

Histology-based treatment: a new scenario in the management of advanced nonsmall cell lung cancer

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Lung cancer is the leading cause of mortality due to cancer worldwide with about 1 300 000 cases diagnosed yearly [1]. Nonsmall cell lung cancer (NSCLC) accounts for more than 80% of all lung cancers. The NSCLC subgroup includes squamous carcinoma, adenocarcinoma and undifferentiated large cell carcinoma. In the past years, the most frequent histology was represented by squamous carcinoma followed by adenocarcinoma and large cell carcinoma. In the last decades, there is an epidemiologic shift from squamous to adenocarcinoma histology, the latter now represented in more than 50% of cases [2]. This can be explained in part by changes in smoking behavior such as the frequency of puff drawing and depth of inhalation and cigarette manufacturing such as an increase in light and filterless cigarettes [3].

The majority of patients have advanced disease at diagnosis, and medical treatment is the cornerstone of management. Platin-based doublets including a third generation drug such as gemcitabine, docetaxel, paclitaxel or vinorelbine showed superimposable efficacy with different toxicity profiles [4]. However, chemotherapy apparently reached a plateau of effectiveness in improving survival of NSCLC patients, and treatment outcomes must still be considered disappointing [4].

The major progresses in the understanding of cancer biology and mechanism of oncogenesis have allowed the development of several potential molecular targets for cancer treatment that are components of signaling pathways or metabolic processes contributing to the acquisition of cancer phenotype. Several targeted agents have been introduced in clinical trials in cancer treatment, and a series of phase III studies have already produced definitive results.

Due to its central role in tumor angiogenesis, the vascular endothelial growth factor (VEGF) and its receptor have

been a major focus in basic research and drug development in the field of oncology, including the treatment of NSCLC. Bevacizumab is an anti-VEGF recombinant humanized monoclonal antibody, and its clinical development, when combined with chemotherapy in the treatment of advanced NSCLC, has produced interesting results. A randomized phase III trial (study E4599) compared the combination of bevacizumab (15 mg/kg, dose selected by a previous phase II study) with chemotherapy (carboplatin and paclitaxel) versus chemotherapy alone in the treatment of advanced nonsquamous NSCLC [5]. In this trial, bevacizumab showed to be the first targeted agent which, when combined with chemotherapy, reported superior efficacy versus chemotherapy alone. After this study, the drug was licensed in combination with carboplatin and paclitaxel for first-line therapy of patients with advanced nonsquamous NSCLC in the United States. Efficacy benefit of bevacizumab has been recently confirmed by the AVAiL (AVAstin in Lung) trial, a randomized, placebo-controlled phase III study that evaluated bevacizumab in combination with cisplatin and gemcitabine in advanced nonsquamous NSCLC [6]. In this trial, chemotherapy was compared with chemotherapy and two different doses of bevacizumab, 7.5 and 15 mg/kg. The primary endpoint was progression-free survival, and statistical significant differences favoring both bevacizumab combinations were reported. Unfortunately, no difference in terms of survival was observed. Some issues such as a better prognosis of study patient population and the impact of further treatments after progression could have affected survival data. After the AVAiL trial, bevacizumab was licensed in Europe in combination with any platin-based chemotherapy. The main issue for bevacizumab is that it needs patient selection, in fact, to date, the drug can be used only in nonsquamous histology due to a high risk of pulmonary bleeding in squamous carcinoma.

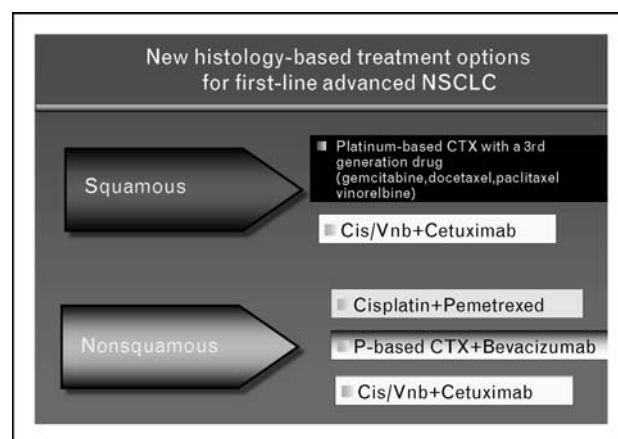
Recently, a phase III randomized trial in advanced NSCLC patients compared the new chemotherapy combination of cisplatin and pemetrexed versus cisplatin and gemcitabine [7]. In the whole patient population, the two regimens showed superimposable efficacy in terms of response rate, progression-free survival and overall survival with a better toxicity profile favoring the pemetrexed arm. Surprisingly, a preplanned subgroup analysis showed a statistically significant advantage in any outcome for cisplatin and pemetrexed

as compared to cisplatin and gemcitabine in nonsquamous histology. On the contrary, the advantage of cisplatin and gemcitabine combination in squamous carcinoma was clear. This result was confirmed by a retrospective analysis of the second-line trial involving pemetrexed versus docetaxel [8] and in the phase III trial of platin-based chemotherapy plus or minus pemetrexed maintenance [9]. This observation has its biological explanation in the higher protein level of thymidylate synthase, the primary target of pemetrexed, observed in squamous cell carcinoma [10]. After this study, pemetrexed was licensed for use in the first-line treatment of advanced nonsquamous NSCLC.

Targeting the epidermal growth factor receptor (EGFR) has played a central role in advancing NSCLC research, treatment and patients' outcome over the last several years. Cetuximab is an anti-EGFR monoclonal antibody approved for use in colorectal carcinoma and head and neck cancer treatment. Very recently, in the FLEX (first-line in lung cancer with erbitux) phase III randomized trial, the combination of cisplatin and vinorelbine along with cetuximab demonstrated superiority in terms of response rate and overall survival compared with the same chemotherapy alone in the first-line treatment of advanced EGFR expressing NSCLC [11]. After a licence awaited by 2009, cetuximab-based chemotherapy could represent a treatment option for all EGFR-positive NSCLC.

The future choice of treatment for squamous carcinoma could be a platin-based doublet including a third generation drug (i.e. gemcitabine, docetaxel, paclitaxel, or vinorelbine) or cisplatin, vinorelbine or cetuximab and for nonsquamous carcinoma cisplatin and pemetrexed or platin-based chemotherapy and bevacizumab (Fig. 1). However, this scenario raises a diagnostic issue: in order to choose an optimal treatment, we need a specific diagnosis, as a general NSCLC diagnosis is not enough. In clinical practice, particularly in patients with metastatic disease, frequent diagnosis is performed by fine needle aspiration biopsy (FNAB) that produces a general cytological NSCLC diagnosis. When possible, we should always try to obtain a tumor sample tissue for a subtype of histological diagnosis, even using more invasive approaches. In a future era of treatments guided by molecular biomarkers, this will be mandatory, though waiting to obtain a molecular characterization of circulating tumor cells that may provide a noninvasive strategy [12]. However, to date, we need a sure diagnosis in order to administer a well tolerated and optimal treatment to our patients.

Figure 1 Histology-based therapeutic options for advanced nonsmall cell lung cancer



CTX, chemotherapy.

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