Cark and Ihde have written an excellent review of small-cell lung cancer (SCLC). My commentary will provide some additional information, as well as explore several issues that require clarification.

As the authors note, the overall survival rates of patients with extensive small-cell lung cancer have not improved significantly during the past 20 years. However, the availability of several new drugs offers hope that this situation may change. On the other hand, in patients with limited-stage SCLC, combined-modality treatment regimens have improved survival times to the point that this disease can be considered curable.

**Unresolved Issues in Limited-Disease SCLC**

In my opinion, the pivotal study in limited-disease SCLC was the well-designed Phase III Intergroup randomized trial, which compared PE (Platinol plus etoposide) administered with concurrent standard radiation therapy to the same drug regimen administered with concurrent hyperfractionated (twice-daily) radiation therapy. Survival rates at 3 years in the two arms were 26.9% and 30.9%, respectively—the latter an excellent survival rate—with the potential that a percentage of these patients will be cured. Toxicities of the two radiation fractionation schemes were identical, except for grade 3 esophagitis, which was more common with hyperfractionated than with standard radiation therapy (25.7% vs 10.9%). Also, survival times for patients receiving twice-daily radiotherapy were prolonged to some extent.

An important question in the management of limited-disease SCLC is whether concurrent chemoradiation therapy, either administered as induction therapy or delayed, is better than sequential therapy. Moreover, if radiation therapy is given after chemotherapy, should it be initiated before all of the chemotherapy is completed? Some clinical trials have shown that radiation delayed until after the completion of six cycles of chemotherapy is less effective than the early administration of radiation, that is, following two to three cycles of chemotherapy. It is speculated that this may be due to the development of resistance to the radiation therapy by the cancer cells. Another important question is which chemotherapeutic regimen should be used to treat patients with limited-stage SCLC. The Radiation Therapy Oncology Group (RTOG) is conducting a phase II study of paclitaxel (Taxol), etoposide, and cisplatin (Platinol) administered with hyperfractionated radiation therapy (45 Gy in 30 fractions [twice daily] beginning on day 1) in patients with limited disease. Cycles 2 to 4 consist of chemotherapy alone.

The Eastern Cooperative Oncology Group (ECOG) trial in limited-disease SCLC, on the other hand, is using the same three drugs for cycles 1 and 2, followed by concurrent chemoradiation therapy for cycles 3 and 4. The radiation therapy regimen consists of daily fractions to a total dose of 63 Gy.

**Unresolved Issues in Extensive-Disease SCLC**

In patients with extensive small-cell lung cancer, although Platinol plus etoposide (PE) and CAV (cyclophosphamide, Adriamycin, and vincristine) are considered equivalent, PE is the more frequently used drug combination. Moreover, many community-based oncologists substitute carboplatin (Paraplatin) for cisplatin because the combination of carboplatin and etoposide is less toxic than PE and equally as effective.

Ifosfamide (Ifex) has demonstrated a response rate of 50% in patients with extensive disease. The Hoosier Oncology Group compared PE to cisplatin, ifosfamide, and etoposide in patients with extensive-stage SCLC. Median survival durations with the two regimens were 7.3 vs 9.1 months; 2-year survival rates were 5% vs 13%; and 3-year survival rates were 0% vs 5%. A number of phase II studies utilizing ifosfamide in similar three-drug combinations to treat patients with extensive disease (carboplatin was substituted for cisplatin in several studies) demonstrated comparable survival times.

Given these results, why are ifosfamide-containing regimens not used more frequently? Several
possible reasons come to mind. They include: (1) no standard schedule of ifosfamide administration; (2) some difficulty in administering the drug on an outpatient basis; and (3) significant neurotoxicity associated with its administration.

**New Drugs, Same Question**

Over a decade ago, we asked the question, is a two-drug combination better than a three- or four-drug combination in the treatment of SCLC? Now, years later, with more effective agents available to treat this disease, the same question is being asked about combinations of these newer agents.

The proposed intergroup randomized phase III study in patients with extensive SCLC will compare the two-drug combination, PE, to the three-drug combination, paclitaxel, etoposide, and cisplatin. Other new drug combinations are also being evaluated. Preliminary results of a study evaluating paclitaxel plus topotecan (Hycamtin) in patients with extensive-stage SCLC produced a 92% overall response rate and a 1-year survival rate of 50%.[3]

The key factor in evaluating all of these new regimens will be whether they can improve survival rates. In that light, it is important that clinical studies report the percentage of patients alive at 2 and 3 years rather than focus on median survival times.

The future may now be brighter for patients who develop SCLC.

**References:**


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