Small-Cell Lung Cancer: Translational Research Enroute to Therapeutic Advances

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Hann/Rudin Article Reviewed. Hann and Rudin have provided a comprehensive and thoughtful review of the current management of small-cell lung cancer (SCLC).

Hann and Rudin have provided a comprehensive and thoughtful review of the current management of small-cell lung cancer (SCLC). As they note, for approaching 2 decades, little has changed in the pretreatment evaluation, staging, or treatment of this disease. As a result, only modest improvements in survival have been seen. During this time, however, a considerable understanding of the biology of this malignancy has emerged, and this knowledge should soon translate into improved therapies for patients with SCLC.

One of the treatment advances discussed in the review is the definitive demonstration by Turrisi et al that radiation to 45 Gy (given concurrently with cisplatin and etoposide) administered in 1.5-Gy fractions twice daily significantly improved survival in patients with limited-stage disease, compared with the prior standard of 1.8-Gy fractions daily for 5 weeks. The authors did not mention that physicians and patients have failed to embrace this regimen due to the practical issues associated with the administration of twice-daily radiation. As a result, several current studies are evaluating whether a radiobiologically similar dose administered in once-daily fractions is safe and effective for patients with limited-stage disease.

Extensive-Stage Disease
In their overview of treatment for extensive-stage disease, the authors point out that a number of chemotherapy agents (pemetrexed [Alimta], irinotecan [Camptosar], topotecan [Hycamtin]) have been evaluated in combination with platinum in recent years as first-line therapy for extensive-stage disease. Despite initial indications that these regimens might be shown to be superior to the current standard of etoposide and a platinum analog (PE), all three failed to demonstrate superiority to PE in phase III randomized trials. As Hann and Rudin then discuss, the one chemotherapy agent currently under evaluation that still appears to hold promise is the synthetic anthracycline amrubicin. Amrubicin has shown significant activity in the second-line setting in both chemosensitive and chemorefractory populations. Currently, a randomized, phase III trial comparing cisplatin/amrubicin with PE as first-line therapy in extensive-stage disease is underway in China (NCT00660504), and in the second-line setting, amrubicin is being evaluated against parenteral topotecan in another phase III trial (NCT00547651).

Somewhat ironically, despite the long-established relative chemosensitivity of SCLC, the only significant advance in the treatment of extensive-stage disease in recent years can be attributed to radiation rather than chemotherapy. The European Organisation for Research and Treatment of Cancer (EORTC) demonstrated in a phase III randomized trial that prophylactic cranial irradiation in extensive-stage SCLC patients whose tumors have responded to first-line therapy more than doubles survival at 1 year from randomization (13% vs 27%).

Underlying Mechanisms
Current research seeks to exploit the ever-increasing understanding of the molecular pathways involved in SCLC. As Rudin and Hann touch on in their review, approaches targeting angiogenesis showed initial promise in this disease. However, thus far, trials combining standard chemotherapy with agents such as bevacizumab (Avastin) and thalidomide (Thalomid) did not demonstrate clear progress over standard treatment. In addition, therapies targeting the c-Kit tyrosine kinase and the antiapoptotic protein Bcl-2 also failed to demonstrate significant activity.

One additional area that deserves mention is the possible identification of the tumor stem cell population in SCLC. Several studies have suggested the presence of a subpopulation of cells (tumor stem cells) in solid tumors that are able to regenerate and propagate the tumor. Recently, Gutova and colleagues identified a rare population of cells in SCLC cell lines that were urokinase-type plasminogen activator receptor (uPAR)-positive and possessed clonogenic activity and marked...
resistance to chemotherapy when compared with the uPAR-negative population that was chemosensitive and did not possess clonogenic activity.[1] Further study is required to demonstrate whether this uPAR-positive group of cells may be the putative stem cell population for SCLC.

**Hedgehog Signaling Pathway**

In addition, the hedgehog pathway (an embryonic signaling pathway) has been shown to be activated in airway epithelium in response to injury, and this is thought to lead to malignant change by repeatedly expanding the airway stem cell pool. The cells within SCLC tumors in vivo that are involved in hedgehog signaling are compartmentalized and appear to recapitulate the process seen in airway development and injury repair. It has therefore been speculated that these cells are maintained as tumor stem cells through ongoing hedgehog signaling.[2,3] Treatment of SCLC cell lines and xenografts with cyclopamine (a specific hedgehog pathway inhibitor) produces tumor growth arrest in both models.[4] Currently, GDC-0449, an orally bioavailable synthetic inhibitor of the hedgehog pathway is in phase I and II studies in patients with solid tumors, including SCLC. Finally, increasing evidence suggests that cancer stem cells are controlled by an epigenetic program and that treatment with epigenetic-targeted agents may convert the cancer stem cells to progenitors with less malignant behavior.[5,6] The outcome of these and future studies will determine whether targeting these cell populations will prove to be a successful therapeutic approach in SCLC.

**References:**


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