Editorial

Durvalumab showed long and durable effects after chemoradiotherapy in stage III non-small cell lung cancer: results of the PACIFIC study

Takehiro Uemura, Toyoaki Hida

Department of Thoracic Oncology, Aichi Cancer Center Hospital, Aichi, Japan

Correspondence to: Toyoaki Hida, MD, PhD. Department of Thoracic Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan. Email: 107974@aichi-cc.jp.

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Lung cancer is the leading cause of death worldwide. Non-small cell lung cancer (NSCLC) makes up about 80% of lung cancer cases, and up to 50% of these cancers are locally advanced when detected (1). Within the stage III classification in NSCLC, the distinction between stages IIIA and IIIB leads to differences in prognosis, treatment options, and long-term outcomes. When first detected, stage IIIA NSCLC is diagnosed as resectable or unresectable, and some patients with stage IIIA are candidates for surgery. However, removal of a stage IIIB primary tumor is problematic due to metastatic disease in lymph nodes located in the contralateral thorax or supraclavicular fossa. Therefore, the treatment of stage III NSCLC patients differs in terms of the extent and location of disease. For this reason, a combination of surgery, radiation, and systemic chemotherapy is often used. Despite this multimodal treatment, the prognosis for unresectable stage III NSCLC remains poor, with a 5-year overall survival (OS) rate of approximately 15% (2,3). The standard of care for patients with stage IIIA and IIIB NSCLC who are not surgical candidates is chemoradiotherapy. For those with stage IIIA disease, the treatment regimen is complex and uncertain. Adjuvant chemotherapy for patients with operable NSCLC improves the OS of patients with stage I–III disease (4), and definitive chemoradiotherapy is the standard of care for stage IIIB and IIIA patients who are not surgical candidates.

Chemotherapy reduces or prevents micrometastasis of inoperable tumors and sensitizes tumors to radiation therapy. The combination of chemotherapy and radiation in patients with advanced NSCLC improves survival compared to supportive care or radiotherapy only (5,6). Selection of chemoradiotherapy agents that control disease and increase survival is complex and not well established. Cisplatin plus etoposide or carboplatin plus paclitaxel are frequently used, and these two regimens were compared in a randomized trial of 191 patients with stage III NSCLC receiving concurrent thoracic radiation (7). After a median follow-up of 73 months, patients who received cisplatin plus etoposide had a higher 3-year survival rate [41.1% *vs.* 26.0%; absolute difference 15%; 95% confidence interval (CI), 2.0–28.0%] and tended to have a better OS [23.3 *vs.* 20.7 months; hazard ratio (HR) 0.76, 95% CI, 0.55–1.05] compared with patients who received carboplatin and paclitaxel.

Recently, interest has been growing in the use of new immunotherapy agents for lung cancer. An international phase III trial investigated tecemotide versus placebo as maintenance therapy in patients with stage III NSCLC who had received chemoradiotherapy (START study) and indicated a potential OS improvement with tecemotide over placebo in the subgroup of patients who had received primary concurrent chemoradiotherapy compared to those who received sequential chemoradiotherapy (8). However, the results in Japanese patients after a long-term follow-up (9)

did not support the START study findings.

Immune checkpoint inhibitors (ICIs), a new class of drugs that have been developed, are showing encouraging results in patients with advanced NSCLC in randomized phase II and III clinical trials. ICIs include anti-programmed death 1 (PD-1) and anti-programmed death ligand 1 (PD-L1). The first ICI to be an effective second-line treatment in two phase III trials in patients with NSCLC was the anti-PD-1 antibody nivolumab (10,11). Another anti-PD-1 antibody, pembrolizumab, is an effective first-line therapy for patients whose tumors show ≥50% PD-L1 positivity. Pembrolizumab provided a median progression-free survival (PFS) of 10.4 months, whereas PFS was only 6.0 months in patients treated with chemotherapy (12). Atezolizumab, an anti-PD-L1 antibody, showed efficacy as a second-line treatment with a median OS of 13.8 months, compared to a median OS of 9.6 months with docetaxel (13). These results can address the current poor prognosis of unresectable stage III NSCLC despite the availability of conventional multimodal treatment by providing newer treatment paradigms that incorporate immunotherapy.

Durvalumab, new anti-PD-L1 antibody, inhibits binding of PD-L1 to PD-1 and B7-1, releasing the ability of T cells to recognize and eliminate tumor cells. In the November 2017 issue of *The New England Journal of Medicine*, Antonia and colleagues showed a longer PFS with durvalumab as consolidation therapy than with placebo in stage III NSCLC patients who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy (14).

PFS and OS were defined as the time from randomization of the patient in the study (within 6 weeks of chemoradiotherapy) to the time at which tumor progression or death occurred or until death from any cause, respectively. The study enrolled patients with stage III, locally advanced, unresectable NSCLC as determined with histology or cytology. These patients had received two or more cycles of platinum-based chemotherapy concurrently with definitive radiation therapy (54–66 Gy). Within 1 to 42 days after chemoradiotherapy, the patients were randomly assigned to receive either intravenous durvalumab or matching placebo in a 2:1 ratio every 2 weeks as consolidation therapy for up to 12 months.

Among a total of 709 of 713 patients who underwent randomization, 473 patients received durvalumab and 236 patients received placebo. The median age of the patients was 64 years, and most were men (70.2%) and current or former smokers (91.0%); 47.1% of enrolled patients had the squamous histologic type of cancer. The two groups had responded similarly to previous chemoradiotherapy. PD-L1 expression in archived tumors prior to chemoradiotherapy was ≥25% in 22.3% of patients, <25% in 41.0% of patients, and unknown in 36.7% of patients. Most patients (67.3%) were negative for mutations in epidermal growth factor receptor (EGFR), and mutations were found in 6.0% of patients.

Patients treated with durvalumab showed a PFS of 16.8 months (95% CI, 13.0–18.1), whereas those treated with placebo showed a PFS of 5.6 months (95% CI, 4.6–7.8; stratified HR for disease progression or death, 0.52; 95% CI, 0.42–0.65; two-sided P<0.001). With durvalumab, the PFS survival rates at 12 and 18 months were 55.9% (95% CI, 51.0–64.0) and 44.2% (95% CI, 37.7–50.5), and with placebo were 35.3% (95% CI, 29.0–41.7) and 27.0% (95% CI, 19.9–34.5), respectively. This improvement in PFS in patients treated with durvalumab was present regardless of whether the tumor was positive for PD-L1 expression before chemotherapy. The HRs were 0.59 (95% CI, 0.43–0.82) and 0.41 (95% CI, 0.26–0.65) in patients showing PD-L1 expression <25% and ≥25%, respectively. This improvement was also present in non-smokers. Durvalumab (28.4%) produced a significantly higher objective response rate than placebo (16.0%; P<0.001).

Approximately one-third of patients (29.9%) treated with durvalumab experienced grade 3 or 4 adverse events compared to 26.1% of patients given placebo. Pneumonia (4.4% in patients treated with durvalumab and 3.8% in those given placebo) was the most common grade 3 or 4 adverse event. Adverse events leading to death were seen in 4.4% of patients given durvalumab and 5.6% of those given placebo. Two-thirds (66.1%) of patients given durvalumab and 48.7% of patients given placebo experienced adverse events of any grade that were of particular interest, regardless of cause; the most frequent of these with durvalumab and placebo were diarrhea in 18.3% and 18.8%, respectively; pneumonitis in 12.6% and 7.7%, respectively; rash in 12.2% and 7.3%, respectively; and pruritus in 12.2% and 4.7%, respectively. Adverse immune events of all grades, any cause, were present in 24.2% and 8.1% of those given durvalumab or placebo, respectively. In 3.4% of the durvalumab group and 2.6% of the placebo group, these events were grade 3 or 4.

OS with durvalumab has not yet been reported, but these encouraging PFS results support the idea that consolidation treatment with durvalumab may become the new standard of care for patients with stage III NSCLC who are not surgical candidates and who did not progress after

receiving platinum-based chemotherapy and concomitant radiotherapy. Responses to durvalumab therapy were durable but those with placebo were not. If consolidation treatment with durvalumab after chemoradiotherapy improves OS, even in resectable stage IIIA patients, the subset of patients who used to be treated with surgery and adjuvant chemotherapy will need only a combination of immunotherapy and chemoradiotherapy instead of surgery. Furthermore, the advent of this new combination therapy may expand its indications among NSCLC patients.

Although radiation activates the immune system by releasing tumor antigens, in addition to killing cancer cells (15), the mechanisms of chemoradiation combined with immunotherapy and its effects on cancer cells remain unknown. The KEYNOTE-001 trial, which aimed to assess disease control and pulmonary toxicity in NSCLC patients who previously received radiotherapy before pembrolizumab, reported that in advanced NSCLC patients who received pembrolizumab, PFS and OS were longer in patients who had previous radiotherapy than in those who did not have previous radiotherapy (16). The phenomenon of the abscopal effect may explain the mechanisms of action of the combination of radiotherapy and immunotherapy. Radiotherapy decreases metastatic disease far from the irradiated site, a phenomenon that may be immune mediated (17,18). Thus, radiotherapy combined with inhibition of PD-1/PD-L1 may be a rational new therapeutic strategy.

In general, chemotherapy kills cancer cells by targeting DNA synthesis and replication and by priming tumor-specific T cells through promotion of tumor antigen presentation after cancer cell death (19,20). Thus, combining chemotherapy with PD-1/PD-L1 inhibition may improve the effectiveness of PD-1/PD-L1 inhibition, especially in tumors that are minimally immunogenic and chemosensitive. Indeed, a recent phase II clinical study (KEYNOTE-021) reported that pembrolizumab combined with pemetrexed/carboplatin enhanced the efficacy of chemotherapy alone for the treatment of metastatic non-squamous NSCLC (21); this treatment has been approved by the Food and Drug Administration. The KEYNOTE-001 trial showed that compared with patients who did not receive previous thoracic radiotherapy, those who did were more likely to have treatment-related pulmonary toxicity after pembrolizumab treatment (63% *vs.* 40%, P=0.052) but had similar rates of grade 3 or worse pulmonary toxicities (4% *vs.* 1%, P=0.44) (16). In the PACIFIC study, although the addition of immunotherapy after chemoradiotherapy raised concerns about development of adverse events, pneumonitis in particular, this side effect was fully manageable. Moreover, two meta-analyses suggested that anti-PD-L1 inhibitors are associated with a significantly lower incidence of pneumonitis than anti-PD-1 inhibitors (22,23). These results verify the safety of the combination treatment of radiotherapy and immunotherapy with anti-PD-L1 inhibitors.

The combination of chemoradiotherapy and immunotherapy can lead to a more effective anti-tumor response compared with that of the individual modalities. The interactions of the immune system with radiation and chemotherapy have become a new area of intense cancer research. In the PACIFIC study, consolidation treatment with durvalumab after chemoradiotherapy achieved desirable results, although some issues remain to be addressed. First, PD-L1 expression was checked using tissue obtained before chemoradiotherapy; therefore, the true PD-L1 expression after chemoradiotherapy was unclear even if a survival benefit was observed regardless of PD-L1 expression. In this study, the risk of disease progression was lower in patients with PD-L1 expression ≥25% (HR, 0.41; 95% CI, 0.26–0.65) than in patients with PD-L1 expression <25% (HR, 0.59; 95% CI, 0.43–0.82). Thus, PD-L1 could serve as a biomarker for effective consolidation treatment with durvalumab. Because PD-L1 expression was reported to be affected by radiotherapy (24), the relationship between PD-L1 expression in tissue obtained by re-biopsy after chemoradiotherapy and the effectiveness of durvalumab are worthy of investigation. The second issue in the PACIFIC study was the uncertain benefit of consolidation treatment with durvalumab in patients harboring driver mutations, such as EGFR mutation. According to a recent meta-analysis, ICIs may not improve the OS in EGFR-mutant advanced NSCLC (25). Therefore, in patients harboring driver mutations, consolidation treatment with durvalumab after chemoradiotherapy may have no clinical benefit, and other treatment strategies, such as the corresponding tyrosine kinase inhibitors, may be needed.

Because the PACIFIC study was the first to demonstrate the efficacy of durvalumab as consolidation treatment, many questions arose. The first is the choice of an adequate ICI among anti-PD-1 inhibitors, anti-PD-L1 inhibitors, and anti-cytotoxic T-lymphocyte antigen 4 inhibitors for use as consolidation therapy. The second is the timing of initiation of consolidation therapy; in this study, a better PFS was observed when durvalumab was initiated within ≤2 weeks of radiation (HR, 0.39; 95% CI, 0.26–058), rather than

Table 1 Ongoing trials combining immunotherapy with chemotherapy and radiation in NSCLC

NCT#	Study phase	Disease stage	IT	Treatment sequence
NCT02400814	I	Recurrent or IV	Atezolizumab	SBRT plus concurrent IT; induction IT → SBRT; SBRT → sequential IT
NCT02434081 (NICOLAS)	II	III	Nivolumab	CRT plus concurrent IT
NCT03102242	II	III	Atezolizumab	induction IT → CRT
NCT03379441 (MP-LALC)	II	III	Pembrolizumab	CRT (concomitant or sequential) → IT; CRT (concomitant or sequential) → observation
NCT02343952	II	III	Pembrolizumab	Concurrent CRT → IT
NCT03053856	II	IIIA	Pembrolizumab	Neoadjuvant concurrent CRT → curative resection → IT
NCT03391869 (LONESTAR)	III	IV	Nivolumab, Ipilimumab	IT; IT → LCT

NSCLC, non-small cell lung cancer; IT, immunotherapy; SBRT, stereotactic body radiation therapy; LCT, local consolidation therapy (surgery and/or radiation); CRT, chemoradiotherapy.

>2 weeks after radiation (HR, 0.63; 95% CI, 0.49–0.80). Moreover, the value of durvalumab consolidation therapy in prolonging PFS and OS remains to be compared among the timing of initiation after chemoradiotherapy, concurrently with chemoradiotherapy, and induction before chemoradiotherapy. Other questions include the duration of consolidation immunotherapy and the need to find an adequate biomarker to help identify the subset of stage III NSCLC patients who will receive great benefit from this consolidation treatment. To answer these questions, the optimal management of stage III NSCLC patients is under active investigation in some trials investigating the combination of chemoradiotherapy and immunotherapy (*Table 1*). Depending on the results of these ongoing clinical trials, new combination treatment with chemoradiotherapy and immunotherapy using different treatment sequences may be approved for lung cancer patients in other clinical stages.

In conclusion, the advent of immunotherapy is currently revolutionizing the field of oncology. At this time, durvalumab has produced reasonably well-tolerated results with a manageable safety profile in the PACIFIC trial. Blockade of PD-L1 following chemoradiation may be a new therapeutic option for patients with stage III lung cancer that is only locally advanced. In addition, its appropriate use may overcome the controversial situation regarding stage III NSCLC treatment. Several questions about this novel combination therapy that includes immunotherapy remain to be fully answered, and further studies of patients with stage III NSCLC are expected.

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Footnote

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