LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Radiation Therapy and Immunotherapy in Locally Advanced NSCLC

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H&O What is standard treatment in locally advanced non–small cell lung cancer (NSCLC)?

PL Standard treatment in locally advanced NSCLC used to be 6 weeks of concurrent chemotherapy and radiation therapy. The landmark phase 3 PACIFIC study, however, established the use of the anti–programmed death ligand 1 (anti–PD-L1) agent durvalumab (Imfinzi, AstraZeneca) for up to 1 year after standard chemoradiotherapy as consolidation therapy. PACIFIC was a phase 3 trial of 713 patients with nonresectable stage III NSCLC. The participants were randomly assigned to durvalumab or placebo in a 2:1 ratio following chemoradiotherapy; results were first published by Antonia and colleagues in the *New England Journal of Medicine* in 2017. In the most recent results, published in 2022 by Spigel and colleagues in the *Journal of Clinical Oncology*, the estimated 5-year overall survival was 43% for durvalumab vs 33% for placebo. As a result, standard treatment is now chemoradiation followed by durvalumab.

The radiation dose remains 60 Gy on the basis of results of the landmark phase 3 RTOG 0617 study from the Radiation Therapy Oncology Group, published by Bradley and colleagues in 2015. This study found that survival was worse with high-dose radiation of 74 Gy than with standard-dose radiation of 60 Gy. The reason why outcome was worse with higher-dose radiation is currently unknown, but some have postulated that higher radiation doses may damage lung and heart tissue, abrogating the benefits of the higher doses. Radiation oncologists are taking steps to reduce the amount of radiation to the heart and lungs, such as with proton therapy or magnetic resonance imaging–guided radiotherapy, to mitigate long-term complications of therapy and improve patients' quality of life. This is particularly relevant because our patients with stage III NSCLC are living much longer than before.

The publication of PACIFIC led to some ongoing discussions about what to do for patients with resectable or borderline-resectable stage III disease. A preplanned primary outcome analysis of the phase 3 IMpower010 trial found that the addition of 1 year of atezolizumab (Tecentriq, Genentech) after completion of cisplatin-based chemotherapy significantly improved disease-free survival in patients with resected stage II-IIIA NSCLC. This study provided direction for the management of patients with resectable disease, although overall survival results have not yet been presented. Also, the addition of nivolumab (Opdivo, Bristol Myers Squibb) to chemotherapy in a neoadjuvant fashion before surgery was recently approved by the US Food and Drug Administration after the positive CheckMate 816 study showed an impressive pathologic complete response score with the addition of nivolumab in this neoadjuvant approach. Therefore, what is currently unclear is the best treatment option for patients with borderline-resectable disease. Should these patients get chemoradiation and immunotherapy, or surgery and immunotherapy?

H&O How much does the prior use of radiation therapy improve the effectiveness of immunotherapy?

PL This is an area of intense research by many groups. The randomized phase 1 KEYNOTE-001 study looked at the anti–programmed death 1 (anti–PD-1) agent pembrolizumab (Keytruda, Merck), which was the first checkpoint inhibitor to be approved for the first-line treatment of NSCLC. The trial showed that the use of pembrolizumab rather than chemotherapy as frontline therapy for patients with locally advanced or metastatic lung cancer improved overall survival. Patients with a PD-L1 tumor proportion score of 50% or higher were most likely to respond to pembrolizumab.

In 2017, when I was at the University of California Los Angeles, our group (Shaverdian and colleagues) published a secondary analysis of KEYNOTE-001 in *Lancet Oncology*, in which we compared patients treated with pembrolizumab who had received prior radiation therapy with those treated with pembrolizumab who had not received prior radiation therapy. We wanted to see whether the prior use of radiation would increase toxicity with pembrolizumab. We also wanted to know whether aspects of the prior use of radiation—including duration and timing—would affect the efficacy of pembrolizumab. We were surprised to find that prior radiation appeared to benefit patients who subsequently received pembrolizumab, in terms of both overall survival and disease-free survival. That finding supports the hypothesis that prior radiation could synergistically increase the efficacy of immunotherapy. I must caution that although KEYNOTE-001 was a randomized, prospective study with an excellent prospective data set, our analysis was not randomized and was done retrospectively.

A phase 1/2 study from Welsh and colleagues also supports the addition of radiation therapy to pembrolizumab in patients with stage IV NSCLC, with an improvement in progression-free survival among patients with a low rate of expression of PD-L1—although the difference was not statistically significant in the overall group. This same group, with Theelen as the first author, subsequently published a pooled analysis of 2 randomized clinical trials that further supported the addition of radiotherapy to pembrolizumab in patients with stage IV NSCLC, with improved progression-free survival. Advances in the treatment of stage IV disease often trickle down to earlier-stage disease, so research in metastatic disease has a wide reach.

H&O Is there a synergistic effect between radiation therapy and immunotherapy?

PL We do not have definite proof of a synergistic effect between radiation therapy and immunotherapy, but that is one of the current hypotheses. The concept is that administering radiation to tumors, especially at a high dose per fraction, rapidly causes the death of tumor cells and the subsequent release of tumor-specific antigens. This primes the immune system to recognize these foreign antigens easily, potentially allowing checkpoint inhibition to be much more effective.

If you have a patient with stage IV NSCLC, for example, who has disease progression after 6 months of response to chemotherapy plus pembrolizumab or pembrolizumab alone, what is the next step? One possibility is switching therapies, including switching from pembrolizumab to another checkpoint inhibitor; another is enrollment in a clinical trial. However, still another approach is to use radiation therapy in an attempt to reinvigorate the immune system so it will once again recognize and respond to immunotherapy. Welsh and colleagues have been studying this approach, which is based on the often-described abscopal effect—the phenomenon in which a significant response to radiation occurs in patients with progressing tumors, even in areas outside the radiation field. His research in animal models, including a study published with Barsoumian as the first author, suggests that low-dose radiation affects the tumor microenvironment, increasing the ability of T cells to infiltrate the tumor.

Data from PACIFIC suggest that the patients with stage III unresectable NSCLC who received durvalumab within 2 weeks after chemoradiation did better than those who received durvalumab at 4 weeks. Patients generally experience toxicity after chemoradiation, which is one of the reasons to postpone immunotherapy. It is possible that these patients do better simply because they have a more favorable clinical profile with better performance status. However, the alternate hypothesis is that the timing and sequencing of radiation and durvalumab treatment make a difference, and the sooner patients receive durvalumab after radiation, the more synergy there may be.

H&O What other studies are looking at immunotherapy and radiation in NSCLC?

PL The phase 3 LONESTAR study here at MD Anderson is looking at whether the addition of consolidation radiation therapy to combination immunotherapy with ipilimumab (Yervoy, Bristol Myers Squibb) and nivolumab can improve overall survival in patients with stage IV NSCLC (NCT03391869). The similar phase 2 NRG-LU002 study is looking at the addition of consolidation radiation therapy to maintenance chemotherapy in stage IV NSCLC (NCT03137771).

In stage III disease, the single-arm phase 2 KEYNOTE-799 study looked at the safety of pembrolizumab with concurrent chemoradiation. This was a nonrandomized study, but it suggested promising antitumor activity

with pembrolizumab plus concurrent chemoradiation in patients with previously untreated, locally advanced NSCLC. This was an encouraging finding because chemoradiation plus pembrolizumab has the potential to be a fairly toxic regimen. Also in stage III disease, the phase 3 PACIFIC-2 study is looking at the addition of durvalumab to concurrent platinum-based chemoradiation in patients with unresectable stage III NSCLC (NCT03519971). I have also initiated the phase 2 ENDURE trial, which is looking at the use of consolidation radiotherapy plus durvalumab with or without chemotherapy in patients with oligoprogressive or polyprogressive stage III NSCLC who were initially treated with chemoradiotherapy and durvalumab (NCT04892953).

H&O Can chemotherapy be omitted when radiation and immunotherapy are both used?

PL It may be possible to omit chemotherapy, which is generally more toxic than immunotherapy, in a subset of patients. We are currently awaiting the results of the phase 1 NRG-LU004 trial, which is looking at the safety of durvalumab plus either hypofractionated or conventionally fractionated radiation therapy in patients with PD-L1–high unresectable stage II or III NSCLC (NCT03801902). Another investigator-initiated trial that we are conducting at MD Anderson is PIN-X, which has nearly completed enrollment (NCT04013542). In this single-arm trial, we are combining ipilimumab and nivolumab with 6 weeks of standard radiation without chemotherapy, followed by 1 year of nivolumab, regardless of the patients' initial levels of tumor PD-L1 expression.

H&O What advances do you hope to see in the next 5 years?

PL We have seen many advances in therapy for stage III NSCLC over the past few years, with incremental improvements in outcome culminating in the landmark PACIFIC trial, which showed significant improvement. Deaths from cancer have decreased overall, in large part because of immunotherapy. In lung cancer, therapeutic advances appear to have been augmented by the use of radiation therapy. I hope that as we learn more about the interaction between radiation therapy and immunotherapy, we can better tailor our treatments to individual patients with lung cancer and minimize toxicities. Over the next 5 years, we should be able to fine-tune our approach so that we will know which patients will benefit from a particular combination of therapies, what is the appropriate sequencing of therapies, and what doses of radiation provide the best synergy with these novel drugs. Then, we can administer the right combination of agents and precisely direct radiation therapy to the right tumors. We expect to see more and better biomarkers that go beyond just PD-L1.

Disclosure

Dr Lee has served on the advisory board of and received honoraria and research grants from AstraZeneca. He has served on an independent data-monitoring committee for Genentech; has been a consultant for the RTOG Foundation (RTOG 3515 RT plan quality review); has served as a consultant for and received honoraria, research grants, and travel expenses from Varian Medical Systems; and has served on the advisory board of, served as a consultant for, and received honoraria, research grants, and travel expenses from ViewRay.

Suggested Readings

Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med.* 2017;377(20):1919-1929.

Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med.* 2018;379(24):2342-2350.

Barsoumian HB, Ramapriyan R, Younes AI, et al. Low-dose radiation treatment enhances systemic antitumor immune responses by overcoming the inhibitory stroma. *J Immunother Cancer.* 2020;8(2):e000537.

Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617). *Lancet Oncol.* 2015;16(2):187-199.

Garon EB, Hellmann MD, Rizvi NA,et al. Five-year overall survival for patients with advanced non−small-cell lung cancer treated with pembrolizumab: results from the phase I KEYNOTE-001 study. *J Clin Oncol.* 2019;37(28):2518-2527.

Gray JE, Villegas A, Daniel D, et al. Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC-update from PACIFIC. *J Thorac Oncol.* 2020;15(2):288-293.

Jabbour SK, Lee KH, Frost N, et al. Pembrolizumab plus concurrent chemoradiation therapy in patients with unresectable, locally advanced, stage III non-small cell lung cancer: the phase 2 KEYNOTE-799 nonrandomized trial. *JAMA Oncol.* 2021;7(9):1-9.

Lin SH, Lin Y, Yao L, et al. Phase II trial of concurrent atezolizumab with chemoradiation for unresectable NSCLC. *J Thorac Oncol.* 2020;15(2):248-257.

Luterstein E, Shaverdian N, Lee P. Radiotherapy: the key to immunotherapy ignition? *Oncotarget.* 2017;8(55):93307-93308.

Patel RR, He K, Barsoumian HB, et al. High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: results of a phase II trial. *Radiother Oncol.* 2021;162:60-67.

Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol.* 2017;18(7):895-903.

Spigel DR, Faivre-Finn C, Gray JE, et al. Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *J Clin Oncol.* doi:10.1200/JCO.21.01308.

Theelen W, Chen D, Verma V, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Respir Med.* 2021;9(5):467-475.

Wakelee HA, Altorki NK, Zhou C, et al. IMpower010: Primary results of a phase III global study of atezolizumab versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIA non-small cell lung cancer (NSCLC) [ASCO abstract 8500]. *J Clin Oncol.* 2021;39(15)(suppl).

Welsh J, Menon H, Chen D, et al. Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial. *J Immunother Cancer.* 2020;8(2).