First-Line Systemic Therapy Practice Patterns and Concordance With NCCN Guidelines for Patients Diagnosed With Metastatic NSCLC Treated at NCCN Institutions

Carrie Zornosa, MSPH[a]; Jonathan L. Vandergrift, MS[a]; Gregory P. Kalemkerian, MD[b]; David S. Ettinger, MD[c]; Michael S. Rabin, MD[d]; Mary Reid, PhD[e]; Gregory A. Otterson, MD[f]; Marianna Koczywas, MD[g]; Thomas A. D'Amico, MD[h]; Joyce C. Niland, PhD[g]; Rizvan Mamet, MS[g]; and Katherine M. Pisters, MD[i]

Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) allow many systemic therapy options for patients with metastatic non–small cell lung cancer (NSCLC). This analysis uses the NCCN NSCLC Outcomes Database to report on first-line therapy practice patterns and concordance with NCCN Guidelines. The analysis was limited to patients diagnosed with metastatic NSCLC between September 2006 and November 2009 at 1 of 8 participating NCCN Member Institutions. Patient characteristics, regimens used, and guidelines concordance were analyzed. Institutional variation and changes in practice over time were also measured. A total of 1717 patients were included in the analysis. Of these, 1375 (80%) were treated with systemic therapy, most often in the form of a carboplatin-based doublet (51%) or carboplatin-based doublet with targeted therapy (17%). Overall, 76% of patients received care that was concordant with NCCN Guidelines. Among patients with good performance status (n = 167), the most common reasons for not receiving first-line therapy were that therapy was not recommended (39%) or death occurred before treatment (33%). The most common reason for receiving nonconcordant drug therapy was the administration of pemetrexed or erlotinib before its incorporation into the NCCN Guidelines for first-line therapy (53%). Most patients in this cohort received care that was concordant with NCCN Guidelines. The NSCLC Outcomes Database is a valuable resource for evaluating practice patterns and concordance with NCCN Guidelines among patients with NSCLC. (*JNCCN* 2012;10:847–856)

From the [a]National Comprehensive Cancer Network, Fort Washington, Pennsylvania; [b]University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan; [c]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore Maryland; [d]Dana-Farber/Brigham and Women's Cancer Center, Boston, Massachusetts; [e]Roswell Park Cancer Institute, Buffalo, New York; [f]The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute, Columbus, Ohio; [g]City of Hope Comprehensive Cancer Center, Los Angeles, California; [h]Duke Cancer Institute, Durham, North Carolina; and [i]The University of Texas MD Anderson Cancer Center, Houston, Texas.

Submitted October 11, 2011; accepted for publication April 2, 2012.

Ms. Zornosa and Mr. Vandergrift have disclosed that they are employees of NCCN. The remaining authors have disclosed that that they have no financial interests, arrangements, or affiliations with the manufacturers of any products discussed in this article or their competitors.

Correspondence: Carrie Zornosa, MSPH, National Comprehensive Cancer Network, 275 Commerce Drive, Suite 300, Fort Washington, PA 19034. E-mail: zornosa@nccn.org

Lung cancer is one of the deadliest and most common cancers in the United States. An estimated 226,000 cases of lung cancer will be diagnosed in 2012, and 56% of these will be distant-stage disease. Prognosis for patients with advanced disease is poor, with only 4% alive 5 years after diagnosis.[1] Most patients with lung cancer are diagnosed with non–small cell lung cancer (NSCLC), which constitutes 85% of diagnoses.[2] Because of the aggressive and incurable nature of metastatic NSCLC, selection of first-line therapy is a critical decision point in the treatment of advanced lung cancer. The oncology provider must balance toxicity, expected survival benefit, and impact on quality of life.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC provide recommendations for the treatment of cancer (available at NCCN.org).[3] Recommendations are based on the most

recent evidence supplemented with expert medical opinion from an interdisciplinary panel of clinicians and researchers. Recommendations are reviewed at least once a year to reflect the emergence of practice-changing evidence. NCCN Guidelines for NSCLC recommendations provide many options for first-line systemic drug therapy. In recent years, recommendations for first-line management have included targeted therapies in addition to chemotherapeutic agents. Furthermore, first-line therapy recommendations have evolved to depend on histology subtype and biomarker test results.

The NSCLC component of the NCCN Outcomes Database was developed in 2007. A primary objective of the NCCN Outcomes Database is to measure the quality of care among patients with cancer through capturing practice patterns at NCCN Member Institutions and comparing these data with NCCN Guidelines recommendations. Currently, the NCCN Outcomes Database Project comprises 5 active disease sites: breast cancer, non-Hodgkin's lymphoma, colon/rectal cancer, ovarian cancer, and NSCLC.

The primary aim of this analysis is to describe first-line therapy patterns for patients with metastatic NSCLC and examine concordance between first-line therapy decisions and NCCN Guidelines recommendations. Because of the recent rapid evolution of evidence and recommendations for first-line metastatic NSCLC and lack of recent data on practice patterns for first-line therapy, a need exists to evaluate first-line therapy practice patterns in a large-scale, multi-institutional setting.

Methods

Data Source

The NCCN NSCLC Outcomes Database is a multi-institutional observational cohort study with participation from the following institutions: City of Hope Comprehensive Cancer Center; Dana-Farber/Brigham and Women's Cancer Center; Duke Cancer Institute; The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute; The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; The University of Texas MD Anderson Cancer Center; Roswell Park Cancer Institute; and University of Michigan Comprehensive Cancer Center.

Patients are eligible for the database if they have presented to a participating NCCN Member Institution with a diagnosis of NSCLC. Patients with a past NSCLC diagnosis (within 2 years of the current NSCLC diagnosis) or a past invasive cancer diagnosis other than NSCLC (within 5 years of the current NSCLC diagnosis) are ineligible. Eligible patients must have a histology consistent with an AJCC defined NSCLC subtype and receive treatment, such as drug therapy, radiation therapy, surgery, or palliative care, at the NCCN Member Institution.

Data collection includes patient, disease, and treatment characteristics that are manually abstracted from medical records by trained data managers at each participating site. Data are abstracted for each patient in 6-month intervals for the first 2 years of follow-up, and annually thereafter. Patients who permanently transfer their care or are diagnosed with a new other cancer are subsequently only followed for survival data.

Reliability and validity of the abstracted data are assessed through several processes, including real-time logic checks, monthly data manager training teleconferences, quarterly quality assurance testing, biannual in-person data manager training, and annual data audits wherein abstracted data are compared with source documentation. Data collection and storage policies have undergone Institutional Review Board review and approval at each participating institution. Two participating centers require patient informed consent for participation, whereas the other participating institutions have deemed this project to be minimal risk research with adequate privacy safeguards and have granted waivers for informed consent.

Patient Cohort

The NCCN NSCLC Outcomes Database was queried to identify 2258 patients diagnosed with metastatic disease (stage IV or IIIB with malignant pleural effusion[4]) between September 2006 and November 2009. Patients were subsequently excluded from the analysis if they did not have at least 90 days of quality follow-up (n = 259; 11%), received any cancer-directed therapy before diagnosis of metastatic disease (n = 75; 4%), initiated first-line therapy at an outside institution (n = 152; 8%), or underwent a resection of primary and metastatic disease sites (n = 55; 3%). After exclusions, 1717 patients were included in the analytic cohort.

Characterization of First-Line Therapy and Guidelines Concordance

First-line therapy was defined as the initial cytotoxic and/or targeted drug therapy regimen each patient received after diagnosis. Drug regimens were analyzed according to drug therapy category and individual regimens.

Patients receiving off-trial first-line therapy were classified as receiving concordant treatment if all drugs within their first-line therapy regimen were recommended as first-line drugs in the NCCN Guidelines and the patient did not have any clinical characteristic, such as poor performance status (PS), that contradicted the guidelines recommendation for first-line therapy. During the study period, 3 versions containing updates to the treatment algorithm of the NCCN Guidelines were published.[5–7] Each version contained a change to the recommendations for first-line therapy. Therefore, patient concordance was assessed against the latest version of the NCCN Guidelines at the time of drug therapy initiation (or diagnosis date for patients who did not receive drug therapy).

Because the NCCN Guidelines state that clinical trials are considered the best management for any patient with cancer, patients receiving any part of first-line drug therapy directed by a clinical trial were classified as concordant. Patients with an unknown parameter relevant to determining patient concordance (i.e., patients with unknown PS or histology subtype) were assumed to have received concordant care in the absence of any clear evidence of nonconcordant care (n = 298). A sensitivity analysis was performed to evaluate the impact of this assumption on the results.

Statistical Analysis

All analyses were performed with SAS v9.2 (SAS Institute Inc., Cary, NC). Significant differences between proportions were assessed using the Pearson χ^2 test. Significant trends over time were assessed using the Cochran-Armitage test for trend. Multivariate logistic regression models were used to compute adjusted odds ratios to assess the association between patient demographic or clinical factors and the odds of receiving systemic drug therapy or enrollment in a clinical trial. All tests were 2-sided, with an alpha of 0.05 as a cut-off for statistical significance.

Results

Cohort Characteristics and Receipt of Systemic Drug Therapy

Demographics and clinical characteristics for the 1717 patients in the cohort are shown in Table 1. Median age at diagnosis was 64 years. The cohort was equally represented by male (51%) and female (49%) patients. Most patients presented with adenocarcinoma (62%), squamous (15%), or unspecified NSCLC histology (19%).

Overall, 80% (n = 1375) of patients received first-line drug therapy, of which 18% (n = 244) received therapy on a clinical trial. When stratified according to treating institution, use of first-line drug therapy ranged from 69% to 90%, whereas the percentage of drug therapy that was protocol-directed ranged from 4% to 30%. In multivariate logistic regression models, patients with poor baseline PS and who were smokers at diagnosis or quit smoking within 1 year of diagnosis were less likely to receive systemic drug therapy ($P < .001$; Table 1).

Among patients receiving first-line therapy, PS was the only analyzed patient characteristic associated with receiving first-line therapy on a clinical trial, with 10% of patients with PS 2 (adjusted odds ratio [OR], 0.4; 95% CI, 0.3–0.8) and 12% of those with PS 3 (adjusted OR, 0.6; 95% CI, 0.2–1.7) enrolled in a trial compared with 20% (n = 198) of patients with PS 0/1. Race was unrelated to enrollment with 18% of Caucasian, 19% of African American, 19% of Hispanic, and 16% of Asian patients enrolled (P = .90).

Characterization of Off-Trial First-Line Therapy

Drug therapy categories for the 1131 patients receiving off-trial first-line drug therapy are shown in Figure 1. Platinum-based doublets (n = 676; 60%) and platinum-based doublets combined with a targeted therapy agent (n = 214; 19%) constituted the most common therapy strategies for this group. Single-agent targeted therapy (n = 148; 13%) and single-agent chemotherapy (n = 91; 8%) were less commonly administered in this setting.

Table 2 reports the specific drug combinations received within each off-trial first-line drug therapy category. Carboplatin (n = 779; 87%) was more commonly used than cisplatin (n = 111; 12%) among 2- and 3-drug platinum-based therapies, although an increase in cisplatin administration was observed over time, with 7%, 9%, and 21% of patients diagnosed in 2007, 2008, and 2009, respectively, receiv-

Table 1 Association Between Demographic and Clinical Characteristics and Receipt of First-Line Therapy (n = 1717)

	Total n (col %)	Received First-Line Drug Therapy		Adjusted OR (95% CI)[a]
		No n (row %)	Yes n (row %)	
Age (y)				
< 50	234 (14)	28 (12)	206 (88)	Ref
50–59	429 (25)	79 (18)	350 (82)	0.6 (0.4–1.1)
60–69	572 (33)	119 (21)	453 (79)	0.6 (0.3–1.0)
≥ 70	482 (28)	116 (24)	366 (76)	0.5 (0.3–0.8)
				P = .09
Sex				
Male	878 (51)	190 (22)	688 (78)	Ref
Female	839 (49)	152 (18)	687 (82)	1.0 (0.7–1.3)
				P = .94
Insurance				
MCO	752 (44)	115 (15)	637 (85)	Ref
Medicare	750 (44)	178 (24)	572 (76)	0.9 (0.6–1.3)
Medicaid	126 (7)	24 (19)	102 (81)	1.2 (0.7–2.0)
Other	77 (5)	21 (27)	56 (73)	0.8 (0.4–1.5)
Unknown	12 (1)	4 (33)	8 (67)	0.9 (0.2–3.5)
				P = .90
Race/Ethnicity				
Caucasian	1337 (78)	263 (20)	1074 (80)	Ref
African American	218 (13)	59 (27)	159 (73)	0.8 (0.6–1.2)
Hispanic	58 (3)	10 (17)	48 (83)	1.1 (0.5–2.5)
Asian/Pacific Islander	82 (5)	6 (7)	76 (93)	1.8 (0.7–4.4)
Other	12 (1)	3 (25)	9 (75)	0.7 (0.2–3.0)
Unknown	10 (1)	1 (10)	9 (90)	2.9 (0.3–27.8)
				P = .54
Smoking Status				
Current	459 (27)	108 (23)	351 (76)	Ref
Quit ≤ 12 mo pre-Dx	216 (13)	58 (27)	158 (73)	0.8 (0.5–1.2)
Quit > 12 mo pre-Dx	720 (42)	142 (20)	578 (80)	1.3 (1.0–1.9)
Never	285 (17)	17 (6)	268 (94)	3.6 (2.0–6.2)
Unknown	37 (2)	17 (46)	20 (54)	0.4 (0.2–0.8)
				P < .001
Performance Status				
Unknown	320 (19)	123 (38)	197 (62)	0.2 (0.1–0.3)
0/1	1092 (64)	108 (10)	984 (90)	Ref
2	218 (13)	59 (27)	159 (73)	0.3 (0.2–0.5)
3	81 (5)	47 (55)	34 (42)	0.1 (0.1–0.1)
4	6 (< 1)	5 (83)	1 (17)	0.0 (0.0–0.3)
				P < .001
Histology				
Adenocarcinoma	1060 (62)	174 (17)	886 (83)	Ref
Squamous	254 (15)	63 (25)	191 (75)	0.8 (0.5–1.1)
NSCLC, NOS	336 (19)	86 (26)	250 (74)	0.8 (0.5–1.1)
Other	67 (4)	19 (28)	48 (72)	0.5 (0.3–1.0)
				P = .13
Total	1717 (100)	342 (20)	1375 (80)	

Abbreviations: col, column; Dx, diagnosis; MCO, managed care organization; NOS, not otherwise specified; NSCLC, non–small cell lung cancer; OR, odds ratio; Ref, reference group.
[a]OR and 95% CI are adjusted for all factors listed in the table.

ing cisplatin-based therapy (*P* for trend < .001). This increase seems to be driven by use of cisplatin/pemetrexed +/– bevacizumab regimens, which increased from 1 patient in 2007 to 32 patients in 2009. Among institutions, the use of cisplatin in platinum-based regimens varied from 4% to 22%.

Paclitaxel was the most common cytotoxic partner agent combined with a platinum agent (n = 402; 45%), followed by pemetrexed (n = 216; 24%), docetaxel (n = 133; 15%), and gemcitabine (n = 102; 11%). The use of cytotoxic partner agents varied by treating institution, with paclitaxel use ranging from 28% to 68%; pemetrexed use ranging from 4% to 41%; and both docetaxel and gemcitabine use ranging from 0% to 29%. For all but one institution, paclitaxel was the most common partner agent used in platinum-based regimens. Across the study period, pemetrexed use increased from 7% in the beginning of 2007 to 46% in the last 6 months of 2009 (*P* for trend < .001; Figure 2). Use of other cytotoxic agents declined during the study period (all *P* for trend < .002).

Among patients treated with platinum-based doublets, 22% were combined with bevacizumab (n = 199), 1% with erlotinib (n = 11), and less than 1% with cetuximab (n = 4). Institutional use of bevacizumab ranged from 12% to 29%, and overall use remained stable across the study period (*P* for trend = .58).

A minority of patients received either single-agent or non–platinum-based systemic drug therapy (Figure 1; n = 241; 21%). Most of these patients received either single-agent erlotinib (n = 148; 61%) or single-agent cytotoxic therapy (n = 91; 38%). Pemetrexed (n = 37; 15%), gemcitabine (n = 24; 10%), and vinorelbine (n = 17; 7%) were the most commonly administered single-agent cytotoxic drugs. Use of single-agent erlotinib remained stable across the study period (*P* for trend = .12).

Concordance With NCCN Guidelines Recommendations

Overall, 76% (n = 1311) of patients received first-line therapy in concordance with NCCN Guidelines recommendations. Institutional concordance ranged from 73% to 81%. Among patients with concordant care, 68% (n = 892) had good, marginal, or undocumented PS (ECOG PS 0/1/2/unknown) and received systemic drug therapy as recommended, 19% (n = 244) were enrolled in a clinical trial, and 13% (n = 175) had poor or undocumented PS (ECOG PS 3/4/unknown) and did not receive systemic drug therapy.

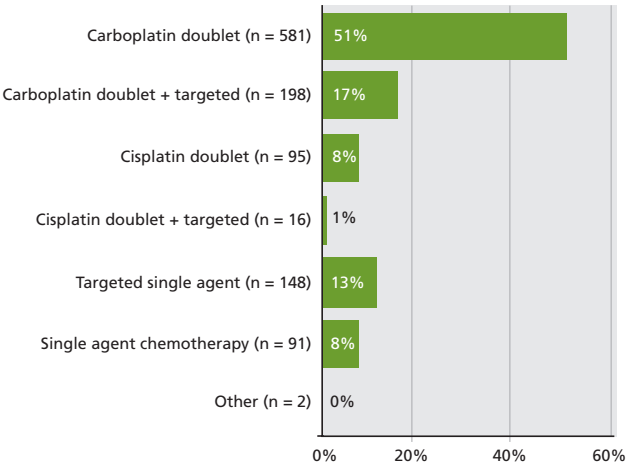

Figure 1 Category of drug therapy received by patients treated with off-trial first-line therapy (n = 1131).

Of the 406 patients who were classified as nonconcordant, 167 (41%; Table 3) had good or marginal PS (ECOG PS 0/1/2) and did not receive any cancer-directed cytotoxic or targeted drug therapy. The most common reasons noted in the medical record for not receiving drug therapy were that therapy was not recommended by the medical oncologist (n = 66; 39%) or the patient expired (n = 56; 33%; median 65 days from diagnosis to death). The remainder of patients classified as nonconcordant (n = 239; 59%; Table 3) received systemic drug therapy wherein at least one aspect of the therapy was nonconcordant with NCCN Guidelines recommendations. The most common reason was the administration of erlotinib or pemetrexed before their inclusion as a first-line therapy option in the NCCN Guidelines (n = 126; 53%). The second most common reason was the administration of erlotinib in current and former smokers who did not undergo epidermal growth factor receptor (EGFR) testing (n = 56; 23%); most of these patients had quit more than 12 months before diagnosis (n = 43; 77%).

A significant increase in concordance was observed across the study period (Figure 3; *P* for trend = .004), from a low of 71% in the second half of 2007 to 84% in the latter 6 months of 2009. After excluding patients who are classified as nonconcordant because of receipt of erlotinib or pemetrexed before the guidelines recommendations (n = 126), the concordance rate remained stable at approximately 82% across the study period (*P* for trend = .35).

Table 2 Off-Trial First-Line Systemic Drug Therapy Combinations Used According to Therapy Type (n = 1131)

Carboplatin Doublet	**n (col %)**
Carboplatin + paclitaxel	270 (46)
Carboplatin + pemetrexed	134 (23)
Carboplatin + gemcitabine	89 (15)
Carboplatin + docetaxel	78 (13)
Carboplatin + etoposide	7 (1)
Carboplatin + vinorelbine	3 (< 1)
Total	581 (100)
Carboplatin Doublet +Targeted Therapy	**n (col %)**
Carboplatin + paclitaxel + bevacizumab	129 (65)
Carboplatin + pemetrexed + bevacizumab	32 (16)
Carboplatin + docetaxel + bevacizumab	22 (11)
Carboplatin + pemetrexed + erlotinib	7 (3)
Carboplatin + gemcitabine + bevacizumab	3 (1)
Carboplatin + paclitaxel + erlotinib	2 (1)
Carboplatin + pemetrexed + cetuximab	1 (< 1)
Carboplatin + gemcitabine + erlotinib	1 (< 1)
Carboplatin + docetaxel + erlotinib	1 (< 1)
Total	198 (100)
Cisplatin Doublet	**n (col %)**
Cisplatin + docetaxel	31 (33)
Cisplatin + pemetrexed	30 (32)
Cisplatin + etoposide	26 (27)
Cisplatin + gemcitabine	7 (7)
Cisplatin + paclitaxel	1 (1)
Total	95 (100)
Cisplatin Doublet + Targeted Therapy	**n (col %)**
Cisplatin + pemetrexed + bevacizumab	9 (56)
Cisplatin + pemetrexed + cetuximab	3 (19)
Cisplatin + gemcitabine + bevacizumab	2 (12)
Cisplatin + docetaxel + bevacizumab	2 (12)
Total	16 (100)
Non–Platinum-Based Drug Therapy	**n (col %)**
Erlotinib	148 (61)
Pemetrexed	37 (15)
Gemcitabine	24 (10)
Vinorelbine	17 (7)
Docetaxel	6 (3)
Paclitaxel	4 (2)
Carmustine	2 (1)
Cytarabine	1 (< 1)
Vinorelbine + pemetrexed	1 (< 1)
Docetaxel + bevacizumab	1 (< 1)
Total	241 (100)

Concordance Sensitivity Analysis

A concordance sensitivity analysis was conducted to evaluate the impact of assuming patients with either an unknown PS or unspecified NSCLC histology received concordant care when all other concordance parameters were met (n = 298). Based on these assumptions, 76% (95% CI, 74%–78%) of patients were classified as concordant (1311/1717). Excluding all patients with unknown PS (n = 232; 110 received first-line therapy and 122 did not) an undefined histology (n = 35), or both (n = 31), a concordance rate of 71% (95% CI, 69%–74%) was observed (1013/1419). If patients with missing PS or undefined histology are assumed to have a similar distribution of PS or histology as was observed in patients with known data, then a concordance rate of 70% (95% CI, 68%–72%) is seen (1202/1717).

Discussion

Main Findings

This article describes patterns of first-line therapy at 8 large NCI-designated academic cancer centers. The most commonly administered therapies in the cohort were platinum-based doublets, of which carboplatin/paclitaxel was the most common. Pemetrexed was the second most common cytotoxic agent combined with a platinum agent, and its use increased considerably over the study period. Although carboplatin was the more common platinum agent, use of cisplatin did increase over time. This increase seems to be driven by the increased use of cisplatin/pemetrexed combination therapy. The proportion of patients receiving first-line therapy in a clinical trial was similar to the 15% accrual rate reported among all patients treated at NCCN Member Institutions.[8]

A 2-drug chemotherapy regimen is the current standard of care for first-line treatment of NSCLC. In select subgroups, targeted agents may be used either in place of or in combination with a chemotherapy doublet. Single-agent chemotherapy is generally not recommended except in patients with marginal PS 2.[3] Adding a third chemotherapy agent has not been shown to improve survival.[9] Despite the consensus surrounding the use cytotoxic doublets, it is not clear which combination of cytotoxic agents constitutes the most effective first-line therapy.[3] This

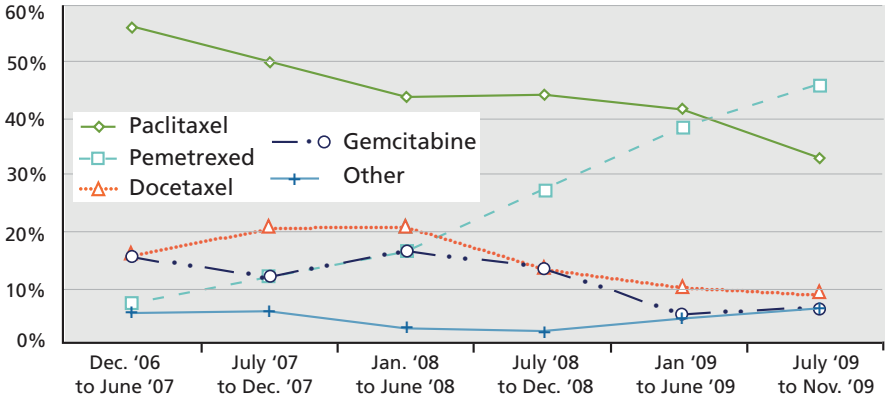

Figure 2 Time trend of the use of cytotoxic partner agents among patients receiving off-trial, platinum-based drug therapy (n = 890). All trends except "other" were statistically significant (all *P* for trend < .002).

lack of consensus is reflected by the considerable institutional variability in cytotoxic agents partnered with a platinum agent. During the study period, Scagliotti et al.[10] published a phase III trial showing a 1.7-month improvement in overall survival and better tolerability with cisplatin/pemetrexed compared with cisplatin/gemcitabine among patients with adenocarcinoma histology. The publication of these data in mid-2008 corresponds with the observed increase in pemetrexed use noted in the current study. This increased use seems to have occurred at each of the institutions examined.

Several studies have demonstrated the efficacy of doublets containing either carboplatin or cisplatin.[11] In a meta-analysis of 15 randomized trials,[12] cisplatin doublets were associated with a statistically significant 16% increased relative 1-year survival advantage (hazard ratio [HR], 1.16, *P* = .001) over non–platinum-based doublets, whereas no statistically significant difference in 1-year survival between carboplatin and non–platinum-based doublets was observed (HR, 0.95; *P* = .42). Despite the improved survival associated with cisplatin, carboplatin was far more commonly used for the patients with metastatic NSCLC reported herein. This likely reflects the better overall tolerability of carboplatin versus cisplatin,[12] and that therapy for metastatic NSCLC is generally focused on disease control and palliation of symptoms. Cisplatin has been associated with an increased risk of severe symptomatic side effects, especially nausea and vomiting.

Concordance

In this cohort, most patients received care that was concordant with the NCCN Guidelines, and the concordance rate was similar among all institutions. Most patients receiving care that was classified as nonconcordant received erlotinib or pemetrexed before their incorporation into the NCCN Guidelines. The physicians in these scenarios may have been practicing according to recently discovered evidence that had not yet been added to the NCCN Guidelines or in anticipation of evidence based on preliminary research findings.[10,13–17] Furthermore, clinical decisions incorporating a patient's preference for less toxic therapy may also result in receipt of nonconcordant treatment. These are examples of how quality care and concordant care are analogous but not interchangeable concepts, wherein nonconcordant care may still be appropriate care. This distinction should be noted when analyses comparing practice patterns to guidelines recommendations are performed.

Use of erlotinib as first-line therapy remained consistent throughout the study period despite its incorporation into the guidelines as a first-line therapy option in August 2007.[6] This may reflect uncertainty over the appropriate patient selection criteria for erlotinib first-line therapy, wherein the initial phase III clinical trials examining first-line efficacy identified a survival advantage for patients classified as never-smokers,[14,15] and retrospective work observed a correlation between select mutations in the EGFR gene and erlotinib effectiveness.[13,16,17] Data from these retrospective studies have subsequently been supported in prospective trials of gefitinib[18] and erlotinib.[19] This evolution in evidence regarding the use of up-front erlotinib therapy can be observed in changes to the NCCN Guidelines: from the initial recommendations to consider use in patients without a smoking history or documented EGFR mutation in version 1.2008,[6] to a recommendation for

Table 3 Reasons for Receiving Nonconcordant Care (n = 406)

PS 0–2 Patients Who Did Not Receive First-Line Therapy	n (col %)
Treatment not recommended	66 (39)
Patient expired prior to therapy	56 (33)
Patient declined therapy	17 (10)
Patient not referred/seen by medical oncologist	16 (10)
Patient transferred care before receiving therapy	3 (2)
Reason unknown	9 (5)
Total	167 (100)
Patients Who Received Nonconcordant Systemic Drug Therapy	**n (col %)**
Pemetrexed/erlotinib initiated before guidelines recommendation	126 (53)
Erlotinib used in current smokers/past smokers without EGFR mutation test	56 (23)
Single agent cytotoxic therapy for patients with PS 0/1	42 (18)
Any therapy for patients with PS 3/4 (including receipt of erlotinib before 11/30/09)	31 (13)
Pemetrexed, bevacizumab, or cetuximab for squamous histology	18 (8)
Bevacizumab for patients with PS 2 (after 8/23/07)	13 (5)
Bevacizumab for patients with untreated CNS metastasis or cetuximab for patients with any CNS metastasis	8 (3)
Cetuximab without documented EGFR overexpression	4 (2)
Erlotinib with negative EGFR mutation test	3 (1)
Therapy not indicated in guidelines (carmustine or cytarabine)	3 (1)
Total	239 (100)

Abbreviations: CNS, central nervous system; col, column; EGFR, epidermal growth factor receptor; PS, performance.

patients with poor PS in version 1.2009,[7] to a recommendation for use only in patients with a documented EGFR mutation in version 1.2010.[20] This uncertainty in effective use likely also explains the nonconcordant use in patients with a smoking history without documented EGFR mutation, because many of these patients may have quit years before diagnosis, leading the treating provider to classify them as nonsmokers when considering therapy options.

This history is in contrast to that for pemetrexed, wherein the initial phase III clinical trial[10] demonstrated efficacy in a subgroup of patients with an adenocarcinoma histology, leading to inclusion in the NCCN Guidelines as a first-line therapy option in September 2008. After the initial release of these data in the fall of 2007 and the subsequent peer-reviewed publication in July 2008 (available online in late May), a rapid increase in pemetrexed use was observed. The contrast in the uptake and concordant use of these 2 agents, both of which have been shown to be effective in the treatment of select subgroups of patients, illustrates the importance of clear definitive evidence on the timely and appropriate use of new agents in everyday clinical practice.

The data from this analysis highlight several opportunities for quality improvement at NCCN Member Institutions. The study revealed a significant percentage of patients with undocumented PS, a key clinical characteristic in determining care for patients with metastatic NSCLC. Although PS was likely considered at the time that treatment decisions were made, the documentation of PS is critical to evaluating whether patients are receiving appropriate care. Furthermore, analysis showed that a subset of patients with good PS did not receive first-line therapy because they were not referred to a medical oncologist or they died before a decision could be made regarding treatment. These situations stress the importance of referral to an appropriate specialist in a timely manner.

Strengths and Limitations

Strengths of the analysis include the high level of quality and completeness of the data, and the ability to report not only whether patients who met the recommendations for receipt of first-line therapy did receive therapy (and vice versa) but also whether the actual therapy received was in accordance with

NCCN Guidelines recommendations based on patient and clinical characteristics. This analysis also reported on the reasons why patients who were of good PS did not receive therapy, such as when patients refused the recommended treatment. Furthermore, because this is a multi-institutional analysis, it can better demonstrate patterns that are common across institutions and draw attention to variations in practice between institutions.

This study includes several limitations. The cohort consists of large NCI-designated cancer centers, and therefore these data may have limited generalizability to smaller community practices. The median age at diagnosis in this cohort (median age, 64 years) was younger than reported in SEER data (median age, 71 years[21]), suggesting that younger patients are more likely to seek care at multidisciplinary cancer centers. In addition, the authors assumed that patients with unknown PS or histology received care that was concordant with the guidelines as long as no other known clinical factor indicated that the patient received nonconcordant care. Although this may have inflated the concordance rate in the cohort (median age, 64 years), sensitivity analyses show that if these patients had been excluded from the concordance analysis, the concordance rate would not have drastically changed.

Conclusions

As the NCCN NSCLC database matures, it will be an invaluable resource for measuring practice patterns and concordance to NCCN Guidelines recommendations over time. The database also allows assessment of quality of care and benchmarking of guideline concordance over time among participating cancer centers. Future work includes examining guideline concordance among other clinical cohorts and points in care, including therapy for nonmetastatic patients, evaluating use of appropriate diagnostic tests, and assessing quality of end-of-life care. In addition, the database has tremendous potential for comparing outcomes among therapy groups and assessing the outcomes of concordant and nonconcordant care.

Examining practice patterns over time allows unique insight into the incorporation of new evidence into clinical practice. During the period examined, a large increase in use of pemetrexed was observed in the first-line setting. Although erlotinib use remained stable during the study period, recent data regarding the appropriate use of erlotinib as first-line therapy in patients with a documented EGFR mutation are expected to lead to an increase in the concordant use of erlotinib. Future work will continue to examine the impact of practice-changing evidence on treatment of NSCLC, including monitoring the uptake of newer agents, changes in use of more traditional cytotoxic agents, such as carboplatin- or cisplatin-based therapy, and characterizing changes in treatment approach, such as use of maintenance therapy.

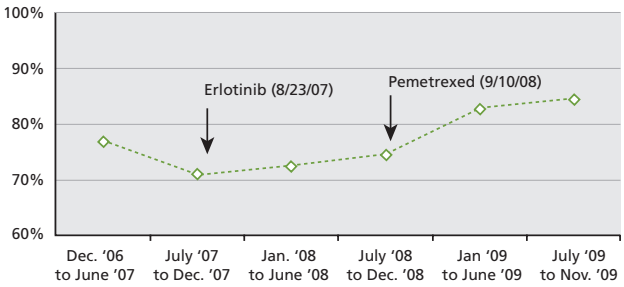

Figure 3 Concordance time trend highlighting a significant increase in concordance (P = .004) across the study period (n = 1717). Arrows indicate dates where either erlotinib (8/23/07) and pemetrexed (9/10/08) were first included as an option for use in first-line therapy.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10–29.
2. Ries LA, Young JL, Keel GE, et al, eds. SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988–2001, Patient and Tumor Characteristics. Bethesda, MD: National Cancer Institute, SEER Program; 2007. Available at: http://seer.cancer.gov/publications/survival/seer_survival_mono_lowres.pdf. Accessed April 25, 2012.
3. Ettinger DS, Akerley W, Borghaei H, et al. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 3, 2012. Available at NCCN.org. Accessed June 1, 2012.
4. Greene FL, ed. AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual, 6th ed. New York, NY: Springer; 2002.
5. Ettinger DS, Akerley W, Bepler G, et al. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 1, 2007. For the most recent and complete version of these guidelines, visit NCCN.org.
6. Ettinger DS, Akerley W, Bepler G, et al. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 1, 2008. For the most recent and complete version of these guidelines, visit NCCN.org.
7. Ettinger DS, Akerley W, Bepler G, et al. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 1, 2009. For the most recent and complete version of these guidelines, visit NCCN.org.
8. Sherman SL, Waldinger MB, Paul DE. The 2010 National Comprehensive Cancer Network (NCCN) research benchmarking

survey (RBS): clinical trials in the academic cancer center [abstract]. J Clin Oncol 2011;29(Suppl):Abstract 6116.

9. Delbaldo C, Michiels S, Syz N, et al. Benefits of adding a drug to a single-agent or a 2-agent chemotherapy regimen in advanced non-small-cell lung cancer: a meta-analysis. JAMA 2004;292:470–484.
10. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543–3551.
11. D'Addario G, Pintilie M, Leighl NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. J Clin Oncol 2005;23:2926–2936.
12. Rajeswaran A, Trojan A, Burnand B, Giannelli M. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials. Lung Cancer 2008;59:1–11.
13. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol 2005;23:5900–5909.
14. Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. J Clin Oncol 2007;25:1545–1552.
15. Herbst RS, Prager D, Hermann R, et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2005;23:5892–5899.
16. Sequist LV, Joshi VA, Janne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. Oncologist 2007;12:90–98.
17. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer—molecular and clinical predictors of outcome. N Engl J Med 2005;353:133–144.
18. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947–957.
19. Rosell R, Gervais R, Vergnenegre A, et al. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomized trial [abstract]. J Clin Oncol 2011;29(Suppl):Abstract 7503.
20. Ettinger DS, Akerley W, Bepler G, et al. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 1, 2010. For the most recent and complete version of these guidelines, visit NCCN.org.
21. SEER Cancer Statistics Review 1975-2008. Table 1.11. National Cancer Institute Web site. Available at: http://seer.cancer.gov/csr/1975_2008/results_single/sect_01_table.11_2pgs.pdf. Accessed April 25, 2012.