Small-Cell Lung Cancer: Treatment Progress and Prospects

This comprehensive, well-written review of small-cell lung cancer by Drs. Clark and Ihde covers nearly all of the important clinical issues. However, a few areas warrant additional comment and discussion.

Diagnosis by Transthoracic Fine-Needle Aspiration

Drs. Clark and Ihde point out that transthoracic fine-needle aspiration is a safe, cost-effective diagnostic technique. However, a word of caution should be raised about its use in patients with peripheral lesions. I have found that certain patients with peripheral lesions actually have neuroendocrine tumors of other varieties, usually carcinoid tumors (either typical or atypical), when a more definitive biopsy or resection is performed. This is particularly true of nonsmokers. More rarely, patients can have mixed small-cell and non-small-cell carcinomas, with only the small-cell component identified in tissue obtained via fine-needle aspiration.

All of these lesions, when localized, require initial surgical resection, which not only is important therapeutically but also is necessary for accurate diagnosis. It is important to understand this particular clinical picture. Although most oncologists currently believe that peripheral lesions should be resected initially, I am not sure whether it is widely appreciated that a number of these tumors represent other varieties of neuroendocrine tumors. For example, I recently saw a patient with small-cell lung carcinoma diagnosed 6 years earlier by fine-needle aspiration of a lung lesion. He had multiple bone metastases and was treated with several sequential chemotherapy regimens. A few weeks previously, hypercorticalism from ectopic adrenocorticotropic hormone secretion was detected. Biopsy of a lymph node revealed a classic carcinoid tumor. The long history of this patient’s neoplasm also suggested an alternative diagnosis. When localized to the lung, the typical or classic carcinoid tumor does not require chemotherapy. It is inappropriate to treat patients with isolated peripheral lesions with chemotherapy initially with the idea of performing surgery at a later date, when the diagnosis is made solely from a fine needle aspiration.

Appropriate Role of Growth Factor Support During Chemotherapy

I would like to emphasize that growth factor support should not be routinely employed during chemotherapy for small-cell lung cancer patients. It is ironic that granulocyte colony-stimulating factor (G-CSF [Neupogen]) gained FDA approval on the basis of a randomized trial in patients with small-cell lung cancer.[1] This trial, however, used a particularly intensive treatment course with cyclophosphamide (Cytoxan, Neosar), etoposide, and doxorubicin. Although G-CSF reduced myelotoxicity in this setting, no form of intensive chemotherapy that produces severe, prolonged myelosuppression has ever been shown to be more effective than modest-dose regimens that routinely produce much less myelosuppression.

The high-dose regimen employed in the trial that gained FDA approval for G-CSF is more toxic, but no more effective, even when administered with the cytokine, than modest doses of cisplatin (Platinol) or carboplatin (Paraplatin) plus etoposide. I see the value of cytokines as a routine part of primary therapy only if extremely intensive regimens become more effective in the future.

Carboplatin in Combination Chemotherapy

Drs. Clark and Ihde should have discussed the role of carboplatin more thoroughly. Carboplatin in combination chemotherapy has many practical advantages over cisplatin in patients with small-cell lung cancer. I do not fully understand why cisplatin continues to be the favored agent. I suspect that historical precedence is a factor, as well as older data with carboplatin before area-under-the-curve (AUC) dosing was routinely used.

The current literature, [2-4] as well as my own experience, convinces me that carboplatin is equally...
effective as and much less toxic than cisplatin. A recent meta-analysis of the several randomized comparisons showed no significant differences between the two agents, except for less toxicity with carboplatin. [P. A. Bunn, Jr., md, personal communication, February 1998] Therefore, I favor the use of carboplatin over cisplatin in patients with small-cell lung cancer.

**Insufficient Study of Newer Agents**

I am also somewhat puzzled as to why the newer agents—paclitaxel (Taxol), docetaxel (Taxotere), topotecan (Hycamtin), irinotecan (Camptosar), vinorelbine (Navelbine), and gemcitabine (Gemzar)—have not been studied as thoroughly in small-cell cancer as in non-small-cell lung cancer. Most of these drugs are more active than older single agents in non-small-cell carcinomas, and even greater efficacy is expected for small-cell carcinoma.

There has been no change in the incidence of either neoplasm. Rather, I think the lack of investigation of the newer agents is more likely a reflection of where the majority of patients are now treated. Not unlike patients with Hodgkin’s disease or non-Hodgkin’s lymphoma, most patients with small-cell lung cancer are now diagnosed and treated in community practices. Small-cell lung cancer has been recognized as a chemoresponsive neoplasm for many years, and multiple reports over the past 20 years have documented several regimens that benefit these patients. These regimens have been used in the community by large numbers of well-trained medical oncologists. Therefore, the number of patients available for new trials at university centers and large referral cancer centers has been substantially reduced. Even cooperative groups sponsored by the National Cancer Institute depend on community oncologists for more than 50% of their patients in large phase III trials.

During the 17 years that I spent at Vanderbilt University Medical Center, I observed the small-cell lung cancer referral population decline from approximately 80 previously untreated patients per year to 10 patients per year. Now that I am affiliated with a large community cancer center, the number of patients seen by our group is quite similar to the annual number that were treated at Vanderbilt 15 to 20 years ago. Certainly, the time has come for community centers to plan and initiate clinical trials, and we have taken an active role in this process.

**Results With Paclitaxel**

A few phase II studies using the newer drugs have been reported and are discussed briefly in this review. Paclitaxel as a single agent is as active as any other single drug. Our center recently published an update of a cooperative community group effort performed by the Minnie Pearl Cancer Research Network in which paclitaxel was used in combination with carboplatin and oral etoposide. [5] It is worth noting that a comparison of two sequential phase II trials showed that slightly higher doses of paclitaxel and carboplatin were associated with higher response rates and longer survivals.

The initial phase II trial in 38 patients used 135 mg/m² of paclitaxel over 1 hour with carboplatin (AUC = 5) and oral etoposide (total dose, 50 mg alternating with 100 mg) for 10 consecutive days. The regimen was repeated every 21 days for four courses. In patients with limited-stage disease, radiotherapy (45 Gy) was given concurrently with the third and fourth courses. This combined-modality regimen was well tolerated, with no unexpected severe toxicity.

The second phase II trial in 79 patients used a similar combined-modality regimen, except that the doses of paclitaxel and carboplatin were increased (to 200 mg/m² and AUC = 6, respectively). Although severe myelosuppression (grade 3/4) increased from 8% to 38% of courses with the higher doses, the incidence of sepsis and hospitalization for neutropenia with fever was no different. Cytokines were not used. The median survival in patients with extensive-stage disease treated with the higher doses was statistically greater (P = .008), and survival in patients with limited-stage disease compared favorably to that reported for other regimens.

A randomized, prospective trial is currently comparing this promising combination to carboplatin plus etoposide.

**Early Results With Other New Agents**

Topotecan shows promising results in early trials, and all of the other newer drugs appear to have some activity. It is important that these agents are rapidly evaluated in this disease, since this is the most likely route for further improving the survival of these patients over the next few years. In fact, these same new drugs appear to have increased the survival of patients with stage III and IV non-small-cell lung cancer in 1998 to a higher level than is currently attainable in patients with limited- and extensive-stage small-cell lung cancer, respectively.

**References:**


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