

A Breath of Fresh Air for Advanced Lung Cancer

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Immunotherapy and stereotactic radiation are making a difference for some patients with advanced lung cancer.

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COURTESY OF JUANITA SEGURA

In June 2014, 46-year-old Juanita Segura couldn't stop wheezing. Within a few months, she developed a persistent cough and started on medications for asthma, though she doubted the diagnosis. In October, she landed in the emergency room with severe shortness of breath and was admitted for possible pneumonia. Again, she questioned the diagnosis, and an X-ray showed what looked like a flattened lung. It turned out that an enlarged lymph node, revealed during a bronchoscopy, was squeezing her lung and airway closed. This diagnosis shocked her: stage 3b ALK-positive adenocarcinoma non-small cell lung cancer (NSCLC). "I was a mother of five in the best shape of my life," she says. "I could do 95 overhead squats, 300 deadlifts and 250 back squats. I had just lost a lot of weight. And I don't even smoke." Between 85 and 90 percent of lung cancers are NSCLC, estimates the American Cancer Society. The remaining 10 to 15 percent are small cell lung cancer. Each year in the United States, more than 234,000 new lung cancer cases are diagnosed. Although Segura isn't a smoker, she's been around secondhand smoke her whole life. Nonsmokers have a 20 to 30 percent greater chance of developing lung cancer if exposed to secondhand smoke, according to the American Lung Association.

Treatment for stage 3 NSCLC hasn't changed much in the last 25 years – typically, chemotherapy and radiation therapy – but immunotherapy approved by the Food and Drug Administration (FDA) in early 2018 has slowed the disease's progression in some patients. Clinicians sometimes also add a more intense and short-term radiation therapy, and researchers continue to look for the best mix of treatments and scheduling.

A LONGTIME STANDARD APPROACH

A stage 3 diagnosis usually means the lung tumor has spread to the lymph nodes, often the mediastinal lymph nodes in the middle of the chest or the supraclavicular nodes at the base of the neck. To stage the cancer and evaluate the patient for treatment, doctors typically order imaging including a chest X-ray, a PET/CT full-body scan to detect cancer in the lungs and elsewhere, and an MRI to look for cancer that may have spread to the brain or spinal cord. Doctors may perform a bronchoscopy or other procedures to determine lymph node involvement. A pulmonary function test gauges lung capacity to see if the patient is a candidate for surgery and aids in radiation planning. Basic blood tests check red and white blood cell counts, and also see if someone's organs can handle the treatment.

Then the patient often sees a multidisciplinary care team, including a medical oncologist, a radiation oncologist and a thoracic surgeon, for a treatment plan. In addition to considering the NSCLC stage, doctors factor in the patient's age, overall health, severity of symptoms, lung capacity and treatment preferences. "I often describe stage 3 as one of the most challenging clinical scenarios because traditionally, there are a variety of opinions without clear data on the direction," says Edward Garon, M.D., an associate professor of hematology and oncology at the David Geffen School of Medicine at UCLA. "Often in our own tumor board, there's significant debate on the likely success from a surgical approach with a stage 3 NSCLC." Opinions and practices vary by the facility. Patients who get surgical resections usually receive chemotherapy or a combination of chemotherapy and radiation before surgery, he says.

However, most stage 3 NSCLCs are unresectable – they can't be surgically removed – due to extensive lymph node involvement or because the tumor location is not amenable to surgery at this spot, says John Heinzerling, M.D., a radiation oncologist at Southeast Radiation Oncology Group in Charlotte, North Carolina. For the past 15 to 20 years, treatment for these unresectable cancers has remained consistent: chemotherapy and radiation, usually at the same time. "Most of the research in the last 20 years has been what chemotherapy to use; whether to use chemotherapy at the same time as radiation; and whether to use it before or after and what radiation dose to use," he says. The current standard of care is to give a two-drug chemotherapy regimen concurrent with radiation. That includes six weeks of radiation, five days a week, and up to six cycles of chemotherapy.

Although chemotherapy is used, radiation is the most effective treatment for lung cancer, says Ronald McGarry, M.D., Ph.D., a clinical professor in the department of radiation medicine at the University of Kentucky in Lexington. "Chemotherapy has two roles in stage 3," he says. "It

makes the cancer cells more sensitive to the killing effect of radiation, and, in theory, it decreases the risk of metastatic disease.”

NEW ON THE BLOCK

Immunotherapy — the use of substances to stimulate the immune system to help the body fight cancer — is the latest option to be added to stage 3 NSCLC treatment.

The FDA approved Imfinzi (durvalumab) for stage 3 unresectable NSCLC in February. The agency based its decision on findings from the phase 3 PACIFIC trial, which showed that patients who received Imfinzi went almost a year longer without worsening disease compared with those who didn't get it (17.2 months versus 5.6 months, respectively). In September, newly published results showed a 24-month overall survival rate of 66.3 percent for those who received Imfinzi compared with 55.6 percent for those who did not.

“That’s the ultimate measure of benefit in oncology — do patients actually live longer?” says Julie Brahmer, M.D., co-director of the upper aerodigestive program at Johns Hopkins Medicine’s Bloomberg-Kimmel Institute for Cancer Immunotherapy in Baltimore. The study showed a significant prolonged overall survival.

Imfinzi blocks the PD-L1 pathway, which in turn stimulates the immune system to kill cancer cells. The drug is associated with a slight rise in toxicity and side effects, but it’s thought to be manageable. Imfinzi’s most common side effects involve the immune system attacking the body’s organs or healthy cells, and making a person more susceptible to infections. Because of the higher risk of complications, some patients with autoimmune disorders might not be offered Imfinzi. “Even that premise is being challenged now, in that there are some published reports indicating that patients with autoimmune diseases who have received it can be safely treated,” Garon says. “One place we’ve seen absolute contraindication is solid organ transplant.” That is due to a risk of organ rejection, he says, noting that clinicians are trying to define the risk factors.

Researchers are looking at different combinations of chemotherapy and radiation, along with adding immunotherapy at the same time as radiation, Brahmer says. Also, some studies are investigating whether Imfinzi treatment time can be shortened with the same benefit; others are looking at combinations of immunotherapies.

RADIATION WITH PRECISION

Stereotactic radiation has been given by radiation oncologists for stage 1 and 2 NSCLC for almost two decades, but now clinicians are testing the best sequence for treating stage 3 disease. Stereotactic radiation delivers a high dose of precisely targeted radiation to a smaller amount of tissue in fewer sessions than traditional radiation therapy. Heinzerling is conducting

a trial, radiating the primary tumor in patients with stage 3 NSCLC in three to five treatments before beginning traditional radiation therapy. “We think that it prompts the immune system more, creating massive death of tumor cells, and that attracts the immune cells to go after the cancer,” he says. He then gives Imfinzi after traditional chemotherapy and radiation therapy, per current standards. He’s investigating whether the four elements provide better control of the chest tumor. Although the study is small, he says that they are seeing some very good responses in addition to low incidences of lung-related and other side effects.

One of his patients, 68-year-old Virginia Huerter, participated in the trial. Her lung cancer was discovered as an incidental finding when she had a septic bowel in February — she had two spots on her left lung, close to her throat. She received five treatments of stereotactic radiation before her radiation and chemotherapy began. “They say if they didn’t do anything, I had six months to a year,” she says. “I was told if they did something, there was a 30 percent chance it would work.” Her most recent CT scan, in August, showed no evidence of cancer, and she was able to skip her last two rounds of chemotherapy. Although Huerter knows about Imfinzi, she was unable to get it because of an autoimmune disorder.

McGarry offers his patients a so-called stereotactic boost after the chemotherapy and radiation are complete. “There’s up to (a) 30 to 40 percent chance the cancer will return in the chest,” he says. “The bigger the mass, the more likely it is to recur.” He gives the patients a little time off after chemotherapy and traditional radiation, then repeats a CT scan. If there’s residual disease, he gives stereotactic radiation treatments over three days and says that outcomes are much better for patients with stage 3a NSCLC. Although a stereotactic boost is not commonly offered, he says, he’s been doing it for 18 years, and insurance pays for it.

TREATMENT TOXICITY

Experts agree that most patients can tolerate receiving chemotherapy and radiation during the same time, but this type of regimen does increase toxicity. The main pulmonary side effects are coughing, shortness of breath and lung scarring. Patients can also develop sore throats, fatigue and an irritated esophagus from the radiation. Chemotherapy raises the risk of infection and anemia, plus nausea. Both medical and radiation oncologists follow up with patients every week or two during treatment to check on side effects and blood counts. “Sometimes we end treatment early or modify it, but that’s pretty uncommon. Most can make it through the regimen,” Heinzerling says. That’s because the treatment is designed for each patient.

Some facilities offer integrative oncology, which combines complementary therapies such as acupuncture, guided imagery, massage and yoga — mainly for side effect management and stress relief — with medical treatment. Heinzerling says that at his facility, a staff member sees patients on an ongoing basis or recommends supplements or other therapies to try before or during treatment. Tips may include simple strategies, such as taking honey to ease pain when swallowing and esophageal irritation from radiation. To combat patients’ fatigue, the integrative staff may advise on dietary changes and ways to keep up with activities.



Diane Spry PHOTO: JILLIAN HOFFMAN

When 30-year-old Diane Spry got chemotherapy for her stage 3 lung cancer, she also received acupuncture to combat side effects, such as anxiety. “I was apprehensive about them sticking needles in me,” she says, but the thin needles inserted into her forehead, arms and legs ultimately helped. Spry also got magnets placed in her ears to help with nausea and vomiting. “Whenever I felt nauseous, I was to pinch my ears,” she says.

FOLLOW-UP CARE

When stage 3 treatment is completed, patients are typically monitored for cancer and side effects for at least five years. “There’s no standard way to follow up and timing of scans is a clinical decision,” Brahmer says, although experts mentioned interim visits with the medical and radiation oncologists, including repeat chest CT scans every three to six months for three years followed by chest CT scans every six months for an additional two years. The scans then change to every year with low dose non-contrast enhanced chest CT scans.

“They’re typically done with every six-month scans at five years,” Brahmer says. Patients are at risk not only of recurrence or spread of the original cancer but also the development of a new lung cancer.

Some clinics offer survivorship visits to discuss quality of life and potential long-term side effects of therapy that could occur in the next five to 10 years. “That way, if they have symptoms, (patients) will bring them to a doctor’s attention, as opposed to ignoring (them) or not telling the oncologist because they are aware that it may be related to their treatment,” Heinzerling says.

For example, three to 12 months after completing radiation, patients can get a pneumonia-like reaction called pneumonitis, which can affect the ability to be active and exercise but is reversible if treated properly with steroids. However, some clinicians confuse the diagnosis with bacterial pneumonia, for which antibiotics are prescribed. Other therapy-related side

effects that may arise later include hormonal deficiencies from immunotherapy's effects on endocrine glands like the thyroid or adrenals, or neuropathy from taxane- or platinum-based chemotherapy.

Metastases pose the biggest challenge in treating stage 3 patients, according to McGarry. "Ultimately, we can get good local control in the chest, and still the median survival is 24 months," he says. "Most die of local failure or metastatic disease," which is why he gives stereotactic radiation.

Both Segura and Spry's lung cancers spread not long after their initial regimen. Segura was treated for stage 4 cancer, but in December 2015 doctors found no evidence of disease, and she takes maintenance chemotherapy daily. "They call me the walking miracle," Segura says. She opened her own CrossFit studio in September 2016 and challenges her clients to exercise to their fullest, just as she does.

Spry's cancer also changed to stage 4 after maintenance chemotherapy. Doctors found cancer cells in the fluid around her heart, plus a related blood clot on her heart valve. She takes medications to treat it. "I'm pretty healthy right now," she says. "I don't get winded very easily. I can still walk around." In the five years since her diagnosis, Spry has gotten married and travels to places like California and the Bahamas. She is now looking for a full-time job. "I'm living my life," she says.

She's learned to be her own advocate by bringing up questions and concerns to her care team. "Sometimes I feel stupid asking questions, but I have to remember I'm paying them to help me," Spry says.

Patients with stage 4 disease have new hope in three FDA approvals. In October, Keytruda (pembrolizumab), an immunotherapy, was approved in combination with carboplatin and either paclitaxel or nab-paclitaxel for first-line treatment of patients with stage 4 squamous NSCLC. The regimen prolonged median overall survival by 4.6 months, compared with placebo, and reduced the risk of disease progression or death by 44 percent.

Two more medications were approved for people who have specific mutations: Lorbrina (lorlatinib) for the treatment of patients with ALK-positive, stage 4 NSCLC who progressed on one or more ALK tyrosine kinase inhibitor, and Vizimpro (dacomitinib) as a frontline treatment of patients with stage 4 NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations.

Although there haven't been many changes in treatment during the last 25 years, clinicians are excited to see some positive momentum with immunotherapy. "For the first time, we're seeing changes in treatment that are significant, and so the hope is that treatments continue to evolve at a more rapid pace and make it easier for patients to get their cancer under control — to tolerate the treatment and make a significant impact on this, even though it's advanced stage disease," Brahmer says.

