Timing Matters When Adding Immunotherapy to Chemoradiation for Patients With Small-Cell Lung Cancer

The activity of immunotherapy is reduced when given simultaneously, likely due to the inherent immunosuppressive effects of radiation.

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People with limited-stage small cell lung cancer may benefit from adding immunotherapy to chemoradiation, but not if both treatments are given at the same time, new research finds. The results suggest that the timing of when immunotherapy is given plays a key role in its ability to extend survival.

Findings of the multi-institutional Phase III trial, which also found that twice-daily radiation treatments offer greater survival benefits than once-daily treatment, were presented at the American Society for Radiation Oncology (ASTRO) Annual Meeting.

The research comes on the heels of a recent study showing immunotherapy given after radiation and chemotherapy are completed can increase overall survival for people with limited-stage small cell lung cancer. Researchers in this new study, the NRG Oncology/Alliance LU005 trial, wanted to test whether there would be a similar benefit when delivering the treatments at the same time.

“The introduction of immunotherapy marked the first significant breakthrough in treating small cell lung cancer treatment in decades. Now, we see that if you give immunotherapy concurrently with chemoradiation, it does not yield the same survival benefit as it does when we add it after standard treatment,” said Kristin Higgins, MD, the principal investigator of the trial and a radiation oncologist, professor and chief clinical officer at City of Hope Cancer Center in Atlanta.

“This seemingly small difference in the timing of when the drug is delivered has a very significant impact on the results. At the same time, we found that changing the way you deliver radiation — giving it twice daily — improved survival rates compared to the once daily approach.”

Lung cancer is the leading cause of cancer deaths for both women and men in the U.S. Small cell lung cancer, an especially aggressive form of the disease, accounts for 10% to 15% of all lung cancers. Standard treatment for patients with limited-stage disease, which has not spread outside the chest and is potentially curable, includes concurrent radiation therapy and chemotherapy.

While treatments can be effective initially — the five-year overall survival rate is 30% — the cancer often recurs, and options for additional treatment have historically been limited.

Earlier this year, the landmark phase III ADRIATIC trial found adding a similar immunotherapy agent (durvalumab [Imfinzi]) six weeks after completion of chemoradiation reduced patients' risk of death by 27%. ADRIATIC and similar trials showing a survival benefit from this new class of drugs were "the first therapeutic improvements for this 'forgotten cancer' in decades," Dr. Higgins said. NRG Oncology/LU005 adds to this progress by shedding light on the importance of when treatment is delivered.

For the study, Dr. Higgins and her colleagues randomized 544 patients at centers across the U.S. (n=500) and Japan (n=44) to receive standard chemoradiation with or without atezolizumab [Tecentriq] immunotherapy. All patients received radiation therapy either twice daily to a total dose of 45 Gy (47.2% of participants) or once daily to a dose of 66 Gy, as well as four cycles of concurrent chemotherapy. For patients on the experimental arm, atezolizumab was also given every three weeks beginning at the start of radiation, for a maximum of one year. Prophylactic cranial irradiation was prescribed at the discretion of the investigator for patients with a complete or near-complete response to chemoradiation. Median follow-up for this second planned interim analysis was 21 months.

Contrary to expectations, concurrent treatment with atezolizumab and chemoradiation did not improve survival rates compared to standard care. After one year, overall survival for patients receiving chemoradiation alone was 82.6%, compared to 80.2% with concurrent chemoradiation and atezolizumab. At two years post-treatment, the rates were 62.9% and 58.6%, respectively, and after three years, 50.3% and 44.7%. Median overall survival for patients on the standard treatment arm was 39.5 months, compared to 33.1 months for those who also received immunotherapy (HR=1.1, 95% CI: 11.3-18.2).

The lack of survival benefit when giving immunotherapy together with chemoradiation, rather than after radiation is completed, indicates that the activity of this type of immunotherapy is reduced when given simultaneously with thoracic radiation, likely due to the inherent immunosuppressive effects of radiation, Dr. Higgins said.

"We know that radiation suppresses the immune system to a certain degree in the immediate sense, and immunotherapy relies on the immune system to be effective," she explained. "Adding these drugs after you give radiation can make the immunotherapy more potent, but you have to allow the immune system time to recover to really see the two work well together."

Adding concurrent immunotherapy to chemoradiation also did not improve progression free survival (median 11.5 months with atezolizumab vs. 12.0 months without) or distant metastasis free survival (13.2 vs. 16.8 months, respectively).

"Sometimes, if you give too much therapy at the same time, it actually yields worse outcomes," Dr. Higgins said. "And this trial demonstrated that. But at the same time, we did see that changing the way you give radiation can help."

There was a benefit to giving radiation twice daily over giving it once daily, regardless of study arm. In both groups, patients treated twice daily lived longer on average; median overall survival for those treated twice daily was 35.4 months, compared to 28.3 months for people treated once per day (HR=1.44, 95% CI: 1.10-1.89).

Most radiation oncologists in the U.S. favor the once-daily approach because it presents fewer logistical challenges for treatment delivery, Dr. Higgins said, but these data suggest a potential need to re-evaluate current practice patterns.

“While this wasn’t the primary endpoint of the study, we see clearly that patients receiving radiation for small cell lung cancer do better when you treat them twice daily,” she explained. “Many doctors and patients may find twice daily radiation more cumbersome, but these data show giving radiation in a more compact way is beneficial for survival.”

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