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Perspective

EGFR Inhibitors for Neoadjuvant and Adjuvant Therapy of NSCLC

Abstract

5-year survival rates of Non-Small Cell Lung Cancer (NSCLC) remain unsatisfactory after surgery with curative intent and disease recurrences, including distant metastases, are frequent. Only a minority of this heterogeneous disease is positive for EGFR mutations and suitable for Tyrosine Kinase-Inhibitor biological agents, which however present limits in terms of stable response to treatment, due to the acquired drug resistances. A few trials administrating EGFR inhibitors combined with surgery, in neoadjuvant or adjuvant settings, have been reported with lack of evidence. The third-generation EGFR inhibitors, with the amelioration of techniques of gene profiling and the knowledge of pathways could extent the spectrum of complementary-to-surgery treatments in NSCLC at high risk of relapse.

5-year survival rates of NSCLC remain unsatisfactory after surgery with curative intent and disease recurrences, including distant metastases, are frequent [1]. These findings suggest a common micrometastatic pattern for NSCLC retained amenable for curative resection. Nowadays the guidelines from the American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) recommend adjuvant cisplatin-based regimen for patients with completely resected stage II or IIIA NSCLC [2], while neoadjuvant therapy has shown promising results when a good pathological response is observed and negative resection margins are achieved [3]. In these trials neodjuvant chemotherapy has been performed exclusively by cytotoxic agents. Despite toxicity progression free survival and overall survival are significantly improved by neoadjuvant and adjuvant treatments in stage III NSCLC, although weaker evidences have been found for stage II NSCLC. Nevertheless strategies for the identification of patients who can obtain the best gain from surgery are still lacking. Gene expression profiling has already been used to detect patients at risk of recurrences and candidates to adjuvant treatment [4]. In this study patients with K-ras mutations did not have benefits by the administration of adjuvant therapy, and patients with the overexpression of p53 had better response despite the poorer prognosis. This auspicious approach leads to the personalized treatment of NSCLC and presumably brings the perspective of a revision of the current staging classification based upon macroscopic tools, clearly insufficient.

Within this context remarquable efforts have been made to assess the real prognostic and therapeutic implications of the EGFR mutations in NSCLC.

A number of trials on EGFR inhibitors for neoadjuvant and adjuvant therapy of NSCLC have been developped in the recent years. The rationale is that complementary to surgery biological agents could represent a cancer signaling-targeted strategy to control the disease, including micrometastases overgrowth, hypotesized to be sustained by the crosstalk with the main mass. EGFR inhibitors could reduce continued dissemination of cancer and the 'seed and soil' interaction with macro and microenvironement. EGFR is in fact strongly involved in lymphatic and hematogenous spread of aberrant cells and in their pro-metastatic interactions with stromal tissue [5]. EGFR mutations play also a role in evasion of tumor immunosurveillance [6]. Molecular-targeted agents could strenght surgery before and after it, even though it has been observed great inter and intra-individual variability in response in non-surgical patients due to the complexity of mitogenic redundant pathways, the heterogeneity of mutations among cancer populations and the possibility of acquired resistance [7].

In 2009 thirty-six patients have been enrolled in the first phase II study on preoperative Gefitinib in an unselected population [8]. Not surprisingly EGFR mutation was the strongest predictor of response. Schaake et al. [9], report a metabolic response at PET scan (defined as >25% standardized uptake value decrease) in 27% of patients using neoadjuvant Erlotinib, but only 5% of responder at CT evaluation according to the Response Evaluation Criteria in Solid Tumors (RECIST). Patients were substantially unselected for EGFR mutations, despite the study population was enriched with never-smokers, females, nonsquamous histology and Asian ethnicity, more likely to have EGFR mutations [7]. Toxicity was well tolerated and lower in comparison with cytotoxic regimens.

In a case report of 2013 it was observed a preoperative down staging using Gefitinib for an EGFR mutation-positive bronchioloalveolar carcinoma, and a complete radiological response after brain recurrence in the adjuvant setting [10].

Monoclonal antibodies are also used for treatment of advanced-stage EGFR mutation-negative NSCLC, and attempts in terms of inductive systemic chemotherapy have been reported with promising results in unselected patients [11]. Panitumumab, the competitor of Cetuximab, has not been used yet as neoadjuvant or adjuvant strategy for NSCLC.

Adjuvant targeted therapy have been better investigated. Evidences of the effectiveness of EGFR inhibitors after surgery are weak [12-14]. Possible explanations include heterogeneity of the study population and the known biases of selection. In addition long term

results are not available yet. It's licit to consider the augmentation of the risk of relapse caused by mutational acquired resistance in a long-term adjuvant treatment. However the preliminary studies on Third-generation EGFR inhibitors have shown promising results of new EGFR-mutant-selective TKIs compounds (AZD9291 and rociletininb). These molecules directed on Thr790Met, the most common mechanism of EGFR inhibitors acquired resistance, seem to overcome the main limit of the biological agents for NSCLC: the stable response to treatment [15]. For this reason they could be hypotetically used combined with surgery in patients suffering from advanced stages of NSCLC, or eventually early stages NSCLC prone to relapse. The amelioration of techniques of gene profiling and the knowledge of pathways could in fact reveal better predictors of outcome, also for early stages NSCLC.

Other trials are ongoing on neoadjuvant and adjuvant treatment of NSCLC, and regularly presented as abstracts at congresses, however planning of studies is difficult for the relative low prevalence of EGFR mutation-positive patients, especially in western countries, and costs. More efforts in research are required.

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