Patterns of Care for Non–Small-Cell Lung Cancer at an Academic Institution Affiliated With a National Cancer Institute–Designated Cancer Center

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Abstract

Purpose: Evidence-based treatment guidelines for non–small-cell lung cancer (NSCLC) exist to improve the quality of care for patients with this disease. However, how often evidence-based decisions are used for care of NSCLC is poorly understood.

Patients and Methods: We examined patterns of care and rate of adherence to evidence-based guidelines for 185 new NSCLC patients seen between 2007 and 2009. Evidence-based care status was determined for 150 patients.

Results: Eighty-one percent of the patients were white, the mean age was 66 years, 49% were women, 11% were never smokers, 83% had Eastern Cooperative Oncology Group performance status 0 to 1, 49.7% of tumors were adenocarcinomas, 57.1% of never smokers had tumors genotyped (*EGFR*, *ALK*, *KRAS*), and 13.3% participated in clinical trials. The rate of evidence-based treatment adherence was 94.1% (16 of 17), 100% (21 of 21) and 100% (36 of 36) in patients with stages I, II, and III NSCLC, respectively. Stage IV disease, with adherence of 76.3% (58 of 76), was correlated with a higher rate of nonadherence when compared with stages I-III (odds ratio 16.33; 95% CI, 1.94 to 137.73). In patients with stage IV disease, the rate of evidence-based adherence was 95% (72 of 76) for first-line therapy, 95.2% (40 of 42) for second-line therapy, and only 33.3% (6 of 18) for third-line therapy ($P < .001$). There was no significant correlation between evidence-based adherence status and the patient's age, sex, performance status, smoking history, ethnicity, or the treating physician.

Conclusion: These data point toward the need for improved evidence-based use of resources in the third-line setting of stage IV NSCLC.

Introduction

Lung cancer continues to lead cancer-related deaths in the United States.[1,2] The two most prevalent sub-types are small-cell lung cancer and non–small-cell lung cancer (NSCLC). NSCLCs comprise the majority of cases, and on the basis of the former sixth-edition tumor-node-metastasis (TNM) classification, the 5-year survival of patients with stage IA NSCLC is approximately 60%; stage IB; 40%, stage II; 25% to 35%; stage IIIA; 15%; stage IIIB, 5%; and stage IV, < 1%.[3]

Despite the shortcomings of therapies in this malignancy, in almost all stages of NSCLC, well-designed randomized trials have been conducted and evidence-based data exist for patient treatment. Many of the recent advances have led to US Food and Drug Administration (FDA) approval of therapies specific for NSCLC. Therefore, evidence-based therapeutic decisions can be made for NSCLC from stages I to IV. Indeed, practice guidelines, which reflect "standard of care" evidence-based data, are available for NSCLC from institutions such as the National Comprehensive Cancer Network (NCCN)[4] and ASCO.[5]

The standard management of stage I NSCLC with a tumor size < 4 cm is surgical resection alone.[4,6] In the case of stage II and III NSCLC, surgical resection is followed by adjuvant therapy. There is a significant 5% to 15% improvement in 5-year survival with the addition of cisplatin-based chemotherapy to surgical resection for stages II to IIIA NSCLC.[6] The same principle may hold true for tumors that have a size > 4 cm.[4] In 2007, ASCO and NCCN put forth recommendations for adjuvant platinum-based chemotherapy in NSCLC that were based on data from multiple randomized trials.[4,6] Patients with unresectable stage IIIA (based on N2 lymph node involvement) or stage IIIB (based on N3 node involvement) NSCLC are treated with concurrent cisplatin-based chemotherapy and radiotherapy.[4]

For stage IV, metastatic NSCLC, the goal of care is palliative. Use of palliative platinum-based chemotherapy has been the standard therapy for patients with stage IV NSCLC for more than a decade.[7,8] The historic response rates (RRs) with different platinum doublets are in the range of 20%, with a median overall survival (OS) of 8-10 months and a 2-year survival of < 15%.[4,5,9] For the fit elderly, the use of platinum doublets has recently gained momentum as the preferred treatment in the first-line setting instead of single-agent chemotherapy, the prior commonly used standard for this age group, and ASCO guidelines already advocated in 2009 that age alone should not influence the choice of a platinum doublet.[5] In NSCLCs with nonsquamous histology and without contraindications to vascular endothelial growth factor (VEGF) inhibitors, the addition of bevacizumab to chemotherapy improves RRs, progression-free survival (PFS), and median OS.[10] The

FDA approved bevacizumab to be used in combination with carboplatin-paclitaxel in this specific patient population as first line therapy. For patients with NSCLC whose tumors harbor activating epidermal growth factor receptor (*EGFR*) gene mutations, EGFR tyrosine kinase inhibitors (TKIs) improve clinical outcomes.[11-13] Randomized trials have reported a RR of 60% to 70% for gefitinib and 30% to 47% for platinum doublets, with a PFS hazard ratio (HR) of 0.30-0.48 favoring gefitinib.[11-13] Erlotinib has a similar spectrum of activity in patients whose tumors harbor *EGFR* mutations.[14] Therefore, for *EGFR*-mutated NSCLC, an EGFR inhibitor is considered an appropriate evidence-based first-line therapy.[4] After failure of first-line palliative chemotherapy in stage IV NSCLC, there are three FDA-approved second line therapies: docetaxel,[15] pemetrexed,[16] and erlotinib.[17] All have been tested in randomized trials; however, the RRs are in the single digits, and the PFS and OS are short.[5] Erlotinib is also approved as a third-line systemic therapy in advanced NSCLC.[4] In 2008, the FDA restricted the use of pemetrexed to NSCLCs with nonsquamous histology on the basis of a preferential benefit of this chemotherapy in adenocarcinomas or large-cell carcinomas.[18]

It is unknown how often academic medical centers in the United States adhere to evidence-based NSCLC care. To better understand the adoption of evidence-based care in an academic medical center affiliated with a National Cancer Institute (NCI) –designated cancer center, we evaluated whether medical oncology providers at Beth Israel Deaconess Medical Center (BIDMC), a Harvard Medical School–affiliated academic medical center and a member of the NCI-designated Dana-Farber/Harvard Cancer Center, adhere to evidence-based guidelines. The data collected here may reflect treatment strategies for an academic medical center with dedicated medical oncologists that focus on NSCLC.

Patients and Methods

Patient Selection

Institutional review board approval was obtained for access to the online medical chart records of patients diagnosed with lung cancer seen at BIDMC (protocol 2009-P-000182/BIDMC). Data were obtained from the Web-based Online Medical Records, BIDMC's electronic health records system. We reviewed all records of new patients with NSCLC seen in the thoracic oncology outpatient clinic at BIDMC between July 1, 2007 and July 31, 2009 for whom care was provided by a medical oncologist. We excluded patients who had already received treatment elsewhere before their first visit to BIDMC and who did not have care provided at BIDMC during the prespecified dates. The data cutoff for analysis of outcomes was set as January 1, 2010. The study was approved by the institutional review board in 2009, and the data were collected retrospectively between July 31, 2009 and July 1, 2010. The variables recorded are described in the Appendix (online only).

Table 1. Summary of Evidence-Based Treatments by NSCLC Stage and, for Stage IV, by Line of Therapy

Stage	Evidence-Based Care
I	Surgery (R0 lobectomy or equivalent)* Radiotherapy for nonsurgical candidate
II	Surgery (R0 lobectomy or equivalent), followed by adjuvant platinum-based chemotherapy† Radiotherapy ± platinum-based chemotherapy for nonsurgical candidate
III	Surgery (R0 lobectomy) ± neoadjuvant or adjuvant systemic chemotherapy (platinum-based)† ± radiotherapy Definitive concurrent chemotherapy with radiotherapy for nonsurgical candidate†
IV‡	
First line	Platinum-based doublet chemotherapy if ECOG PS 0-2†§ ± bevacizumab Platinum-based doublet or single agent chemotherapy acceptable for elderly with ECOG PS 0-2 If activating *EGFR* mutation, EGFR TKI, independent of ECOG PS If ECOG PS 3-4, best supportive care only
Second line	If ECOG PS 0-2, docetaxel,† pemetrexed,† or erlotinib†‖ If ECOG PS 3-4, best supportive care
Third line	If ECOG PS 0-2, erlotinib† or best supportive care If ECOG PS 3-4, best supportive care

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer; R0, complete surgical resection with negative margins; TKI, tyrosine kinase inhibitor.

* For tumors > 4 cm, use of adjuvant chemotherapy is acceptable.[4,6]

† Based on randomized phase III trial.

‡ Staging was based on the 6th TNM, except for our classification of malignant pleural effusion as stage IV.

§ For patients with ECOG PS 2, single-agent chemotherapy is also acceptable.[5]

‖ If *EGFR* activating mutation, systemic chemotherapy with evidence-based single agent or doublet accepted as second-line therapy.

Determination of Evidence-Based Versus Non–Evidence-Based Therapies

Once all the data had been entered into the database, the researchers determined the evidence-based therapy status for each individual patient on the basis of available clinical trials and treatment guidelines for NSCLC. Table 1 summarizes evidence-based treatment recommendations for all stages of NSCLC that were used for this study (Appendix, Methods). Patients for whom there was insufficient information to determine evidence-based status were considered "undetermined."

Statistical Methods

Descriptive statistics were used to describe the patterns of patients seen and care delivered. To determine whether there was any correlation between the examined variables and evidence-based care status, individual Pearson χ^2 tests or Fisher's exact tests, when appropriate, and logistic multivariate regressions were performed. All data analyses were done in SAS statistical software (SAS Institute, Cary, NC).

Results

Identification of Patients

We were able to identify 185 new patients who fit the initial inclusion criteria and had NSCLC (Appendix, Results). Of

Table 2. Clinical, Pathologic, and Molecular Characteristics of the Identified Patients

Value	All Patients (N = 185) No.	%	Only Patients With Determined Evidence-Based Care Status (n = 150) No.	%
Age, years				
Mean	66.4		65.7	
< 41	3	1.6	3	2
41-50	15	8.1	14	9.3
51-60	32	17.3	25	16.7
61-70	65	35.1	53	35.3
71-80	53	28.6	43	28.7
> 80	17	9.2	12	8.0
Sex				
Male	94	51	78	52
Female	91	49	72	48
Stage				
I	18	10	17	11
II	22	12	21	14
III	43	23	36	24
IV	101	55	76	51
Genetic (tumor genotype)				
Unknown	152	82.2*	125	83.3*
EGFR WT	23	12.4*	18	12.0*
EGFR mutation positive	9	4.9*	6	4.0*
ALK non-translocated	6	3.2*	5	3.3*
ALK translocated	2	1.1*	2	1.3*
KRAS WT	6	3.2*	5	3.3*
KRAS mutation positive	2	1.1*	2	1.3*
ECOG PS				
0/1	132	83.0	111	84.1
2	18	11.3	14	10.6
3	8	5.0	7	5.3
4	1	0.6	0	0
Smoking				
Unknown	26	—	18	—
Never	21	11.4	18	12.0
Former	131	70.8	104	69.3
Current	33	17.8	28	18.7
Histology				
Adenocarcinoma	92	49.7	75	50.0
Squamous cell carcinoma	33	17.8	30	20.0
Large-cell carcinoma	15	8.1	12	8.0
NOS	45	24.3	33	22.0
Physician of record				
A	58	31.4	55	36.7
B	65	35.1	52	34.7
C	62	33.5	43	28.7
Ethnicity				
White	151	81.6	122	81.3
Black	14	7.6	11	7.3
Hispanic	4	2.2	4	2.7
Asian/other	16	8.6	13	8.7
Clinical trials				
Enrolled	22	13.3	22	15.8
Not enrolled	143	86.7	117	84.2

Continued on next column

Table 2. (Continued)

NOTE. Dashes indicate data not used for calculation of percentages.
Abbreviations: ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; NOS, not otherwise specified; WT, wild type.
* Percentages do not add up to 100% as a result of overlapping mutations.

these, evidence-based treatment status was determined for 150 patients, whereas we could not determine evidence-based status in 35 patients (25 had stage IV NSCLC). Of these, 18 patients (17 with stage IV) had data censoring before start of cancer therapy and 17 patients (8 with stage IV) had incomplete documentation.

Patient and Tumor Characteristics

Table 2 lists the characteristics of the identified patients. There was no significant difference between the total cohort and the subset of patients with determined evidence-based treatment status (data not shown). The overall cohort was 81% white, and the mean age at time of diagnosis was 66 years, with the above 61-year-old group making up 72.9% of all patients. Forty-nine percent of patients were women. The majority (55%) of patients had stage IV disease. Most patients (83%) had a good (0 or 1) Eastern Cooperative Oncology Group performance status (ECOG PS) (0/1) at their first office visit. Almost half (49.7%) of all tumors had adenocarcinoma histology. Never smokers made up 11.4% of the patients and former smokers 70.8%. The 185 patients were evenly distributed among the three main medical thoracic oncology physicians. Clinical trial participation was noted for 13.3% of the patients (Table 2).

Smoking Status and Tumor Genotype

Smoking status was found to be correlated to the frequency of genotyping. Tumor genotype was performed in 18% of all patients (Table 2), with never smokers being genotyped much more frequently (12 of 21 patients; 57.1%) than former/current smokers (21 of 164 patients; 12.8%) ($P < .001$, Fisher's exact test).

Of the 32 patients genotyped for *EGFR*, nine had mutations, with five of 12 never smokers (41.6%) harboring an

Table 3. Rate of Adherence to Guidelines by Stage

Stage	Evidence-Based Care		Non–Evidence-Based Care		No. of Uncertain Evidence-Based Care Status	Total No. of Determined Evidence-Based Care Status	Total
	No.	%	No.	%			
I	16	94.1	1	5.9	1	17	18
II	21	100	0	0	1	21	22
III	36	100	0	0	7	36	43
IV	58	76.3	18	23.7	25	76	101

EGFR mutation. Of the eight patients genotyped for anaplastic lymphoma kinase (*ALK*) translocation, two had translocations, with one of four never smokers (25%) having this translocation. Only eight patients were tested for V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation, and two tumors from smokers were positive.

Adherence to Evidence-Based Treatment Strategies

We were able to determine evidence-based care status for 150 patients. Overall, the rate of adherence to evidence-based practices was 16 of 17 (94.1%), 21 of 21 (100%), 36 of 36 (100%), and 58 of 76 (76.3%) in patients with stages I, II, III, and IV NSCLC, respectively (Table 3). Only one of 17 (5.9%) patients with stage I disease received non–evidence-based care, whereas 18 of 76 (23.7%) patients with stage IV disease received non–evidence-based care. All patients with stage II and stage III disease received evidence-based therapies.

We were interested in examining whether patient characteristics and other variables affected adherence to evidence-based treatment allocation (Appendix Table A1, online only). Pearson χ^2 tests and logistic multivariate regression analyses revealed that that the only variable that correlated with evidence-based status was disease stage, when stages I to III were grouped together as nonadvanced and stage IV as advanced stage (Table A1). The odds ratio for the nonadvanced versus the advanced stage was 16.33 (95% CI, 1.94 to 137.73). Performing the same logistic multivariate regression (Table 4, Online only) or separate Pearson χ^2 tests or Fisher's exact tests when the number of patients was ≤ 5 (data not shown), we found no significant correlation between evidence-based status and the patient's age, sex, PS, smoking history, ethnicity, or physician of record.

Adherence to Evidence-Based Treatment Strategies in Stage IV NSCLC

We then examined the subset of patients with stage IV NSCLC and the type of care provided. Each line of therapy (first, second, or third) was analyzed separately (Appendix, Results).

When these patients with stage IV NSCLC were examined, the rate of non–evidence-based care increased with lines of therapy: 5% (four of 76) in first-line therapy, 4.8% (two of 42) in second line, and 63.7% (12 of 18) in third line (Table 5, Online only). Only 18 (23.7%) of the 76 patients with stage IV NSCLC reached the third-line setting of care by our data cutoff. There was a statistically significant difference in rate of adherence to evidence-based care when the third-line treatment group was compared with the first- and second-line treatment groups ($P < .001$, Fisher's exact test). The most common non–evidence-based practice was the use of cytotoxic chemotherapy as third-line regimen in patients with stage IV disease (four patients treated with pemetrexed, three with gemcitabine, two with docetaxel, two with vinorelbine, and one case with carboplatin). Other non–evidence-based practices were seen: in two patients for whom vinorelbine was used as a second-line regimen, two patients for whom erlotinib was used as a first-line regimen when the patients had not been genotyped for *EGFR* mutations, and two patients with ECOG PS of 3 who still received cytotoxic chemotherapy.

When we examined (using Pearson χ^2 tests or Fisher's exact tests when the number of patients was ≤ 5 and logistic multivariate regression analyses) the subset of patients with stage IV disease who received at least three lines of therapy, there was no significant correlation between evidence-based status and the patient's age, sex, performance status, smoking history, ethnicity, or physician of record (data not shown). However, the limited number of patients in this cohort (18) compromised statistical power to detect a significant correlation between the characteristics analyzed and the type of care received.

Discussion

Overall, we found that the patients with NSCLC seen at our hospital, in the thoracic oncology clinic, were overwhelmingly white, were mostly former or current smokers, and had good PS. The rate of adherence to the evidence-based practices was generally high, with 94.1%, 100%, 100%, and 76.3% adherence in patients with stages I, II, III, and IV NSCLC, respectively. The high overall adherence for patients with stages I to III NSCLC may be explained by two factors. The first is the broad treatment approaches that we allowed as evidence-based care in Table 1. These were meant to encompass all possible evidence-based strategies and guidelines for stages I to III NSCLC between 2007 and 2010. Second is the multidisciplinary care model available at our institution, where all patients are seen and discussed in a common clinic by medical oncologists, thoracic surgeons, interventional pulmonologists, and radiation oncologists. It has been recently shown that multidisciplinary cancer care and meetings enhance the adherence to guideline- and evidence-based care in NSCLC.[19,20]

The stage at diagnosis was the only factor shown to correlate with the treatment guideline adherence rate in our cohort, with patients with advanced (stage IV) NSCLC having a higher rate

of nonadherence to treatment guidelines. The most common practice that deviated from evidence-based care was the use of cytotoxic chemotherapies of unproven value as a third-line regimen in patients with stage IV NSCLC. We could not find any other patient, tumor, or provider characteristics that contributed to nonadherence to treatment guidelines. A study from an nonacademic practice[21] examining the patterns of care for NSCLC in an outpatient community setting demonstrated that the economic costs of providing non–guideline-based treatment to patients with advanced-stage NSCLC, with no resultant survival benefit, are not insignificant. The authors evaluated eight practices in the US Oncology network and showed that outpatient costs were 35% lower for providers using an evidence-based pathway, which took into account cost of therapy, when compared with providers who did not use such a pathway, with an average 12-month cost of US $18,042 and $27,737, respectively. No difference in OS was observed in the two groups overall or by line of therapy provided.[21] This set of data indicates that use of a pathway-based care model that uses both evidence-based and cost-saving strategies may improve resource allocation for practices treating NSCLC, without compromising patient outcomes.

Because most of the nonadherence to evidence-based care in our cohort occurred in the third-line setting among patients with stage IV NSCLC, we attempted to understand the causal factors underlying this incidence. Although we could not find a single patient, tumor, or provider-related factor that correlated with nonadherence to evidenced-base care, we know that this setting of care for NSCLC is chronically understudied, with very few phase III trials available to establish evidence-based recommendations.[22] The only study that has evaluated patients, in a randomized fashion, in the third-line setting of stage IV NSCLC was the BR.21 clinical trial[17] (Appendix, Discussion). Erlotinib is the only systemic therapy currently recommended by NCCN and ASCO guidelines for patients with stage IV NSCLC who have an adequate PS and reach the third-line setting of care.[4,5] Other evidence-based approaches in the third-line setting include inclusion on a clinical trial or best supportive care (Table 1). Although other cytotoxic chemotherapies - such as vinorelbine, gemcitabine, pemetrexed and taxanes - have activity either as single agents or as part of doublets in stage IV NSCLC, these have never been compared with placebo or erlotinib in well-designed randomized trials in the third-line setting.[4,5,22] Therefore, it is unclear whether use of these agents can improve patient outcomes. In our own data set, the use of nonstandard cytotoxic chemotherapies invariably explained all incidents of nonadherence among patients with stage IV NSCLC in the third-line setting. Only three of the patients in the third-line setting of our cohort were part of a clinical trial. The clinical trial participation rate for all patients with NSCLC in our clinic was approximately 13%, and this rate does not differ significantly from participation rates cited in previous studies.[23,24] Patients with advanced NSCLC who had experienced failure of more than two lines of systemic therapy could have been offered enrollment into clinical trials of novel agents instead of unproven chemotherapies, although the clinical benefit of clinical trials in the third-line setting of NSCLC is unknown. It is possible that the third or subsequent line settings of care for stage IV NSCLC may be the Achilles' heel of assessing evidence-based compliance in a multidisciplinary academic clinic, as patients and physicians may have a biased expectation that continued therapy is superior to best supportive care alone. Unfortunately, our study methodology was unable to capture whether patients or physicians were the main determinants of use of cytotoxic chemotherapy. This will need to be explored in future cohorts evaluating evidence-based adherence in NSCLC. The use of dedicated palliative care providers[25] may be an interesting treatment paradigm to explore in the third-line setting of care.

We also found that tumor genotype was obtained in only 18% of our patients with NSCLC. However, the rate of tumor genotype was much higher, at approximately 57%, for patients who were never smokers. Never smokers make up a specific subgroup of NSCLC that is enriched for tumors harboring *EGFR* mutations and *ALK* translocations.[26-28] On the basis of data from clinical trials of never smokers with advanced NSCLC, it is clear that the *EGFR* mutational status of the tumor is the main predictor of RR and PFS of an EGFR TKI when compared with platinum-based chemotherapy.[11-13] In addition, the novel ALK TKI crizotinib has shown impressive activity in pretreated patients with NSCLC harboring *ALK* translocations.[29] As the cost of tumor genotype decreases and further evidence-based data emerge of the predictive role of these biomarkers, we believe that most new patients with NSCLC will be tested for *EGFR*, *KRAS*, *ALK*, and other genetic mutations.

The present study had some limitations and significant strengths (Appendix, Discussion). Therefore, we believe our database and results can be representative of the patterns of care provided by medical oncologists that specialize in NSCLC. It is unclear whether this set of data can be generalized to small, medium, and large academic medical centers affiliated with an NCI-designated cancer center. Future research comparing the patterns of adherence to evidence-based care for NSCLC in academic and nonacademic settings is warranted.

In summary, we examined the patterns of care provided by dedicated oncologists to patients with NSCLC at an academic center. The rate of adherence to evidence-based treatment strategies was generally high; however, we identified several shortcomings, especially in the care of patients with advanced-stage disease after failure of first and second lines of systemic therapy. These observations present valuable opportunities for improvements in the pattern of care for patients with stage IV NSCLC and point toward the need for more clinical trials for patients with this deadly disease.

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References

1. Jemal A, Siegel R, Xu J, et al: Cancer statistics, 2010. CA Cancer J Clin 60:277-300, 2010

2. Sun S, Schiller JH, Gazdar AF: Lung cancer in never smokers–a different disease. Nat Rev Cancer 7:778-790, 2007

3. Mountain CF: Revisions in the International System for Staging Lung Cancer. Chest 111:1710-1717, 1997

4. Ettinger DS, Akerley W, Bepler G, et al: Non-small cell lung cancer. J Natl Compr Cancer Netw 8:740-801, 2010

5. Azzoli CG, Baker S Jr, Temin S, et al: American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non–small-cell lung cancer. J Clin Oncol 27:6251-6266, 2009

6. Pisters KM, Evans WK, Azzoli CG, et al: Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non–small-cell lung cancer guideline. J Clin Oncol 25:5506-5518, 2007

7. Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92-98, 2002

8. Ardizzoni A, Boni L, Tiseo M, et al: Cisplatin- versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: An individual patient data meta-analysis. J Natl Cancer Inst 99:847-857, 2007

9. Ohe Y, Ohashi Y, Kubota K, et al: Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 18:317-323, 2007

10. Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542-2550, 2006

11. Mok TS, Wu YL, Thongprasert S, et al: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947-957, 2009

12. Mitsudomi T, Morita S, Yatabe Y, et al: Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. Lancet Oncol 11:121-128, 2010

13. Maemondo M, Inoue A, Kobayashi K, et al: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362:2380-2388, 2010

14. Rosell R, Moran T, Queralt C, et al: Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 361:958-967, 2009

15. Shepherd FA, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095-2103, 2000

16. Hanna N, Shepherd FA, Fossella FV, et al: Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589-1597, 2004

17. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123-132, 2005

18. 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 26:3543-3551, 2008

19. Vinod SK, Sidhom MA, Gabriel GS, et al: Why do some lung cancer patients receive no anticancer treatment? J Thorac Oncol 5:1025-1032, 2010

20. Vinod SK, Sidhom MA, Delaney GP: Do multidisciplinary meetings follow guideline-based care? J Oncol Pract 6:276-281, 2010

21. Neubauer MA, Hoverman JR, Kolodziej M, et al: Cost effectiveness of evidence-based treatment guidelines for the treatment of non–small-cell lung cancer in the community setting. J Oncol Pract 6:12-18, 2010

22. Noble J, Ellis PM, Mackay JA, et al: Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: A systematic review and practice guideline. J Thorac Oncol 1:1042-1058, 2006

23. Tejeda HA, Green SB, Trimble EL, et al: Representation of African-Americans, Hispanics, and whites in National Cancer Institute cancer treatment trials. J Natl Cancer Inst 88:812-816, 1996

24. Go RS, Frisby KA, Lee JA, et al: Clinical trial accrual among new cancer patients at a community-based cancer center. Cancer 106:426-433, 2006

25. Temel JS, Greer JA, Muzikansky A, et al: Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363:733-742, 2010

26. Nguyen KS, Kobayashi S, Costa DB: Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. Clin Lung Cancer 10:281-289, 2009

27. Sharma SV, Bell DW, Settleman J, et al: Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer 7:169-181, 2007

28. Shaw AT, Yeap BY, Mino-Kenudson M, et al: Clinical features and outcome of patients with non–small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 27:4247-4253, 2009

29. Kwak EL, Bang YJ, Camidge DR, et al: Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 363:1693-1703, 2010