Perspective

Turn on the TORCH before treat your patients: a lesson from a first line study in advanced NSCLC

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The first line treatment of (EGFR unselected) stage IV non small cell lung cancer (NSCLC), in Western countries, is driven by the disease (histology) and by the patient [age and performance status (PS)]. Infact non-squamous NSCLC benefits more of pemetrexed based-chemotherapy and older or poor PS are prescribed more often monochemotherapy rather than platinum-based doublet. On the contrary, in patients with known, positive, EGFR mutations status, the first line choice is an anti-EGFR tyrosine kinase inhibitor (TKI) as erlotinib or gefitinib according also to data of EURTACH study (1).

In this trial, European patients with NSCLC and EGFR mutations (exon 19 deletion or L858R mutation in exon 21) and with no history of chemotherapy for metastatic disease, were randomized to oral erlotinib or ciplatin/gemcitabine. The median PFS was 9.7 months (95% CI, 8.4-12.3 months) in the erlotinib group, compared with 5.2 months (4.5-5.8 months) in the standard chemotherapy group (hazard ratio 0.37, 95% CI, 0.25-0.54; P<0.0001). This study confirmed that in EGFR-selected patients, even in Western countries, the first line choice should be an anti-EGFR TKI. In Asiatic countries similarly, where number of patients harboring EGFR mutations is much higher, starting with erlotinib or gefitinib confers a PFS benefit in EGFR mutated patients according to at least 4 phase III trials (2-5).

The screening for mutations, where possible, should precede the choice of first line treatment. Infact if tumor is EGFR mutated a course of an EGFR TKI should be prescribed due to greater efficacy data. Instead if lung cancer is EGFR wild type chemotherapy should be obviously the first choice. In some cases, however, data of EGFR mutation status is not available due to technical (not availability of tissue for analysis or lack of a dedicated local laboratory) or clinical reasons (rapid symptoms worsening and deterioration of patients PS that needs treatment initiation). In these "EGFR-unselected" patients, the expected mutations rate in Western countries is about 16% according to Rosell data (6). So in absence of a confirmatory mutation analysis starting with erlotinib or gefitinib is not a labeled indication of these drugs and so a first line (platinum-based) chemotherapy should be started. After progression of disease, data of BR21 trial permits to offer erlotinib after chemotherapy failure.

Confirmatory data comes from TORCH trial (7), which reaffirms that in "EGFR-unselected", Western population of advanced NSCLCs, starting with erlotinib is detrimental, compared to starting with cisplatin/gemcitabine combination. This phase III trial, lead by Gridelli and colleagues, was designed to test whether first-line erlotinib followed at progression by cisplatin-gemcitabine was not inferior in terms of survival to the standard inverse sequence. Seven hundred sixty patients (median age, 62 years; range, 27-81 years) had been randomly assigned. Median survival was 11.6 months (95% CI, 10.2 to 13.3 months) in the standard arm and 8.7 months (95% CI, 7.4 to 10.5 months) in the experimental arm. Adjusted HR of death in the experimental arm was 1.24 (95% CI, 1.04 to 1.47). Rate of EGFR mutation was 14%, similarly to Rosell publication. Median PFS was 5.4 and 2.2 months after first-line chemotherapy and first-line erlotinib respectively, and total PFS (PFS of first plus PFS of second line therapy) was 8.9 and 6.4 months in the standard arm and the experimental arm, respectively [adjusted HR of progression was 1.21 (95% CI, 1.04 to 1.42)]. A significant qualitative interaction

was found in first-PFS analysis, showing higher efficacy of erlotinib in the presence of EGFR mutation and higher efficacy of chemotherapy in EGFR wild-type tumors. The data is more difficult to obtain for survival due to crossover. Even response rate is expected as a function of mutation status, infact among patients with EGFR mutations, response rate after first line treatment was 25.0% with chemotherapy and 42.1% with erlotinib and response rate after both lines of therapy is however similar: 45.0% in the standard arm and 42.1% in the experimental arm.

The conclusion of the trial is that in unselected patients with advanced NSCLC, first-line erlotinib followed at progression by cisplatin-gemcitabine was significantly inferior in terms of overall survival (OS) compared with the standard sequence of first-line chemotherapy followed by erlotinib. We agree with these conclusions that respect the current literature data and the present labeled indications of erlotinib and gefitinib.

It is important to stress some points. First, is confirmed in a large number of patients that in EGFR wild type disease, chemotherapy is significantly better than EGFR TKIs (8). The data already reported by Mok in IPASS trial confirms that in Western countries patients where the frequence of EGFR mutations is lower that Asiatic countries, if data about mutation status is unknown, starting with chemotherapy is less hazardous. In particular, if EGFR mutation status is wild type, erlotinib would be indeed detrimental for survival. Infact median OS for standard and experimental arms were 9.6 and 6.5 months in EGFR wild type patients. Also, from TORCH trial is evident that EGFR mutated patients fared better both with chemotherapy than with erlotinib than EGFR wild type counterpart (median OS 32.5/18.1 months and 9.6/6.5 months for chemotherapy/erlotinib in EGFR wild type and mutated populations): this highlights that EGFR status is a predictive but also a prognostic factor for NSCLC patients.

Second, what is evident from Gridelli trial is the lower number of patients that have been offered second line treatment in experimental arm (41.7% *vs*. 28.5% did not received the preplanned second line therapy as for study design). So it seems that the outcome of patients with EGFR unselected status would be influenced also by the chance to receive an active second line after first line failure. The risk substantially is that a faster clinical deterioration would be observed in patients progressing after first line erlotinib. The cause of this data is not clear but it confirms that starting with a less efficacious therapy could be deleterious for unselected patients.

Third the histology of the patients enrolled in TORCH study is mixed (about half squamous and half adenocarcinoma). It is well known infact that squamous cell carcinoma of the lung portend a different biology compared to adenocarcinomas. Infact EGFR mutations can be detected in 30% of adenocarcinoma patients and in only 2.0% of non-adenocarcinoma NSCLC patients. Also in EGFR mutated non-adenocarcinoma NSCLC patients, EGFR TKIs performed worse than the adenocarcinoma counterpart for response rate and PFS, from a pooled analysis of literature (9). So the totally unselected population of TORCH trial (both for histology and mutation status) could have influenced the overall outcome results.

Finally this trial highlights the importance of achieving sufficient tissue for biomarker analysis in NSCLC patients. Mutation status of exon 19 and exon 21 were infact available from 36% of the entire study population. This data appears fair deluding in light of the present need of biomarker selection of NSCLC patients.

The lesson learned from the TORCH study so is complex. The NSCLC population (at least in Western countries) is a mixed one for biology, outcome and response to treatment. All possible informations should be obtained from the disease and obviously from the patients. The histology selection permits to orient at least the type of platinum doublet (pemetrexed *vs*. other agents-based). The mutations selection clearly settles the choice between chemotherapy and an EGFR TKIs. Finally the patients selection permit to decide the intensity and urgently of treatment. In patients for whom the disease is symptomatic and performing the mutations analysis could risk an excessive treatment delay, a course of chemotherapy should be initiated. In case of more indolent disease, where some weeks of waiting before start the treatment does not appear deleterious, EGFR status should be assessed and so the treatment decided accordingly. In patients with EGFR mutation status unknown, unfit for chemotherapy or which desire an oral treatment, a course with an EGFR TKI could be started monitoring for response earlier (after few weeks). In these cases the appearance of the typical skin toxicity after some weeks of treatment for example, could reassure both clinician and patient about the higher chance of response, according to a recently published meta-analysis analyzing the predictive role of skin rash with EGFR TKIs in lung cancer (10).

Overall, at least in EGFR mutated NSCLCs of TORCH study, whichever sequence (chemotherapy followed by an EGFR TKI or viceversa) is selected the final OS is similar

with the 2 strategies. And also in all NSCLC patients starting a first line platinum-based chemotherapy, an EGFR TKIs could be offered to patients later, as maintenance or second line treatment, according to present literature data and independently of mutational status.

In all cases however the TORCH should be immediately turned on to select at best our NSCLC patients for first line therapy.

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