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

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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.

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

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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

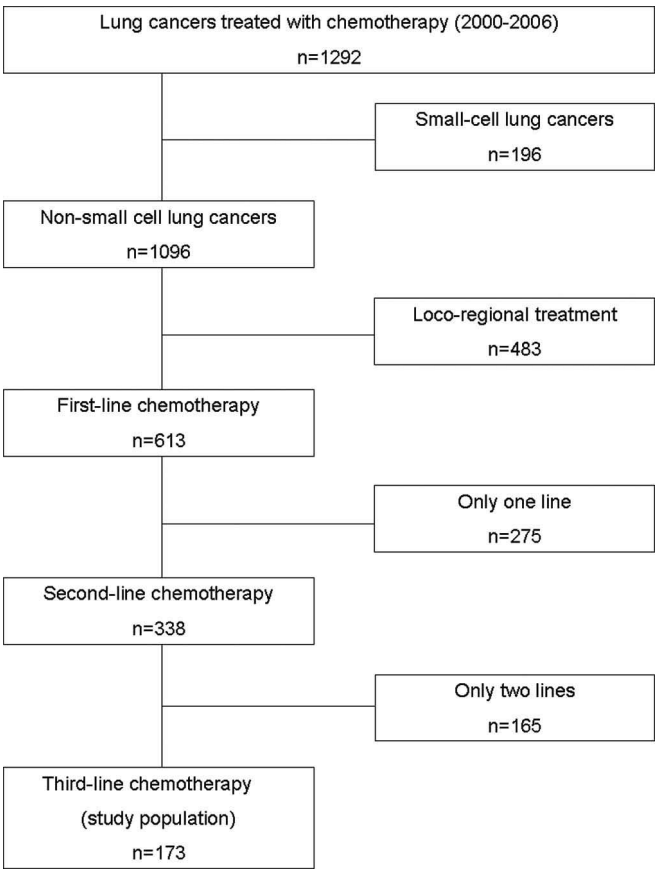

FIGURE 1. Study population.