Original Study

Modern Treatments in Advanced Non–Small-Cell Lung Cancer: Temporal Trends and Effect on Survival. A French Population-Based Study

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Abstract

Extrapolation of clinical trials results to the general population is always challenging. We analysed 1047 patients diagnosed with an advanced stage disease between 1998 and 2005 in a french administrative department and found a good spread of modern chemotherapy since 1998 and targeted therapy since 2002. Moreover, the outcomes in patients treated according to guidelines are very proximal from those obtained in clinical trials.

Background: Management of metastatic non–small-cell lung cancer has considerably evolved during the past 2 decades. In this study we aimed to assess how treatments have spread at a population-based level and their effect on survival. **Patients and Methods:** Medical records of patients diagnosed from 1998 to 2005 in the French department of Bas-Rhin were checked to collect data on patient characteristics and treatments received. Multivariate analysis of survival was performed using pretherapeutic and therapeutic factors including targeted therapies received as third-line treatment. **Results:** We included 1047 patients with stage IIIB to IV non–small-cell lung cancer. The proportion of patients who underwent chemotherapy increased from 373/471 (79.2%) to 491/576 (85.2%) over the 1998 to 2001 and 2002 to 2005 periods, and there was an increased use of third-generation drugs associated with platin. Third-line treatment was gefitinib or erlotinib in 73/155 (47.1%) of the cases among patients diagnosed from 2002 to 2005. Compared with older agents, targeted therapy administered as third-line treatment was associated with a longer survival but there was no significant difference in survival with recent chemotherapy agents in multivariate analyses (hazard ratio, 0.773; 95% confidence interval, 0.445-1.343). **Conclusion:** Results of our study showed a good spread of modern chemotherapy and targeted therapy use at a population-based level. However, even if the general outcomes were improved along the years, the results observed in real clinical practice were slightly different from those reported in clinical trials.

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Introduction

Of all cancer types, lung cancer is the leading cause of mortality with 1.5 million deaths estimated worldwide; 167,000 in the United States and 267,000 in the European Union in 2012.[1] In France, lung cancer in 2012 brought 39,000 new cases, and was responsible for 30,000 deaths.[2] Approximately 84% of lung cancers are non–small-cell lung cancer (NSCLC),[3] with approximately 50% being metastatic at time of diagnosis.[4] Previous decades have seen considerable changes in histological distribution, with increased adenocarcinoma subtype incidence over the past 2 decades in France, whereas squamous cell carcinoma took precedence during the 1980s and 1990s.[5]

Treatment of Stage IIIB "wet" and IV disease (sixth tumor, node, metastases classification) is based on chemotherapy. In physically fit patients, a platinum-based doublet was recommended in 1997[6] and

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confirmed in more recent recommendations.[7] Results obtained with this chemotherapy type plateaued in the early 2000s, with a median overall survival of approximately 8 months and 1-year survival rates of 33% in phase III clinical trials,[8-10] regardless of the third-generation drug associated with either cisplatin or carboplatin. Additionally, third-generation agents like docetaxel[11] and pemetrexed[12] have been approved by the Food and Drug Administration as single agents for second-line therapy after platinum-based doublet therapy.

From this era onward, the concept of personalized treatment has considerably modified the management of metastatic NSCLC. From 2002, tyrosine kinase inhibitors (TKIs) namely gefitinib and erlotinib, were used with particular clinical benefit observed in Asian patients, women, adenocarcinoma cases, and never-smokers. Moreover, the 2004 discovery of activating mutations of the *epidermal growth factor receptor* (*EGFR*) gene allowed for these mutations to be correlated with response to TKIs.[13,14] Median overall survival time in patients with *EGFR* mutations was approximately 19 to 21 months,[15] to 31 to 33 months in recent phase III studies that evaluated afatinib.[16] TKI efficacy has also been assessed in second- and third-line therapy for patients with or without *EGFR* mutations. Compared with best supportive care (BSC), even in the absence of *EGFR* mutations, TKIs were associated with survival benefits.[17]

When treatments evolve to such an extent, it is always useful to determine if changes to guidelines are applied to the general population, and if the results reported in clinical trials are consistent with those observed at the whole-population level.

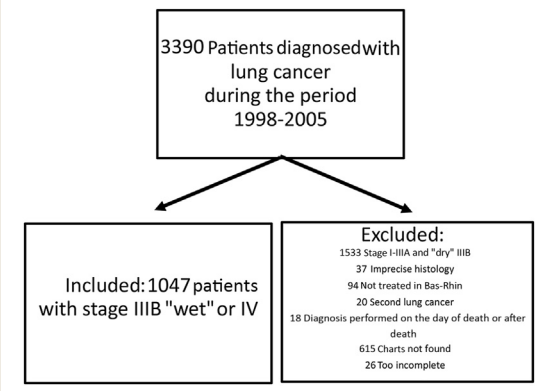
To address these issues, we conducted a retrospective study to analyze management and outcome of patients from the "département" of Bas-Rhin, a French administrative region of approximately 1 million inhabitants, who had received a diagnosis of advanced stage IIIB "wet" or IV NSCLC between 1998 and 2005 and followed-up until 2009.

Patients and Methods

Patients

Using the Bas-Rhin population-based cancer registry, we were able to compile the list of all patients diagnosed with NSCLC during the 8-year period of 1998 to 2005, comprising a 4-year period (2002-2005) during which first-generation TKIs could be used without knowledge of the existence of *EGFR* mutations. Overall, 3390 patients were diagnosed with lung cancer in this 8-year period (Figure 1). Of these patients, 1533 were excluded from analysis because of stage I to IIIA or "dry" stage IIIB disease, and 37 because of imprecise histology. In addition, 94 patients were excluded because they were not treated in the Bas-Rhin, 20 because their cancer was a second lung cancer, and 18 because the diagnosis was made on the day of death or even after death. Medical records for 615 cases could not be found for various reasons, such as difficult access to private practitioner records, and 26 were too incomplete.

Figure 1 Flow Chart



Data Collection

Medical records were checked to collect data about age; sex; smoking habits, less than a hundred cigarettes during life for never-smokers, at least 1 year smoke-free for former smokers, and current smokers; performance status (PS) of 0 to 1 versus ≥ 2; histological subtype; date of diagnosis; investigations performed for diagnosis and disease extent assessment; number of metastatic sites; and location.

With regard to treatment variables, first-line chemotherapy, second-, third-, and greater than third-line chemotherapy, TKI treatment, radiation therapy, surgery, and BSC alone were recorded. Chemotherapy types were classified as platinum-based (cisplatin or carboplatin), older or unusual drugs, and third-generation agents, such as vinorelbine, gemcitabine, paclitaxel, docetaxel, and pemetrexed. TKIs administered were gefitinib or erlotinib.

Statistical Analyses

A descriptive analysis of the data set was performed. The type of treatment received was analyzed according to year of NSCLC diagnosis, with a particular focus on the different types of chemotherapy used (older or unusual, third-generation, and targeted therapy).

Survival time was first defined from the date of NSCLC diagnosis and the date of death, last known vital status, or September 30, 2009, whichever came first.

Because targeted therapies were more frequent as third-line chemotherapy in our data set, we also performed a specific survival analysis among patients who underwent 3 lines of chemotherapy. In this case, survival time was therefore defined from the beginning of the third-line chemotherapy and the date of death, last known vital status, or September 30, 2009, whichever came first.

Survival curves were constructed using the Kaplan–Meier method and comparisons were performed using the log-rank test. Multiple regression analyses using Cox proportional hazard models were done to assess the effect of chemotherapy on survival, adjusted with other prognosis factors. The proportionality assumption was verified through assessment of interaction with time.

All analyses were performed using SAS software version 9.3 (SAS institute, Cary, NC).

Results

Descriptive Analysis

The study population included 1047 patients with stage IIIB "wet" or stage IV NSCLC (Figure 1). Of those, 641 patients