Does the order of factors affect the product? Lessons learned from the TORCH trial

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Lung cancer is the leading cause of cancer-related deaths globally, with a low 5-year survival rate [approximately 15 percent - *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). non-small cell lung cancer. National Comprehensive Cancer, Network 2012*]. Non-small cell lung cancer (NSCLC) is the most common subtype. Traditionally, platinum-based chemotherapy has been the main frontline treatment modality for advanced NSCLC (1). Despite the many active combination chemotherapy regimens, median overall survival (OS) for advanced NSCLC remains 10-12 months. Due to a growing understanding of molecular abnormalities related to tumorigenesis and the intricacies of drug-target interactions, there has been a paradigm shift in clinical trial design, incorporating current knowledge into a trend towards personalized medicine. More recently, in many diseases including lung cancer, some of the targeted approaches have led to significant improvements in efficacy.

Over the past decade, several studies have been published utilizing drugs that target the epidermal growth factor receptor (EGFR) in NSCLC patients, through the use of small molecule tyrosine kinase inhibitors (2-4) or antibodies directed towards the extracellular domain of the receptor (5). The EGFR family of tyrosine kinase based enzymes is responsible for controlling multiple signaling pathways, including Ras/MAP-K, PI3K/Akt and activators of transcription (6). Specific mutations in the genes encoding these enzymes lead to tyrosine kinase ligand-independent activity, resulting in proliferation and dissemination of malignant cells (7). Initial phase II trials of EGFR tyrosine-kinase inhibitors (EGFR-TKIs), particularly erlotinib and gefitinib, yielded optimistic results, with prolonged periods of remission and improvement in quality of life in some patients whose tumors were refractory to standard chemotherapy (8,9). Despite promising single agent responses, preclinical chemo-combinatorial data, and the lack of overlapping toxicities, the addition of EGFR-TKIs to standard chemotherapy did not lead to improved efficacy (10).

The BR.21 trial shed new light on the potential of EGFR-TKIs, and led to renovated interest in the use of these drugs in NSCLC (2). Shepherd *et al*. randomized patients with stage IIIB or IV NSCLC, previously treated with one or two standard chemotherapy regimens, to receive either erlotinib or placebo. Patients in this study were not selected based on EFGR expression or presence of EGFR mutations. Treatment with erlotinib resulted in a 2 month survival advantage when compared to best supportive care, with tolerable side effects. This was the first trial showing a survival advantage with the use of an EGFR-TKI. Intriguingly, analysis of the molecular aspects of the study (11) implied an increased rate of response in patients whose tumors expressed *EGFR* (11 percent *vs.* 4 percent) and, particularly, who had polysomy or amplification of *EGFR* (20 percent *vs.* 2 percent). Univariate analysis of tumor sample sequencing for *EGFR* mutations revealed no significant difference in survival associated with erlotinib therapy, as compared with placebo (hazard ratio for death, 0.65; 95% confidence interval, 0.24 to 1.75; P=0.39).

Initially, the mechanism for selective responses to EGFR-TKIs in NSCLC patients was not known, but analysis of Phase II studies suggested that female sex, adenocarcinoma, Asian origin, and never or light smoking history were associated with responses in patients with non-small cell lung cancer treated with the EGFR TKIs erlotinib or gefitinib (12-14). Several groups described

mutations in the EGFR tyrosine kinase domain (exons 18 through 21) that sensitized cell lines to the effects of EGFR inhibition. Retrospective molecular analysis of patients with NSCLC responding to EGFR TKIs supported this hypothesis (12-14). The majority of mutations are either a deletion of a conserved sequence in exon 19 or a single point mutation in exon 21 (L858R). These activating mutations result in ligand-independent tumor-cell dependence on *EGFR* signaling and were found to be more common in people of Asian origin, women and never smokers.

The importance of clinical characteristics to select patient populations more likely to harbor a response to EFGR targeted therapy was significantly underscored in 2009 by two simultaneously published studies (15,16). The IPASS (Iressa Pan-Asia Study) trial (15) randomized a selected population of never or light ex-smoker Asian patients with adenocarcinoma NSCLC to receive gefitinib or carboplatin-paclitaxel as first-line therapy. In the intent-to-treat analysis, patients receiving gefitinib had improvements in the primary objective of PFS, response rate and quality of life. Retrospective analysis of the presence of activating *EGFR* mutations revealed that expression of an exon 19 or 21 *EGFR* mutation was predictive of a PFS improvement when receiving gefitinib as first-line therapy, whereas patients with *EGFR* wild-type tumors had an improvement in PFS when treated with carboplatin-paclitaxel. In this cross-over study, an advantage in overall survival was not identified.

The European study by Rosell *et al*. (16) provides substrate for the large-scale screening of *EGFR* mutations in patients with advanced NSCLC. Those who presented with tumors harboring activating *EGFR* mutations were eligible for therapy with erlotinib, in a non-randomized fashion. Patients could receive erlotinib as first, second or third line therapy. When compared to historical controls treated with standard chemotherapy, there was a numerical improvement in median PFS and overall survival favoring erlotinib. It is important to underline that, in this Western population, only 16.6% of the 2,105 patients screened had *EGFR* mutations. As expected, *EGFR* activating mutations were more common in women, never-smokers and in those with adenocarcinomas.

These two studies were important in leading to the approval of EGFR-TKI as first-line therapy in patients with advanced NSCLC whose tumors harbor an *EGFR* mutation and established the now standard of care of screening patients with advanced NSCLC for such mutations. Despite the remarkable improvements seen in PFS, response rates, and quality of life, for patients receiving therapy with EGFR-TKIs, to date, no statistical improvement in overall survival (OS) has been reported, possibly due to the cross-over design of such studies, which could negatively impact OS evaluation.

Recently published by Gridelli *et al*., the well-conducted TORCH (Tarceva OR CHemotherapy) trial aimed to provide a rationale for sequential therapy with erlotinib followed by cisplatin-based chemotherapy (in combination with gemcitabine) in an unselected population of patients with advanced NSCLC (17). This trial was designed to establish non-inferiority of first-line erlotinib, followed by cisplatin-gemcitabine chemotherapy at progression, when compared to the inverse sequence (i.e., chemotherapy followed by erlotinib). This trail concept was designed prior to a clear understanding of the relationship between response and *EGFR* mutation status, which has now been well established.

While 900 patients were planned, the study was terminated early due to crossing the inferiority boundary for the experimental arm at the first planned interim analysis, after 760 patients were randomized. Overall survival was worse in the experimental arm, with an adjusted HR of 1.24 (95% CI, 1.04 to 1.47), irrespective of other factors (i.e. gender, histology, or smoking status). This study was closed in November 2009, only two months after the publication of the IPASS trial results. The TORCH trial was the first to compare, head-to-head, an EGFR-TKI followed by platinum-based chemotherapy as first line treatment for NSCLC in an unselected Western population. This is an important feature, since there is a known lower incidence of *EGFR* mutations which may predict EGFR-TKI efficacy [a base-pair deletion at exon 19 (del746_A750) or a point mutation at exon 21 (L858R)] in the Western world, when compared to Asian populations.

Given the emerging importance of *EGFR* mutation status after study planning, tumor samples were retrospectively evaluated for activating *EGFR* mutations. Thirty-nine patients (14.2 percent) had *EGFR* mutation-positive tumors: 20 in the standard arm and 19 in the experimental arm. This percentage is consistent with other studies conducted in Western populations (16), and is compatible with the population enrolled in the TORCH trial (33.7 percent were females, 20.7 percent were never smokers, and 55.5 percent had adenocarcinoma, with most patients being white and 3.2 percent having East Asian ethnicity). First-line response rates for patients with *EGFR* mutation-positive tumors were significantly better for those receiving erlotinib (42.1 percent)

versus those receiving chemotherapy (25 percent).

With the publication of the TORCH trial, the current evidence for use of EGFR-TKIs in advanced NSCLC suggests that: (I) EGFR-TKIs are effective, as single agents, in increasing response and prolonging PFS in patients whose disease is refractory to standard chemotherapy, irrespective of the presence of *EGFR* mutations (2,11); (II) EGFR-TKIs prolong PFS and OS when used as maintenance therapy for patients who received first line therapy with a platinum doublet and whose disease has not progressed, irrespective of the presence of *EGFR* mutations (4); (III) the concurrent use of EGFR-TKIs with standard chemotherapy failed to show clinical benefit in unselected patient populations (10); (IV) the use of EGFR-TKIs as single agents for first-line therapy in patients whose tumors harbor specific *EGFR* mutations improves PFS, response rate, and quality of life (15,18); (V) in an unselected population, first-line therapy with EGFR-TKIs followed by platinum-based chemotherapy at progression is worse than the inverse sequence (17).

As understanding of the intricate mechanisms involving targeted therapies evolves, novel therapeutic combinations may come to fruition. Addition of the anti-EGFR monoclonal antibody cetuximab to standard chemotherapy has been shown to improve overall survival in unselected patients with advanced NSCLC, although this benefit was modest and this strategy has not been widely adopted (5). This contrasts with the lack of additional efficacy when combining EGFR-TKIs with chemotherapy, most likely due to the different mode of action between these two therapeutic entities and the fact that the antibody can down-regulate cell surface receptors and possibly mediate immune effects. Although there is still a need to identify biomarkers that may predict response to cetuximab in advanced NSCLC, an interesting treatment option would be to combine antibody-mediated EGFR targeting with tyrosine kinase based EGFR inhibition, either for an unselected population with chemotherapy-refractory advanced NSCLC or as first-line therapy for patients with *EGFR*-mutation-positive tumors. Indeed, this concept is currently being tested, with early suggestions of improved efficacy (19).

Beyond EGFR, distinct molecular subsets that are related to prognosis and response to therapy have been well described. For instance, the targeted agent crizotinib, which is directed to the *EML4-ALK* translocation which is present in 3-7% of patients with lung adenocarcinoma, was studied, yielding significant response rates, duration of response and advantageous OS trends, leading to its approval in patients possessing such translocation (20,21).

Other biomarkers potentially involved in NSCLC tumorigenesis and tumor cell survival include upregulation and polymorphisms of *VEGF*, an important proangiogenic molecule that may have prognostic significance in patients with NSCLC (22); *B-RAF* mutations, which have been detected in approximately 5% of lung adenocarcinomas and have been shown to be a negative prognostic factor (23); *MET* expression, which may predict benefit of MET inhibition when combined with an EGFR inhibitor (24); and point mutations in *KRAS*, found in up to 25% of Caucasian and African-American patients with NSCLC, which confer constitutive KRAS signaling and an overall worse prognosis (25). While these biomarkers and others are interesting targets for therapeutic development, additional trials in selected populations are warranted to establish their true importance.

While systemic chemotherapy remains useful in NSCLC patients without EGFR or ALK pathway perturbations, current evidence regarding targeted therapy and the available targeted agents make molecular testing paramount for the proper evaluation and treatment of NSCLC patients. With that in mind, it is important for medical oncologists to work together with interventionists to ensure that adequate tissue is obtained for such tests. In the absence of molecular testing (specifically *EGFR* mutation testing), the results by Gridelli *et al.* clearly establishes chemotherapy as the best first-line option for patients (17).

Overall, these data support the current evolution of the treatment of lung cancer, from a histology-based approach to a molecular-based approach. Moreover, these data confirm the heterogeneity of NSCLC, and provide a basis for clinical trial design where patient selection should be driven by the presence or absence of biomarkers whenever feasible.

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