LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

Section Editor: Edward S. Kim, MD, MBA

The Next Targets for Small Cell Lung Cancer

Ravi Salgia, MD, PhD
Professor and Chair
Department of Medical Oncology & Therapeutics Research
City of Hope Comprehensive Cancer Center
Duarte, California

H&O What are the goals of treatment in small cell lung cancer (SCLC)?

RS Our ultimate goal is cure, but we know that SCLC is a difficult disease to treat. In the more than 30 years that I have been in practice, we have not made as many advances in SCLC, which accounts for 15% of cases of lung cancer, as we have in non-SCLC, which accounts for the other 85%. If we can detect SCLC at an early stage, which rarely happens, we try to cure the disease with chemotherapy and radiation therapy. If the disease is advanced, however, it becomes very hard to cure.

H&O What are the limitations of the existing agents and regimens for SCLC?

RS We have not been able to break the code in terms of getting a better survival. We can get a good response to treatment in early disease, when it is sensitive to treatment. Limited disease can be successfully treated with moderately intensive chemotherapy consisting of 4 to 6 cycles of etoposide plus cisplatin and radiotherapy. This treatment has been shown to produce a response in 65% to 90% of patients with limited disease, although the 5-year survival rate is only 21%. Extensive disease is treated with 4 to 6 cycles of combination chemotherapy; radiotherapy to the chest or brain is sometimes used as well. Combination chemotherapy has been shown to produce response rates of 70% to 85% in patients with extensive disease, but the 5-year survival rate is only 3%. The problem is that SCLC soon becomes resistant to current treatment approaches, and most patients relapse within 1 year. The prognosis is very poor for patients with relapsed SCLC, whose expected survival is only 4 to 6 months. We need to acquire a better understanding of what drives this resistance and learn how to get rid of treatment-resistant tumor cells. Are stem cells persisting that we are unable to kill? What is happening in terms of tumor heterogeneity and molecular evolution? When we better understand the mechanisms of resistance, we will be able to develop better treatments for both early- and late-stage disease.

H&O What new approaches are being investigated?

RS A lot of new approaches are being investigated, including new chemotherapy agents, immunotherapy, and targeted therapy. New data have suggested that SCLC is associated with certain germline alterations, so targeting these alterations with drugs may help us treat patients with SCLC. Targets of interest include programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), CD80, BCL2, protein phosphatase 2 (PP2A), poly(ADP-ribose) polymerase (PARP), ATR, CHK1, CDC25A, CDK2, and WEE1.

Many trials are ongoing. Regarding chemotherapy, phase 3 trials are looking at amrubicin, and phase 2 trials are looking at the use of nab-paclitaxel (Abraxane, Bristol Myers Squibb), nanoliposomal irinotecan (nal-IRI; Onivyde, Ipsen), belotecan, and temozolomide.

The US Food and Drug Administration has approved the use of several immunotherapy agents in extensive-disease SCLC. Nivolumab (Opdivo, Bristol Myers Squibb)

received approval in 2018 as third-line treatment, although the company withdrew the indication in 2020. Similarly, pembrolizumab (Keytruda, Merck) received approval in 2019 as third-line treatment, but the company withdrew this indication in 2021. Atezolizumab (Tecentriq, Genentech) in combination with chemotherapy received approval in 2019 as first-line treatment, durvalumab (Imfinzi, AstraZeneca) in combination with chemotherapy received approval in 2020 as first-line treatment, and lurbinectidin (Zepzelca, Jazz/PharmaMar) received approval in 2020 as second-line treatment. Pembrolizumab also received approval in 2020 as second-line treatment for SCLC with a high tumor mutation burden.

Ongoing phase 2 and 3 trials are looking at the addition of agents such as atezolizumab (NCT04028050, NCT03811002), durvalumab (NCT04449861), nivolumab (NCT03382561), the anti–PD-L1 antibody SHR-1316 (NCT03711305), and the anti–PD-1 antibody HLX10 (NCT04063163) to chemotherapy. The phase 3 SKYSCRAPER-02 trial is comparing the addition of the anti–TIGIT (anti–T-cell immunoreceptor with Ig and ITIM domains) antibody tiragolumab vs placebo to treatment with atezolizumab, carboplatin, and etoposide; this study has completed accrual (NCT04256421). Studies are also looking at atezolizumab alone or in combination with radiation therapy (NCT04402788) and atezolizumab alone vs observation (NCT03540420). In addition, studies are evaluating combinations of nivolumab plus ipilimumab (Yervoy, Bristol Myers Squibb; NCT02046733) and durvalumab (Imfinzi, AstraZeneca) plus the anti–CTLA-4 antibody tremelimumab (NCT03703297).

Targeted therapy is another promising area of research. A phase 3 trial is looking at lurbinectedin, which targets CG-rich promoter sequences. Phase 2 trials are looking at navitoclax, which targets BCL2; BMS-986012, which targets FucGM1; vistusertib, which targets mammalian target of rapamycin complex 1 and 2 (mTORC1/2); and olaparib (Lynparza, AstraZeneca), talazoparib (Talzenna, Pfizer), veliparib, rucaparib (Rubraca, Clovis Oncology), and niraparib (Zejula, GSK/Tesaro), all of which target PARP. Here at City of Hope, we are conducting a phase 1 trial of LB-100, which is an inhibitor of the enzyme PP2A, in combination with chemotherapy and immunotherapy in extensive-stage SCLC (NCT04560972). Preclinical studies in our laboratory showed promising results with LB-100 alone and in combination with carboplatin or etoposide and immunotherapy. Other phase 1 trials are looking at DLL3-targeting agents such as the bispecific antibody AMG 757 (NCT03319940) and the chimeric antigen receptor T-cell therapy AMG 119 (NCT03392064) against DLL3. Dr Taofeek Owonikoko presented encouraging early data on AMG 757 at the American Society of Clinical Oncology 2021 Annual Meeting.

Research on rovalpituzumab tesirine (Rova-T), the antibody-drug conjugate against DLL3, has been discontinued because the agent has been shown to be ineffective in SCLC.

We need to be able to attack the small cells in every venue possible. We are not quite sure which approach will crack the code, but it is time for us to revolutionize our thinking and go beyond the standard of care. We need to have good therapeutic strategies, and we need to define biomarkers that will tell us in advance whether a patient's disease will respond to a particular therapy.

H&O What other questions would you like to see researchers address?

RS SCLC should be one of our highest priorities, because decades and decades of research have not improved survival in a very significant way. Even though we can often cure early-stage disease, most of the time SCLC is caught at a late stage. We need much better options for these patients. It is very important that we invest more in lung cancer research, and that we seek out clinical trials for our patients.

Disclosure

Dr Salgia has served as a consultant to Iovance Biotherapeutics, AbbVie, and Novartis; a consultant and speaker for AstraZeneca and Janssen; and on the ad board of Sanofi.

Suggested Readings

Cortinovis D, Bidoli P, Canova S, et al. Novel cytotoxic chemotherapies in small cell lung carcinoma. *Cancers (Basel)*. 2021;13(5):1152.

Esposito G, Palumbo G, Carillio G, et al. Immunotherapy in small cell lung cancer. *Cancers (Basel)*. 2020;12(9):2522.

Mirzapoiazova T, Xiao G, Mambetsariev B, et al. Protein phosphatase 2A as a therapeutic target in small cell lung cancer. *Mol Cancer Ther*. 2021;20(10):1820-1835.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Small Cell Lung Cancer. v.2.2022. https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf. Updated November 24, 2021. Accessed December 7, 2021.

Owonikoko TK, Champiat S, Johnson ML, et al. Updated results from a phase 1 study of AMG 757, a half-life extended bispecific T-cell engager (BiTE) immuno-oncology therapy against delta-like ligand 3 (DLL3), in small cell lung cancer (SCLC) [ASCO abstract 8510]. *J Clin Oncol*. 2021;39(15)(suppl).

Poirier JT, George J, Owonikoko TK, et al. New Approaches to SCLC therapy: from the laboratory to the clinic. *J Thorac Oncol*. 2020;15(4):520-540.

Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7-33.