Non-small-cell lung cancer: targeted therapies

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Chemotherapy: is it still enough?

The major progresses in understanding cancer biology and the mechanism of oncogenesis have allowed the development of several potential molecular target drugs for cancer treatment, which are components of signaling pathways or metabolic processes contributing to the acquisition of cancer phenotype. A general better tolerability, owing to a milder toxicity profile than conventional chemotherapy, better target selectivity, availability for chronic treatment and, in some cases, oral administration, have marked these new targeted compounds as the most promising investigational drugs for cancer therapy. Several targeted agents have been extensively employed for the treatment of lung cancer, which remains the main killer. In fact, lung tumors are the leading cause of mortality due to cancer, with approximately 1.35 million new diagnoses and 1.18 million deaths worldwide in 2002 [1]. Lung cancer includes two main groups: non-small-cell lung cancer (NSCLC), which accounts for more than 80% and comprises squamous carcinoma, adenocarcinoma and undifferentiated large-cell carcinoma, and small-cell lung cancer (SCLC) [2].

The majority of people diagnosed with NSCLC are unsuitable for surgery due to advanced disease, thus, palliation and patient quality-of-life are still the primary goal of therapy. Advanced disease represents the main field in which the new targeted agents have been employed. Progresses with chemotherapeutic agents in advanced NSCLC seem to have reached a plateau [3], with a recent study showing that the combination of pemetrexed and cisplatin compared with gemcitabine plus cisplatin statistically improved the median survival time (MST) in patients with nonsquamous histology [4]. The outcome advantage of pemetrexed in nonsquamous histology was confirmed by a retrospective analysis of a second-line trial involving pemetrexed versus docetaxel [5], and in a Phase III trial of platinum-based chemotherapy followed, or not, by pemetrexed maintenance [6]. This observation has its biological explanation in the higher protein level of thymydilate-synthase, the primary target of pemetrexed, observed in squamous cell carcinoma [7]. After this study, pemetrexed was licensed for use in the first-line treatment of advanced nonsquamous NSCLC. Nevertheless, new treatment approaches are needed.

Targeted therapies: what do we know?

Targeting EGFR and VEGF and their receptors has played a central role in advancing NSCLC research, treatment and patient outcome over recent years. Approaches targeting EGFR and VEGF include monoclonal antibodies (mAbs) and small molecules that inhibit corresponding receptor-tyrosine kinase activity.

To date, only two new targeted agents have been licensed worldwide for clinical practice use in the treatment of advanced NSCLC. Bevacizumab, an anti-VEGF recombinant humanized mAb, in combination with first-line chemotherapy statistically improved the main end point of two Phase III randomized trials, and is currently licensed for use in combination with carboplatin plus paclitaxel in the USA, or in addition to platinum-based chemotherapy in Europe for first-line therapy of patients with advanced nonsquamous NSCLC [8,9]. To date, the main issue for bevacizumab is that it requires patient selection, as the drug can be used only in nonsquamous histology patients due to a high risk of pulmonary bleeding in squamous carcinoma.

Erlotinib, an EGFR tyrosine-kinase inhibitor, is the second agent being used in clinical practice. In the Phase III randomized trial BR.21, erlotinib improved the MST, quality-of-life and related symptoms of an unselected population of

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advanced NSCLC patients in the second- or third-line setting, compared with the best supportive care [10].

Gefitinib, another EGFR tyrosine-kinase inhibitor, failed to show any advantage when compared with best supportive care in pretreated NSCLC patients, and is, currently, only licensed in Asian countries [11]. The results of a large Phase III randomized trial, named IRESSA NSCLC Trial Evaluating Response and Survival against Taxotere (INTEREST), comparing gefitinib to docetaxel chemotherapy in second- and third-line setting of NSCLC, have recently become available [12]. In a noninferiority design, gefitinib showed similar efficacy to docetaxel (MST of 7.6 and 8 months, respectively), with a lower toxicity profile and a better quality-of-life score. These results support licensing gefitinib for second- and third-line therapy worldwide.

Factors that might predict the efficacy of erlotinib and gefitinib, including clinical, pathologic and molecular features, have been investigated. It has been shown that a substantial percentage of tumors responding to gefitinib or erlotinib therapy harbor somatic mutations in the *EGFR* gene. These mutations are more frequently detected in NSCLC patients with clinical characteristics reported as predictive of response to gefitinib or erlotinib, such as never-smoking status, female gender, Asian race and adenocarcinoma with bronchioloalveolar features, once again, nonsquamous histotype. In addition, a high EGFR copy number, detected by fluorescence *in situ* hybridization, seems to have a predictive role of outcome for EGFR tyrosine-kinase inhibitors. Overall, never-smoking history and EGFR mutations seem to be the strongest predictive factors. However, it is important to note that the main information on the predictive role of clinical and biomolecular markers came from retrospective analyses, where gefitinib or erlotinib were compared with the best supportive care [10,11,13]. In fact, gefitinib unexpectedly failed to show a survival advantage versus docetaxel, not only in patients who were EGFR fluorescence *in situ* hybridization-positive, but also for all the other clinical and biomolecular factors [12], thus raising doubts about their predictive role. However, this is the first prospective analysis in a large Phase III randomized trial comparing these new biologic agents to chemotherapy.

Very recently, in the First-line in Lung cancer with Erbitux (FLEX) Phase III randomized trial, the combination of cisplatin and vinorelbine plus cetuximab, a chimeric (human–murine) anti-EGFR mAb, demonstrated superiority in terms of response rate and MST compared with the same chemotherapy alone in the first-line treatment of advanced EGFR-expressing NSCLC [14]. This trial supports the licensing of cetuximab-based chemotherapy, a treatment option for EGFR-positive NSCLC, independently from histotype.

> *"The results reported by the INTEREST and INVITE studies underline the need for further prospective clinical trials to better understand the predictive and/or prognostic role of clinical and biomolecular markers."*

Future perspective

In the last few years, the impact of targeted therapies in the clinical practice therapy of NSCLC has raised at least two major issues to arise. First, could clinical, pathologic and molecular features be prognostic and not predictive factors? Better understanding of the molecular mechanisms targeted by new biologic agents calls for further investigation of chemotherapy interference with cellular pathways. The randomized, Phase II trial named IRESSA in NSCLC versus Vinorelbine Investigation in the Elderly (INVITE) showed similar efficacy of gefitinib and vinorelbine with a lower toxicity profile and a better quality-of-life favoring gefitinib. Surprisingly, in this case EGFR fluorescence *in situ* hybridization-positive patients reported better outcomes with vinorelbine than with gefitinib [15]. The results reported by the INTEREST [12] and INVITE [15] studies underline the need for further prospective clinical trials to better understand the predictive and/or prognostic role of clinical and biomolecular markers.

Secondly, the prognostic difference between squamous and nonsquamous histology is becoming more evident. This difference could subdivide lung cancer into three main groups: nonsquamous carcinoma, squamous carcinoma and SCLC. This distinction is also based on the different approaches derived by key trials. In fact, nonsquamous carcinoma benefits from cisplatin plus pemetrexed or platinum-based chemotherapy plus bevacizumab, whereas these regimens are not licensed for squamous carcinoma, which may benefit from platinum-based doublets including a third-generation drug (gemcitabine, docetaxel, paclitaxel and vinorelbine). The forthcoming cetuximab-based chemotherapy use does not depend on histotype. In this view, CP-751,871, a fully human anti-insulin-like growth factor-I receptor mAb,

seems to improve the outcomes of squamous NSCLC in combination with chemotherapy and is, at present, in development in a Phase III randomized trial [16].

"The prognostic difference between squamous and nonsquamous histology is becoming more evident. This difference could subdivide lung cancer into three main groups: nonsquamous carcinoma, squamous carcinoma and SCLC."

As a consequence, this scenario rises a diagnostic issue. In clinical practice, and particularly in patients with metastatic disease, diagnosis is frequently performed by fine-needle biopsy, which produces a general cytological NSCLC finding. However, based on the previous statements, an optimal treatment calls for a specific diagnosis. Therefore, should we still use invasive approaches to obtain a tumor sample tissue for a subtype of histological diagnosis? To administer the optimal treatment to patients, a more definite diagnosis is mandatory. In the future, the possibility of obtaining a molecular characterization of circulating tumor cells [17] could help avoid an invasive strategy for diagnosis.

In second-line treatment, the choice of erlotinib or chemotherapy, represented by docetaxel or pemetrexed, should be guided by first-line therapy outcomes, performance status, and/or clinical and biomolecular factors, of which, as reported before, never-smoking history and EGFR mutations seem to be the strongest. Erlotinib is the only drug registered for third-line therapy.

Several new biologic agents are being evaluated in clinical research and some of them, such as ZD6474, sunitinib, histone deacetylase or m-TOR inhibitors, due to evidence of anti-tumor activity, good toxicity profiles and an oral route of administration, seem to be promising targeted agents for NSCLC treatment.

Finally, despite the statistical improvement in survival reported with the aforementioned new biologic agents, many doubts exist concerning their proper administration in clinical practice. In fact, these new therapeutic agents are far from being a cure for advanced NSCLC, and only definition of the populations who might benefit from these treatments will help in optimizing their therapy and outcomes.

"In the future, the possibility of obtaining a molecular characterization of circulating tumor cells could help avoid an invasive strategy for diagnosis."

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