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Association of Patient Characteristics with Chemotherapy Receipt among Depressed and Non-Depressed Patients with Non-small Cell Lung Cancer

Donald R Sullivan, MD, MA^{1,2}, Linda Ganzini, MD, MPH^{1,3}, Ariel Lopez-Chavez, MD⁴, and Christopher G Slatore, MD, MS^{1,2,5}

¹Health Services Research & Development, Portland VA Medical Center, Portland, OR

²Division of Pulmonary & Critical Care Medicine, Department of Medicine, Oregon Health & Science University; Portland, OR

³Department of Psychiatry, Oregon Health & Science University, Portland, OR

⁴Division of Hematology and Medical Oncology, Department of Medicine, Oregon Health & Science University; Portland, OR

⁵Section of Pulmonary & Critical Care Medicine, Portland VA Medical Center; Portland, OR

Introduction

Lung cancer patients suffer considerable morbidity and mortality along with substantial psychological distress [1]. Lung cancer patients with diagnoses of depression experience greater mortality than their non-depressed peers [2], but the causes of this increased mortality are not well understood. For patients with advanced stage non-small cell lung cancer (NSCLC), platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care [3]. The utilization of chemotherapy and patient factors impacting its receipt have not been characterized in depressed patients.

The National Comprehensive Cancer Network (NCCN) has established Clinical Practice Guidelines for the treatment of lung cancer [3]. Previous studies have revealed that patients' age and comorbidities affect receipt of recommended therapies [4], which is in accordance with guidelines. Other patient characteristics, such as black race, reduce the likelihood of chemotherapy receipt and represent an important treatment disparity [5–7]. It is unclear to what extent patients' psychological comorbidities, such as a diagnosis of depression, influence utilization of guideline recommended chemotherapy. In addition, interactions

Corresponding author: Donald R Sullivan, 3710 SW US Veterans Hospital Rd., R&D 66, Portland, OR 97239; Office: 503.220.8262 x58087, Fax: 503.273.5367, sullivanad@ohsu.edu.
Reprints: Christopher G. Slatore, 3710 SW US Veterans Hospital Rd., R&D 66, Portland, OR 97239; Office: 503.220.8262 x52018, Fax: 503.273.5367, Christopher.slatore@va.gov

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between patient characteristics, such as race and depression, and their impact on chemotherapy receipt have not been explored. We examined chemotherapy receipt among lung cancer patients with a diagnosis of depression, including an analysis of patient risk factors associated with reduced receipt, in order to determine if differences in receipt may contribute to increased mortality.

Methods

We identified patients who were diagnosed with advanced stage (III & IV) NSCLC as recorded in the Veterans Integrated Service Network 20 (VISN20) Veterans Affairs Central Cancer Registry (VACCR) between January 1, 1995-December 31, 2010. Veterans Affairs (VA) registrars perform identification, abstraction and follow-up activities of lung cancer patients with adherence to the Commission on Cancer and an external audit found their case capture rate was comparable to Surveillance, Epidemiology, and End Results (SEER) data. We identified patients with a diagnosis of depression as recorded in the VISN20-data warehouse (DW) according to ICD-9 codes (296.2x/296.3x/311.xx/309.1x/300.4x/309.0x/298.0x). We used the following criteria to define depression within two years prior to the lung cancer diagnosis date: (i) 1 primary diagnosis as an inpatient or outpatient; (ii) 1 secondary diagnosis during any inpatient stay; or (iii) 2 secondary diagnoses as an outpatient on different days, no more than 12 months apart. A detailed description of study methods has been reported [2].

The primary outcome was first-line chemotherapy received within 180 days of cancer diagnosis. Chemotherapy receipt was obtained from the prescription data files of the VISN20-DW. Within the VISN20-DW records, chemotherapy receipt was defined as administration of: carboplatin, cisplatin, paclitaxel, docetaxel, gemcitabine, vinorelbine, etoposide, irinotecan, ifosfamide, cyclophosphamide, or vincristine. Individual chemotherapy cycles were defined as administration of an agent within a 19–23 day interval from a previous chemotherapeutic agent. Platinum-based doublets were defined as carboplatin or cisplatin combined with any other agent. Since 1996, the NCCN has recommended 3–4 cycles of a platinum-based doublet as the initial treatment in NSCLC patients [3, 8].

Analysis

Descriptive and comparative statistics were used to categorize patient characteristics at time of diagnosis from the VACCR and included: race/ethnicity, gender, tobacco use, tumor stage, year of diagnosis, radiation treatment receipt. Age at diagnosis and Charlson Comorbidity Index (CCI) score [9] at were collected from the VISN20-DW.

We used logistic regression to calculate odds ratios to evaluate the association of patient characteristics among depressed and non-depressed patients with any chemotherapy receipt. Separate models were created for each patient characteristic. Logistic regression modeling was used to calculate odds ratios to evaluate the association of chemotherapy receipt and distance (per 100 miles) from patients' ZIP at home residence to the nearest tertiary Veterans Affairs Medical Centers (VAMC). We adjusted for the following covariates in our

models: age, race/ethnicity, tobacco use, cancer stage, year of diagnosis, distance to nearest VAMC and CCI.

P values of <0.05 were considered significant. Statistical software: Stata Corp. 2011. *Stata Statistical Software: Release 12: StataCorp, LP.*

Results

Among 1966 advanced stage (III & IV) NSCLC patients, 265 (16%) were identified as having a diagnosis of depression. Refer to Table 1 for patient characteristics. Overall, 698/1966 (36%) of patients received any chemotherapy, 40% of depressed and 35% of non-depressed patients (Table 1). There were no significant differences in chemotherapy receipt between all advanced stage patients with and without a diagnosis of depression (adjOR 0.98, 95% CI: 0.73–1.30, $p=0.88$). Patients who received any chemotherapy survived a median of 309 days (IQR, 163–595) versus 90 days (IQR, 34–241) among patients who did not receive chemotherapy.

Regarding chemotherapy characteristics among depressed patients who received any chemotherapy, 56% received 1 cycle of a platinum-based doublet. Overall, only 36% of depressed patients who received any chemotherapy received 3–4 cycles of a platinum-based doublet (Table 1). No significant differences in total number of cycles or platinum-based cycles among patients with and without a diagnosis of depression were observed.

Among patients with a diagnosis of depression the following patient characteristics were associated with a significantly decreased likelihood of chemotherapy receipt: age ≥ 75 years (adjOR 0.26, 95% CI: 0.11–0.63, $p=0.003$), black race (adjOR 0.19, 95% CI: 0.05–0.74, $p=0.02$), CCI ≥ 4 (adjOR 0.44, 95% CI: 0.21–0.91, $p=0.03$), and stage IV disease (adjOR 0.24, 95% CI: 0.14–0.44, $p<0.0001$). Additional patient characteristics associated with decreased likelihood of chemotherapy receipt among non-depressed lung cancer patients, were tobacco use at diagnosis (OR 0.67, 95% CI: 0.53–0.85, $p=0.00$) and greater distance from patients' ZIP code of their home residence to the nearest VAMC (per 100 miles) (OR=0.95, CI: 0.92–0.996, $p=0.03$) (Table 2).

Discussion

This population based study of Veterans diagnosed with depression with advanced stage (III & IV) NSCLC provides the only available data on chemotherapy receipt and the impact of patient characteristics on receipt. A minority of patients, both with and without a diagnosis of depression, received any chemotherapy and even fewer received NCCN guideline recommended initial chemotherapy. Advanced age, four or more comorbidities, black race and stage IV disease were each associated with reduced chemotherapy receipt among patients diagnosed with depression. Accounting for sample size constraints, patient characteristics that were associated with chemotherapy receipt appeared similar among patients with and without a diagnosis of depression. However, black race seemed to have a greater impact on chemotherapy receipt among patients with a diagnosis of depression.

Recommended by the NCCN, platinum-based chemotherapy improves outcomes compared to best supportive care for advanced stage lung cancer patients [3, 8]. Improved outcomes are consistent even among advanced stage patients aged ≥ 70 years [10]. Despite these superior outcomes, low utilization rates persist in these patients [4, 11]. Reasons for low utilization rates in clinical practice are not entirely clear. However, our results demonstrate that patient characteristics which may impact their performance status, such as age and comorbidities, significantly reduce recommended therapies received, in accordance with guidelines. Participants in trials demonstrating benefit are likely healthier than patients in our population [12]. Over time, advanced stage disease patients' likelihood of receiving chemotherapy is increasing [4, 11], which may reflect better management of toxicities. Our study was consistent with this utilization trend, although it failed to reach statistical significance.

Black patients with lung cancer are less likely to receive guideline recommended treatment and these treatment differences contribute to worse mortality [6, 7, 13]. Treatment disparities among racial/ethnic groups have been attributed to numerous characteristics such as increased number of medical comorbidities [14], patient-provider interactions [15, 16], and treatment access [17]. Among patients with advanced stage lung cancer the racial and ethnic disparities in the receipt of chemotherapy persist despite adjustment for comorbidities and uniform health insurance [5, 18]. Our finding of a possible effect modification of a diagnosis of depression on decreased likelihood of chemotherapy receipt among black lung cancer patients is striking. This relationship may help explain the racial disparities in treatment and mortality among these patients.

We found that distance from a tertiary VAMC might influence chemotherapy receipt among Veterans with advanced stage disease. Within the VISN-20 system, chemotherapy administration occurs almost exclusively at tertiary-care medical centers. Veterans, especially those with supplemental insurance, may receive chemotherapy at non-VA hospitals. However, this occurred infrequently in our cohort based on VACCR estimates. Although many Veterans receive transportation assistance, there are likely many obstacles, system and patient-related, that impact chemotherapy receipt for Veterans that live far from a VAMC.

There are several study limitations. The population consisted of mostly white, male Veterans from the Pacific Northwest. We studied patients with a diagnosis of depression, not depressed patients. We did not have data regarding performance status, which may be a predictor of chemotherapy receipt. However, it is unlikely that poor performance status alone accounts for the low utilization rates. Even among young patients and those with 0–1 comorbidities less than half received chemotherapy. In addition, chronologic age and comorbidities have been shown to dominate clinicians' NSCLC treatment decisions [4, 11]. In 2009, erlotinib was added to NCCN guidelines as a first-line treatment option for epidermal growth factor receptor (EGFR) mutation positive advanced stage patients. Receipt of erlotinib was not included in our analysis.

Conclusions

Despite clinical guidelines and demonstrated superior outcomes, utilization of chemotherapy and platinum-based agents among Veterans with advanced stage NSCLC is low. Utilization rates among patients with and without a diagnosis of depression appeared similar, as are most patient characteristics that decrease the likelihood of receipt with one exception. Notably, black race seemed to have a greater impact on chemotherapy receipt among patients with a diagnosis of depression. Chemotherapy receipt likely does not explain the increased overall mortality among depressed lung cancer patients; therefore, future research is needed to investigate the mechanism(s) underlying this finding.

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Table 1

Characteristics of Depressed and Non-Depressed Advanced Stage (III & IV) NSCLC Patients.

Characteristics	Depressed	Non-Depressed
	n=265	n=1701
Age, years, mean (SD)	64 (10.1)	68 (9.4)
Male, n (%)	255 (96)	1666 (98)
Race/ethnicity, n (%)		
White	220 (83)	1526 (90)
Black	23 (9)	79 (5)
Other	22 (8)	96 (6)
Current Tobacco Use, n (%)	159 (60)	923 (54)
Charlson Comorbidity Index (CCI), mean (SD)	4.5 (3.8)	4.4 (3.6)
NTM-AJCC Stage, n (%)		
III	108 (41)	684 (40)
IV	157 (59)	1017 (60)
Radiation Therapy Receipt, n (%)	130 (49)	742 (44)
Chemotherapy Receipt, n (%)	107 (40)	591 (35)
Total Cycles *, mean (SD)	2.5 (1.4)	2.7 (1.5)
Platinum-based Doublet Cycles *, mean (SD)	2.3 (1.5)	2.3 (1.7)
1–2 cycles, n (%)	60 (56)	300 (51)
3–4 cycles, n (%)	32 (30)	156 (26)
5 cycles, n (%)	6 (6)	67 (11)
Single Agent, Non-platinum Cycles *, n (%)		
Gemcitabine	10 (9)	81 (14)
Vinca Alkaloid	6 (6)	38 (6)
Other#	0	6 (1)

* Cycles defined as chemotherapy received <180 days from diagnosis at 19–23 day intervals; # includes paclitaxel, docetaxel, etoposide, irinotecan, and ifosfamide; p value >0.05 for all comparisons.

Abbreviations: NTM-AJCC = tumor, node, and metastasis Classification of Malignant Tumors - American Joint Committee on Cancer.

Table 2
Patient Characteristics and Chemotherapy Receipt among Depressed and Non-Depressed Patients.

Patient Characteristic	Depressed Patients n=265					Non-Depressed Patients n=1701				
	Chemotherapy (%) n=107	No Chemotherapy (%) n=158	Adj OR* (95%CI)	p		Chemotherapy (%) n=591	No Chemotherapy (%) n=1110	Adj OR* (95%CI)	p	
Age at diagnosis, years										
64	45	55	Ref			45	55	Ref		
65–74	44	56	0.78 (0.37–1.65)	0.52		35	65	0.62 (0.48–0.79)	<0.0001	
75	21	79	0.26 (0.11–0.63)	0.003		20	80	0.26 (0.19–0.36)	<0.0001	
Race/ethnicity										
White	41	59	Ref			35	65	Ref		
Black	22	78	0.19 (0.05–0.74)	0.02		30	70	0.67 (0.42–1.09)	0.11	
Other	50	50	1.48 (0.49–4.52)	0.49		27	73	0.65 (0.39–1.09)	0.1	
Tobacco Use at Diagnosis										
Not Current	37	63	Ref			37	63	Ref		
Current	43	57	1.01 (0.53–1.92)	0.98		34	66	0.63 (0.50–0.81)	<0.0001	
Charlson Comorbidity Index (CCI)										
0–1	49	51	Ref			45	55	Ref		
2–3	48	52	0.81 (0.37–1.76)	0.59		39	61	0.77 (0.58–1.04)	0.09	
4	31	69	0.44 (0.21–0.91)	0.03		26	74	0.50 (0.38–0.66)	<0.0001	
NTM-AJCC Stage										
III	56	44	Ref			44	56	Ref		
IV	29	71	0.24 (0.14–0.44)	<0.0001		29	71	0.55 (0.44–0.69)	<0.0001	
Year of Diagnosis										
1995–2000	25	75	Ref			33	67	Ref		
2001–2005	42	58	1.70 (0.63–4.59)	0.29		34	66	1.07 (0.80–1.43)	0.65	
2006–2010	42	58	2.34 (0.91–6.02)	0.08		37	63	1.29 (0.96–1.72)	0.09	

Patient Characteristic	Depressed Patients n=265				Non-Depressed Patients n=1701			
	Chemotherapy (%)	No Chemotherapy (%)	Adj OR* (95%CI)	p	Chemotherapy (%)	No Chemotherapy (%)	Adj OR* (95%CI)	p
	n=107	n=158			n=591	n=1110		
Radiation Therapy								
No	34	66	Ref		28	72	Ref	
Yes	46	54	1.17 (0.65–2.11)	0.61	44	56	1.69 (1.35–2.12)	<0.0001
Distance from home to nearest VAMC (per 100 miles)			0.98 (0.86–1.11)	0.71			0.95 (0.92–0.996)	0.03

* Odds ratios were calculated with the use of multivariable logistic regression. An odds ratio of more than 1 represents a greater likelihood of chemotherapy receipt. Adjusted by age, race/ethnicity, tobacco use, CCI, lung cancer stage, year of diagnosis, and distance from home to nearest Veterans Affairs Medical Center.

Abbreviations: NTM-AJCC = tumor, node, and metastasis Classification of Malignant Tumors American Joint Committee on Cancer; VAMC = Veterans Affairs Medical Center.