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Referral patterns in advanced non-small cell lung cancer: Impact on delivery of treatment and survival in a contemporary population based cohort

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ABSTRACT

Introduction: Chemotherapy improves overall survival (OS) in advanced non-small cell lung cancer (NSCLC), yet low rates of chemotherapy utilization have been observed. We sought to characterize the clinical effectiveness of chemotherapy in the general population by evaluating referral patterns, predictors of chemotherapy receipt and outcomes.

Methods: All referred cases of stage IIIB/IV NSCLC in British Columbia from January 1 to December 31, 2009 were retrospectively reviewed. Patient demographics, tumor characteristics and treatments were extracted. OS was estimated using the Kaplan–Meier method. Cox Proportional Hazards modeling was used to control for confounding variables. Multiple logistic regression was used to assess factors that predicted for chemotherapy treatment.

Results: 1373 patients were identified. Median age 70 years, 53% male, 37% ECOG $\geq$ 3. Histology: 34% non-squamous, 21% squamous and 46% NOS. 748 (54%) patients were assessed by medical oncology and 417 (30%) received chemotherapy. Predictors of chemotherapy treatment were younger age, ECOG 0–2, living in a rural area and not receiving radiotherapy. There was an improvement in OS in patients who received chemotherapy at 13.1 months versus best supportive care 5.4 months ($p < 0.0001$). This remained statistically significant when controlling for ECOG, sex, age, histology (HR 0.68, CI 0.59–0.78).

Conclusions: In this population-based setting, 37% of patients had an ECOG $\geq$ 3 at the time of referral, 54% were assessed by a medical oncologist and only 30% received chemotherapy. This is despite the awareness that chemotherapy significantly improves survival. Strategies to optimize appropriate referral such that patients do not miss out on life-prolonging therapy should be evaluated.

1. Introduction

Lung cancer is the leading cause of cancer deaths in both males and females with an estimated 224,000 new cases and 159,000 deaths in the US in 2014 and 25,500 new cases and 20,200 deaths in Canada in 2013 [1,2]. Eighty-five percent of lung cancer cases are NSCLC, and of these 75% are diagnosed as advanced NSCLC [3–5]. Palliative systemic therapy has been shown to improve survival in advanced NSCLC patients [6–9].

Within this past decade, the population of patients who are candidates for palliative systemic therapy has expanded. Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors have shown to be effective in EGFR mutated and ALK-rearranged patients respectively, and can be safely given to older patients with poorer ECOG performance status [10,11]. While there is data showing efficacy of palliative systemic therapy in elderly patients [12–14] as well as patients who are ECOG 2 [15], delivery of chemotherapy to these patient populations is not as consistent as with younger fit patients. The availability of targeted oral treatments may facilitate systemic treatments in those who would have otherwise been excluded in the past.

Many of the studies evaluating treatment utilization patterns in the literature are in selected patient populations, such as Surveillance Epidemiology and End Results (SEER)-Medicare,

Abbreviations: OS, overall survival; NSCLC, non-small cell lung cancer; BC, British Columbia; CPH, Cox Proportional Hazards; MLR, Multinomial logistic regression; MO, medical oncology; RO, radiation oncology; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; BSC, best supportive care; EGFR, Epidermal Growth Factor Inhibitor; ALK, Anaplastic Lymphoma Kinase; TKI, tyrosine kinase inhibitor; PS, performance status.

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Health Maintenance Organization (HMO) populations or institutional reviews. These results may be influenced by referral bias, insurance coverage and access to care. Population-based data provides more realistic and accurate data about referrals, and treatments. While this may differ to some extent by health care system, this information is critical for informing policy-makers of resource utilization and to inform clinicians of true clinical effectiveness of treating patients and reveal the extent of unmet need for those not given systemic therapy. Currently, there is a paucity of studies evaluating referral patterns and their impact on outcomes in the modern era.

British Columbia has a publicly funded system that provides care to a population of 4.5 million through a centralized cancer program, allowing the opportunity to evaluate referral patterns and treatment utilization in a population-based fashion. The British Columbia Cancer Agency (BCCA) has 6 cancer centers and operates the Community Oncology Network to provide care in rural sites.

The BCCA reports to the Canadian Cancer Registry, the administrative database that collects information on cancer incidence from all provincial and territorial cancer registries in Canada. As part of an initiative with Canadian Partnership Against Cancer (CPAP) the BCCA adopted collaborative staging. Collaborative staging is method of conversion between the TNM staging system of the American Joint Committee on Cancer (AJCC) and the Surveillance and Epidemiology and End Result program (SEER) Summary Staging System that records detailed tumor, nodal and metastasis information on patients that can be translated easily to different staging versions. This enabled our study to establish the number of patients who had advanced staged NSCLC in the province as our denominator when determining the proportion referred. Of all the diagnoses of advanced NSCLC in the province, 90% are referred under the umbrella of the BCCA for management. Data on the remaining 10% could not be captured as they were not evaluated at a BCCA center.

We conducted a retrospective review of our advanced NSCLC population. Our primary objective was to evaluate referral patterns and receipt of radiation and chemotherapy. Secondarily, we sought to identify predictors of chemotherapy receipt, and assess survival outcomes in the general population.

2. Patients and methods

A retrospective review was conducted of all patients referred to the BCCA with histologically confirmed diagnosis of stage IIIB/IV NSCLC from January 1, 2009 to December 31, 2009. Patient demographics including age, gender, Eastern Cooperative Group (ECOG) performance status (PS), smoking status, histology and geographic location were collected by oncologists at the time of first BCCA consult. Rural and urban were defined by matching the patient's postal code with the population density of each census block as per the Statistics Canada's Postal Code Conversion File. Treatment and outcomes were abstracted from the patients' electronic record.

Data about referral events were collected through the Outcomes and Surveillance Integrated System (OaSIS). Patients were triaged by BCCA oncologists specialized in thoracic oncology to be assessed by medical oncology and/or radiation oncology by reviewing the information in the electronic record. All referred patients were triaged to medical oncology, radiation oncology, or both. Time from diagnosis to referral was defined as time from pathologic diagnosis to receipt of referral at the BCCA. All of the patients has a histologic diagnosis. Time from referral to medical oncology consult (MOC) or radiation oncology consult (ROC) was from receipt of patient referral to being seen by a medical or radiation oncologist. Diagnosis to chemotherapy/radiotherapy was the time from pathologic diagnosis to first receipt of treatment by the respective modality. Time from MOC/ROC to chemotherapy/radiotherapy was the time from being first seen by the oncologist to the first treatment by the respective modality.

Ethical approval for the study was obtained from the institutional research ethics board.

The primary outcome measures were proportions of advanced NSCLC patients who were referred to radiation oncology (RO), medical oncology (MO), and who received radiation and chemotherapy. Secondarily, predictors of receipt of MO consult and chemotherapy were evaluated. Overall survival (OS) was defined as the time from diagnosis to death.

Chi-squared, and Wilcoxon tests were used to compare characteristics between groups. *p*-values were two-sided, with a significance level of 0.05. The association between patient

Table 1
Baseline characteristics of all referred patients with histologically confirmed stage IIIB/IV NSCLC including all patients, patients seen by a medical oncologist and patients who were not seen by a medical oncologist.

	Entire cohort $n = 1373$ (%)	MO consult $n = 748$ (%)	No MO consult $n = 625$ (%)	Univariate *p*-value
Sex (%)				
Male	725 (53%)	391 (52%)	334 (53%)	0.704
Female	648 (47%)	357 (48%)	291 (47%)	
Geographical site				
Rural	237 (17%)	142 (19%)	95 (15%)	0.073
Urban	1136 (83%)	606 (81%)	530 (85%)	
Age (median, range)	70 (29–96)	66 (29–90)	75 (43–96)	<0.0001
20–49	65 (5%)	53 (7%)	12 (2%)	
50–59	194 (14%)	152 (20%)	42 (7%)	
60–69	389 (28%)	257 (34%)	132 (21%)	
70–75	281 (20%)	146 (20%)	135 (22%)	
76–80	231 (17%)	87 (12%)	144 (23%)	
81–85	150 (11%)	40 (5%)	110 (18%)	
86–90	53 (4%)	13 (2%)	40 (6%)	
>90	10 (1%)	0 (0%)	10 (2%)	
ECOG PS				
0–1	544 (40%)	386 (52%)	158 (25%)	<0.0001
2	317 (23%)	184 (25%)	133 (21%)	
3–4	512 (37%)	178 (24%)	334 (53%)	
Histology				
Non-squamous	464 (34%)	305 (41%)	159 (25%)	<0.0001
Squamous	284 (21%)	135 (18%)	149 (24%)	
NOS	625 (46%)	308 (41%)	317 (51%)	

Abbreviations: MO – medical oncology, PS – performance status, NOS – not otherwise specified. Level of significance, $p < 0.05$.