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Uptake of Adjuvant Durvalumab After Definitive Concurrent Chemoradiotherapy for Stage III Nonsmall-cell Lung Cancer

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Objectives: The addition of adjuvant durvalumab improves overall survival in locally advanced nonsmall-cell lung cancer (NSCLC) patients treated with definitive chemoradiation, but the real-world uptake of adjuvant durvalumab is unknown.

Materials and Methods: We identified patients with stage III NSCLC treated with definitive concurrent chemoradiation from January 2018 to October 2020 from a statewide radiation oncology quality consortium, representing a mix of community (n = 22 centers) and academic (n = 5) across the state of Michigan. Use of adjuvant durvalumab was ascertained at the time of routine 3-month or 6-month follow-up after completion of chemoradiation.

Results: Of 421 patients with stage III NSCLC who completed chemoradiation, 322 (76.5%) initiated adjuvant durvalumab. The percentage of patients initiating adjuvant durvalumab increased over time from 66% early in the study period to 92% at the end of the study period. There was substantial heterogeneity by treatment center, ranging from 53% to 90%. In multivariable logistic regression, independent predictors of durvalumab initiation included more recent month (odds ratio [OR]: 1.05 per month, 95% confidence interval [CI]: 1.02-1.08, $P = 0.003$), lower Eastern Cooperative Oncology Group score (OR: 4.02 for ECOG 0 vs. 2+, 95% CI: 1.67-9.64, $P = 0.002$), and a trend toward significance for female sex (OR: 1.66, 95% CI: 0.98-2.82, $P = 0.06$).

Conclusion: Adjuvant durvalumab for stage III NSCLC treated with definitive chemoradiation was rapidly and successfully incorporated into clinical care across a range of community and academic settings in the state of Michigan, with over 90% of potentially eligible patients starting durvalumab in more recent months.

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Adjuvant durvalumab after definitive concurrent chemoradiation for unresectable stage III nonsmall-cell lung cancer (NSCLC) became the standard-of-care after the publication of PACIFIC in 2018, which showed an 11% absolute overall survival benefit at 2 years compared with placebo.[1,2] Durvalumab was approved by the Federal Drug Administration (FDA) for this indication on February 16, 2018, but it is unclear how quickly durvalumab has been incorporated into routine care since approval. In this study we studied the rate of adjuvant durvalumab initiation in a diverse consortium of community and academic radiation oncology practices across the state of Michigan.

MATERIALS AND METHODS

Data Source and Patient Selection

We identified patients with newly diagnosed stage III (American Joint Committee on Cancer 8th edition) NSCLC treated with definitive concurrent chemoradiation through the Michigan Radiation Oncology Quality Consortium (MROQC). MROQC is a statewide quality improvement effort that tracks implementation of best practices in radiation oncology across a range of academic and community centers in Michigan. Patient-level demographic, comorbidity, staging, treatment, and toxicity data are collected within a centralized database by trained data abstractors. As durvalumab was approved as adjuvant therapy in stage III NSCLC on February 16, 2018, we included patients who started definitive chemoradiation between January 31, 2018 through October 1, 2020. The database was last updated on April 30, 2021 to allow adequate time for follow-up in assessing adjuvant therapy initiation. Among 1908 stage III NSCLC patients, we excluded patients treated with radiotherapy outside of the date window (n = 1245), patients treated with radiation alone or surgery following radiation (n = 132), missing adjuvant therapy information (n = 63), and patients treated with immunotherapy other than durvalumab (n = 47), leaving a final cohort of 421 patients. This study was institutional review board exempt.

TABLE 1. Characteristics of the Sample

Variable	Durvalumab, n (%)	No Durvalumab, n (%)	*P*
Sample size	322 (76.5)	99 (23.5)	
Age in years, mean (SD)	65.5 (8.56)	67.4 (10.2)	0.06
Male	173 (53.7)	59 (59.6)	0.31
Race			
Caucasian	277 (86.0)	84 (84.9)	0.90
African American	34 (10.6)	12 (12.1)	
Other	11 (3.42)	3 (3.03)	
Insurance			
Medicare	149 (46.3)	47 (47.5)	0.45
Medicaid	32 (9.94)	8 (8.08)	
Commercial	77 (23.9)	25 (25.3)	
Other	64 (19.9)	18 (18.2)	
Uninsured	0	1 (1.01)	
Married	156 (48.5)	45 (45.5)	0.60
Academic hospital setting	47 (14.6)	13 (13.1)	0.72
Supplemental O_2 at baseline	27 (8.39)	10 (10.1)	0.60
ECOG			
0	184 (57.1)	52 (52.5)	0.001
1	107 (33.2)	23 (23.2)	
2+	17 (5.28)	17 (17.2)	
Unknown	14 (4.35)	7 (7.07)	
Smoking			
Current	141 (43.8)	29 (29.3)	0.03
Former	166 (51.6)	62 (62.6)	
Unknown	15 (4.66)	8 (8.08)	
Comorbidities			
Hypertension	187 (58.1)	65 (65.7)	0.18
Diabetes	66 (20.5)	17 (17.2)	0.47
COPD	160 (49.7)	46 (46.5)	0.58
Cardiac disease*	51 (15.8)	18 (18.2)	0.58
Connective tissue disease†	5 (1.55)	4 (4.04)	0.14
Vascular disease‡	32 (9.94)	10 (10.1)	0.96
Renal disease	17 (5.28)	6 (6.06)	0.77
Liver disease	11 (3.42)	4 (4.04)	0.77
Other malignancy	20 (6.21)	11 (11.1)	0.10
Histology			
Adenocarcinoma	151 (46.9)	40 (40.4)	0.26
Squamous cell carcinoma	171 (53.1)	59 (59.6)	
AJCC 8th summary stage			
IIIA	201 (62.4)	68 (68.7)	0.26
IIIB	121 (37.6)	31 (31.3)	
Tumor stage			
T1	54 (16.8)	12 (12.1)	0.55
T2	68 (21.1)	26 (26.3)	
T3	63 (19.6)	21 (21.2)	
T4	137 (42.6)	40 (40.4)	
Nodal stage			
N0	42 (13.0)	9 (9.09)	0.04
N1	18 (5.59)	12 (12.1)	
N2	197 (61.2)	62 (62.6)	
N3	65 (20.2)	15 (15.2)	
NX	0	1 (1.01)	
Cumulative radiation dose			
< 59 Gy	9 (2.80)	8 (8.08)	0.10
60-65 Gy	211 (65.5)	61 (61.6)	
> 65 Gy	88 (27.3)	24 (24.2)	
Unknown	14 (4.35)	6 (6.06)	

*Cardiac disease includes congestive heart failure, arrhythmia, and prior myocardial infarction.
†Connective tissue disease includes scleroderma, lupus, rheumatoid arthritis, and other connective tissue disease.
‡Vascular disease includes cerebrovascular disease, peripheral vascular disease, or hemiplegia.
AJCC indicates American Joint Committee on Cancer; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; Gy, Gray.

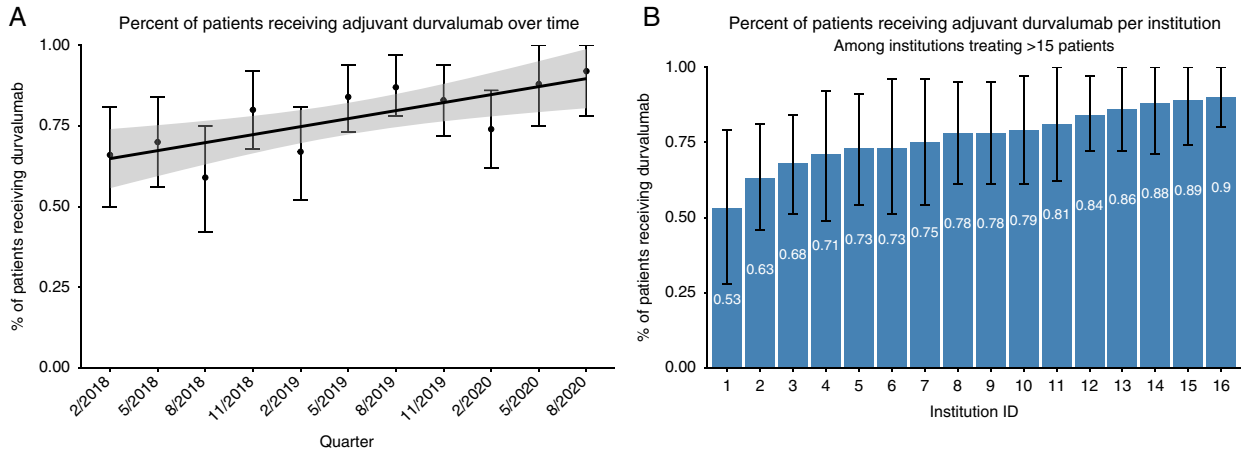

FIGURE 1. Adjuvant durvalumab therapy initiation rates. Rates of adjuvant durvalumab initiation over time (A) and within individual treatment centers (B). The analysis by treatment center was restricted to the 16 centers (of 27 total) that treated at least 15 patients over the study period. Error bars represent 95% confidence interval. full color online

Outcomes and Covariates

The primary outcome was initiation of adjuvant durvalumab after completion of definitive chemoradiation. This was assessed through physician-completed forms at routine 1, 3, and 6-month follow-up after completion of chemoradiation.

TABLE 2. Results of Multivariable Logistic Regression for Odds of Initiating Durvalumab

Variable	OR for Initiating Durvalumab (95% CI)	*P*
Age (per 10 y)	0.81 (0.61-1.07)	0.14
Month of follow-up (per month)	1.05 (1.02-1.08)	0.003
Female sex	1.66 (0.98-2.82)	0.06
Academic hospital setting	1.21 (0.58-2.54)	0.61
Married	1.02 (0.60-1.72)	0.95
Race		
Caucasian	(ref)	(ref)
African American	0.65 (0.29-1.42)	0.28
Other	0.91 (0.22-3.75)	0.89
Tumor stage		
T1	(ref)	
T2	0.62 (0.27-1.44)	0.27
T3	0.75 (0.32-1.76)	0.5
T4	1.12 (0.46-2.75)	0.8
Nodal stage		
0	(ref)	(ref)
1	0.40 (0.13-1.27)	0.12
2	0.89 (0.34-2.38)	0.82
3	1.53 (0.50-4.72)	0.46
Supplemental oxygen at baseline	1.10 (0.44-2.74)	0.84
COPD	1.25 (0.74-2.12)	0.41
Diabetes	1.45 (0.76-2.77)	0.26
Cardiac comorbidity	0.77 (0.40-1.49)	0.44
ECOG performance status		
0	(ref)	(ref)
1	1.30 (0.73-2.33)	0.37
2+	0.25 (0.10-0.60)	0.002

Odds ratio > 1 indicates greater odds of initiating durvalumab.
CI indicates confidence interval; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio.

Baseline covariates assessed before the start of chemoradiation included age, sex, race, insurance, married status, academic versus community center setting, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, use of supplemental oxygen, baseline comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, cardiac disease [including congestive heart failure, arrhythmia, or prior myocardial infarction], connective tissue disease, vascular disease including prior stroke, peripheral arterial disease, hemiplegia, renal disease, liver disease, or other malignancy), tumor histology (adenocarcinoma vs. squamous cell), tumor stage, nodal stage, and cumulative radiation dose planned to the primary tumor.

Statistics

Baseline demographics and treatment information were compared with the *t* test for continuous variables and the χ^2 test for categorical variables. We modeled the odds of adjuvant immunotherapy initiation using multivariable logistic regression. Predictors in the model were chosen a priori and included age, calendar quarter, sex, academic hospital setting, marriage status, race, tumor stage, nodal stage, use of supplemental oxygen at baseline, chronic obstructive pulmonary disease, diabetes, cardiac disease, and ECOG score. Analyses were performed with SAS 9.4 (SAS Institute, Cary, NC) and R 4.0.4 (R Core Team, Vienna, Australia).

RESULTS

The cohort included 421 patients with stage III NSCLC treated with definitive chemoradiation, of whom 322 (76.5%) initiated adjuvant durvalumab. The cohort spanned 27 treatment centers in total, 5 of which were associated with an academic hospital setting (accounting for 14% of the patient cohort). The cohort was predominately Caucasian (85.7%) with excellent performance status (86.9% with ECOG 0 or 1); the mean age was 65.9 years (SD: 8.9). Patients who did not receive adjuvant durvalumab were slightly older (mean age: 67.4 vs. 65.5 years, $P = 0.06$), had worse performance status (17.2% vs. 5.3% with ECOG 2 or higher, $P = 0.001$), and were less likely to be current smokers (29.3% vs. 43.8%, $P = 0.03$) compared with patients who received durvalumab. The groups were otherwise

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broadly similar in demographic, stage, and comorbidity profiles (Table 1).

The percentage of patients receiving adjuvant durvalumab increased over time, from 66% (95% confidence interval [CI]: 50%-81%) at the beginning of the study period to 92% (95% CI: 78%-100%) in the most recent quarter (mean 2.5% increase per quarter, $P = 0.006$ for correlation; Fig. 1A). There was heterogeneity in this percentage across the 16 centers that treated at least 15 patients over the study period, from 53% (95% CI: 28%-79%) to 90% (95% CI: 80%-100%) (Fig. 1B). In multivariable logistic regression, independent predictors of durvalumab initiation included more recent month (odds ratio [OR]: 1.05 per month, 95% CI: 1.02-1.08, $P = 0.003$) and worse performance status (OR: 4.02 for ECOG 0 vs. 2+, 95% CI: 1.67-9.64, $P = 0.002$). Female sex trended toward significance (OR: 1.66, 95% CI: 0.98-2.82, $P = 0.06$) (Table 2).

DISCUSSION

In this study of contemporary practice patterns in the state of Michigan, we found that adjuvant durvalumab was quickly introduced into routine practice after FDA approval. The percentage of potentially eligible patients who started durvalumab increased substantially over time and varied across the 27 treatment centers in the study, though patients treated at community centers were just as likely to receive durvalumab as those treated at academic centers. Patients who did not receive durvalumab tended to be male and to have worse performance status before chemoradiation, but there were reassuringly no other differences by race, insurance status, or comorbidity.

These findings suggest that durvalumab is being successfully incorporated into routine care across a range of practice settings and reflect the rapid uptake seen after immunotherapy approvals for metastatic tumors in other studies.[3,4] The rapid pace of uptake may be influenced by providers' previous experience administering immunotherapy, the large survival benefit seen in PACIFIC, and information dissemination on new standard-of-care practices by MROQC. Within MROQC, FDA approval of durvalumab in stage III NSCLC was discussed during lung working group calls as well as consortium-wide meetings. Each disease site has an assigned clinical champion who is charged with disseminating relevant information to their clinics, and these data are then shared with the consortium physician members. Further, when there are changes made in elements of data collection, these are reviewed in detail with clinical coordinators and care providers. Since the addition of durvalumab is considered level 1 evidence, this was not specifically included in the quality consortium consent.

While some concern has been raised about the proportion of real-world stage III NSCLC patients who are eligible for durvalumab under strict PACIFIC inclusion criteria,[5] we found that over 90% of our cohort started adjuvant durvalumab in the most recent months of our study period. Similarly, despite the substantial economic cost of 12 months of durvalumab infusions,[6] there was no difference in the odds of receiving durvalumab by insurance status. This may reflect recognition of the likely cost-effectiveness of adjuvant durvalumab relative to the costs of disease progression, including expensive salvage chemoimmunotherapy regimens and hospital care.[6] Of note, our data do not include patient-level financial toxicity in the form of potentially significant out-of-pocket costs.[7,8] Overall our findings are reassuring that consolidation durvalumab—which carries a substantial survival benefit[1]—is reaching most eligible patients regardless of demographics, insurance coverage, or geography.

Limitations include the predominately Caucasian cohort and single state setting in Michigan, which may limit generalizability. Further, the limited number of patients who did not start durvalumab (99 patients) limits our power to detect more subtle differences in comorbidity or demographic profiles that may influence durvalumab initiation. Given the consortium's focus on educating practitioners on changes in the standard-of-care, it is possible that MROQC itself may have caused increased uptake or that those participating in the consortium elected to do so because they embrace changes in the standard-of-care more readily than others, such that durvalumab use may be lower among providers outside of the consortium. Finally, we did not have access to patient-level documentation detailing the reasons why potentially eligible patients did not start durvalumab. As MROQC does not routinely collect data on disease progression, it is possible that a subset of patients had progression after definitive chemoradiation and were therefore ineligible. Additional avenues of investigation using these data could include the effect of durvalumab on patient-reported symptoms, adverse events, and quality of life, which are collected by MROQC at regular intervals. Analysis of quality of life data from PACIFIC[9] suggested no clinically significant differences between treatment arms, though toxicity and quality of life profiles could differ in real-world populations.

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