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Behavioral and Psychological Predictors of Chemotherapy Adherence in Patients with Advanced Non-Small-Cell Lung Cancer

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Abstract

Objective—Dose delays and reductions in chemotherapy due to hematologic toxicities are common among patients with advanced non-small-cell lung cancer (NSCLC). However, limited data exist on behavioral or psychological predictors of chemotherapy adherence. The goal of this study was to explore the frequency and clinical predictors of infusion dose delays and reductions in this patient population.

Methods—Fifty patients newly diagnosed with advanced NSCLC of high performance status (ECOG PS=0-1) completed baseline assessments on quality of life (FACT-L) and mood (HADS) within eight weeks of diagnosis. Participants were followed prospectively for six months. Chemotherapy dosing data came from medical chart review.

Results—All patients received chemotherapy during the course of the study, beginning with either a platinum-based doublet (74%), an oral epidermal growth factor receptor-tyrosine kinase inhibitor (14%), or a parenteral single agent (12%). Forty percent (N=20) of patients had either a dose delay (38%) and/or reduction (16%) in their scheduled infusions. Fisher's exact tests showed that patients who experienced neutropenia, smoked at the time of diagnosis, or reported heightened baseline anxiety were significantly more likely to experience dose delays or reductions. There were no associations between chemotherapy adherence and patient demographics, performance status, or quality of life.

Conclusion—In this sample, over one-third of patients with advanced NSCLC experienced either a dose delay or reduction in prescribed chemotherapy regimens. Behavioral and psychological factors, such as tobacco use and anxiety symptoms, appear to play an important role in chemotherapy adherence, though further study is required to confirm these findings.

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Keywords

non-small-cell lung cancer; chemotherapy; adherence

Introduction

The standard of care for patients diagnosed with advanced NSCLC includes some form of chemotherapy, which may consist of either platinum-based doublets, a single agent, or oral epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI's).¹ However, treatment with any of these anti-cancer regimens often leads to impairing side effects, such as cytopenia, emesis, and nephrotoxicity, that compromise patient adherence to chemotherapy. Of these, hematologic toxicities most commonly cause infusion dose delays, though some data suggest that neutropenia may actually serve as a useful biological marker of chemotherapy dose intensity for patients with advanced NSCLC.² Therefore, identifying dose-limiting factors is critical not only for maximizing chemotherapy delivery but also for evaluating patient response to treatment.

While hematologic-related dose delays are well-documented, few data exist regarding the effects of behavioral and psychological variables on chemotherapy adherence.³ Investigators have linked some of these factors, such as quality of life,⁴ smoking behavior⁵ and mood symptoms,⁶ to worse mortality among patients with NSCLC, which may be mediated through poor adherence to treatment. Up to 40% of patients with NSCLC report smoking at the time of diagnosis,⁷ increasing the risk of thromboembolic events⁸ and infections,⁹ factors that potentially complicate adherence. Also, patients experiencing psychological difficulties may be less adherent to cancer therapy, perhaps due to exacerbations of treatment side effects. Researchers have observed that anxiety symptoms are related to delayed emesis and poorer response to anti-nausea medication after use of platinum-based chemotherapy.¹⁰

To further research in this area, we examined the following: 1) the frequency of chemotherapy dose delays and reductions in a sample of patients with advanced NSCLC and 2) the extent to which behavioral and psychological factors relate to treatment adherence.

Materials and Methods

Patient Selection

The data for this observational study came from a pilot investigation of early palliative care services for patients with newly diagnosed advanced NSCLC. Eligible participants included patients within eight weeks of diagnosis of stage IIIb (with pericardial or pleural effusions) or stage IV NSCLC. These disease stages are considered incurable and treated with similar protocols. Participants also had to be greater than 18 years old, literate in English, and of high performance status (i.e., Eastern Cooperative Oncology Group PS = 0 or 1). The Dana-Farber/ Partners Cancer Care IRB approved the project protocol prior to the initiation of the study.

Procedure

From October 2003 through June 2005, participants enrolled in a single-arm, prospective study to test the feasibility and acceptability of integrated oncologic and palliative care services over the course of illness. Patients were scheduled to consult with the Massachusetts General Hospital Palliative Care Team monthly while simultaneously receiving standard ambulatory oncology services. Patients completed baseline assessments of their quality of life and mood in the thoracic oncology clinic prior to or within one month of initiating chemotherapy. Participants were followed for a six-month period.

Measures

Functional Assessment of Cancer Therapy-Lung (FACT-L).¹¹—The FACT-L is a 33-item questionnaire that assesses health-related quality of life across multiple domains including physical, social, emotional, and functional wellbeing. Responses are scored on 5-point scales assessing quality of life during the previous week. The Lung Cancer Subscale (LCS) of the questionnaire addresses seven symptoms specific to lung cancer, such as shortness of breath.

Hospital Anxiety and Depression Scale (HADS).¹²—The HADS is a 14-item questionnaire designed for medically-ill populations that contains two subscales assessing anxiety and depression symptoms during the past week. We utilized a cutoff score of 8 or greater on each subscale to identify patients with possible depression and anxiety based on published guidelines.¹²

Chart Review

A board-certified oncologist conducted a retrospective review of patients' electronic medical records to identify chemotherapy agents prescribed and frequency of any infusion dose delays or reductions during the six-month study period. Such modifications to chemotherapy regimens were defined as instances in which patients either did not receive or received a reduced dose of the prescribed chemotherapy on the date scheduled by the oncology team. Reasons for altering chemotherapy regimens, such as fatigue or neutropenia (i.e., absolute neutrophil count <1000), were also documented in the electronic medical record and accessible by chart review. Finally, data were collected on patient history of tobacco use, including smoking status at the time of diagnosis and pack years of smoking.

Statistical Methods

Analyses were conducted with SPSS (version 14.0), beginning with calculation of the frequencies, means, and standard deviations for the study variables. Fisher's exact tests and point-biserial correlation coefficients were computed to explore the bivariate relationships between chemotherapy adherence and patient demographic, psychosocial, health behavior, and clinical characteristics. Two separate logistic regression models were analyzed to identify independent baseline predictors of chemotherapy dose delays and reductions, controlling for neutropenia.

Results

Sample Characteristics

Fifty participants were consecutively enrolled for the original palliative care trial. Although four patients withdrew from the study, all baseline self-report and six-month chart review data were available for this analysis, with no data lost to follow-up. Ninety-four percent of participants (N=47) had newly diagnosed stage IV NSCLC, with 6% having stage IIIb disease (with effusions). The demographic characteristics of the sample are listed in Table 1; all participants identified themselves as White. Clinically significant anxiety and depression symptoms were present in 31% and 21% of the sample, respectively. Forty-five patients (90%) had a history of tobacco use, 13 of whom (26%) were still smoking at the time of diagnosis. Mean pack years for the sample was 40.53 (SD=26.36), with no significant differences observed between current and former smokers. Finally, patients indicated impaired quality of life and the presence of lung cancer symptoms on the baseline FACT-L (see Table 1).

Types of Chemotherapy and Frequency of Dose Delays and Reductions

Initial chemotherapy included either a platinum-based doublet (74%, e.g., carboplatin and paclitaxel), an oral EGFR-TKI (14%, e.g., gefitinib), or a parenteral single agent (12%, e.g., vinorelbine). The majority of patients (60%) received second-line chemotherapy, and many (38%) underwent third-line therapy or greater. Forty percent (N=20) of participants experienced either a dose delay (38%) and/or reduction (16%) in their scheduled regimens. Documented reasons for chemotherapy non-adherence included: neutropenia (40%), thrombocytopenia (35%), fatigue (20%), anemia (15%), nausea/vomiting (15%), neuropathy (10%), patient preference (10%), thromboembolic event (5%), upper-respiratory infection (5%), febrile illness (5%), elevated liver function tests (5%), and failure to thrive (5%). The number of infusion cycles did not relate to chemotherapy dose delays or reductions ($r_{pb} = .17, p=.28$).

Predictors of Chemotherapy Dose Delays or Reductions

Bivariate associations displayed in Table 1 indicate that the presence of neutropenia as well as current smoking and heightened anxiety symptoms at the time of diagnosis of advanced NSCLC predicted greater likelihood of having a chemotherapy dose delay or reduction during the subsequent six-month period. Controlling for neutropenia only, separate logistic regression analyses showed that patient smoking ($OR=11.21, p=.01$) and anxiety symptoms ($OR=4.28, p=.04$) remained significantly associated with chemotherapy dose delays and reductions. P-values for the Hosmer and Lemeshow goodness-of-fit tests were .71 and .53, respectively.

Discussion

As expected, one of the strongest predictors of chemotherapy dose delays and reductions in this homogeneous sample of patients with advanced NSCLC was neutropenia. Adjusting for the hematologic toxicity, other significant predictors of poor chemotherapy adherence included current smoking and elevated anxiety. The mechanism by which smokers are more

likely to have chemotherapy dose delays or reductions remains unclear. Yet, smoking is associated with worse medical outcomes, including mortality,⁵ the causes of which are likely multifactorial and potentially include altered metabolism of chemotherapeutic agents.¹³ Moreover, given that tobacco use increases the risk of thromboembolic events⁸ and infections,⁹ smokers with NSCLC may simply be more ill and unable to tolerate prescribed doses of chemotherapy.

The high rates of anxiety and depressive symptoms in this sample are consistent with previous research on the rates of psychological distress in this population.¹⁴ Patients with heightened anxiety may experience worse cancer-related symptoms that reduce adherence to treatment. For example, researchers have observed that anxiety symptoms are associated with fatigue in anemic patients with lung cancer¹⁵ and more severe physical symptoms in a sample of patients with diverse malignancies undergoing chemotherapy.¹⁶ Evidence suggests that this relationship between anxiety and physical symptoms during chemotherapy may be mediated by patients' illness beliefs about the efficacy of cancer treatment.¹⁶ Further study is needed to understand the course of anxiety comorbid with NSCLC, to assess patients' expectations and interpretations regarding their disease, and to determine the extent to which chemotherapy adherence is complicated by toxic treatment side effects.

The findings from the present study, while novel, are preliminary and warrant confirmation through prospective large-scale studies, without the potential selection biases and intervention effects related to patient enrollment in the early palliative care trial. Due to the small sample size, an examination of adherence by type of medication regimen was not feasible and the results of the logistic regression analyses ought to be interpreted cautiously. Therefore, follow-up longitudinal investigations, that are sufficiently powered, are needed to further elucidate the factors that both predict anxiety and smoking in this patient population, as well as to identify the relevant covariates that may clarify the direction and underlying mechanisms of the complex associations among chemotherapy adherence and psychological factors. As these mediating mechanisms become apparent, tailored interventions targeting smoking behavior and anxiety symptoms could then be developed and tested to enhance adherence to therapy, ideally improving both medical and psychological outcomes in patients with advanced NSCLC.

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Table 1

Participant Characteristics for Entire Sample and by Chemotherapy Dose Status

Predictor Variable	Entire Sample	No Chemotherapy Dose Delay or Reduction	Chemotherapy Dose Delay or Reduction	P-value *
	N (%) or M (SD)	N (%) or M (SD)	N (%) or M (SD)	
Sex				.77
Female	30 (60)	17 (57)	13 (65)	
Male	20 (40)	13 (43)	7 (35)	
Age in years				.39
Mean (SD)	65.70 (8.67)	66.57 (9.85)	64.40 (6.56)	
ECOG PS [†]				.74
0	11 (22)	6 (20)	5 (25)	
1-2	39 (78)	24 (80)	15 (75)	
Neutropenia				.02
No	26 (52)	20 (67)	6 (30)	
Yes	24 (48)	10 (33)	14 (70)	
Smoker at Diagnosis				.02
No	36 (72)	25 (86)	11 (55)	
Yes	13 (26)	4 (14)	9 (45)	
HADS-Anxiety [‡]				.03
0-7	33 (69)	23 (82)	10 (50)	
8	15 (31)	5 (18)	10 (50)	
HADS-Depression [‡]				.72
0-7	38 (79)	23 (82)	15 (75)	
8	10 (21)	5 (18)	5 (25)	
FACT-L [§]				.58
Mean (SD)	94.37 (16.37)	95.45 (18.02)	92.80 (13.93)	
FACT-LCS [§]				.52
Mean (SD)	19.84 (4.38)	20.17 (4.63)	19.35 (4.06)	

* P-values derived from two-sided Fisher's exact tests when both variables are dichotomous and point-biserial correlation coefficients when one variable is continuous and the other dichotomous (r_{pb} coefficients for Age=-.12, FACT-L=-.08 and LCS=-.09).

[†] ECOG PS (Eastern Cooperative Oncology Group Performance Status) – note: one participant had an ECOG PS=2

[‡] HADS (Hospital Anxiety and Depression Scale) – Scores ≥ 8 probable case of anxiety or depression

[§] FACT-L (Functional Assessment of Cancer Therapy-Lung) – Out of a total score 132 with higher values indicating better QOL; LCS (Lung Cancer Subscale) – Out of a total score of 28 with higher values indicating fewer symptoms