Third-Line Chemotherapy in Advanced Non-small Cell Lung Cancer: Identifying the Candidates for Routine Practice

Nicolas Girard, MD,† Pascale Jacoulet, MD,* Marie Gainet, MD,* Rami Elleuch, MD,* Didier Pernet, MD,* Alain Depierre, MD,* Jean-Charles Dalphin, MD, PhD,* and Virginie Westeel, MD, PhD**

Background: The interest of first- and second-line treatments in non-small cell lung cancer (NSCLC) has been demonstrated by successive randomized trials. Improvements in lung cancer care have routinely allowed a significant proportion of patients to be considered for third-line treatment.

Methods: A retrospective analysis was performed, including all consecutive patients with advanced NSCLC, who received at least three lines of systemic antineoplastic treatment at our institution.

Results: From a population of 613 patients treated with first-line treatment, a total of 173 patients received third-line treatment (cytotoxic chemotherapy in 131 patients; epidermal growth factor (EGFR) tyrosine kinase inhibitors in 42 patients). Only 13 patients (8%) received less than 75% of the theoretical dose intensity; 22 patients (13%) presented with severe toxicities. Symptom relief and performance status (PS) improvement were observed in 121 (92% of the 131 patients with symptoms) and 90 patients (52%), respectively. Using multivariate analysis, survival after third-line treatment was significantly increased in patients younger than 70 years-old (hazard ratio [HR] = 0.73, 95% confidence interval [CI]: 0.53–0.99, $p = 0.047$), who smoked less than 10 pack-years (HR = 0.82, 95% CI: 0.57–0.93, $p = 0.036$), with no cancer-related symptoms (HR = 0.75, 95% CI: 0.61–0.92, $p = 0.007$), a weight loss inferior to 5 kg since the beginning of second-line (HR = 0.63, 95% CI: 0.52–0.75, $p = 0.013$), a PS 0 to 1 (HR = 0.81, 95% CI: 0.76–0.86, $p = 0.008$), and no extrathoracic tumor spread at initiation of third-line treatment (HR = 0.67, 95% CI: 0.47–0.94, $p = 0.042$). Disease control after both first- and second-line treatments was the strongest predictor of prolonged survival after third-line treatment (HR = 0.47, 95% CI: 0.33–0.67, $p = 0.001$).

Conclusions: Patients with advanced NSCLC may benefit from third-line treatment. The best candidates can be identified using standard prognostic factors, such as PS, and disease control after first- and second-line treatments.

Key-Words: Non-small cell lung cancer, Advanced stage, Third-line treatment, Chemotherapy, Tyrosine Kinase Inhibitor.

(*J Thorac Oncol.* 2009;4: 1544–1549)

Chemotherapy is the standard treatment of advanced non-small cell lung cancer (NSCLC).[1–4] Two-drug, platinum-based regimens with third-generation agents significantly improve overall survival and quality of life.[1,5] For second-line treatment, three agents have been approved so far, based on randomized phase III trials: two cytotoxic drugs, that is, docetaxel and pemetrexed, and one targeted therapy, erlotinib.[6–8] These drugs, although providing a modest 1-year survival benefit (ranging from 6 to 10%), significantly improve quality of life and cancer-related symptoms.[6–8] Erlotinib is the only specifically approved agent for third-line treatment, as half of the patients included in the landmark trial comparing erlotinib with best supportive care had previously received two chemotherapy regimens.[3,8] Interestingly, a significant proportion of third-line patients, up to 35%, were also included in the second-line trials evaluating docetaxel.[6,9] Collectively, these studies showed the overall benefit of single-agent treatment in the second-line setting and beyond.

The clinical improvements provided by first- and second-line treatment in NSCLC have led a higher proportion of patients to be considered for third-line treatment, rising from 6% in 1990s[10] to 26% after 2000.[11] Meanwhile, more patients are willing to receive treatment for lung cancer, especially if quality of life improvements are likely to occur.[12] Although a survival benefit may also exist in some cases, the main aim of third-line treatment should be palliation of symptoms, while minimizing side effects.

As no prospective study specifically addressed the role of third-line treatment in NSCLC, we conducted a retrospective analysis to determine which patients may benefit from third-line treatment, using symptom relief, disease control, and overall survival as major endpoints.

*Service de Pneumologie, Centre Hospitalier Universitaire de Besançon, Université de Franche Comté, Besançon, France and †Université Claude Bernard-Lyon 1, Université de Lyon, Lyon, France.

Disclosure: NG received travel grants from the French Lilly Institute and the French College des Professeurs de Pneumologie (CEP)/AstraZeneca.

Address for correspondence: Nicolas Girard, Service de Pneumologie, Hôpital Louis Pradel, 28 avenue doyen Lépine, 69500 Lyon (Bron). E-mail: nggirard@gmail.com

ISSN: 1556-0864/09/0412-1544

MATERIALS AND METHODS

Study Population

We included all consecutive patients with NSCLC, who received at least three lines of systemic antineoplastic treatment between January 1, 2000 and December 31, 2006 in the Department of Respiratory Medicine and Thoracic Oncology of the University Hospital of Besançon, France. All chemotherapy treatments were administered in this single outpatient clinic, using standardized guidelines. Patients were identified using the pharmacy database. Inclusion criteria were: (1) pathologically proven primary NSCLC (adenocarcinoma, squamous cell carcinoma, or large cell carcinoma)[13]; (2) American Joint Committee on Cancer stage IIIB or IV at time of diagnosis[14]; (3) treatment with systemic antineoplastic drugs (cytotoxic chemotherapy or epidermal growth factor receptor [EGFR] tyrosine kinase inhibitors [TKIs]); (4) without any focal treatment on the lung tumor, at any time of the therapeutic management; and (5) administration of at least one course of third-line treatment. We excluded from the analysis patients with any previous history of invasive malignancy. As per standard recommendations, third-line treatment was initiated only at the time of progression after second-line treatment. All patients experiencing recurrence or progression after second-line treatment and in a sufficient medical condition to receive another line of treatment were treated with third-line treatment. All patients had a subsequent follow-up in our department.

Clinical Review

A retrospective review of the clinical history of eligible patients was performed. According to French laws, such analyses do not require the approval of an institutional review board. At time of initial diagnosis, all cases had been assessed with a complete history, physical examination, fiberoptic bronchoscopy, imaging investigations (chest radiography and computed tomography [CT]; brain CT-scan or magnetic resonance imaging; abdomen ultrasound or CT-scan; and bone scintigraphy in some patients), pathologic reports, and blood tests results. Progression or recurrence after second-line treatment was usually diagnosed using CT-scan of the chest and of target lesions when appropriate. Patients were categorized as never smokers (less than 100 lifetime cigarettes), former smokers (quit more than 1 year ago), or current smokers (quit less than 1 year ago). Duration of first-, second-, and third-line treatment was calculated from the first to the last day of treatment. Best response to chemotherapy was evaluated according to the World Health Organization criteria.[15] Disease control rate was defined as the addition of objective response and stabilization rates. Chemotherapy dose intensity was calculated as the following: (total administered dose, $mg/m^2/wk$)/(theoretical total dose, $mg/m^2/wk$), for the first four planned cycles.[16] Toxicities were assessed using the National Cancer Institute grading system.[17]

Cancer-Related Symptoms

Cancer-related symptoms and Eastern Cooperative Oncology Group performance status (PS) were systematically evaluated and routinely recorded for every patient visit to the clinic. For this study, we collected the presence or absence of each of the following cancer-related manifestations before and along the duration of third-line treatment: dyspnea, chest pain, cough, hemoptysis, fever, thrombosis, metastasis-related pain, para-neoplastic disease, cachexia, and fatigue.

Statistical Analyses

All patients were included in the statistical calculations. Follow-up was obtained in all cases and was censored on December 31, 2008. Categorical variables were compared using the χ^2 test and continuous variables by the Mann-Whitney nonparametric test. Logistic regression was used to study correlations between disease control after first-, second-, and third-line treatment. Survival was assessed using the Kaplan-Meier method.[18] Relevant parameters were studied for influence on survival by univariate analysis using the log rank test and by multivariate analysis using a stepwise Cox proportional hazards method (entry and exit, $p = 0.10$). Results were considered significant at the 0.05 level. Statistical analyses were performed using the SPSS software program (Chicago, IL), version 17.0.

RESULTS

Study Population

A total of 173 patients received third-line treatment during the study period, what corresponds to 28% of the 613 patients with unresectable stage IIIB or IV NSCLC treated with first-line chemotherapy (Fig. 1). Baseline characteristics of these 173

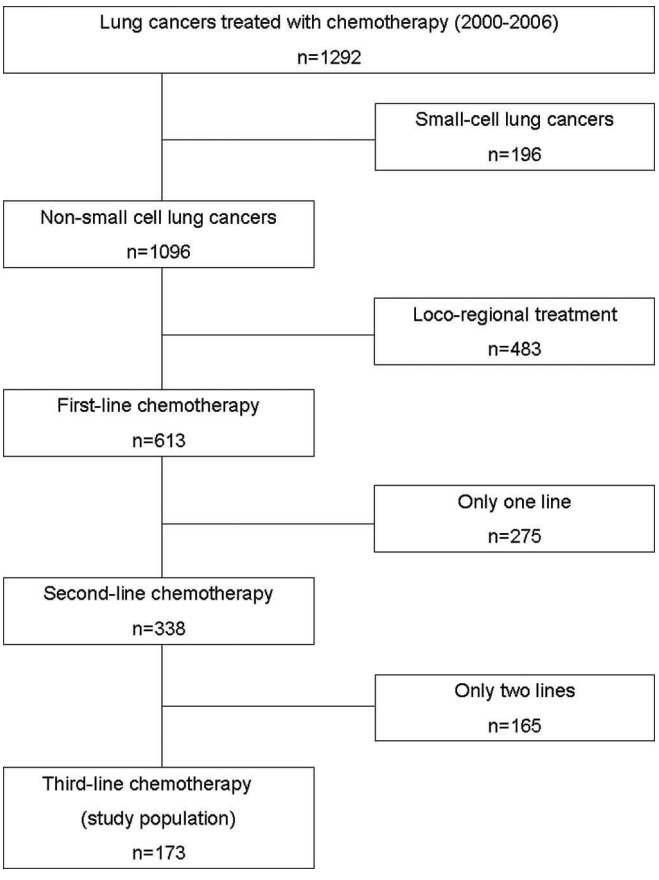

FIGURE 1. Study population.

TABLE 1. Baseline Characteristics of the Study Population

Characteristics	*n*	%
Total	173	100
Gender		
Male	128	74
Female	45	26
Age at diagnosis		
≤70 yr	129	75
>70 yr	44	25
Smoking characteristics		
Smoking status		
Current smoker	75	43
Former smoker	72	42
Never smoker	26	15
Smoking quantity		
<10 pack-years	32	18
≥10 pack-years	141	82
Tumor characteristics		
Histology		
Adenocarcinoma	110	64
Squamous cell carcinoma	38	22
Large-cell carcinoma	25	14
Staging[a]		
Tumor		
T1	13	8
T2	67	39
T3	17	10
T4	76	44
Nodal		
N0	34	20
N1	21	12
N2	43	25
N3	75	43
Metastasis		
M0	52	30
M1	121	70

[a] As of Ref. [14].

patients are presented in Table 1. The first two lines of treatment mostly consisted of chemotherapy, as per the standard recommendations at time of the study (Table 2). First-line treatment was a platinum-based doublet in 142 patients (82%), and second line was single-agent chemotherapy (mostly docetaxel, gemcitabine, or pemetrexed) in 156 patients (90%).

Third-Line Treatment Characteristics

Third-line treatment was cytotoxic chemotherapy for 131 patients (76%) and EGFR TKIs for 42 patients (24%; Table 2). Chemotherapy consisted of a single agent for 125 patients (72%). Most frequently administered drugs were gemcitabine (62 patients), docetaxel (30 patients), and pemetrexed (20 patients). Third-line treatment was different from that delivered as first- and second-line treatment for all patients. Median duration of third-line treatment was 2.1 months (95% CI: 1.9–2.2 months), when compared with 3.3 months (95% CI: 3.0–3.6 months) and 2.3 months (95% CI: 2.1–2.5 months), for first- and second-line treatments, respectively ($p = 0.534$).

TABLE 2. Characteristics of First-, Second-, and Third-Line Treatment

	Third-Line Treatment		First-Line Treatment		Second-Line Treatment	
	n	100%	*n*	100%	*n*	100%
Total	173	100	173	100	173	100
Patient characteristics at day 1						
Performance status						
0–1	88	51	150	87	130	75
≥2	85	49	23	13	43	25
Loss of weight since previous line						
<5 kg	139	80	N/A	N/A	131	76
≥5 kg	34	20	N/A	N/A	42	24
Treatment						
Regimen						
Triplet[a]	0	0	8	5	0	0
Doublet						
Platinum based	3	2	142	82	12	7
Nonplatinum based	3	2	4	2	1	1
Single-agent chemotherapy	125	72	19	11	156	90
Docetaxel	32	18	1	1	62	36
Pemetrexed	20	12	0	0	46	27
Gemcitabine	62	36	8	5	43	25
Vinorelbine	2	1	6	3	2	2
Paclitaxel	9	5	3	2	3	2
Tyrosine kinase inhibitor	42	24	1	1	4	2
Number of cycles						
1–2	45	26	31	18	60	35
3–4	51	29	83	48	64	37
5–6	35	20	48	28	30	17
>6	0	0	10	6	15	9
N/A[b]	42	24	1	1	4	2
Grade III–IV acute toxicities						
Hematological	17	10	18	10	8	5
Digestive	16	9	7	4	1	1
Neuropathy	9	5	7	4	1	1
Hepatic	1	1	2	1	0	0
Renal	0	0	1	1	0	0
Others	18	10	5	3	3	2
Tumor control						
Complete response	0	0	6	3	0	0
Partial response	10	6	66	38	24	14
Stabilization	52	30	62	36	52	30
Progression	111	64	39	23	97	56

[a] Combination of cisplatinum, ifosfamide, and vinorelbine.
[b] Not applicable for patients who received tyrosine kinase inhibitors.
N/A, not applicable.

Third-line treatment was highly feasible as 127 patients (73%) received at least 90% of the theoretical dose intensity. Only 13 patients (8%) received less than 75% of the theoretical dose intensity. Only 22 patients (13%) presented with grade 3 to 4 acute toxicities (Table 2), including hematolog-

ical complications in 10 cases, febrile neutropenia in 7 cases, digestive disorders in 16 cases, and neuropathy in 9 cases. Severe toxicity rate was similar in patients receiving chemotherapy or TKIs (13 and 12%, respectively). Treatment was discontinued following severe toxicity in 15 patients (9%), 10 of whom had completed more than four cycles of third-line chemotherapy or 3 months of treatment for EGFR TKIs. Treatment discontinuation rate was not statistically different in patients receiving chemotherapy or TKIs (8 and 10%, respectively).

Cancer-Related Symptoms Relief and PS Improvement

Of the 173 patients, 131 (76%) had cancer-related symptoms at initiation of third-line treatment. Most frequent symptoms included dyspnea (76 patients), chest pain (62 patients), thromboembolic disease (32 patients), cough (31 patients), metastasis-related pain (25 patients), and hemoptysis (20 patients). Partial or complete symptom relief was observed in 121 patients (92%) during third-line treatment. In the 59 patients who became completely asymptomatic, initial symptoms consisted of dyspnea (26 patients), chest pain (18 patients), cough (16 patients), and hemoptysis (16 patients).

Even if PS was 0 to 1 for 88 patients (51%) at initiation of third-line treatment (Table 2), PS improvement of at least 1 point was observed in 90 patients (52%). PS was stable in additional 69 patients (40%).

Disease Control

Disease control rate after third-line treatment was 36%, which was significantly lower than after first- and second-line treatments (77 and 44%, respectively; $p < 0.001$; Table 2). Disease control after third-line treatment was significantly associated with disease control after second-line treatment (hazard ratio [HR] = 2.51, 95% confidence interval [CI]: 1.32–4.65, $p = 0.006$), but not after first-line treatment (HR = 1.83, 95% CI: 0.81–4.13, $p = 0.135$).

TABLE 3. Significant Prognostic Factors on Overall Survival from the Initiation of Third-Line Treatment

	Univariate Analysis				Multivariate Analysis		
	Median Survival (mo)	Hazard Ratio	95% CI	*p*	Hazard Ratio	95% CI	*p*
Patient characteristics							
Gender							
Female	6.5	0.73	0.51–1.05	0.092	0.72	0.50–1.04	0.113
Male	4.9	1			1		
Initial tumor stage							
IIIB	6.0	0.96	0.68–1.35	0.811	0.99	0.80–2.38	0.767
IV	5.8	1			1		
Histology							
Adenocarcinoma	6.0	0.65	0.68–1.27	0.649	0.84	0.61–1.15	0.263
Others	5.1	1			1		
Smoking history							
<10 pack-year	11.9	0.55	0.36–0.84	0.003	0.82	0.57–0.93	0.036
≥10 pack-year	5.0	1			1		
Characteristics at initiation of third-line treatment							
Age							
<70 yr	8.8	0.72	0.53–0.98	0.034	0.73	0.53–0.99	0.047
≥70 yr	4.9	1			1		
Symptoms at initiation of third-line treatment							
No	6.9	0.53	0.37–0.76	<0.001	0.75	0.61–0.92	0.007
Yes	4.1	1			1		
Weight loss since the end of second-line treatment							
<5 kg	11.8	0.61	0.53–0.81	0.001	0.63	0.52–0.75	0.013
≥5 kg	4.0	1			1		
Performance status at initiation of third-line treatment							
0–1	6.0	0.62	0.52–0.75	<0.001	0.81	0.76–0.86	0.008
2–3	3.2	1			1		
Absence of extra-thoracic tumor lesion							
Yes	6.9	0.64	0.46–0.89	0.007	0.67	0.47–0.94	0.042
No	4.6	1			1		
Response to previous treatments							
Disease control after first- and second-line	10.3	0.45	0.32–0.62	<0.001	0.47	0.33–0.67	0.001
Progression after first- and/or second-line	4.0	1			1		

Overall Survival

At the time of analysis, all 173 patients were dead (169 from tumor progression and 4 from intercurrent disease). Overall median, 6-, and 12-month survival from first-line treatment were 16.4 months, 93 and 69%, respectively. Median, 6-, and 12-month survival after third-line treatment were 5.8 months, 47, and 25%, respectively. Survival after third-line treatment was higher than 3 months in 121 patients (70%) and higher than 6 months in 83 patients (48%).

Results of univariate analysis are presented in Table 3. The following variables were included in the multivariate analysis: gender, smoking history, weight loss, PS, presence of extrathoracic tumor spread, response to first- and second-line treatment. Survival after third-line treatment was significantly increased in patients less than 70-years old (HR = 0.73, 95% CI: 0.53–0.99, $p = 0.047$), who had smoked less than 10 pack-years (HR = 0.82, 95% CI: 0.57–0.93, $p = 0.036$), with no cancer-related symptoms (HR = 0.75, 95% CI: 0.61–0.92, $p = 0.007$), a weight loss less than 5 kg since the beginning of the second line (HR = 0.63, 95% CI: 0.52–0.75, $p = 0.013$), a PS of 0 to 1 (HR = 0.81, 95% CI: 0.76–0.86, $p = 0.008$), and no extrathoracic tumor spread at initiation of third-line treatment (HR = 0.67, 95% CI: 0.47–0.94, $p = 0.042$; Table 3). Disease control after first- and second-line treatments was the strongest predictor of prolonged survival after third-line treatment (HR = 0.47, 95% CI: 0.33–0.67, $p = 0.001$; Table 3, Fig. 2).

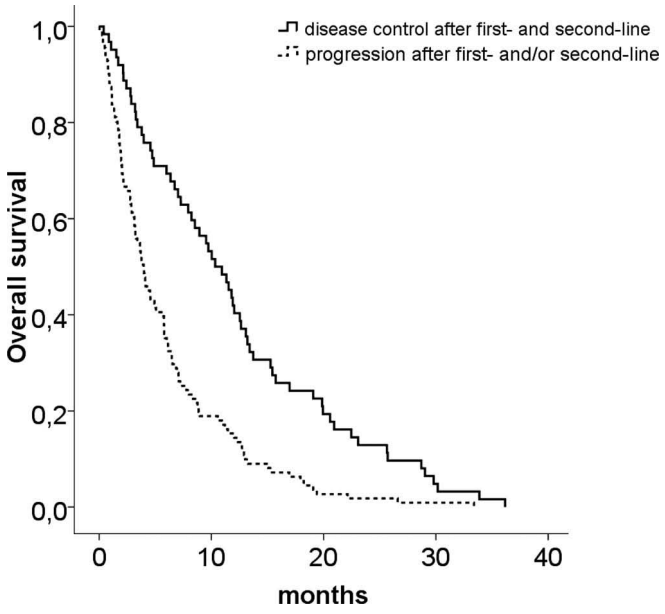

FIGURE 2. Overall survival from the initiation of third-line treatment, according to disease control after first- and second-line treatment. Median survival was 10.3 months in case of disease control after first- and second-line treatment and 4.0 months in case of progression after first- and/or second-line treatment (HR = 0.45, 95% CI: 0.32–0.62, $p < 0.001$ at univariate analysis).

DISCUSSION

This study is the largest reported series of patients who were given third-line chemotherapy for advanced NSCLC. Our analysis showed that third-line treatment was highly feasible in the selected population, as 73% of patients received at least 90% of the theoretical dose intensity and less than 10% experienced severe toxicity leading to discontinue the treatment. Third-line treatment led to symptom relief and PS control in more than 90% of patients. Disease control was achieved in 36% of patients. Survival after third-line treatment was significantly longer in case of disease control after both first- and second-line treatment.

In this study, third-line treatment was delivered to nearly 30% of patients with advanced NSCLC. Patients who are considered for third-line treatment definitely represent a selected population of advanced NSCLC with better prognosis. In our cohort, baseline PS was 0 to 1 in 87% of cases (Table 1), what is one of the strongest prognostic factors in NSCLC.[19] Second, response rate to first-line treatment (41%) and overall survival from diagnosis (16.4 months) were nearly twice the ones observed in patients included in randomized trials with doublet chemotherapy (20% and 7.9 months, respectively, in the study reported by Schiller et al[5]). Finally, a significant proportion (55%) of patients had no extrathoracic tumor spread at time of diagnosis, a favorable prognostic factor recently identified in the Lung Cancer Staging Project analysis.[20]

In our study, the clinical benefit from third-line treatment was striking, as PS was stable or increased in 92% of patients and cancer-related symptoms relief was obtained in more than 90% of patients during treatment. As the majority of patients had symptoms when third-line treatment was considered, this may represent a better end point than response rate, which, as expected, was lower than after the first two lines. Regarding survival, nearly half of our patients were alive more than 6 months after the initiation of third-line treatment, which suggests that third-line treatment may serve as a salvage treatment after second-line treatment for a significant proportion of patients.[21] Interestingly, we did not identify any differences between chemotherapy and EGFR TKIs regarding response rate and survival.

Finally, despite its limitations (retrospective design and single institution recruitment) our study may help the decision making when facing a patient with advanced NSCLC presenting with tumor progression after second-line treatment. Our analysis showed that well-recognized favorable prognostic factors identified for first-line chemotherapy were still relevant for third-line treatment: age less than 70 years, PS 0 to 1, the absence of cancer-related symptoms and weight loss,[19,22] a short smoking history,[23] and the absence of extrathoracic metastases.[20] Interestingly, survival benefit after third-line treatment was strongly associated with disease control after the first two lines of treatment. Such association has previously been suggested for second-line treatment using docetaxel and pemetrexed.[24] For clinical practice, our analysis suggests that patients whose tumor was never controlled by previous treatments may not be good candidates for conventional third-line treatment.

To conclude, patients with advanced NSCLC may benefit from third-line treatment. Most prognostic factors identified for first-line treatment are still relevant in a third-line setting. Disease control after first- and second-line treatment was the most reliable prognostic factor at the initiation of third-line chemotherapy. As no prospective study has specifically been reported in this setting, this study provides relevant data for routine practice and future prospective trials evaluating third-line treatment strategies for advanced NSCLC.

ACKNOWLEDGMENTS

The authors thank Samuel LIMAT from the Hospital Pharmacy of the University Hospital of Besançon, for helpful assistance in recovering chemotherapy information.

REFERENCES

1. NSCLC Meta-Analyses Collaborative Group. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. *J Clin Oncol* 2008;26:4617–4625.
2. Pfister DG, Johnson DH, Azzoli CG, et al.; American Society of Clinical Oncology. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22:330–353.
3. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf. Accessed on August 5, 2009.
4. D'Addario G, Felip E; ESMO Guidelines Working Group. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2008;19S2:ii39–ii40.
5. Schiller JH, Harrington D, Belani CP, et al.; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
6. 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* 2000;18:2095–2103.
7. 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* 2004;22:1589–1597.
8. Shepherd FA, Rodrigues Pereira J, et al.; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–132.
9. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000;18:2354–2362.
10. Massarelli E, Andre F, Liu DD, et al. A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small-cell lung cancer. *Lung Cancer* 2003;39:55–61.
11. Murillo JR Jr, Koeller J. Chemotherapy given near the end of life by community oncologists for advanced non-small cell lung cancer. *Oncologist* 2006;11:1095–1099.
12. Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. *BMJ* 1998;317:771–775.
13. Travis WB, Brambilla A, Muller-Hermelinck HK, Harris CC. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press, 2004. p. 10.
14. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest* 1997;111:1710–1717.
15. World Health Organization. WHO Handbook for Reporting Results of Cancer Treatment. Geneva, Switzerland: WHO Offset Publications; 1979.
16. Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 1984;2:1281–1288.
17. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0. Development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;13:176–181.
18. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
19. Sculier JP, Chansky K, Crowley JJ, Van Meerbeeck J, Goldstraw P; International Staging Committee and Participating Institutions. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th Edition of the TNM Classification of Malignant Tumors and the proposals for the 7th Edition. *J Thorac Oncol* 2008;3:457–466.
20. Postmus PE, Brambilla E, Chansky K, et al.; International Association for the Study of Lung Cancer International Staging Committee; Cancer Research and Biostatistics; Observers to the Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. *J Thorac Oncol* 2007;2:686–693.
21. Chen YM, Perng RP, Shih JF, et al. Salvage therapy for Chinese non-small cell lung cancer patients who failed previous chemotherapy. *J Thorac Oncol* 2006;1:545–550.
22. Hoang T, Xu R, Schiller JH, Bonomi P, Johnson DH. Clinical model to predict survival in chemonaive patients with advanced non-small-cell lung cancer treated with third-generation chemotherapy regimens based on eastern cooperative oncology group data. *J Clin Oncol* 2005;23:175–183.
23. Janjigian Y, Kris MG, Miller VA, Riely G. Pack years of cigarette smoking as a predictor of survival in 2,010 patients with stage IIIb/IV non-small cell lung cancer (NSCLC). *J Clin Oncol ASCO Annu Meet Proc* 2008;26:8005 [abstract].
24. Weiss GJ, Rosell R, Fossella F, et al. The impact of induction chemotherapy on the outcome of second-line therapy with pemetrexed or docetaxel in patients with advanced non-small-cell lung cancer. *Ann Oncol* 2007;18:453–460.

