Small-Cell Lung Cancer: Is There a Standard Therapy?

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For more than 25 years, chemotherapy has been the cornerstone of treatment for small-cell lung cancer. Many studies have tested a wide variety of drugs in different combinations, resulting in a number of standard

In the late 1960s, it became clear that small-cell lung cancer (SCLC) is distinct from other histologic types of lung cancer and could be differentiated in a number of ways. At the time of diagnosis, for example, small-cell lung cancer usually manifests as a central tumor, with dissemination to the locoregional lymph nodes and signs of dissemination to distant sites in the vast majority of patients. Further, it is often associated with paraneoplastic signs like inappropriate antidiuretic hormone production, Cushing’s syndrome, and Eaton-Lambert syndrome.

The general consensus about the approach to treating this tumor changed considerably after it became clear that despite any apparent success of local treatment, ie, radiotherapy or surgery in selected patients, the short- and long-term prognosis for patients with small-cell lung cancer was very poor. In fact it was questionable whether therapy offered any benefit over no treatment, which resulted in a median survival of 6 weeks for patients with extensive disease and 3 months for those with limited disease. Despite the questionable success of radiotherapy as a single-treatment modality for limited-disease patients, the staging system for this tumor is still based on the potential to create a radiotherapy field that will encompass all known tumor sites.

The first small step forward in the treatment of small-cell lung cancer came after some effect was seen with the alkylating agent cyclophosphamide (Cytoxan, Neosar), one of the cytotoxic drugs available at that time.[1] Since then, small-cell lung cancer has been considered to be a systemic disease that requires systemic therapy.

The Historic Development of Chemotherapy for SCLC

Following the first clinical trial using cyclophosphamide, several other drugs were tested (Table 1). Of the chemotherapeutic drugs available in the 1970s—methotrexate, doxorubicin (Adriamycin), vincristine (Oncovin), procarbazine (Matulane), and the nitrosoureas (lomustine [CCNU], carmustine [BiCNU])—only doxorubicin and vincristine are still in use for small-cell lung cancer, and both are near the point of being replaced by more active and/or less toxic drugs. Several drugs that remain important in the treatment of small-cell lung cancer first became available for clinical use in the 1980s. This list includes etoposide (VePesid), teniposide (Vumon), ifosfamide (Ifex), epirubicin, cisplatin (Platinol), and carboplatin (Paraplatin).

During the first half of the 1990s, still other drugs were tested and found to be active in this tumor. These include docetaxel (Taxotere), paclitaxel (Taxol), topotecan (Hycamtin), irinotecan (Camptosar), and gemcitabine (Gemzar). The ultimate roles of these drugs—if they have any—depend on several factors, as will be discussed.

Combination Regimens

With all drugs listed in the second and third columns of Table 1, it is possible to form many different combination chemotherapy regimens. In general, combinations are more active than their individual components. Hundreds of publications have focused on many of these regimens without demonstrating any major differences in activity. Nevertheless, during the last decade, the combinations described in Table 2 have been used widely in clinical trials and may be considered standard combination chemotherapy for small-cell lung cancer.

Emerging Concepts in the Management of SCLC

During the last 25 years, chemotherapy has been the cornerstone of treatment for small-cell lung cancer. That some degree of myelotoxicity had to be accepted to obtain sufficient antitumor activity was recognized quite early. Based on this assumption, several regimens were evaluated and then given until tumor progression or intolerability. This approach often resulted in chemotherapy being
administered for the remaining lifetime of the patient with small-cell lung cancer or for 18 months for the rare patient who achieved a long-term response. Whether this management course resulted in optimal quality of life, especially for patients facing a limited survival time, was questionable.

The Role of Maintenance Chemotherapy
The role of maintenance treatment was therefore addressed in a number of large, randomized trials.[2] Although the design of these studies differed somewhat, the overall consensus was that maintenance chemotherapy prolongs the disease-free period without significantly affecting overall survival. Currently, short-term chemotherapy is considered standard, and in most trials four to six courses are given over a period of 3 to 6 months. Reducing this period any further would probably not improve quality of life for the patients and might impair it. Apparently, patients with small-cell lung cancer benefit most from maximal tumor reduction, which usually corresponds to two to four courses of chemotherapy.

Alternating Chemotherapy
Another management approach evolved from experiments with tumor xenografts and resulted in the Goldie-Coldman hypothesis of the potential benefit of alternating non-cross-resistant chemotherapy. Theoretically, this hypothesis is very attractive, and initial results of clinical trials involving the alternating use of two active chemotherapy regimens seemed to support its validity in the treatment of solid tumors and lymphomas. However, it soon became clear that translating this laboratory concept to the clinical environment is not that simple. Basic information was needed concerning the individual regimens to be alternated before it could be decided whether the regimens were suitable for alternation.

Comparable Activity and Non-Cross-Resistance
Two important points have to be considered before embarking on a randomized trial: First, the activity of both regimens has to be comparable, and second, the regimens must have some degree of non-cross-resistance. In practice, this means that regimen A should be active in patients who were initially treated with regimen B, but whose disease subsequently progressed during or shortly after treatment, and vice versa.[3]

If all regimens used in the different trials had been evaluated in this way before large randomized trials were initiated, many patients would have been treated otherwise. The apparent degree of non-cross-resistance between the two most frequently used combinations—CAV (cyclophosphamide/Adriamycin/ vincristine) and EP (etoposide/Platinol)—in these trials was so small that no clinically valuable difference could be demonstrated between the alternating arm and the standard arm using one of the two combinations. Further, the activity of the two regimens differs somewhat, in favor of the EP schedule. Only two combinations—CDE (cyclophosphamide, doxorubicin, and etoposide) and VIMP (vincristine, ifosfamide, mesna, and Paraplatin)—with comparable first-line activity and a sufficient degree of non-cross-resistance have been evaluated, and these combinations failed as well.[3,4]

Unless new drugs or combinations are developed that are truly non-cross-resistant with currently available agents, the idea of alternating chemotherapy will be no more than a concept without any clinical value.

Weekly Chemotherapy With Dose Intensification
Using the drugs listed in the second and third columns of Table 1, it was possible to design multiple-drug regimens given by alternating schedules every week to increase the dose-intensity of chemotherapy. In a number of randomized trials, this approach was shown to be feasible, although the dose-intensity achievable was not much higher than was possible with standard administration.[5] With regard to efficacy, all trials failed to show any improvement in survival.

Radiotherapy to the Primary Tumor
The problem of demonstrating sufficient gain from the addition of a local therapy to chemotherapy has been the topic of many randomized trials, which showed only marginal or no clear benefit for combined-modality therapy. In a meta-analysis of 13 trials, combined modalities proved somewhat more effective than chemotherapy alone in patients with limited disease. At 3 years, a survival rate of 14% after combined-modality therapy compared favorably with the 9% rate associated with chemotherapy alone.[6] Currently, radiotherapy to the primary tumor should be considered standard, although many questions concerning timing, schedule, fractionation, field size, and interaction with chemotherapy have not been answered sufficiently—or at all.

Treatment of Brain Metastases
For decades, brain metastasis has been treated with radiotherapy, based probably on the assumption that it signals tumor progression in an area inaccessible to chemotherapy because of the blood-brain barrier. From several studies, however, it has now become clear that brain metastases respond to chemotherapy in the same way as do all other metastases of lung cancer.[7]
The choice of treatment for this type of metastasis should therefore be based not on misleading assumptions but on the goal of improving the quality of life for the individual patient. It is, therefore, possible to start with chemotherapy as well as with radiotherapy, or even a combination of the two. The main advantage of chemotherapy in this situation is the possibility of starting treatment immediately, without concerns over the possibility of a waiting time until the start of radiotherapy.

**Optimal First-Line Therapy**

Decisions about the choice of therapy for an individual patient are based on physical investigation and staging procedures like chest x-ray, bronchoscopy, and computed tomography of the thorax, abdomen, and brain. Further, performance status is an important prognostic factor, and age should be considered in a number of situations as well.

**Patients With Limited Disease and ECOG Performance Status 0 to 2**

It is now accepted that patients with limited disease and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 should be treated with cisplatin and etoposide, with radiotherapy to the primary tumor. Results of a National Cancer Institute of Canada (NCIC) trial suggest that it is better to combine radiotherapy and chemotherapy early in the treatment course.[8] For this concurrent approach it is necessary to use a chemotherapy regimen associated with limited myelosuppression and no interaction with radiotherapy. For this purpose, the combination of cisplatin and etoposide is more suitable than are regimens based on doxorubicin, which causes much more myelotoxicity and probably more esophagitis as well.

**Therapy for Patients With Extensive Disease**

For patients with extensive disease, several other treatment regimens are available, as shown in Table 2. In Europe, for example, the CDE (cyclophosphamide, doxorubicin, and etoposide) regimen has become particularly popular. It has proven to be a relatively mild regimen that can be given in the outpatient clinic, and its activity is comparable with that of cisplatin/etoposide but without the problem of platinum-induced nephrotoxicity.

**Modifications for Patients With Poor Performance Status**

Treatment of patients with a poor performance status can be a problem regardless of disease stage because standard-dose chemotherapy is often poorly tolerated by this group of patients. In such a population, lower-dose induction chemotherapy might be safer, followed—if possible—by standard-dose chemotherapy.

**Considerations for Elderly Patients**

The treatment of elderly patients with small-cell lung cancer has often been disputed. Currently, patients up to age 75 years are accepted for most clinical trials, and there is no reason to withhold standard chemotherapy from these patients. Using a combined modality with cisplatin-etoposide and local radiotherapy is potentially more toxic in this older age group. In a number of phase II studies, monotherapy with oral etoposide has resulted in acceptable response rates and median and long-term survival times, especially in patients older than 75 years of age. However, in two recently published randomized studies, single-agent oral etoposide was demonstrated to be less effective and to improve the quality of life to a lesser extent than standard-dose combination chemotherapy.[9,10] Nevertheless, oral etoposide may be useful as a simple therapy for the elderly patient who is not considered to be a good candidate for intravenous combination chemotherapy.[11]

**Treatment of Patients With Brain Metastases at Diagnosis**

About 10% of all patients with small-cell lung cancer present with brain metastases at the time of diagnosis. Often, these patients are excluded from clinical trials. On the basis of a number of small studies, it might be concluded that initiating treatment with usual chemotherapy would be considered standard. However, in patients for whom the brain is the only site of metastatic disease, the favorable results obtained with chemotherapy and whole brain radiotherapy indicate that these patients will benefit more if combined treatment is administered.[12]

**Research Areas**

**The Value of Dose Escalation**

The potential value of higher-dose chemotherapy is being evaluated in several studies. At least four different approaches have been investigated, each probably differing in terms of antitumor mechanism and efficacy (Table 3). Because smaller studies were not able to establish a clear picture of the effects of accelerated chemotherapy, with some studies showing positive and some negative results, higher-dose chemotherapy is now being evaluated in a number of large, randomized studies.[5]
High-dose induction chemotherapy and late intensification were tested in the 1980s and results were not promising. If other studies concerning dose intensity do not show more positive outcomes, it may not be necessary to continue with further testing of these approaches.

**Second-Line Therapy**

Unfortunately, regardless of response achieved after chemotherapy, the majority of patients with small-cell lung cancer eventually will experience disease progression, for which further treatment is mandatory. Since short-term chemotherapy became generally accepted as standard, the prospects for patients treated with second-line chemotherapy have improved. Patients with disease progression during chemotherapy are usually resistant to other cytotoxic drugs as well, which may explain the negative connotations that developed about treatment at relapse before short-term chemotherapy became standard.

**Sensitive vs Resistant Tumors** During the last decade, clear guidelines for second-line chemotherapy have been formulated and shown to be effective. Patients whose disease progresses during, or shortly after, first-line chemotherapy usually have tumors that are resistant to the drugs used in the first-line regimen. These patients should, therefore, be treated with drugs that have at least some degree of non-cross-resistance to the first-line chemotherapy. For patients treated with CDE, the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group developed the VIMP regimen, which is associated with a response rate of at least 50% in this population.[3] Recently, investigators from Groningen and Amsterdam evaluated the combination of carboplatin and paclitaxel, which resulted in an amazingly active response rate of at least 70% (Harry J. M. Groen, md, phd, personal communication, August 1997).

Patients whose disease relapses after a longer treatment-free period (> 3 months) usually have tumors that are still sensitive to the drugs used in their first-line regimen or their analogues. Grouping tumors into the categories of sensitive or resistant is a useful guide to treatment at relapse (Table 4).[13]

**How to Evaluate New Drugs**

The best means of testing new cytotoxic drugs remains unclear. Currently, two scenarios are popular: One calls for evaluation of previously untreated patients[14] and the other for evaluation of patients with recurrent or progressive disease.[15]

**Previously Untreated Patients** In the United States in particular, testing in previously untreated patients with extensive disease [14] has become popular. New drugs are given to patients who are in good condition with extensive disease, and response is evaluated after every course of the investigational therapy. As soon as progression occurs, or after two cycles if no more than stable disease has been reached, the salvage regimen (usually cisplatin and etoposide) is given. Patients who respond to the new drug continue that treatment until the disease progresses or they reach a maximum number of cycles. The main advantage of this method is that the experimental drug can be tested at full dose level, because such patients do not suffer from toxicity induced by their previous chemotherapy.

**Recurrent or Progressive Disease** In comparison, testing new drugs in patients with disease recurrence or progression [15] comprises two separate patient groups: those with a so-called resistant tumor and those with a so-called sensitive tumor. The main disadvantage of this method is the companion to the advantage given for testing untreated patients: There is the possibility of greater toxicity, particularly myelosuppression, due to previous chemotherapy and subsequent suboptimal dosing of the experimental regimen. The major advantage of this method is that it becomes very clear whether a new drug adds any benefit to the currently available drugs. The response in the sensitive group will be more or less comparable with that achievable in previously untreated patients, whereas the response in the resistant group provides valuable information about possible non-cross-resistance with the previous chemotherapy. Drugs that are active in patients with resistant disease are particularly promising for further improvement of first-line therapy.

This testing approach also makes it possible to evaluate the activity of new combinations as well as to detect possible non-cross-resistance with other combinations. The new drugs listed as investigational in Table 1 have been tested in some of the above-described test settings. Results are shown in Table 5.

**Introducing New Drugs Into First-Line Therapy**

New drugs with proven activity against small-cell lung cancer have to be considered as candidates for replacing other drugs or as additions to currently used regimens. Historically, the drugs introduced into first-line therapy have been analogues of known drugs. So far, only carboplatin, an active analogue of cisplatin with a different toxicity profile, has achieved wide-scale use. Attempts to
give epirubicin in place of doxorubicin have not been very successful; the same can be said for substitution of teniposide and vindesine.

Of the new drugs listed in Table 1, those with activity against so-called resistant tumors are probably the most interesting. However, drugs with a different mechanism of cytotoxicity, like the topoisomerase I inhibitors, also might be worth further testing if their activity is related to an interaction with another drug, like etoposide, a topoisomerase II inhibitor.

A possible approach to introducing a new drug is to combine it with a drug or drugs with known activity, evaluate the new combination in a phase II setting, and subsequently test it in a randomized comparison with a known combination. Unfortunately, this would be a very time-consuming and patient-consuming procedure. Examples of combinations with known toxicity profiles are topotecan and cisplatin, and paclitaxel and carboplatin; both of these combinations have been tested in other solid tumors.

**Conclusion**

During the last 25 years some progress has been made in the treatment of small-cell lung cancer. In this overview some aspects of old, new, and experimental therapies have been discussed. For selected groups of patients the goal of treatment is more than simple palliation. Much research is still needed, however, to improve the outcome for the majority of patients with small-cell lung cancer.

**References:**


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