LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Updates in Small Cell Lung Cancer

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H&O How common is small cell lung cancer (SCLC), and who is at risk?

JS Lung cancer is the second most common cancer type in men and women, with an estimated 238,340 adults in the United States expected to be diagnosed with lung cancer in 2023. SCLC accounts for approximately 13% of all lung cancers.

Nearly everyone who receives a diagnosis of SCLC has a significant smoking history and probably qualifies for lung cancer screening with low-dose computed tomography (CT). The technique is far from perfect, and SCLC can grow so rapidly that it goes from being undetectable one year to widespread the next. However, screening is still very important for early detection of lung cancer. Screening is considered the most effective intervention for the reduction of lung cancer mortality.

H&O Could you describe treatment of limited-stage disease?

JS Patients with limited-stage disease are treated with surgery and chemotherapy; chemotherapy and radiation therapy; or surgery, chemotherapy, and radiation therapy. The goal is to cure the patients of the cancer. It is important to monitor patients after treatment because recurrence is common. Fortunately, many patients are effectively cured.

Surgery is generally performed in patients with limited-stage disease who have a single nodule in the lung and no evidence of disease spread. Regardless of the size or extent of disease, all patients with SCLC receive chemotherapy after surgery in case the nodule has shed cancerous cells into the rest of the body. Surgery is sometimes performed in patients who have limited-stage disease with lymph node involvement, but the more common approach for patients with a greater degree of disease spread is to administer chemotherapy and radiation therapy.

Although patients with limited-stage disease do not have any evidence of cancer in the brain based on magnetic resonance imaging (MRI), microscopic disease may be present in the central nervous system. As a result, researchers have been investigating whether prophylactic cranial irradiation (PCI) can lead to improved survival. Historical studies have shown improved survival with PCI, but they were conducted before MRI was used to detect disease spread to the brain. Now that MRI has become standard testing to determine which patients have brain metastases, the possibility has been raised that earlier studies showed improvement with PCI because they were treating disease that had not been detected because MRI had not been performed. The ongoing phase 3 MAVERICK trial, which is sponsored by the SWOG Cancer Research Network, is examining the question of whether the addition of PCI affects survival in patients with non–small cell lung cancer (NSCLC) who receive MRI surveillance (NCT04155034). A 2017 study from Japan in patients with extensive-stage disease showed that long-term outcomes were similar whether patients received MRI monitoring of the brain every few months

or PCI. The MAVERICK trial also includes individuals with extensive-stage disease.

H&O Could you describe treatment of extensive-stage disease?

JS Patients with extensive-stage disease, which has metastasized to distant parts of the body, typically receive systemic therapy with chemotherapy and immunotherapy. Chemotherapy consists of carboplatin or cisplatin plus etoposide. The US Food and Drug Administration (FDA) has approved the use of the immunotherapy agents durvalumab (Imfinzi, AstraZeneca) or atezolizumab (Tecentriq, Genentech) with chemotherapy in patients with extensive-stage SCLC. The introduction of immunotherapy in the treatment of patients with extensive-stage NSCLC has represented a revolutionary change over the last 5 years to the standard of care.

One option for patients who do not feel strongly about receiving prophylactic cranial irradiation is enrolling in the MAVERICK clinical trial.

Durvalumab and atezolizumab, which I consider to be essentially interchangeable, are an important part of initial treatment. These immunotherapies have been shown to control a subset of cancers for years, leading to improved overall survival. Serplulimab, a checkpoint inhibitor available in China, led to improved outcomes when given with chemotherapy as first-line treatment. Chen and colleagues presented these results at the 2022 American Society of Clinical Oncology annual meeting.

Another consideration in extensive-stage SCLC is whether to use PCI after chemotherapy and before immunotherapy maintenance. As I mentioned earlier, a study from Japan did not show a significant improvement with the addition of PCI to MRI monitoring, so this has become less common. It is still used, however, so the possibility is important to discuss with patients. One option for patients who do not feel strongly about receiving PCI is enrolling in the MAVERICK clinical trial.

Cure is not considered realistic for patients with extensive-stage SCLC, and most patients with extensive-stage disease will experience progression and need next-line treatments. Having said that, some of my patients with extensive-stage disease still have disease control after many years of treatment. Although we need another 10 years of data to have realistic statistics regarding the potential for actual cure of extensive-stage SCLC, I expect to see that some patients will never need another treatment. It is unfortunate that only a subset of patients has that kind of response, but immunotherapy works exceptionally well in a small number of cases. As a result, we need to focus on making it work in more people rather than making it work better.

H&O How can oncologists determine which patients will benefit from immunotherapy?

JS We do not have a perfect answer to that right now. Some studies have shown that response may be somewhat better in patients with high expression of programmed death ligand 1 (PD-L1), but some cancers with high PD-L1 expression do not respond well, whereas others with no PD-L1 expression do respond. There is simply no biomarker that is good enough to affect the way that we treat individuals.

That may change once we can identify specific subtypes of SCLC that respond differently to treatment. Research by Gay and colleagues suggests that the inflamed subtype of SCLC responds better than noninflamed lung cancer to immunotherapy, although not all SCLC responds to immunotherapy. We are working toward determining which patients with SCLC might benefit from the addition of agents that make cancer cells more susceptible to the immunotherapy.

H&O What is second-line treatment in extensive-stage disease?

JS Two agents have received FDA approval for use as second-line treatments in SCLC: topotecan and lurbinectedin (Zepzelca, Jazz/PharmaMar). Topotecan has been in use the longest and is still widely used, but it is quite toxic. I tend to use lurbinectedin, which is newer and less toxic. Tolerability is an especially big concern in the second-line setting because treatments are less likely to be as effective as in the first-line setting. Additional second-line options are irinotecan or paclitaxel, which do not have FDA approval for this use but are included in the National Comprehensive Cancer Network guidelines for SCLC.

H&O What other approaches to SCLC are being investigated?

JS One promising approach that is being studied is the

use of bispecific antibodies, which bind the cancer cells to immune cells. For example, the phase 2 DeLLphi-301 study is looking at the bispecific antibody tarlatamab in patients with relapsed or refractory SCLC after 2 or more prior lines of treatment (NCT05060016). Additionally, a phase 1/2 study is looking at the bispecific antibody HPN328 in advanced cancers that express DLL3, including SCLC (NCT04471727).

Another exciting approach that is being studied is the use of antibody-drug conjugates, which allow for targeted delivery of chemotherapy. For example, a phase 2 study is looking at the antibody-drug conjugate ifinatamab deruxtecan in patients with extensive-stage SCLC who received at least 1 prior line of platinum-based chemotherapy (NCT05280470).

Another approach that is still very early in SCLC is the use of chimeric antigen receptor (CAR) T-cell therapy, in which immune cells are removed and altered to identify cancer cells and attack them. CAR T-cell therapy has changed the landscape in the treatment of lymphoma and other blood cancers and is just now being looked at as a possible treatment for SCLC.

Now is an exciting time in the treatment of SCLC. A lot of promising treatments are available in clinical trials, and I expect to see some of these trials lead to advances in treatment.

Disclosures

Dr Sands has served as a consultant to or on the scientific advisory board of Arcus Biosciences, Amgen, AstraZeneca, Boehringer Ingelheim, Curadev Pharma, Daiichi Sankyo, Guardant Health, Janssen, Jazz Pharmaceuticals, Medtronic, PharmaMar, Sanofi, and Takeda.

Suggested Readings

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