Small Cell Lung Cancer: Will Recent Progress Lead to Improved Outcomes?

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Abstract

Small cell lung cancer (SCLC) is an aggressive neuroendocrine malignancy with a unique natural history characterized by a short doubling time, high growth fraction, and early development of widespread metastases. Although a chemotherapy- and radiation-sensitive disease, SCLC typically recurs rapidly after primary treatment, with only 6% of patients surviving 5 years from diagnosis. This disease has been notable for the absence of major improvements in its treatment: Nearly four decades after the introduction of a platinum-etoposide doublet, therapeutic options have remained virtually unchanged, with corresponding little improvement in survival rates. Here, we summarize specific barriers and challenges inherent to SCLC research and care that have limited progress in novel therapeutic development to date. We discuss recent progress in basic and translational research, especially in the development of mouse models, which will provide insights into the patterns of metastasis and resistance in SCLC. Opportunities in clinical research aimed at exploiting SCLC biology are reviewed, with an emphasis on ongoing trials. SCLC has been described as a recalcitrant cancer, for which there is an urgent need for accelerated progress. The NCI convened a panel of laboratory and clinical investigators interested in SCLC with a goal of defining consensus recommendations to accelerate progress in the treatment of SCLC, which we summarize here. Clin Cancer Res; 21(10): 2244–55. ©2015 AACR.

See all articles in this CCR Focus section, “Progress in Lung Cancer.”

Introduction

Small cell lung cancer (SCLC) remains a worldwide public health problem. In the United States, the decrease in prevalence of tobacco use has resulted in a gradual decrease in SCLC incidence over the past decade; nonetheless, SCLC remains a major cause of cancer mortality, currently accounting for 14% of all lung cancers, or approximately 30,000 patients annually (1, 2). Tobacco exposure is strongly associated with the development of SCLC, with only 2% to 3% of patients being never-smokers (3, 4). Outcomes for SCLC have not changed dramatically as the majority of patients, including those with limited-stage disease and those initially responsive to chemotherapy and radiation, develop chemoresistance. As a result, overall 5-year survival rates are a dismal 6% (1, 2).

Few improvements have been made in the fundamentals of SCLC treatment in the past few decades, with most advances being restricted to improved approaches to radiotherapy. Notably, the standard chemotherapy regimen of cisplatin or carboplatin plus etoposide used for the first-line treatment of limited-stage (LS-SCLC) and extensive-stage (ES-SCLC) disease has not changed over the past four decades. Radiotherapy is administered to those patients with LS-SCLC, whose cancer is confined to the chest in a single tolerable radiation field. The superiority of hyperfractionated radiotherapy and early initiation of radiation, either during the first or second cycle, has been suggested in numerous clinical trials (3–12), although the question of standard hyperfractionation versus a higher total dose of radiation is being revisited in a large national cooperative group study using modern radiotherapy techniques (NCT00632853). Those patients with LS-SCLC and ES-SCLC who show a response to first-line platinum-based therapy generally are offered prophylactic cranial irradiation (PCI), which has been shown to decrease the risk of intracranial recurrence and improve overall survival (OS; refs. 13, 14).

First-line treatment for SCLC yields optimal tumor response rates as high as 60% to 80%, which, unfortunately, translate to cure in only approximately 20% of patients with LS-SCLC (15). Essentially all patients with ES-SCLC, and the majority of patients with LS-SCLC, suffer relapse within months of completing initial therapy. The strongest predictor of outcome for patients with relapsed SCLC is the duration of remission. Patients with sensitive disease who maintain a response to initial treatment for 3 months or longer have a median survival of approximately a 25% response rate to additional chemotherapy and a median survival from the time of relapse of approximately 6 months. In contrast, those patients with refractory disease who either have no response to initial therapy, or progress within 3 months, rarely benefit from additional treatment, with response rates less than 10% and median survival of 4 months.

Topotecan is the only FDA-approved agent for recurrent or progressive SCLC, based on the results of three phase III trials (16–18). There are no accepted regimens for patients whose
Recent Progress in SCLC May Lead to Improved Outcomes

The inherent biology of SCLC presents numerous challenges, further hindering potential advancements.

**Challenges in SCLC**

SCLC has a complex molecular biologic pathogenesis with many mutations but few obvious therapeutic targets.

First, the molecular pathology of SCLC is particularly complex. SCLC is most strongly linked to long-term high exposure to tobacco carcinogens, leading to an exceptionally high degree of genomic alterations, including mutations, insertions, deletions, large-scale copy number alterations, and gross inter- and intrachromosomal rearrangements (25–27). With approximately 8.88 mutations per megabyte, the only other malignancy with a higher mutational burden than SCLC is melanoma, caused by ultraviolet light, another potent carcinogen (26–28).

Most of the mutations observed in SCLC tumors are passengers, i.e., those that do not meaningfully contribute to growth, progression, or invasion of disease. Furthermore, the most commonly recurrent mutations that are seen in this disease are inactivating mutations in the tumor suppressor genes TP53 (75%–90%; ref. 29) and RB1 (60%–90%; ref. 30, 31), which cannot be targeted directly.

Two independent, comprehensive genomic studies, which included exome, whole genome, transcriptome, and copy number alteration data from primary SCLC patient samples (together over 100 samples) have provided some initial insights into the fuller landscape of genetic alterations in this disease (26, 27). The results of these studies confirm TP53 and RB1 inactivation and the exceptionally high degree of genomic alteration in this tumor type. The two studies emphasize that, unlike lung adenocarcinoma, the genomic landscape of SCLC is not broadly characterized by a set of mutually exclusive, targetable driver oncogenes involved in activation of kinase signaling. Other processes, such as transcriptional deregulation, histone modification (e.g., mutations in CREBBP, EP300 and MLL), and dysregulation of the cytoskeleton (e.g., mutations in SLIT2 and EPHA7), are implicated by mutational data. Additional alterations of interest in SCLC defined by the two studies include amplification of MYC, MYCN, and MYCL1; a recurrent fusion involving MYCL1 (9%); inactivation of PTEN (10%) and mutations of other factors in the same signaling pathway; and amplification of the tyrosine kinase FGFR1 (6%) and of the developmental regulator and transcription factor SOX2 (27%; refs. 26, 27). It is notable that the less common genomic alterations detected in each of the reports differed, indicating that these current studies have been insufficiently powered to reliably identify recurrent mutations present in <10% of patients with SCLC; clearly, such efforts should be expanded further, as the functional and therapeutic implications of the large majority of the genetic alterations documented to date in SCLC have not been defined.

**Mechanisms of primary and acquired resistance to chemotherapy are unknown**

Second, while all patients with ES-SCLC, and the majority of patients with LS-SCLC, suffer relapse within months of completing initial therapy, the mechanisms of resistance and properties of the chemoresistant cell population remain unknown. In standard clinical practice, patients with SCLC are not given a second biopsy upon recurrence, given that disease progression is expected and
often symptomatic, necessitating urgent treatment. In the context of limited treatment options, such biopsies have been considered unwarranted. However, following upon the experience with molecularly driven NSCLC, in which we have an increasingly clear understanding of the mechanisms of resistance for EGFR-mutated and ALK-rearranged tumors, as discussed elsewhere in this CCR Focus section (32, 33), research programs to obtain acquired resistance biopsies should be considered for SCLC. Identifying specific molecular aberrations in SCLC tumors upon recurrence may help us understand the mechanisms of acquired resistance to first-line chemotherapy, may identify factors that contribute to the variable responses observed with standard treatment, and may define opportunities to tailor effective treatment options for patients with SCLC (Fig. 1).

Improved Research Strategies in SCLC

Mouse models of SCLC

Given the complexity of SCLC and the relatively limited number of available patient samples, animal models of this disease play a key role in translational research. These include both genetically engineered mouse models (GEMM) and patient-derived xenograft (PDX) models. GEMM. Many GEMMs have been developed that recapitulate the spectrum of human SCLC and other high-grade neuroendocrine cancers (34). Loss-of-function mutations in RB1 and TP53 genes are hallmarks of SCLC and are therefore the “backbone” of most GEMMs, to which additional alterations can be added to hasten tumor development or to study the contribution of a specific gene alteration. Mice with conditional loss of Trp53 and Rb1 in the lung develop spontaneous SCLC tumors that behave similarly to human tumors (e.g., development of metastatic disease and the sites of those metastases). Genomically, these models have lower mutational burdens overall (presumably due to the absence of tobacco exposure) but still undergo both genetic and clonal progression (including the development of Mycl1 amplification and Pten loss; refs. 35, 36). Therefore, while GEMMs do not fully capture the genetic complexity of human SCLC tumors, they nevertheless provide an important tool for studying the contribution of key genes while minimizing "noise" from passenger mutations characteristic of human SCLC. Finally, from a therapeutic standpoint, the use of GEMMs to test therapeutic interventions can be highly informative (37), despite being labor-intensive and costly given the time required to develop cancer (e.g., ≥9 months in models with Rb1 and Trp53 inactivation). In particular, GEMMs (unlike xenografts) allow for the investigation of SCLC within an immunocompetent context—a valuable feature for studying the role of the immune system and immunotherapies in SCLC.

Figure 1. Chemoresistance and potential for research and change in treatment. A, SCLC is very sensitive to first-line chemotherapy, with a 60% to 80% response rate. However, there is almost uniform relapse or progression of disease. Such relapse likely is due to the behavior of the chemoresistant cell population, which may also have enhanced tumorigenic potential (blue-colored cells). B, opportunities for research and drug development. Patients with newly diagnosed advanced SCLC could be enrolled into tissue acquisition protocols and their tumors biopsied prior to initiating treatment, facilitating comprehensive molecular studies, including but not limited to genome, transcriptome, proteomic, and methylome profiling. Furthermore, these samples could subsequently be available for creation of PDX (not shown). At the time of progression or recurrent disease, patients could be approached to undergo repeat biopsy. Evaluation and comparisons of molecular features of paired samples from the same patient could identify pathways of resistance to standard first-line therapy, define new biomarkers, and provide opportunities for targeted drug development. Pathways of interest could be evaluated further in GEMM (not shown). C, once agents are found to have benefit against chemoresistant cells, these drugs could be incorporated into clinical trials and potentially lead to responses, and importantly, more durable outcomes. EP, etoposide and platinum; GEMM, genetically engineered mouse model; PDX, patient-derived xenograft.
**GEMMs: transgenic mouse models of SCLC.** Initial genetic mouse models of SCLC used tissue-/cell-type–specific promoters to drive expression of oncogenes or proto-oncogenes, such as Simian virus 40 (SV40) large T antigen (Tag) a transforming oncogene that disrupts several key functions of RB1 and TRP53; refs. 38, 39) and MYC (38). Limitations of early transgenic models included a lack of an efficient method for gene deletion (but rather for addition or misexpression) and an absence of inducible systems. As such, oncogene expression depends upon the onset of promoter expression, regardless of age or stage of development of the mouse. The inability for these transgenic models to target neuroendocrine cells may therefore be due to promiscuity of transgene expression during early lung development (40).

**GEMMs: conditional mouse models of SCLC.** Genes can be conditionally deleted in mice using such methods as cell-type–specific adenoviral vectors or by crossing to recombinant mice. Loss of RB1 and Trp53 resulted in tumors expressing neuroendocrine markers that have morphologic similarities to SCLC within 6 to 9 months (41–43).

The addition of any of several third alleles, such as p130 (Rh2; ref. 44), Rh2 and Smo or SmoM2 (45), and Pten (36, 42), to RB1 and Trp53 loss can accelerate tumor formation and metastasis. Mice with loss of RB1, Trp53, and Rh2 develop SCLC tumors and liver metastases within 5 to 6 months and do not survive until 9 months (44). While this triple model results in accelerated SCLC formation, Rh2 mutation is not commonly found in human SCLC. Mice with constitutively active Hedgehog signaling (RB1; Trp53; SmoM2) form SCLC tumors with greater volume and higher mitotic index. Conversely, attenuation of Hedgehog signaling combined with the accelerated, triple model described by Schaffer and colleagues (RB1; Trp53; Rh2; Smo; ref. 44) resulted in fewer and smaller SCLC tumors (45), supporting the idea that Hedgehog signaling is essential for SCLC tumor formation and progression. One of the most aggressive mouse models of SCLC incorporates deletion of the tumor suppressor Pten together with Trp53 and RB1 loss. These mice develop hyperplastic lesions within 2 to 4 weeks; display neuroendocrine hyperplasia, tumor invasiveness and large cell tumors within 2 to 3 months; and do not survive beyond 3 months (42).

Primary benefits of these genetic models of SCLC include the ability to study the malignancy in a tightly manipulable system, to evaluate the characteristics of metastases that arise endogenously, and, in particular, the opportunity to assess the contribution of specific genetic lesions (e.g., Smo, Pten) in the context of RB1 and Trp53 loss (without the large burden of passenger mutations typical of human tumors). Mouse SCLC shares many characteristics with human SCLC, including cell morphology, gene expression profiling, and metastatic patterns. Interestingly, tumors arising in these mouse models are heterogeneous (46), a feature they share with human SCLC.

**PDX.** PDX models, which depend on the immediate transfer of human SCLC from patients to recipient immunodeficient mice without intervening tissue culture or cell line derivation ex vivo (47), provide an opportunity to study the fuller extent of human tumor heterogeneity, to expand original biopsies into a larger supply of tumors that can then be used more successfully for molecular profiling (e.g., DNA sequencing, proteomics), and to investigate response to drugs and other therapeutic approaches. Recently, the feasibility of using circulating tumor cells (CTC) from the blood of patients with SCLC to establish animal models (CTC-derived xenografts, CDX) was demonstrated (48). These models may prove to be particularly transformative for the field, as they do not rely on actual invasive biopsies to obtain tissue, but rather a "liquid biopsy," and further, allow for studying mechanisms of drug resistance and SCLC biology through sequential sampling of blood from the same patient at the time of initial diagnosis and relapse.

**Comprehensive molecular profiling**

As summarized above, two recent independent studies focused primarily on comprehensive genomic analyses of human SCLC (26, 27). However, beyond alterations in DNA, analysis of additional layers of cancer-specific dysregulation, including epigenetic alterations, changes in gene and miRNA expression profiles, and, ultimately, changes in the proteome, will be instrumental in the understanding of the malignant transformation, clonogenic potential, tumor growth, and metastatic spread of SCLC and have already begun to yield potentially clinically relevant insights. For example, proteomic profiling of a large panel of SCLC cell lines led to the identification of increased expression of the DNA repair proteins, PARP1 and checkpoint kinase 1 (Chk1), as well as the chromatin modulator, enhancer of zest 2 polycomb repressive complex 2 subunit (EZH2; ref. 49). It will be necessary to use large numbers of patient samples in real time to more comprehensively characterize the landscape of potential targets.

**Drug screening and bioinformatics**

The Developmental Therapeutics Program at the NCI has been investigating drug sensitivity of more than 400 targeted drugs and more than 100 FDA-approved oncology agents in a panel of more than 60 SCLC cell lines. Results from this drug screen, as well as others, coupled with intense analyses of the pathways affected by the indicated agents using the comprehensive methods indicated above, may provide indications for future clinical trials (50).

An attractive modality of therapeutic discovery is drug repositioning using novel bioinformatic approaches (51). An advantage of repurposed candidate drugs is that they can often enter clinical trials much more rapidly than drugs in preclinical development. Recently, a computational drug repositioning approach identified agents that can be repurposed to treat SCLC. Top candidates were validated in a comprehensive series of assays with SCLC cells, in culture and in vivo (37, 51). This approach identified tricyclic antidepressants (TCA), including imipramine and desipramine as potent inhibitors of SCLC growth, which led to a clinical trial evaluating the latter drug in patients with SCLC (NCT01719861).

**Novel Therapeutic Strategies in SCLC**

In light of the therapeutic plateau achieved with chemotherapy, investigators have studied a wide range of novel therapies in the hopes of improving outcomes (see Table 1).
Unfortunately, although often these trials were rationally designed based on existing data at the time, in general, their outcomes have not been favorable. The genomic studies highlighted above, as well as additional proteomic, high-throughput drug screening and pathway-specific investigations, have yielded new insights and new potential therapeutic targets for this aggressive disease. Building upon these findings and continued focus on the biology of the disease to design future studies may lead to improved outcomes for patients with SCLC.

### Table 1. Agents that have undergone testing in SCLC

<table>
<thead>
<tr>
<th>Agent (ref.)</th>
<th>Mechanism of action</th>
<th>Study design</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNα (106–109)</td>
<td>Immuno/modulator</td>
<td>Phase III (multiple)</td>
<td>Two studies with improved survival in limited-stage patients, two studies with no survival benefit</td>
</tr>
<tr>
<td>IFNγ (110, 111)</td>
<td>Immuno/modulator</td>
<td>Phase III (multiple)</td>
<td>No improvement in survival</td>
</tr>
<tr>
<td>IL2 (112)</td>
<td>Immuno/modulator</td>
<td>Phase II</td>
<td>21% response rate but excessive toxicity</td>
</tr>
<tr>
<td>Ipilimumab (104)</td>
<td>Humanized anti–CTLA-4 antibody</td>
<td>Randomized phase II</td>
<td>Improved immune-related PFS when administered with carboplatin/paclitaxel in phased dosing schedule in chemo-naive extensive stage SCLC</td>
</tr>
<tr>
<td>Marimastat (113)</td>
<td>Matrix metalloproteinase inhibitor</td>
<td>Phase III</td>
<td>No improvement in progression-free or OS</td>
</tr>
<tr>
<td>Tanomastat (114)</td>
<td>Matrix metalloproteinase inhibitor</td>
<td>Phase III</td>
<td>No improvement in PFS or OS</td>
</tr>
<tr>
<td>Imatinib (115–117)</td>
<td>c-KIT tyrosine kinase inhibitor</td>
<td>Phase II (multiple)</td>
<td>No responses</td>
</tr>
<tr>
<td>Temsirolimus (118)</td>
<td>mTOR inhibitor</td>
<td>Randomized phase II</td>
<td>Higher dose level demonstrated improved survival compared with lower dose level when given post-first-line therapy; both doses showed improvement in outcome compared with historical control</td>
</tr>
<tr>
<td>Everolimus (119)</td>
<td>mTOR inhibitor</td>
<td>Phase II</td>
<td>Limited antitumor activity in relapsed SCLC</td>
</tr>
<tr>
<td>Tipifarnib (120)</td>
<td>Farnesyl transferase inhibitor</td>
<td>Phase II</td>
<td>No responses</td>
</tr>
<tr>
<td>Cixutumumab (83)</td>
<td>Monoclonal IGF-1R antibody</td>
<td>Randomized phase II</td>
<td>No improvement in PFS when added to cisplatin/etoposide in chemo-naive extensive-stage SCLC</td>
</tr>
<tr>
<td>Vismodegib (83)</td>
<td>Hedgehog pathway inhibitor</td>
<td>Randomized phase II</td>
<td>No improvement in PFS when added to cisplatin/etoposide in chemo-naive extensive-stage SCLC</td>
</tr>
<tr>
<td>Oblimersen (121)</td>
<td>Bcl-2 antisense</td>
<td>Randomized phase II</td>
<td>No improvement in response rate</td>
</tr>
<tr>
<td>Navitoclax (122)</td>
<td>Bcl-2 and bcl-x, inhibitor</td>
<td>Phase II</td>
<td>Limited activity in recurrent and progressive disease</td>
</tr>
<tr>
<td>Obatoclax mesylate (123, 124)</td>
<td>BH3-mimetic exhibits binding affinity for bcl-2 family members, including bcl-2, bcl-XL, and mcl-1</td>
<td>Randomized phase II</td>
<td>No increased response rate when added to topotecan in relapsed SCLC</td>
</tr>
<tr>
<td>Vandetanib (129)</td>
<td>Tyrosine kinase inhibitor of VEGFR-2 and EGFR</td>
<td>Randomized phase II</td>
<td>Trend toward improved response rate, PFS, and OS in chemo-naive extensive stage SCLC</td>
</tr>
<tr>
<td>Bortezomib (125)</td>
<td>Proteasome inhibitor</td>
<td>Phase II</td>
<td>One response in refractory patient (2% overall response rate)</td>
</tr>
<tr>
<td>BEC-2 + BCG adjuvant (126)</td>
<td>Ganglioside (GD3) anti-idiotype vaccine</td>
<td>Phase III</td>
<td>No improvement in PFS or OS</td>
</tr>
<tr>
<td>Thalidomide (127, 128)</td>
<td>Multiple immunomodulatory effects, also inhibits VEGF</td>
<td>Phase III</td>
<td>Improved survival from 8.7 to 11.7 months, but not significant (HR, 0.74; P = 0.16)</td>
</tr>
<tr>
<td>Vandetanib (129)</td>
<td>Tyrosine kinase inhibitor of VEGFR-2 and EGFR</td>
<td>Randomized phase II</td>
<td>No improvement in any parameters</td>
</tr>
<tr>
<td>Sorafenib (130)</td>
<td>RAF, VEGFR-2,VEGFR-3, PDGFRα Inhibitor</td>
<td>Phase II</td>
<td>No improvement in PFS</td>
</tr>
<tr>
<td>Cediranib (131, 132)</td>
<td>VEGFR-1, VEGFR-2,VEGFR-3, PDGFRβ, c-KIT inhibitor</td>
<td>Phase I</td>
<td>Minimal activity as a single agent in relapsed disease</td>
</tr>
<tr>
<td>Bevacizumab (133–136)</td>
<td>Monoclonal antibody to VEGF</td>
<td>Phase II (multiple)</td>
<td>8-month PFS with cisplatin and etoposide</td>
</tr>
<tr>
<td>Sunitinib (137)</td>
<td>VEGFR-1, VEGFR-2,VEGFR-3, PDGFRα, RET, c-KIT, FLT3</td>
<td>Randomized phase II</td>
<td>Improved PFS for bevacizumab, but not in OS</td>
</tr>
</tbody>
</table>

Abbreviation: PFS, progression-free survival.

Harnessing known molecular alterations in SCLC

Approximately 20% of SCLC patient tumors harbor alterations in the MYC gene family members of transcription factors, which are contributors to oncogenesis (52). Previous efforts to inhibit MYC activity were disappointing, yet the newer Aurora kinase or bromodomain inhibitors may prove to be promising (53–55). MYC is a transcriptional regulator of Aurora kinases A and B, which, in the absence of p53, provide a growth advantage (56–59). Preclinical models of SCLC suggest that tumors with MYC alterations may be most sensitive to Aurora kinase inhibitors (56, 60). The Aurora kinase A inhibitor, alisertib, was evaluated in a phase II clinical trial of patients with recurrent or progressive SCLC and demonstrated a response rate of 21% (61). Notably, patients with refractory disease were found to have the highest response rates. Furthermore, these drugs may be active when administered with taxanes, as Aurora kinase A has a key role in mitotic spindle assembly. An ongoing clinical trial is evaluating paclitaxel with or without alisertib for the second-line treatment of patients with SCLC (NCT02038647). If the activity of the Aurora kinase inhibitors is preferentially restricted to MYC-amplified tumors, MYC amplification may represent the first genotypically defined subset of SCLC that is clinically relevant.

As noted above, FGFR1 is amplified in 6% of SCLC, and sensitivity to FGFR inhibitors has been described in some, but not all, SCLC tumors (54). Although the extent to which this subset of SCLC is dependent on the FGFR pathway is not known, clinical studies are currently evaluating drugs targeting the FGFR family members for patients with SCLC, including INI 42756493 (a pan-FGFR inhibitor; NCT01703481) and BIBF1120 (a multitargeted drug that inhibits FGFR, VEGF receptor, and platelet-derived growth factor receptor; NCT01441297).

Exploiting the epigenome

Epigenetic alterations encompass somatically heritable differences in gene expression not attributable to alterations in the primary sequence of DNA but rather to alterations in chromatin and other associated factors that modify the ability of genes to be transcribed (62). Aberrations in gene promoter methylation patterns and histone acetylation are two of the many epigenetic processes dysregulated in cancer. Histone acetylation, which leads to increased accessibility of promoter regions and increased transcription of genes, is controlled by the interplay of acetyltransferases and deacetylases (HDAC; refs. 63, 64). The histone deacetylase inhibitors vorinostat and belinostat have shown synergistic activity when added to topotecan and cisplatin/etoposide, respectively (65, 66). We are awaiting results of two clinical trials investigating the combination of vorinostat (NCT00702962) and belinostat (NCT01090926) with platinum and etoposide in first-line treatment of patients with ES-SCLC. Notably, HDAC inhibitors have been shown to downregulate expression of c-Myc (67–69). GS11258762 is a small-molecule inhibitor of the BET (bromodomain and extraterminal) family of bromodomain-containing proteins, which prevents interaction of BET proteins with acetylated histones, leading to focal chromatin remodeling and altered expression of a number of potential target genes of interest, including MYC, as noted above. This agent is being evaluated in a phase I clinical trial that includes patients with SCLC (NCT01587703).

DNA repair

SCLC has been characterized by aberrant expression of a number of genes implicated in DNA damage repair. Frequent aberrant methylation and epigenetic silencing of the MGMT gene, which encodes the DNA repair protein O6-alkylguanine (O6-AG) DNA alkyltransferase (MGMT; refs. 70–72), has been demonstrated. Proteomic profiling of a large panel of SCLC cell lines has shown increased expression of PARP-1 and Chk1 (49). Altered expression of additional DNA repair proteins has been noted in SCLC when compared with NSCLC, including high levels of BRCA-1 and RAD51, with known roles in DNA double-strand break repair (49). Multiple DNA repair pathways may represent attractive targets in SCLC.

Epigenetic silencing of MGMT via hypermethylation of specific CpG islands of its promoter leads to loss of MGMT activity and increased sensitivity to alkylating agents (70, 72). Left unrepaired, chemotherapy-induced lesions trigger apoptosis. Temozolomide, an oral alkylating agent that crosses the blood–brain barrier, showed an overall response rate of 20% in a phase II clinical trial of patients with relapsed sensitive or refractory SCLC. Responses also were noted in patients receiving temozolomide as third-line treatment and in those with brain metastases. On the basis of these data, temozolomide has been added to compendia of agents recommended for use in the treatment of SCLC (73).

Subsequent to the observation that PARP is overexpressed in SCLC, PARP inhibitors were investigated preclinically and exhibited single-agent activity in cell lines and/or animal models (49, 74). There are active studies evaluating the PARP inhibitors, BMN673 and veliparib, either alone or in combination with chemotherapy for SCLC (NCT01286987, NCT01642251, NCT02289690, NCT01638546). BMN673 has shown single-agent activity in sensitive relapsed patients with SCLC (75). An ongoing multicenter randomized phase II study is comparing veliparib plus temozolomide with temozolomide alone in patients with relapsed SCLC (NCT01638546).

Developmental pathways: the Hedgehog and Notch pathways

SCLC is a relatively undifferentiated airway epithelial tumor that may recapitulate aspects of early lung development (76, 77). Hedgehog and Notch pathways have been noted to be essential in early lung development and to regulate stem cell self-renewal; thus, when abnormally activated, these pathways can cause neoplastic proliferation, representing an early event in tumorigenesis (78–80). These pathways are being explored as potential targets in SCLC. They are hypothesized to be of particular interest in the clonogenic subset of SCLC cells that persistently gives rise to disease recurrence and metastatic spread (81, 82).

In vivo and in vitro studies have suggested that Hedgehog antagonists can inhibit SCLC growth, and when administered following chemotherapy, these agents may delay or prevent recurrence of residual disease (77). The ECOG 1508 phase II randomized trial in patients with ES-SCLC included an arm evaluating the addition of vismodegib, a Hedgehog inhibitor, to cisplatin and etoposide, which unfortunately did not lead to an improvement in progression-free survival (PFS; ref. 83). Two ongoing studies are evaluating other Hedgehog inhibitors, the results of which have not yet been reported (NCT01579929, NCT01722292).
The Notch pathway is complex and multipartite: Depending on the cellular content, Notch signaling can have oncogenic or tumor-suppressive effects and influences multiple other oncogenic pathways (84). Notch2 and Notch3 receptors and target genes have been noted to be overexpressed in SCLC. Tarextumab (OMP-59R5), a fully human monoclonal antibody that selectively inhibits the function of Notch2 and Notch3 receptors, has been shown to delay tumor recurrence following the discontinuation of chemotherapy in preclinical models of SCLC and to decrease cancer stem cell frequency and tumorigenicity (85). A phase I study of tarextumab with etoposide/platinum in patients with ES-SCLC has been completed, and a randomized phase II study is ongoing (NCT01859741).

Achaete-scute homolog-1 as a lineage oncogene

A highly expressed gene in SCLC and other neuroendocrine lung cancers is the lineage-specific transcription factor achaete-scute homolog 1 (ASCL1; refs. 86–90). ASCL1 is necessary to establish the lineage of pulmonary neuroendocrine cells and for the continued survival of the large fraction of SCLCs that express ASCL1 (86–89). ASCL1 is not amplified or mutated but remains overexpressed in SCLCs (88, 89). Knockdown of ASCL1 or targeting some of its downstream regulated genes leads to SCLC death (87, 89, 90). Thus, an attractive strategy in SCLC may be to develop new therapeutics targeting ASCL1 pathways.

Immunotherapy

Several lines of evidence support modulating the immune response in SCLC as a treatment modality. The disease is associated with immunogenic effects, evidenced by the prolonged survival of patients with autoantibodies (i.e., anti-Hu) and neurologic paraneoplastic syndromes (91). The expression of MHC antigens is reduced in SCLC, and this may play a role in this tumor’s ability to escape immunosurveillance (92, 93). Interestingly, effector T cells associated with cytolytic responses are present in larger numbers in the peripheral blood of patients with LS-SCLC compared with those with ES-SCLC and in long-term disease-free survivors relative to those with recurrent disease (94). Most recently, the programmed death-1 (PD-1) and programmed death ligand-1 (PD-L1) pathway, a major target of antitumor immunotherapy, has been interrogated in SCLC using immunohistochemistry and RNA expression (95). While there appears to be only low-level PD-L1 expression in SCLC tumor cells, PD-L1 is expressed in tumor-infiltrating macrophages and correlates with the presence of tumor-infiltrating lymphocytes (95).

Soria and colleagues detail studies suggesting that smokers with lung cancers are most likely to benefit from PD-1/PD-L1 blockade (96–99). The anti-PD-1 antibody nivolumab recently was approved for second-line treatment of patients with squamous cell lung cancer, a subtype that, like SCLC, is tightly linked to tobacco use (100, 101). Mutational burden appears to be an important determinant of response to these immune checkpoint inhibitors. In a recent study analyzing tumor mutational burden in patients with NSCLC treated with the PD-1 antibody pembrolizumab, higher mutational burden was associated with improved objective response, durable clinical benefit, and PFS (102). The association between response to PD-1 inhibitors, mutation burden, and tobacco exposure may have important implications for SCLC, as this disease is strongly associated with smoking and has a markedly elevated mutation burden, as highlighted previously.

Therefore, immune checkpoint blockade, either alone or in combination with chemotherapy, represents a potentially promising approach to treatment in this malignancy. Ipilimumab, a humanized IgG1 monoclonal antibody against cytotoxic T-lymphocyte antigen-4 (CTLA-4), was evaluated in a randomized, double-blind, three-arm phase II trial in patients with untreated stage IIIB/IV NSCLC or ES-SCLC to assess its efficacy and safety with paclitaxel and carboplatin on two dosing schedules (103). Among the 130 patients with SCLC, the phased dosing schedule, in which ipilimumab was started in cycle three of paclitaxel and carboplatin, appeared to improve immune-related PFS (median 6.4 months for the phased ipilimumab arm vs. 5.3 months for the control arm; P = 0.03), immune-related best overall response rate [71%; 95% confidence interval (CI), 55–84 vs. 53%; 93% CI, 38–68], and OS (median, 12.9 vs. 9.9 months; P = 0.13), compared with paclitaxel and carboplatin, whereas the concurrent regimen did not lead to improved outcomes (104). Given these favorable results, a randomized, multicenter, double-blind phase III trial comparing the efficacy of platinum/etoposide with or without ipilimumab in patients with newly diagnosed ES-SCLC, with OS as the primary end-point, has completed accrual and results are anticipated (NCT01450761). Ongoing early-phase studies for patients with relapsed SCLC are evaluating nivolumab, with and without ipilimumab (NCT01928394) and MEDI4736, the humanized IgG1x monoclonal antibody directed against PD-L1 (NCT01693562), for whom we would anticipate favorable responses based on previous outcomes of these agents in patients with cancers that harbor increased mutational burden.

Moving Forward in SCLC

The pathogenesis of SCLC is driven by multiple aberrant pathways and mutations, leading to its unique biology and clinical features. Clinically meaningful progress has been slow in SCLC, although recent preclinical and clinical correlative analyses have pointed to a number of new targets of interest. Genomic and proteomic studies, as well as additional high-throughput drug screening and pathway-specific investigations, have led to clinical studies attempting to target MYC- and FGFR1-amplified SCLC and to disrupt DNA repair pathways to cause apoptosis. Furthermore, mouse models have been instrumental at exploring the Hedgehog and Notch pathways, among others, leading to the development of additional trials. Ongoing studies in mouse models will allow us to further define the basic molecular and cellular changes in this disease, further fostering the development of novel therapeutic strategies. Importantly, immune checkpoint inhibitors may prove to be effective in this smoking-related disease.

Nevertheless, there continues to be a critical need for a better understanding of this malignancy and the mechanisms that lead to the shift from initial therapeutic sensitivity to ultimate therapeutic resistance. The necessity for accelerated progress in SCLC research and treatment recently has been recognized by the NCI, in response to the Recalcitrant Cancer Research Act of 2012 (105). This Congressional bill charged the NCI with developing plans to accelerate progress in recalcitrant tumors, defined as those with 5-year survival rates of less than 20%.
Recent Progress in SCLC May Lead to Improved Outcomes

SCLC, along with pancreatic cancer, has been identified as an initial focus by the NCI. During the summer of 2013, clinical, translational, and basic science investigators came together at the NCI to develop recommendations for how we might accelerate the pace of SCLC research and clinical progress. Several consensus recommendations were proposed to address the challenges facing those who study and treat SCLC. These included recognition of the need for (i) improved research tools for the study of SCLC (including collaborative efforts to increase the collection and quality of SCLC tumor tissue collection from treatment-naive and -refractory tumors, as well as the continued development of preclinical SCLC models); (ii) high-quality molecular analysis of SCLC patient cohorts (including profiling of relapsed SCLC to investigate potential therapeutic vulnerabilities); (iii) promotion of the most promising drug targets into high-quality clinical trials; and (iv) support for SCLC research and investigators both financially and through academic initiatives to create a community of investigators, medical professionals, advocates, and others to promote collaborations and career development within the field (24).

Multidisciplinary and collaborative approaches across institutions with an emphasis on collecting adequate tissue from patients sequentially throughout their disease, with advances in technology to interrogate samples and translation of molecular findings into rational clinical trials, have the potential to advance the field. Recent discoveries based on these principles continue to inspire the next generation of innovative clinical trials for SCLC.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.C. Pietanza
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.C. Pietanza, L.A. Byers, J.D. Minna
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