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ORIGINAL ARTICLE

Effect of durvalumab on local control after concurrent chemoradiotherapy for locally advanced non-small cell lung cancer in comparison with chemoradiotherapy alone

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Keywords
Concurrent chemoradiotherapy; durvalumab; local control; locally advanced non-small cell lung cancer.

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Abstract

Background: Durvalumab after concurrent chemoradiotherapy (CCRT) for locally advanced non-small cell lung cancer (LA-NSCLC) has been found to significantly improve overall survival (OS). However, the effect of durvalumab on local control remains unclear. Here, we evaluated the effect of the durvalumab on local control in comparison with the clinical result of patients treated with CCRT alone.

Methods: A total of 120 LA-NSCLC patients including 76 patients with CCRT alone and 44 patients with CCRT followed by durvalumab were analyzed. Baseline patient characteristics of CCRT alone cohort and durvalumab cohort were compared with student's *t* test or Mann–Whitney U test for continuous variables and with chi-squared test for categorical variables. Local control (LC), progression free survival (PFS) and OS rates were estimated using the Kaplan–Meier method and compared with the log-rank test.

Results: There were 19 patients with stage II disease and 101 patients with stage III disease. Age, sex, histopathological type, T classification, N classification, clinical stage, tumor volume and dose fractionation schedule were not significantly different between the CCRT alone and durvalumab cohorts. The one-year LC rate was significantly higher in the durvalumab cohort (86%) compared with the CCRT alone cohort (62%) (P = 0.005), whereas no significant difference was observed in either PFS (P = 0.864) or OS (P = 0.443) between the CCRT and durvalumab cohorts.

Conclusions: The one-year LC rate was significantly higher in the durvalumab cohort compared with the CCRT alone cohort. Although the follow-up period was too short to draw definitive conclusions, the study revealed that durvalumab might have a significant effect on LC.

Key points

Significant findings of the study: Effect of durvalumab on local control after chemoradiotherapy for locally advanced non-small cell lung cancer is unclear

What this study adds: The one-year local control rate of chemoradiotherapy followed by durvalumab was significantly higher compared with chemoradiotherapy alone.

Introduction

Lung cancer is a major cause of cancer death worldwide.[1,2] For unresectable locally advanced non-small cell lung cancer (LA-NSCLC), concurrent chemoradiotherapy (CCRT), which combines platinum-based chemotherapy and radiotherapy, is the mainstay of treatment.[3,4] Recently, durvalumab consolidation therapy after CCRT has been reported to significantly improve progression-free survival (PFS) and overall survival (OS) of LA-NSCLC patients in the PACIFIC trial.[5,6] However, limited data exists on the effect of durvalumab on local control in the PACIFIC trial. Because local control (LC) is an important factor associated with OS after CCRT for LA-NSCLC,[7,8] great efforts have been made to improve LC, including the use of radiation dose-escalation.[7–10] On the other hand, the combination of radiotherapy and immune checkpoint inhibitors in lung cancer patients has attracted increasing interest regarding improvements in outcomes, including local control.[11,12] Based on this background, in the study reported here we evaluated the effect of the durvalumab on local control in comparison with the clinical result of patients treated with CCRT alone at our institution.

Methods

Patients

LA-NSCLC patients who underwent CCRT alone between July 2007 and December 2017 or CCRT followed by durvalumab between April 2018 and December 2019 at our hospital were retrospectively analyzed. During April 2018 to December 2019, four patients were treated with CCRT but did not receive durvalumab. Among the four patients who did not receive durvalumab, two patients refused treatment, one patient developed radiation pneumonitis at the end of CCRT and one patient developed disease progression at the end of CCRT. The outcome of CCRT alone for LA-NSCLC at our institution has been previously reported,[8] together with the analysis of toxicity of CCRT followed by durvalumab for LA-NSCLC.[13,14] Some of the patients in the present study overlapped with these studies. Most primary tumors were histologically diagnosed, but for some patients, tumors were clinically diagnosed because of medical reasons. The clinical stage was classified according to the eighth edition of the Union for International Cancer Control (UICC) classification of malignant tumors with contrast-enhanced computed tomography (CT), gadolinium-enhanced head magnetic resonance imaging (MRI), and fluorodeoxyglucose-positron emission tomography (FDG-PET). This study was approved by the Institutional Review Board (Approval number: 18095).

Treatment methods

For most patients, the prescribed dose was 60 Gy in 30 fractions with 10 MV X-ray beams. The treatment technique was conventional three-dimensional conformal radiotherapy (3D-CRT) in all patients. A CT image of both expiratory and inspiratory phases was acquired, and the gross tumor volume was delineated on both expiratory and inspiratory CT images to determine the internal target volume (ITV). The clinical target volume (CTV) was generated with a 5 mm margin in all directions from the ITV and prophylactic lymph node area. The prophylactic lymph node area was basically defined as hilar, subcarina and upper mediastinal lymph nodes for the tumor at the upper and middle lobe, and hilar and subcarinal lymph nodes for the tumor at the lower lobe. The planning target volume (PTV) was defined as the CTV plus 5 mm of setup margin. Patients were treated with platinum-based chemotherapy concurrent with radiation. Durvalumab was intravenously administered at 10 mg/kg every two weeks. Complete blood cell counts, differential counts, routine chemistry measurements, physical examinations, and toxicity assessments were performed weekly. Toxicity was graded using the Common Terminology Criteria for Adverse Events version 5.0.

Evaluation

Treatment efficacy and adverse events were evaluated every 2–3 months for the first year and then every 3–6 months. Blood tests and CT were performed every 2–3 months for the first two years and then every 3–6 months. In addition, MRI and FDG-PET were acquired if disease progression was indicated. OS was defined as the time between the initiation of CCRT and the last follow-up date or death. LC was defined as being free from recurrence in the irradiated field. Distant metastasis was defined as metastatic disease progression according to the eighth edition of the UICC classification of malignant tumors. PFS was defined as the time from the initiation of CCRT to any disease progression or death.

Statistical analysis

Patients were divided into two cohorts. One was treated with CCRT alone (CCRT alone cohort), and the second was treated with CCRT followed by durvalumab (durvalumab cohort). LC, distant metastasis, PFS, and OS rates were calculated using the Kaplan–Meier method and compared with the log-rank test between the two groups. Mean parameters between the two groups were compared using Student's *t*-tests, and median parameters between the two groups were compared using the Mann–Whitney U

test. Differences in categorical variables between the two groups were evaluated with the chi-squared test. Values of $P < 0.05$ were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (SPSS Inc., Armonk, NY, USA).

Results

Patient characteristics

In the CCRT alone cohort, there were 76 patients, including 65 men and 11 women. The median age was 70 years old. There was one patient with stage IIA, 10 patients with stage IIB, 28 patients with stage IIIA, 30 patients with stage IIIB, and seven patients with stage IIIC disease. The mean gross tumor volume was 113 cm^3. The total dose of radiotherapy was 54 Gy in one patient, 60 Gy in 68 patients, 64 Gy in three patients, and 66 Gy in four patients. Regarding the chemotherapy regimen, 28 patients received cisplatin plus docetaxel, 26 patients received carboplatin plus paclitaxel, 15 patients received carboplatin plus docetaxel, five patients received daily low-dose carboplatin, one patient received carboplatin plus nab-paclitaxel, and one patient received cisplatin plus vinorelbine. In the durvalumab cohort, there were 44 patients, including 34 men and 10 women. The median age was 73 years old. There were eight patients with stage IIB, 17 patients with stage IIIA, 16 patients with stage IIIB, and three patients with stage IIIC disease. The mean gross tumor volume was 134 cm^3. The total dose of radiotherapy was 60 Gy for all patients. Regarding the chemotherapy regimen, 20 patients received carboplatin plus paclitaxel, 16 patients received daily low-dose carboplatin, four patients received cisplatin plus docetaxel, three patients received cisplatin plus TS-1, and one patient received carboplatin plus docetaxel. The median time from CCRT completion to the first administration of durvalumab was 13 days (range: 1–52 days). These characteristics are summarized in Table 1. The median number of durvalumab cycles was nine of 44 patients; 30 patients discontinued durvalumab. The reasons for durvalumab treatment discontinuation were grade 2 or greater radiation pneumonitis in 11 patients, disease progression in 13 patients, grade 2 arthralgia in one patient, grade 2 myalgia, grade 3 myasthenia gravis in one patient, grade 2 hypothyroidism in one patient, grade 3 eosinophilia in one patient and grade 2 lung infection in one patient.

Treatment efficacy

In the CCRT alone cohort, 76 patients received CCRT alone between July 2007 and December 2018. The median follow-up period was 26 months (range: 6–132 months). The one-year cumulative LC, distant metastasis, PFS, and OS rates calculated from the start of CCRT in this cohort were 62%, 31%, 57%, and 89%, respectively. PFS events were local recurrence in 19 patients (25%), distant metastasis in 16 patients (21%), both local and distant metastasis in 15 patients (20%) and death from radiation pneumonitis in one patient (1%).

Of 35 patients (46%) with distant metastasis, seven had solitary metastasis, and 28 had multiple metastases. The median time to develop distant metastasis was seven months. In the durvalumab cohort, 44 patients received CCRT followed by durvalumab between April 2018 and December 2019. The median follow-up period was 17 months (range: 4–30 months). The one-year cumulative distant metastasis, PFS, and OS rates calculated from the start of CCRT were 29%, 58%, and 84%, respectively. PFS events were local recurrence in four patients (9%), distant metastasis in 13 patients (30%) and both local and distant metastasis in three patients (7%), death from other disease in two patients (5%) and death from radiation pneumonitis in one patient (2%). Cause of death of patients who died from other disease were fatal arrhythmia in one patient and lung abscess in one patient. The one-year LC rate in the durvalumab cohort was 86%, which was significantly higher ($P = 0.005$) compared with 62% in the CCRT alone cohort (Fig 1). Of 15 patients (34%) with distant metastasis, two had solitary metastasis, and 13 had multiple metastases. The median time to develop distant metastasis was seven months. We compared the one-year LC rate in stage III patients between the durvalumab and CCRT alone cohorts. When we limited our analysis to patients with stage III disease, the one-year LC rate in the durvalumab cohort was significantly higher than that in the CCRT alone cohort (85% vs. 60%; $P = 0.024$). We also calculated the LC rate including patients in which durvalumab was intended to be administered at the beginning of CCRT but who did not actually receive it. As detailed above, there were four patients who did not receive durvalumab during the same period as the durvalumab cohort. A one-year LC rate of intention to receive durvalumab cohort was 82% which was still significantly higher than that of the CCRT alone cohort ($P = 0.019$).

Toxicity

In the CCRT alone cohort, there were three patients (4%) without radiation pneumonitis, 47 patients (62%) with grade 1 radiation pneumonitis, 19 patients with grade 2 (25%), five patients (7%) with grade 3, one patient (1%) with grade 4, and one patient with grade 5 (1%). In the durvalumab cohort, there were four patients (9%) without radiation pneumonitis, 24 patients (54%) with grade

Table 1 Patient and treatment characteristics (n = 120)

Characteristics	CCRT alone (n = 76)	CCRT+ durvalumab (n = 44)	P-value
Age, years, median (range)	70 (39–88)	73 (52–81)	0.317
Sex, n (%)			
Male	65 (86)	34 (77)	0.204
Female	11 (14)	10 (23)	
Histopathological type, n (%)			
Adenocarcinoma	36 (47)	24 (55)	0.607
Squamous cell carcinoma	33 (43)	15 (34)	
Others	6 (8)	5 (11)	
Not identified	1 (2)	0 (0)	
T classification, n (%)			
T1b	2 (3)	6 (13)	0.173
T1c	9 (12)	5 (11)	
T2a	10 (13)	3 (7)	
T2b	14 (18)	4 (9)	
T3	18 (24)	13 (30)	
T4	23 (30)	13 (30)	
N classification, n (%)			
N0	3 (4)	5 (11)	0.354
N1	17 (22)	11 (25)	
N2	41 (54)	23 (52)	
N3	15 (20)	5 (11)	
Clinical stage			
IIA	1 (1)	0 (0)	0.870
IIB	10 (13)	8 (18)	
IIIA	28 (37)	16 (36)	
IIIB	30 (40)	17 (39)	
IIIC	7 (9)	3 (7)	
GTV, cm^3, mean (±SD)	113 (±13)	134 (±36)	0.552
Radiation dose, n (%)			
54 Gy in 27 fractions	1 (1)	0 (0)	0.175
60 Gy in 30 fractions	68 (89)	44 (100)	
64 Gy in 32 fractions	3 (4)	0 (0)	
66 Gy in 33 fractions	4 (5)	0 (0)	

GTV, gross tumor volume.

1 radiation pneumonitis, 13 patients with grade 2 (30%), two patients (5%) with grade 3, and one patient (2%) with grade 5. No significant difference was observed in the incidence of radiation pneumonitis between the CCRT alone and durvalumab cohorts (P = 0.752).

Discussion

We reported the outcomes of CCRT followed by durvalumab for LA-NSCLC in comparison with CCRT alone. Compared with CCRT alone, the one-year LC rate was significantly higher in the durvalumab cohort without an increase in lung toxicity. Similarly, Offin *et al.* previously reported that the LC was improved in patients treated with chemoradiation and durvalumab compared with the historical data of those treated with CCRT alone.[11] Our study directly compared the results between the CCRT alone and durvalumab cohorts using raw data obtained from patients treated at our hospital, which may support and validate the conclusion of Offin *et al.* Although the follow-up period was too short to draw definitive conclusions, durvalumab might have a significant effect on LC.

In this study, the one-year LC rate was significantly higher in the durvalumab cohort (86%) compared with the CCRT alone cohort (62%) (P = 0.005). The one-year LC rate of patients treated with CCRT alone in the literature ranges from 63%–76%,[7,15,16] and thus the one-year LC rate in the durvalumab cohort in this study is also higher than the reported outcomes of patients administered CCRT alone. Patient and tumor characteristics, such as age, sex, histopathological type, T classification, N classification, clinical stage, tumor volume and dose fractionation schedule, were not significantly different between the CCRT alone and durvalumab cohorts. Our previous study revealed that a larger tumor volume was strongly correlated

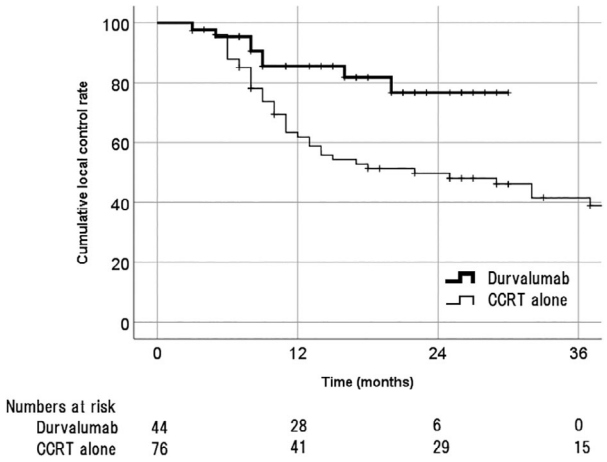

Figure 1 Cumulative local control in the concurrent chemoradiotherapy (CCRT) alone and durvalumab cohorts. The one-year local control rate was 86% in the durvalumab cohort and 62% in the CCRT alone cohort (P = 0.005) (——) Durvalumab, and (——) CCRT alone.

with a lower LC rate.[8] In this study, tumor volume was not significantly different between the CCRT alone and durvalumab cohorts, which indicated that tumor volume did not produce an advantage for the durvalumab cohort with regard to LC. We believe that the higher LC rate in the durvalumab cohort resulted from its effect and not the bias from differences in patient and tumor characteristics.

In our durvalumab cohort, the one-year PFS and OS calculated from the administration of the first durvalumab cycle were 58% and 77%, respectively. In the PACIFIC trial, the one-year PFS and OS were 56% and 83%, respectively, in the durvalumab cohort,[5] which were calculated from randomization. Offin *et al.* reported that the one-year PFS and OS were 65% and 85%, respectively, which were calculated from the initiation of durvalumab. The results obtained in the durvalumab cohort in our study were comparable to these reports. In this study, the one-year PFS and OS calculated from the initiation of CCRT were 58% and 84%, respectively, in the durvalumab cohort, whereas those in the CCRT cohort were 57% and 89%, respectively. No significant difference was observed in either PFS (P = 0.864) or OS (P = 0.443) between the CCRT and durvalumab cohorts. In the placebo cohort of the PACIFIC trial, the one-year PFS and OS were 34% and 75%, respectively.[5] Therefore, the PFS and OS in our CCRT cohort were slightly improved compared with those in the placebo cohort in the PACIFIC trial. This may explain why no significant difference in PFS or OS was found between the durvalumab and CCRT cohorts in this study. However, we believe that the result of the PACIFIC trial was reproduced in our durvalumab cohort with real-world settings.

Offin *et al.* reported the pattern of distant metastasis after CCRT followed by durvalumab for LA-NSCLC. In their reports, oligometastatic disease was observed in 47% of patients who developed distant metastasis.[11] In the PACIFIC trial, 45% of distant metastases were single extrathoracic lesions at first progression.[17] In contrast, only two patients (13%) developed oligometastasis at first progression in this study. The reason for this difference remains unknown, and further studies with a larger number of patients are necessary to clarify the effect of durvalumab on distant metastasis.

There are limitations to the present study that should be noted. First, this study was retrospective with a small number of patients, which may cause bias regarding the baseline patient characteristics. Second, the short-term follow-up period may lead to an underestimation of the incidence of adverse events, such as local failure or distant metastasis. Further studies with a larger number of patients and a longer follow-up period are necessary to clarify the effect of durvalumab on LC after CCRT for LA-NSCLC.

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Disclosure

No authors report any conflict of interest.

References

1 Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; **143**: e1S–e29S. https://doi.org/10.1378/chest.12-2345.

2 Cheng TY, Cramb SM, Baade PD, Youlden DR, Nwogu C, Reid ME. The international epidemiology of lung cancer: Latest trends, disparities, and tumor characteristics. *J Thorac Oncol* 2016; **11**: 1653–71. https://doi.org/10.1016/j.jtho.2016.05.021.

3 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Non-small cell lung cancer, Version 7. 2020. [Cited 14 Sep 2020.] Available from URL: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

4 Aupérin A, Le Péchoux C, Rolland E *et al.* Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010; **28**: 2181–90. https://doi.org/10.1200/jco.2009.26.2543.

5 Antonia SJ, Villegas A, Daniel D *et al.* Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N*

Engl J Med 2018; **379**: 2342–50. https://doi.org/10.1056/nejmoa1809697.
6 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**: 288–93. https://doi.org/10.1016/j.jtho.2019.10.002.
7 Machtay M, Paulus R, Moughan J *et al*. Defining local-regional control and its importance in locally advanced non-small cell lung carcinoma. *J Thorac Oncol* 2012; **7**: 716–22. https://doi.org/10.1097/JTO.0b013e3182429682.
8 Abe T, Kobayashi N, Aoshika T *et al*. Pattern of local failure and its risk factors of locally advanced non-small cell lung cancer treated with concurrent chemo-radiotherapy. *Anticancer Res* 2020; **40**: 3513–7. https://doi.org/10.21873/anticanres.14339.
9 Kong FM, Ten Haken RK, Schipper M *et al*. Effect of midtreatment PET/CT-adapted radiation therapy with concurrent chemotherapy in patients with locally advanced non-small-cell lung cancer: A phase 2 clinical trial. *JAMA Oncol* 2017; **3**: 1358–65. https://doi.org/10.1001/jamaoncol.2017.0982.
10 Saitoh JI, Shirai K, Abe T *et al*. A phase I study of hypofractionated carbon-ion radiotherapy for stage III non-small cell lung cancer. *Anticancer Res* 2018; **38**: 885–91. https://doi.org/10.21873/anticanres.12298.
11 Offin M, Shaverdian N, Rimner A *et al*. Clinical outcomes, local-regional control and the role for metastasis-directed therapies in stage III non-small cell lung cancers treated with chemoradiation and durvalumab. *Radiother Oncol* 2020; **149**: 205–11. https://doi.org/10.1016/j.radonc.2020.04.047.
12 Chicas-Sett R, Zafra-Martin J, Morales-Orue I *et al*. Immunoradiotherapy as an effective therapeutic strategy in lung cancer: From palliative care to curative intent. *Cancers (Basel)* 2020; **12**: E2178. https://doi.org/10.3390/cancers12082178.
13 Miura Y, Mouri A, Kaira K *et al*. Chemoradiotherapy followed by durvalumab in patients with unresectable advanced non-small cell lung cancer: Management of adverse events. *Thorac Cancer* 2020; **11**: 1280–7. https://doi.org/10.1111/1759-7714.13394.
14 Saito S, Abe T, Kobayashi N *et al*. Incidence and dose-volume relationship of radiation pneumonitis after concurrent chemoradiotherapy followed by durvalumab for locally advanced non-small cell lung cancer. *Clin Transl Radiat Oncol* 2020; **23**: 85–8. https://doi.org/10.1016/j.ctro.2020.05.006.
15 Jaksic N, Chajon E, Bellec J *et al*. Optimized radiotherapy to improve clinical outcomes for locally advanced lung cancer. *Radiat Oncol* 2018; **13**: 147. https://doi.org/10.1186/s13014-018-1094-y.
16 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): A randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015; **16**: 187–99. https://doi.org/10.1016/s1470-2045(14)71207-0.
17 Raben D, Rimner A, Senan S *et al*. Patterns of disease progression with durvalumab in stage III non-small cell lung cancer (PACIFIC). *Int J Radiat Oncol Biol Phys* 2019; **105**: 683.

