Management of Small-Cell Lung Cancer: Time to Move Forward

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Small-cell lung cancer (SCLC) is a pathologically distinct malignancy of the lung, characterized by rapid growth, propensity for early metastatic spread, and responsiveness to chemotherapy and radiation. Despite its generally good initial response, the relapse and subsequent mortality rate remain very high. Only 3% to 8% of all patients survive 5 years, and median survival for extensive stage disease is 8 to 13 months.[1,2]

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While the incidence of SCLC is decreasing, SCLC still accounts for approximately 13% of lung cancers—nearly 30,000 diagnoses per year.[3] In this article, Dr. Ganti and colleagues offer an excellent, comprehensive discussion of the diagnosis, staging, and treatment of SCLC. The article serves to underscore how advances in the treatment of SCLC have lagged behind advances in treating non–small-cell lung cancer (NSCLC). It also highlights promising approaches and agents under investigation.

Staging
As Ganti and colleagues note, there are two different staging systems for SCLC. The Veterans Administraion Lung Study Group system categorizes tumors as either limited disease or extensive disease, based on the ability of a reasonable radiation port to encompass all disease. Although this system has been widely used because of its simplicity and utility in clinical decision making, the authors argue for moving towards tumor-node-metastasis (TNM) staging. They note that the lung cancer staging project of the International Association for the Study of Lung Cancer found that TNM staging groups correlated better with survival.[4-6]. However, this improved correlation with survival seems to be driven largely by results in a few specific groups of patients. The first group includes patients with disease that is amenable to complete surgical resection.[7] Unfortunately, this scenario is seen in a small minority of cases,[8,9] and in practice, surgery has often been offered to these patients. The other populations are patients with pleural effusions and those with supraclavicular lymph node involvement. Thus, as Dr. Ganti reports, the prognostic impact of these findings is still unclear.[10,11] Consequently, a switch in the staging system is unlikely to significantly affect treatment in the vast majority of patients, pending future clinical trials. Although the new staging system showed utility in SCLC, all of the data used to generate the new stage groupings came from patients with NSCLC.[12] An ideal SCLC staging system would be generated from prognostic data from SCLC patients. Hopefully, this will be the case with future systems.

Dr. Ganti describes a role for induction chemotherapy followed by surgery with postoperative radiation and chemotherapy. If such an approach were to become more common, the more descriptive TNM staging approach would gain utility.[13-15] However, before this approach becomes more widely used, randomized trials should show that it has an advantage over definitive chemoradiotherapy.

Chemoradiotherapy
The authors acknowledge the lack of significant innovation with regard to front-line chemotherapy, which has not changed significantly in decades. As they describe, a combination of etoposide and platinum is the standard first-line therapy for most patients with SCLC (combined with radiation in patients without extensive-stage or stage IV disease).[16-18] In the last 10 years, the introduction of erlotinib, pemetrexed, and bevacizumab have altered NSCLC treatment. However, oral topotecan as a second-line agent is one of the few advances in the treatment of SCLC to become clinically available[19-21] during that time. Chemotherapy can be followed by prophylactic cranial irradiation (PCI) in patients who show a good response to initial treatment.[22] Interestingly, data support PCI in limited-stage disease with a complete response or in extensive-stage disease with a partial...
response; however, there are not good data for PCI in limited-stage disease with partial response. In practice, PCI is often offered to any patient with SCLC who has had a response to chemotherapy. One promising cytotoxic agent described in the article is the synthetic anthracycline amrubicin. In two randomized phase II trials comparing amrubicin to topotecan in relapsed disease,[23-25] a higher response rate was seen with amrubicin (38% vs 13%, and 36% vs 8%). Amrubicin is also being tested as a first-line agent for elderly patients with good performance status. In a phase II study of elderly patients (aged 70 years or older) with either limited-stage or extensive-stage SCLC, amrubicin plus cisplatin was well tolerated, with an overall response rate of 89% and an 18.6-month median survival.[26]

**Targeted Therapy**

Although not discussed in this article, targeted therapy is another area of exploration in the treatment of SCLC. Not only does SCLC have distinct behavioral characteristics, but its molecular profile differs from that of NSCLC. Deletion of 3p is seen, as is loss of Rb function. Mutations in the p53 gene are common, as is high-level expression of myc and c-kit.[27-29] Still, despite the existence of several potential targets, development of targeted therapies for SCLC remains far behind the development of such therapies for NSCLC. With rare exceptions, SCLC does not harbor EGFR mutations and is generally unresponsive to EGFR inhibition.[30] Likewise, although c-kit provided a theoretical target for imatinib, significant responses were not seen with this agent, even in tumors with c-kit expression.[31-33] Angiogenesis inhibition has emerged as an effective strategy in NSCLC,[34,35] but results in SCLC have been mixed.[36-38] The frequent use of radiation in the treatment of SCLC, along with some concerning safety issues with bevacizumab and radiation, has also limited the development of angiogenesis inhibitors in SCLC.[39]

Other ongoing lines of research include inhibition of bcl-2, mammalian target of rapamycin (mTOR), insulin-like growth factor type I receptor (IGF-1R), and histone deacetylase (HDAC). Thus far, however, no single agent has demonstrated a clear and consistent impact on the disease. A better understanding of the biology of SCLC is needed in order to move the field forward. One limitation has been the lack of available tissue for research purposes. Since surgery is rare in SCLC, and since patients who do undergo surgery may have a biologically distinct disease, available tissue is limited. The authors advocate an increased use of surgery after neoadjuvant therapy. If more patients were to undergo surgery, more tissue would be available. Even recognizing that these specimens would be from previously treated patients, it would be an advance to have greater availability of tissue for study.

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