. The role of radiotherapy in ED-SCLC is largely restricted to palliation of tumor-related symptoms such as bone pain and bronchial obstruction.

PROPHYLACTIC CRANIAL IRRADIATION

Prophylactic cranial irradiation (PCI) should be considered in all patients with either LD-SCLC or ED-SCLC who have responded well to initial therapy. A meta-analysis including seven trials and 987 patients with LD-SCLC who had achieved a complete remission after upfront chemotherapy yielded a 5.4% improvement in overall survival for patients treated with PCI. In patients with ED-SCLC who have responded to first-line chemotherapy, a prospective randomized phase III trial showed that PCI reduced the occurrence of symptomatic brain metastases and prolonged disease-free and overall survival compared to no radiation therapy. Long-term toxicities, including deficits in cognition, have been reported after PCI but are difficult to sort out from the effects of chemotherapy or normal aging.

SUMMARY

The management of NSCLC has undergone major change in the past decade. To a lesser extent, the same is true for SCLC. For patients with early-stage disease, advances in radiotherapy and surgical procedures as well as new systemic therapies have greatly improved prognosis in both diseases. For patients with advanced disease, major progress in understanding tumor genetics has led to the development of