Small-Cell Lung Cancer: Therapeutic Changes

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Almost 40% of patients with newly diagnosed small-cell lung cancer (SCLC) have disease confined to the ipsilateral hemithorax and within a single radiation port, ie, limited-stage disease. The median survival for this group of patients after treatment is approximately 15 months, with one in every four patients surviving 2 years. Current optimal treatment consists of chemotherapy with platinum/etoposide, given concurrently with thoracic radiation. Surgery may represent an option for very early-stage disease, but its added value is uncertain. Prophylactic cranial irradiation (PCI) is used for patients with limited-stage SCLC who have achieved a complete response following initial therapy, as it decreases the risk of brain metastases and provides an overall survival benefit. Newer targeted agents are currently being evaluated in this disease and hold the promise of improving current outcomes seen in patients with early-stage disease.

Small-cell lung cancer (SCLC) is one of the most aggressive solid tumors. Although its incidence is decreasing and modest improvements in outcome have been observed in the past 3 decades, long-term survival is observed only in approximately 10% of patients with limited disease. (In contrast, the outcome in patients with extensive disease is uniformly fatal.)[1] The review by Drs. Ganti, Zhen, and Kessinger presents an excellent update on current therapeutic options for patients with limited-stage SCLC and provides insights into future clinical research developments. In this commentary, we would like to outline ongoing discussions with regard to challenges in the optimal management and current clinical trials in the disease.

Chemotherapy

The Japan Clinical Oncology Group (JCOG) reported with great enthusiasm the results of a phase III clinical trial comparing the combination of the topoisomerase I inhibitor irinotecan (Camptosar) and cisplatin (Platinol)—known as IP—to the standard etoposide/cisplatin regimen (EP) in extensive-stage SCLC patients.[2] This trial was terminated after an interim analysis met predefined early-stopping rules favoring the experimental arm with irinotecan. An improvement in median survival from 9.4 to 12.8 months was observed, corresponding to a hazard ratio of 0.60 (95% confidence interval = 0.43-0.83). The results of this trial prompted the integration of irinotecan into chemoradiotherapy protocols in limited-stage SCLC.

Two phase II clinical studies evaluated concurrent radiotherapy (45 Gy twice daily) during the first cycle of EP chemotherapy followed by three cycles of IP.[3,4] Both studies showed acceptable toxicity and encouraging median survivals of 20 and 23 months. In both trials, isolated local relapses were extremely rare, and grade 3/4 esophagitis was noted in less than 10% of patients.

A phase III clinical trial (JCOG 0202) is currently randomizing limited-disease patients after upfront chemoradiotherapy during the first cycle of EP to either continuation of EP (standard arm) or three cycles of IP (experimental arm). Unfortunately, an extensive-disease phase III clinical study conducted in the United States with a slightly different IP schedule did not result in improved survival, compared to the EP regimen.[5] The pharmacogenomic differences between US and Japanese populations are a potential cause of this discrepancy. A polymorphism of the UGT1A1 gene, which encodes a protein involved in irinotecan metabolism, is currently being studied and may account for ethnic differences in irinotecan efficacy.

A similar study of oral topotecan, another topoisomerase inhibitor, was conducted in Europe.[6] In first-line treatment of patients with extensive SCLC, topotecan/cisplatin proved to have efficacy similar to that of the standard EP schedule.

Given the negative results of these phase III trials, evidence for further development of topoisomerase I inhibitors in limited-stage SCLC is less compelling. However, different dosing schedules of these drugs should be investigated before definitive conclusions can be made. Results from a large prospective randomized study of irinotecan/cisplatin vs etoposide/cisplatin in extensive-stage SCLC conducted in Norway will be presented at the 2007 annual meeting of the American Society of Clinical Oncology.
Radiotherapy
The role of radiation therapy as a means of improving local control and overall survival in the management of limited-stage SCLC was established in the early 1990s.[7] Turrisi et al reported the landmark study of thoracic radiotherapy, showing that twice-daily irradiation to 45 Gy leads to a 10% improvement in the 5-year survival rate, compared to the same dose administered once daily.[8] Twice-daily radiotherapy appears to better counteract accelerated repopulation of clonogenic tumor cells during radiotherapy. The control arm of this study used a dose regarded as suboptimal, and many radiation oncologists in the United States and Europe continue to treat their patients with doses ranging from 60 to 74 Gy using once-daily fractionation. A clinical trial comparing these two approaches is planned.

Controversies also exist with regard to the role of elective nodal irradiation in limited disease. The omission of uninvolved mediastinal nodes resulted in acceptable local control in a relatively small series of patients,[9] but more data are needed to establish this approach as standard of care in limited-stage SCLC. Technical advances with respiratory gating and breath control techniques enable radiation oncologists to minimize treatment volumes in order to prevent treatment-related toxicities and safely deliver higher radiation doses.

Prophylactic cranial irradiation (PCI) after a complete or near-complete response to chemotherapy and thoracic radiotherapy has proven value in reducing brain relapse rates and improving survival in patients with limited disease.[10] An Intergroup study conducted in the United States by the Radiation Therapy Oncology Group (RTOG-0212) and other groups worldwide is comparing two doses of PCI (36 Gy once or twice daily vs 25 Gy once daily) to determine the optimal regimen with regard to efficacy and toxicity. The accrual to this study is completed, and the results are awaited.

Targeted Therapies and Other Novel Approaches
Several clinical studies with low-molecular-weight heparins (LMWHs) conducted in multiple advanced cancer types have indicated the possibility of improved survival with these agents.[11,12] The anticancer properties of LMWHs appear to depend on mechanisms far beyond the prevention of vascular-thromboembolic events, and may include antiangiogenic effects, inhibition of cell adhesion and metastasis formation, and induction of apoptosis. These mechanisms are particularly appealing given the biology of SCLC.

A small randomized study, conducted in 84 patients with limited- and extensive-stage SCLC, assessed the efficacy of cyclophosphamide, epirubicin (Ellence), and vincristine with or without dalteparin (Fragmin) administered once daily for the duration of chemotherapy.[13] This study showed improved response rates (69.2% vs 42.5%), median progression-free survival (10 vs 6 months), and median overall survival (13 vs 8 months) in favor of dalteparin, with acceptable toxicity. The treatment schedule used in this trial was different from the standard of care in most North American institutions.

It is also generally acknowledged that the results of small randomized studies may overestimate treatment benefit.[14] Therefore, larger phase III clinical trials are ongoing, in an effort to define the role of LMWHs in the management of both limited- and extensive-stage SCLC.

Thalidomide (Thalomid) is an anti-inflammatory and sedative agent with antiangiogenic properties, showing significant clinical activity in patients with multiple myeloma. French investigators studied 92 extensive-disease patients who responded to two cycles of chemotherapy (cisplatin, etoposide, epirubicin, and cyclophosphamide), randomizing them to four additional cycles of chemotherapy with or without the addition of thalidomide.[15] Thalidomide was associated with improved overall survival (hazard ratio = 0.48; 95% confidence interval = 0.24-0.93) at the expense of increased toxicity. A large phase III clinical study of thalidomide is currently ongoing in Europe in patients with limited or extensive SCLC.

Most cases of SCLC demonstrate abundant expression of c-kit, the stem-cell factor receptor. Despite promising in vitro data, the results of phase II clinical studies with imatinib (Gleevec), a tyrosine kinase inhibitor of c-kit, failed to demonstrate any activity in c-kit-positive SCLC patients who failed previous chemotherapy.[16,17] In vitro cosignaling through the insulin-like growth factor (IGF) pathway has provided a possible explanation for the lack of c-kit inhibitor efficacy observed in these studies,[18] and trials exploiting inhibition of both targets are contemplated in SCLC. Other phase I and II trials currently recruiting patients will explore the efficacy of antiangiogenic agents and mammalian target of rapamycin (mTOR) inhibitors.

Conclusions
Multidisciplinary management of limited-stage SCLC patients is critical to achieve the best chance
for long-term survival. Several large clinical studies are currently underway to optimize systemic and radiation therapy for these patients. More effective systemic therapies are needed, and the rational design of studies with novel chemotherapeutics and targeted agents will present a challenge for investigators in both basic and clinical sciences.

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Disclosures:
The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

References:


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