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Do HIV-infected Non-Small Cell Lung Cancer Patients Receive Guidance-Concordant Care?

Jeannette Y. Lee, Ph.D.,

Department of Biostatistics, University of Arkansas for Medical Sciences, 4301 West Markham, #781, Little Rock, Arkansas 72205-7199, Phone: (501) 526-6712, Fax: (501) 526-6729

Page C. Moore, Ph.D., and

Department of Biostatistics, University of Arkansas for Medical Sciences, 4301 West Markham, #781, Little Rock, Arkansas 72205, Phone: (501) 526-6724, Fax: (501) 526-6729

Matthew A. Steliga, M.D.

Department of Surgery, University of Arkansas for Medical Sciences, 4301 West Markham, #713, Little Rock, Arkansas 72205, Phone: (501) 686-7884, Fax: (501) 686-8503

Jeannette Y. Lee: jylee@uams.edu; Page C. Moore: pmoore@uams.edu; Matthew A. Steliga: masteliga@uams.edu

Abstract

Background—The incidence of lung cancer cases among HIV-infected individuals is increasing with time. It is unclear whether HIV-infected individuals receive the same care for lung cancer as immunocompetent patients due to comorbidities, the potential for interaction between antiretroviral agents and cancer chemotherapy, and concerns regarding complications related to treatment or infection.

Objectives—The objective of this study was to assess the effect of HIV infection on receipt of guidance-concordant care, and its impact on overall survival among non-small cell lung cancer (NSCLC) Medicare beneficiaries.

Design—Matched case-control design where each HIV patient was matched by age group, gender, race and lung cancer stage at diagnosis with 20 controls randomly selected among those who were not HIV-infected.

Subjects—Medicare beneficiaries diagnosed with NSCLC between 1998 and 2007, qualified for Medicare based on age, and were 65 years of age or older at the time of the lung cancer diagnosis. HIV infection status was based on Medicare claims data. A total of 174 HIV cases and 3480 controls are included in the analysis.

Measures—Odds ratios (OR) for receiving guidance concordant care; hazard ratios (HR) for overall survival

Results—HIV infection was not independently associated with the receipt of guidance concordant care. Among stage I/II patients, median survival times were 26 and 43 months, respectively, for those with and without HIV infection (OR=1.48, P=0.021).

Conclusions—HIV infection was not associated with receipt of guidance concordant care, but reduced survival in early stage patients.

Introduction

The incidence of lung cancer cases among HIV-infected individuals [1, 2] is increasing with time. Much of the increase can be attributed to the longer life expectancy of HIV-infected individuals with the widespread use of highly active antiretroviral therapy (**HAART**), and the higher prevalence of cigarette smoking in this population [3]. The demographic characteristics of the HIV-infected lung cancer cases are similar to those of HIV-infected individuals overall: predominantly male, young, from minority groups, and never married [2].

It is unclear whether HIV-infected individuals receive the same care for lung cancer as immunocompetent patients, and whether HIV infection has an effect on overall mortality. Factors that may influence their care include comorbidities [4, 5], the potential for interaction between antiretroviral agents and cancer chemotherapy [6], and their risk for complications related to treatment or infection.

The objective of this study was to assess the effect of HIV infection on receipt of guidance-concordant care, and its impact on overall survival. Since disparities in treatment and mortality related to age, gender and race are well established [7–13], a matched case-control approach was used to eliminate the effects of those factors.

Methods

The patient population for this study has been previously described [2]. The basis for this study was the SEER-Medicare database which links Medicare claims data with patients identified through cancer registries as part of the Surveillance Epidemiology and End Results (SEER) program (www.seer.cancer.gov). This study includes patients who were diagnosed with non-small cell lung cancer between 1998 and 2007 as their first cancer, were covered by Medicare Parts A and B continuously for 6 months preceding lung cancer diagnosis and 2 months after diagnosis, qualified for Medicare based on age, and were 65 years of age or older at the time of the lung cancer diagnosis.

HIV patients were identified based on the International Classification of Diseases, version 9, “042” diagnosis reported in the databases of Medicare claims for health care services given between 1998 and 2009. Prevalent cases of HIV were defined as cases with an initial Medicare claim with an HIV diagnosis that either preceded the diagnosis of lung cancer or occurred within 90 days after lung cancer diagnosis. Other comorbidities were identified through Medicare claims using the ICD-9 codes for selected morbidities from the Charlson morbidity index using the coding algorithm of Quan et al [14]: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease (COPD), peptic ulcer disease, diabetes, liver disease and renal disease, and preceded the diagnosis of lung cancer by no more than 90 days. Age at diagnosis was categorized in 5-year intervals (65–69, 70–74, 75–79, 80–84, 85+). For purposes of this study, they were further grouped into 3 age groups: 65–74, 75–84, and 85

years of age and older). The areas of residence for patients were classified as Big Metro (residing in counties with populations in excess of 1 million) or Other (residing in counties with populations less than 1 million). Marital status was classified as married or other. For each case with HIV, 20 controls matched by age group, gender, race and lung cancer stage at diagnosis were randomly selected from the non-HIV population. Receipt of surgery or radiation therapy was based on information in the SEER database. Receipt of chemotherapy was determined based on the Medicare claims data.

National Comprehensive Cancer Network (NCCN) guidelines recommend that stage I/II patients be treated initially with surgery and chemotherapy is recommended after surgery in stage II patients. Chemotherapy is recommended for all stage IV patients. In general, treatment for stage III patients consists of chemotherapy and radiation. For select stage IIIA patients, surgery can be recommended in addition to radiation and chemotherapy; however, most patients with stage IIIA disease are not surgical candidates due to the extent of their nodal disease. Because it was difficult to distinguish between IIIA and IIIB patients in the database, and stage IIIA and IIIB patients should receive chemotherapy and radiation, assessment of adequate initial treatment for stage III patients was based on whether they received radiation therapy and/or chemotherapy. Patients were classified as receiving guidance concordant treatment if their initial treatment date was within two months of their date of diagnosis, and they received the appropriate initial treatment for their stage of disease. Survival duration was taken as the time of diagnosis until death or date of last Medicare claim for patients who were alive at last follow-up.

Fisher's exact test was used to compare the HIV and non-HIV patients with respect to demographic characteristics. Conditional logistic regression analyses, adjusting for clusters, were used to determine if specified factors were associated with receipt of guidance concordant case per disease stage (Stage I/II, Stage III, Stage IV). Each cluster was composed of a case and its 20 pair-matched controls, and the following factors were explored in each conditional logistic regression in a multivariable analysis: HIV status, number of comorbidities (>1 vs 0–1), residence in a large metropolitan area, and marital status. Odds ratios were estimated with their point estimates and Wald's 95% confidence intervals. Stratified proportional hazards models were used to evaluate whether the same factors and receipt of guidance concordant treatment were associated with survival duration from diagnosis after adjusting for clusters at each disease stage. Hazard ratios and their 95% Wald confidence intervals were estimated.

Results

Due to matching, cases and controls did not differ with respect to age, gender, race and stage of disease (Table 1). In comparison to non-HIV infected individuals, those with HIV had more comorbidities, were more likely to reside in a large metropolitan area, and were less likely to be married.

Overall, 59.5% patients received guidance-concordant care: 58.0% among HIV infected individuals and 59.6% among those who were not infected with HIV. In multivariable analyses, HIV infection was not independently associated with receipt of guidance-

concordant treatment across all stages of disease; however marital status was positively associated (Table 2; Figure 1). Multiple comorbidities were negatively associated with receipt of appropriate treatment for stage I/II patients (Figure 1A). For both stage I/II and III patients (Figures 1B and 1C), residents of large metropolitan areas were less likely to receive treatment in accordance with guidelines than residents of smaller communities which may reflect the disparity in racial composition. In large metropolitan areas, 60% of the patients were from minority groups in contrast to 20% among patients who resided in less heavily populated areas. Among early stage patients, survival duration was negatively associated with HIV infection and multiple comorbidities, and positively associated with receipt of guidance-concordant care (Table 3; Figure 2). For stage III patients, none of the factors evaluated had a significant impact on survival. Although receipt of chemotherapy among stage IV patients was negatively associated with survival, the difference in median survival months between those who received chemotherapy and those who did not was only one month.

Discussion

The higher number of comorbidities among HIV infected patients as compared to those who are not HIV infected has been previously reported [15]. The role of antiretroviral agents in the development of comorbidities is unclear [16–19]. There are reports that abacavir exposure is related to cardiovascular events [17] and cerebrovascular disease [18], but other investigators have found no association [16, 19].

Across stages, the overall proportion of patients who received guidance concordant care was higher than reported previously [4, 7]. Receipt of guidance concordant care did not differ between HIV and non-HIV lung cancer cases across all stage of disease. This finding may reflect the uniform access to medical care for Medicare patients. Stage I/II patients with multiple comorbidities were less likely to receive guidance-concordant than those with no more than a single comorbidity, probably due to concerns related to surgical risk. HIV patients who had progressed to AIDS with poorly controlled opportunistic infections might not be considered for surgery as their condition would be viewed as life limiting. Poor pulmonary function as a result of opportunistic pulmonary infections such as pneumocystis carinii pneumonia might preclude surgery. The presence of multiple comorbidities has been cited as a reason that patients with early stage disease decide not to undergo surgical intervention [5]. Patients with a higher number of comorbidities are at higher risk of having their lung cancer surgery performed at a hospital that performs a low volume of resections which may place them at higher risk for poor outcomes [20].

Comorbidities did not have an impact on whether patients received radiation or chemotherapy for more advanced stages of disease. It is possible, however, that comorbidities may have had an impact on the chemotherapy or radiation regimen prescribed, detail that could not be easily determined from the database. The positive association between being married and receiving appropriate care corroborates another report that social support has a positive effect on receiving appropriate cancer care [7]. Because sexual orientation is not captured as part of the SEER database, it is possible that the larger proportion of HIV infected individuals who are not married may receive social support

through same-gender relationships. The lower adherence to guidance-concordant among stage I/II and III patients who were residents of urban areas may reflect the higher proportion of minority patients in these areas. The racial disparity across urban and rural areas has been previously described [21].

The decreased survival associated with stage I/II HIV-infected individuals treated surgically confirms a previous report in which HIV-infected individuals had a median survival time of 26 months in comparison to 48 months for their immunocompetent counterparts [22]. Comorbidities were negatively correlated with survival in early stage findings, corroborating previous reports [23, 24].

For more advanced stages of NSCLC, the lack of association of HIV with outcome is consistent with studies in lymphoma [25, 26] and cervical carcinoma [27]. Survival for HIV-positive and HIV-negative patients did not differ for Hodgkin and non-Hodgkin lymphoma patients treated with autologous peripheral blood stem cell transplantation [26], or for adult Burkitt lymphoma patients treated with intensive chemotherapy [25]. Among cervical cancer patients, HIV was not an independent factor for response to chemoradiation [27]. Poorer response among HIV-infected patients in this study was due to their more advanced stage of disease at presentation [27].

There are no specific guidelines for management of HIV-infected lung cancer cases. Esophageal toxicities have been reported in HIV-infected lung cancer cases who received radiotherapy, but more data is required to determine whether HIV patients should be treated differently from the immunocompetent population [28]. Postoperative pulmonary and infectious complications among surgically treated non-small cell lung cancer patients occurred more frequently among HIV infected individuals than among those whose HIV status was indeterminate, and resulted in poorer outcomes for those with HIV [22]. While HIV infection did not decrease adherence with guidelines for treatment of NSCLC patients, concordance with guidelines was beneficial for stage I/II patients.

There are a number of limitations to this study. In comparison to the U.S. population as a whole the SEER database population is more urban, affluent and highly educated [29]. The SEER-Medicare database does not capture information on risk factors for lung cancer such as smoking history or measures of immune deficiency (e.g. CD4 counts or HIV viral load). As our study is limited to those who are 65 years of age and older, the lack of disparity between HIV and non-HIV patients may not be applicable to the younger HIV patients with lung cancer. **Since details on HAART and specific oncologic drugs were not available, it was difficult to determine if treatment decisions were influenced by concerns regarding potential drug interactions.** This study demonstrates that HIV is not independently associated with receipt of guidance-concordant care in NSCLC lung cancer cases aged 65 years and older covered by Medicare. HIV infection is, however, associated with poorer survival in stage I/II patients. **It is unclear whether this association is related to potential comorbidities rather than to HIV infection. Future research is needed to further elucidate the role of HIV infection in outcomes among early stage NSCLC patients.**

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Figure 1.
Odds ratios for receiving guidance-concordant treatment

Figure 2.
Hazard ratios for overall survival

Table 1

Demographic Characteristics

	HIV (N=174)	Non-HIV (N=3480)
Age in years		
65–74	106 (60.9)	2120 (60.9)
75	68 (39.1)	1360 (39.1)
P-value *	1.000	
Gender		
Male	118 (67.8)	2360 (67.8)
Female	56 (32.2)	1120 (32.2)
P-value *	1.000	
Race		
White	102 (58.6)	2040 (58.6)
Non-white	72 (41.4)	1440 (41.4)
P-value *	1.000	
Stage of disease		
I/II	57 (32.8)	1140 (32.8)
III	55 (31.6)	1100 (31.6)
IV	62 (35.6)	1240 (35.6)
P-value *	1.000	
Comorbidities		
0–1	105 (60.3)	2577 (74.1)
>1	69 (39.6)	903 (25.9)
P-value	P<0.001	
Urban/Rural		
Big Metro	142 (81.6)	1770 (50.9)
Other	32 (18.4)	1710 (49.1)
P-value *	<0.001	
Married		
Yes	65 (37.4)	1796 (51.6)
No	109 (62.6)	1684 (48.4)
P-value	P<0.001	

* Based on Fisher's exact test

Table 2

% Received Guidance-Concordant Treatment

Factor	Stage I/II (%)	Stage III (%)	Stage IV (%)
All patients	64.5	63.1	51.6
HIV			
Yes	61.4	58.2	54.8
No	64.7	63.4	51.4
Odds ratio (95% CI)	1.22 (0.69, 2.18)	1.01 (0.57, 1.77)	1.15 (0.68, 1.94)
P-value *	0.494	0.986	0.602
Comorbidities			
0–1	67.8	65.4	51.9
>1	56.8	57.1	50.6
Odds ratio (95% CI)	0.66 (0.50, 0.86)	0.78 (0.59, 1.03)	1.08 (0.83, 1.41)
P-value *	0.003	0.078	0.572
Urban/Rural			
Big Metro	56.2	57.4	49.7
Other	72.4	69.6	54.1
Odds ratio (95% CI)	0.55 (0.41, 0.75)	0.58 (0.42, 0.78)	1.06 (0.80, 1.40)
P-value *	<0.001	<0.001	0.694
Married			
Yes	69.3	67.8	56.6
No	58.1	58.8	47.2
Odds ratio (95% CI)	1.42 (1.01, 1.85)	1.37 (1.05, 1.78)	1.33 (1.05, 1.69)
P-value *	0.008	0.019	0.020

* Based on a multivariate conditional logistic regression model

Table 3

Median Overall Survival

Factor	Stage I/II Survival (mos) Median (95% CI)	Stage III Survival (mos) Median (95% CI)	Stage IV Survival (mos) Median (95% CI)
HIV			
Yes	26 (15–59)	12 (7–16)	6 (4–6)
No	43 (38–47)	10 (9–11)	6 (6–7)
Hazard ratio (95% CI)	1.48 (1.06, 2.07)	0.98 (0.72, 1.32)	1.27 (0.97, 1.67)
P-value *	0.021	0.876	0.082
Receipt of guidance concordant treatment			
Yes	63 (57–69)	10 (10–11)	6 (5–6)
No	21 (18–23)	9 (8–12)	7 (6–8)
Hazard ratio (95% CI)	0.35 (0.30, 0.41)	0.98 (0.85, 1.12)	1.27 (1.13, 1.44)
P-value *	<0.001	0.733	<0.001
Comorbidities			
0–1	50 (43–55)	11 (10–12)	6 (6–7)
>1	29 (25–37)	9 (8–10)	5 (5–6)
Hazard ratio (95% CI)	1.39 (1.17, 1.64)	1.11 (0.96, 1.28)	1.06 (0.92, 1.22)
P-value *	<0.001	0.151	0.451
Urban/Rural			
Big Metro	38 (33–43)	10 (9–11)	6 (5–6)
Other	47 (41–55)	11 (10–12)	7 (6–8)
Hazard ratio (95% CI)	0.98 (0.81, 1.18)	1.05 (0.89, 1.22)	1.01 (0.87, 1.17)
P-value *	0.796	0.578	0.871
Married			
Yes	47 (41–54)	11(10–12)	6 (6–7)
No	36 (32–41)	10 (9–11)	6 (5–6)
Hazard ratio (95% CI)	0.89 (0.76, 1.04)	0.89 (0.78, 1.02)	0.92 (0.81, 1.04)
P-value *	0.155	0.085	0.199

* Based on multivariate stratified proportional hazards model