Emerging Targeted Therapies in Small-Cell Lung Cancer

Background

Small-cell lung cancer (SCLC) is an aggressive carcinoma with neuroendocrine properties that accounts for 13% to 15% of all lung cancer cases.[1] SCLC is the seventh most common cause of cancer-related death in the US, and the 5-year overall survival rate for SCLC is around 6%.[2] SCLC occurrence has a strong correlation with smoking history, especially heavy smoking (>30 pack-years in North America).

The main prognostic factors in SCLC are the extent of the disease and response to initial therapy. Several staging systems have been proposed for SCLC, including those from the American Joint Committee on Cancer (AJCC) TNM, Veterans Administration Lung Study Group (VALG), and the International Association for the Study of Lung Cancer (IASLC).[2] Of these, the VALG staging system is the most commonly used, and it categorizes SCLC into two forms: limited-stage (LS) SCLC is confined to the thorax in a single radiation field, and extensive-stage (ES) SCLC is cancer that has metastasized beyond the ipsilateral lung and regional lymph nodes and is not encompassed in a single radiation field.[2-3] Due to the naturally aggressive course of this cancer, about two-thirds of patients have metastatic SCLC at the time of diagnosis.[4] The rapid doubling time and the early and wide metastasis pattern of SCLC likely also accounts for its high mortality rate (95%).[5]

The current National Comprehensive Cancer Network (NCCN) guidelines recommend pathologic mediastinal staging and surgical resection for all patients with clinically node negative T1 and T2 SCLC.[6] The standard first-line SCLC treatment in the United States and Europe is a chemotherapy regimen with platinum-based chemotherapy, with or without concurrent radiotherapy.[7] In patients with LS-SCLC, radiation therapy is initiated after chemotherapy. Thoracic radiation therapy is also being utilized in patients with ES-SCLC, following response to chemotherapy. Prophylactic intracranial radiation therapy is recommended following response to the first-line chemotherapy in both LS- and ES-SCLC to reduce the risk of intracranial recurrence and improve overall survival rates.[8,9]

Unlike the recent advances in management of non-SCLC (NSCLC), including incorporation of molecular-targeted therapies and immunotherapies, there has been a dearth of new therapeutic options. Recent genomic and proteomic studies, along with those focused molecular pathways altered in SCLC, may generate additional strategies for improving survival and therapeutic options, especially in patients with ES-SCLC and refractory/relapsed disease. Clinicians need to be made aware of these new

developments in understanding the genetics and biology of SCLC and emerging therapies currently under investigation.

The aim of this initiative is to identify the gaps in knowledge and practice in management of SCLC and to describe learning objectives for the target audience (physicians) upon completion of the educational Initiative.

Gap #1: Clinicians may not be aware that surgery is recommended for stage I or LS SCLC and that recent studies have reported the underuse of surgery in patients with early-stage disease, despite improvements in clinical outcomes with surgical resection.

Current Practices and Options in Management of SCLC

Platinum-based chemotherapy, with a combination of cisplatin-etoposide or cisplatin-irinotecan or cisplatin-topotecan, with or without concurrent radiation, is the current standard of care for first-line therapy in SCLC.[9-11] First-line chemotherapy is associated with response rates of 60% to 80% in SCLC; however, cure rates are low (20%) and are restricted to LS-SCLC patients.[1,10] Development of drug resistance and relapse is often rapid in patients with ES-SCLC; the 2-year survival in this patient group is approximately 5%.[4] In patients with ES-SCLC who are responsive to initial chemotherapy for at least 3 months (sensitive), additional chemotherapy yields a response rate of 25%, with a median survival of 6 months. In patients with refractory disease, response rates to additional treatment are low (10%), and the median survival is 4 months.[1] Only one second-line agent has been FDA-approved as second-line treatment for relapsed SCLC: topotecan.[1] To date, there are no third-line therapies available for SCLC.

The current NCCN guidelines recommend surgery in patients with SCLC that is clinical stage I (T1-2, N0), after standard staging evaluation.[6] Less than 5% of SCLC patients are diagnosed with stage I disease. The small population size likely accounts for the lack of any randomized clinical trials that have assessed the utility of surgery in LS or stage I SCLC. The authors found that surgery was associated with longer survival in all cohorts analyzed. They also concluded that surgical resection provided the greatest survival benefit for patients with stage I (median overall survival [OS], 38.6 vs. 22.9 months; hazard ratio [HR], 0.62) and T1–T2 N0 tumors (median OS, 40.1 months; vs. 23.0 months), but not in patients with stage II tumors. Of note, the authors concluded that in the cohort of patients who obtained R0 resection, surgical therapy with adjuvant chemotherapy (and radiation, in cases with nodal disease) was associated with significantly longer survival when compared with chemoradiation alone (median OS 48.6 months vs. 28.7 months).

Another retrospective study conducted in Japan concluded that surgery was effective for patients with stage I SCLC, and even in some patients with stage II or III SCLC.[12] The

authors found that the 5-year survival rates of the patients was improved with surgery (5-year survival rates with and without surgical resection in patients with stage I was 62% vs 25%, stage II was 33% vs 24%, and stage III was 18% vs 18%, respectively). In 44 propensity score-matched pairs with stage II or III disease, the 5-year survival rates were better in patients with surgical resection than in those without surgery ($p = 0.04$).

An earlier report analyzed the incidence, treatment patterns, and outcomes of 2214 patients with early-stage SCLC (1690 with stage I and 524 with stage II) identified from the Surveillance, Epidemiology, and End Results (SEER) database from 1988 to 2005.[13] The authors found that patients treated with lobectomy (or larger resections) without radiotherapy had longer median survival (50 months) than those treated with sublobar resections without radiotherapy (30 months) or those treated with radiotherapy alone (20 months). Moreover, patients who underwent sublobar resections without radiotherapy also demonstrated superior survival than patients receiving radiotherapy alone. The 2-, 3-, and 5-year actuarial OS with sublobar resection without radiotherapy was 62.5%, 41.7%, and 28.5%, respectively, compared with 39.6%, 28.3%, and 17.2%, respectively, with radiotherapy alone.

Despite the recommendation for consideration of surgery in early stage or limited disease in NCCN and other guidelines, and the evidence supporting improvements in clinical outcomes with surgical resection, surgery is underused.[14,15] One recent retrospective cohort analysis of patients with early-stage (LS) SCLC identified from the National Cancer Database (NCDB), 2004 to 2013, found that surgery is rarely used in the United States in treatment of potentially eligible SCLC patients.[11] The study population consisted of patients diagnosed with clinical stages I to IIIA, with pathologically-confirmed invasive SCLC. Similarly, a recent retrospective analysis of SEER data (between 2007 to 2013) reported that fewer than one-third of all patients with stage I SCLC underwent surgical resection.[14]

Best Practice

Clinicians need to be aware of the significance of surgery in treatment of SCLC, especially in patients with early stage (stage I or LS) SCLC.

Learning Objective

Describe the patient population for whom surgery is recommended in SCLC and the impact of surgery on clinical outcomes.

Gap #2: Clinicians may not be aware of recent advances in genomic sequencing and molecular profiling of SCLC

Current practice

The aggressive course of SCLC and the low likelihood of surgery (<1%) in management of SCLC has resulted in a paucity of tumor tissues available for conducting translational SCLC research.[16] Moreover, repeat biopsies of recurrent SCLC tumors are uncommon, further limiting the use of such tissues in examining mechanisms of resistance.

Genomic analysis has helped identify molecular targets for therapy in other lung cancers, including squamous cell carcinoma, a histological subtype of NSCLC strongly associated with tobacco-driven carcinogenesis.[17-19] Researchers have used preclinical models of SCLC, such as patient-derived xenografts, cell lines, and mouse models, in lieu of recently-biopsied or surgically-resected SCLC tumor specimens.[16] Recent studies have utilized integrative genome/exome analysis methods to identify potential biomarkers of clinical interest in patients with SCLC.

Best Practice

A recent integrative analysis of exomes, genomes and transcriptomes using SCLC tumor specimens was enabled by the establishment of a global lung cancer genome research consortium that provided access to 6600 surgically-resected lung cancer specimens.[20] The analysis identified inactivating mutations in *TP53* and *RB1*, as well as recurrent mutations in genes with a function in chromatin modification, including *CREBBP*, *EP300*, and *MLL*. The authors posited that the focal amplifications in *FGFR* and mutations in *PTEN* identified in their integrative genome analysis provide potential molecular targets for therapy in SCLC. They also identified histone-modifying enzymes, the second most frequently mutated class of genes based on function, as additional tractable targets of therapy in SCLC.

Another study established a prospective clinicopathological database of SCLC patients treated at one center and performed targeted- and whole-exome sequencing on tumor tissues from patients with predominantly ES-SCLC.[21] The authors analyzed the correlation between the genomic mutation spectrum and clinical outcomes. In addition to confirming that *TP53* and *RB1* were the most frequently mutated genes in SCLC, they also found frequent mutations in epigenetic regulators (*CREBBP* and *EP300*), as well as *FGFR* amplifications. Furthermore, a subgroup of patients lacking mutations in *RB1* gene had a poor response to chemotherapy, a finding that may be of immediate clinical significance.

In a prospective pilot study of 12 evaluable patients with advanced SCLC, the researchers used comprehensive genomic profiling using next-generation sequencing (NGS) to

identify therapeutically actionable targets.[22] Two or more clinically actionable targets were identified in each patient, and 6 patients received treatment identified by NGS. Partial responses were seen in 2 patients who received a combination of pembrolizumab, an inhibitor of the cell surface receptor programmed death-1 (PD-1; indicated by *PMS2* mutation) and irinotecan (indicated by *MLH*1 alteration). Clinical deterioration occurred in the remaining patients before the NGS-recommended therapy could be initiated.

The identification of potential oncogenic drivers may help improve treatment outcomes in SCLC patients, by identifying biomarker signatures for targeted molecular therapy, akin to those identified for NSCLC. As a proof-of-principle, pembrolizumab and irinotecan provided partial responses in two patients with advanced SCLC in the pilot study discussed above.[22] Multi-target tyrosine kinase inhibitors (TKIs) capable of targeting *FGFR* mutations and amplifications in various cancers are also being investigated, including a phase 2 clinical trial of nintedanib in lung cancer.[23] These recent studies highlight the potential for including currently available or new targeted therapies in SCLC treatment based on the altered genetic profile in individual patients.

Learning Objective

Summarize recent genome/exome studies in SCLC and their therapeutic implications.

Gap #3: Clinicians who manage patients with SCLC may not be aware of the emerging therapies targeting SCLC

Current practice

SCLC has been labeled as a recalcitrant cancer and is frequently identified as being understudied, underfunded, and without therapeutic advances over the past few decades. Over 60 agents have been evaluated in SCLC, including VEGFR, mTOR, EGFR, and IGFR inhibitors, none of which have provided improvements in outcomes.[24,25]

However, recent studies have identified additional targets for therapy in SCLC, as evidenced by ongoing/completed clinical studies addressing the utility of immunotherapies, antibody-drug conjugates, and other molecular-targeted agents.

Best Practice

Immunotherapy

Two recent clinical studies have addressed the utility of immune-modulatory therapy with an antibody against programmed death ligand-1 (PD-L1), alone or in combination with an antibody targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA4).[26,27]

The first trial, denoted the CheckMate032 study, was an open-label randomized phase 1/2 trial of nivolumab, another anti-PD-L1 antibody, with or without the CTLA4-

targeting antibody ipilimumab in patients with advanced SCLC whose disease had progressed with prior platinum-based therapies.[26] Objective response rates of 11% for nivolumab (13% and 8% in platinum-sensitive and -resistant disease, respectively) and 25% for the combination of nivolumab and ipilimumab (25% and 24% in platinum-sensitive and -resistant disease, respectively) were noted. Although the median OS was 4.1 months for nivolumab and 7.9 months for the combination, there was risk of toxicity. Any grade treatment-related adverse events were noted in a significant proportion of the patients (60% for nivolumab alone and 82% for the combination).

The second trial, the KEYNOTE-028 study, was an open-label phase 1b study of the PD-L1 monoclonal antibody pembrolizumab in patients with pre-treated ES-SCLC.[27] All patients in this study had received prior platinum plus etoposide as first-line treatment, and 11 of the 24 patients had been treated with either topotecan or irinotecan as second-line treatment. Although an objective response rate of 33% was noted by the authors, adverse events were noted in the entire cohort of 24 patients, including one patient with Grade 5 colitis as well as asthenia and intestinal ischemia and another with seriously elevated bilirubin levels.

Additional data from phase 2/3 trials of PD-L1 inhibitors and a protocol for including PD-L1 expression analysis is needed to address the utility of pembrolizumab and other PD-L1 antibodies in SCLC.

Epigenetic modifier-targeted therapies in SCLC

Epigenetic dysregulation has been identified as a driver of carcinogenesis in many cancers. Frequent mutations in histone-modifying enzyme-encoding genes, including *CRBPP*, *EP300*, and *MLL*, have been identified in genome/exome sequencing studies.[20,21] The results from a phase 1 trial of belinostat, a histone deacetylase inhibitor, in advanced solid tumors, including SCLC, were recently reported.[28] The authors concluded that the combination treatment of belinostat plus cisplatin and etoposide was safe and effective in SCLC and in other neuroendocrine tumors. The maximum tolerated dose was noted as belinostat (500 mg/m/24 h), cisplatin (60 mg/m), and etoposide (80 mg/m). The authors noted the need for additional phase 2 studies for identifying patients at high risk for adverse events.

Preclinical studies have shown that histone deacetylase inhibitors, such as vorinostat, may enhance anti-cancer effects of other agents in SCLC.[29,30] In addition, a proliferation screen using various cancer cell lines helped identify the sensitivity of SCLC cell lines to a lysine demethylase 1 (LSD1) inhibitor.[31] However, a trial of LSD1 inhibitor in SCLC (NCT02034123) and two phase 1/2 clinical trials of vorinostat in SCLC (NCT00702962 and NCT00697476) have been terminated. It remains to be seen whether these histone-modifying enzymes are actionable molecular targets in SCLC.

RRx-001

RRx-001, a dinitroazetidine derivative, mediates anticancer immunomodulatory effects. RRx-001 can directly promote repolarization of tumor-associated macrophages (TAMs) or indirectly promote immunomodulation through vascular normalization and increased T-lymphocyte infiltration.[32,33] Moreover, RRX-001 promotes upregulation of oxidative stress, anti-angiogenesis, as well as epigenetic modulation by reactivation of viral genes to provoke an immune response. Based on these effects, RRx-001 is being studied as a radio- and chemo-sensitizer in various cancers.

In an ongoing phase 2 study, denoted the QUADRUPLE THREAT (NCT02489903), RRx-001 is to be utilized as a single agent until RECIST version 1.1-defined progression, at which point first-line platinum doublets are sequentially reintroduced in third-line or in resistant/refractory SCLC and in three other cancer types. In over 50% of evaluable patients, RRx-001 has thus far shown reversal of resistance to the reintroduced first-line platinum-based agents.[25]

The data with RRx-001 in SCLC are encouraging, especially considering the low likelihood of adverse events with RRx-001 in many cancers, and potential protective effects of RRx-001 again cisplatin-mediated bone marrow and renal toxicities.[25,34]

Antibody-drug conjugates

Antibody-drug conjugates are comprised of an antibody targeting a defined antigen on cancer cells, a linker, and a cytotoxic drug. Two such conjugates have been considered in SCLC.

Rovalpituzumab tesirine (Rova-T) is an antibody-drug conjugate that is directed at delta-like protein 3 (DLL3), which is expressed on the surface of SCLC cells (one study found that 83%of Japanese SCLC patients were DLL3-positive[35]), but not healthy cells. Although a modest improvement in OS (from a historic average of 4.7 months for third-line SCLC to 5.8 months with Rova-T) was observed in one study, significant toxicity (≥grade 3 in 29%of patients treated with Rova-T) is a concern.[36] Currently, 3 clinical studies of Rova-T are ongoing (NCT03086239, a phase 1 study in Japan; NCT03061812, a phase 3 randomized trial in advanced/metastatic SCLC; and NCT03033511, as phase 3 randomized multinational study of Rova-T as maintenance therapy following first-line platinum-based therapy).

Another conjugate that is under investigation is sacituzumab govitecan, a conjugate of an antibody to the cell-surface glycoprotein Trop-1 and SN-38. Trop-1 is highly expressed in many cancers, including SCLC, and SN-38 is an FDA-approved active metabolite of irinotecan. In a phase 2 trial of 49 patients with recurrent metastatic SCLC, both platinum-

sensitive and -resistant, and a median of two prior therapies, an overall response rate of 14% and a median OS of 7.5 months were reported.[37] Neutropenia (34%), fatigue (13%) and diarrhea (9%) were the main toxicities (grade 3 or 4) observed. Sacituzumab govitecan has received the FDA Fast Track Designation in SCLC for expedited review.

Other targets

SCLC cells overexpress poly ADP ribose polymerase (PARP). Veliparib, a PARP inhibitor, in combination with a DNA-alkylating agent, temozolomide, was compared with temozolomide alone, in a recent phase 3 trial of patients with relapsed SCLC.[38] A significantly higher response rate was seen in patients treated with veliparib and temozolomide, compared to those treated with temozolomide alone (39% vs 14%). However, median OS remained comparable, and grade 3/4 thrombocytopenia (50% vs 9%) and neutropenia (31% vs. 7%) occurred with higher frequency with the combination treatment than with temozolomide alone.

A phase 1/2 trial of veliparib in combination with topotecan in sensitive or refractory SCLC is currently ongoing (NCT03227016). Ongoing phase 1/2 studies are also evaluating olaparib, another PARP inhibitor, in combination with CRLX101, a nanoparticle-drug conjugate containing camptothecin, in relapsed/refractory SCLC (NCT02769962), or in combination with cediranib maleate and standard chemotherapy in SCLC (NCT02899728).

A phase 3 study (ATLANTIS; NCT02566993) is comparing a combination of doxorubicin and lurbinectedin, a RNA II polymerase inhibitor that is structurally-related to trabectedin, to topotecan, or to the combination of cyclophosphamide, doxorubicin, and vincristine (VCR) in second-line therapy of SCLC patients after failure of first-line platinum-based therapy. Although the results of this study are not yet available, a phase I dose escalation study with lurbinectedin and doxorubicin as second-line treatment in SCLC reported a confirmed response rate of 67%, with grade 4 neutropenia, thrombocytopenia, or anemia in 86%, 19%, and 5%, respectively, and febrile neutropenia (grade 3/4) in 29% of patients.[39] Given the toxicity, prophylactic G-CSF support for managing chemotherapy-induced febrile neutropenia is implicated in phase 3 trials that include lurbinectedin in SCLC.

Learning Objective

Identify emerging targeted therapies in SCLC.

Faculty List

Agenda

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