Editorial

EGFR TKIs as maintenance therapy in NSCLC: finding the old in the new INFORMation

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Data from phase III studies indicate that a consistent proportion of metastatic non-small cell lung cancer (NSCLC) patients treated with front-line chemotherapy, at the time of progression, are not able to receive additional therapies mainly because of worsening clinical conditions related to a rapid tumor growth (1,2). An important clinical end-point, particularly for patients with aggressive tumors, is to guarantee that the vast majority of patients could be treated with drugs that, in second-line setting, demonstrated to prolong survival, preserving quality of life and delaying disease-related symptoms. Beyond any semantic questions about the type of agent employed (i.e. continuation maintenance versus switch maintenance), the use of an effective drug in the absence of disease progression following platinum-based chemotherapy means maintenance therapy. During the last few years, several studies (1-4) have been conducted in metastatic NSCLC to assess the role of maintenance therapy. Although in the majority of trials a clear survival improvement has not been demonstrated, in all studies, irrespective of the used drug, the hazard ratio (HR) for overall survival slightly favored maintenance therapy. As a consequence, recent guidelines consider maintenance strategies as a suitable option to offer to NSCLC patients who did not progress after their planned first line chemotherapy and presenting in good clinical condition and without any persistent chemo-related toxicity (5,6). Ideally a maintenance regimen might be of proven efficacy, easy to administer, well tolerated and, most importantly, well accepted by the patient. For these reasons erlotinib and gefitinib, two inhibitors of the tyrosine kinase domain of the epidermal growth factor receptor (EGFR-TKI), seemed both good candidates to be tested in this setting.

Two years ago, we (4), first demonstrated the usefulness of switch maintenance with an EGFR-TKI. The phase III SATURN (Sequential Tarceva UnResectable NSCLC) trial randomly assigned 889 advanced NSCLC patients without disease progression after completion of 4 cycles of standard platinum based chemotherapy to receive erlotinib or placebo. Notably, tissue collection was mandatory for enrollment. The trial met its primary end point of PFS, demonstrating a significant improvement for patients receiving erlotinib (median PFS 12.3 versus 11.1 weeks; HR 0.71, 95% CI, 0.62-0.82, P<0.0001). The co-primary end point of the study, PFS in the subgroup of EGFR immunohistochemistry positive (defined as EGFR expression on the membrane of >10% of cells) patients, was also met (HR 0.69, 95% CI, 0.58-0.82, P<0.0001). In the whole population, the PFS benefit in the active arm translated in survival benefit (median OS 12.0 versus 11.0 months; HR 0.81, 95% CI, 0.70-0.05, P=0.009). In this trial an extensive biomarkers analysis was performed, including *EGFR* mutational status. As expected, patients having an *EGFR* mutation had a significant PFS improvement (median PFS 44.6 versus 13 weeks; HR 0.10, 95% CI, 0.04-0.25, P<0.001); furthermore, also for *EGFR* wild type population the PFS favored the erlotinib arm (HR 0.78, 95% CI, 0.63-0.96, P=0.02).

The WJTOG0203 trial (7), randomized 604 Japanese patients with advanced NSCLC after completion of 3 cycles of platinum doublet chemotherapy, to receive three additional cycles of the same regimen or gefitinb. The study failed to meet its primary end point of overall survival. However, maintenance gefitinib significantly prolonged

PFS (4.6 versus 4.3 months; HR 0.68, 95% CI, 0.57-0.80, P<0.001), with the greatest benefit observed in patients with adenocarcinoma histology (5.1 versus 4.4 months; HR 0.60, 95% CI, 0.50-0.73, P<0.001), that is the histotype classically associated with presence of *EGFR* mutations.

Sequential gefitinib after first line standard chemotherapy was also tested in white population enrolled in the EORTC 08021 trial (8). With the main limits of a low accrual - leading to early closure of the trial - and an ambitious statistical design - in which primary end point was to improve survival of 28% (from 11 to 14 months) - patients receiving gefitinib had longer PFS than those receiving placebo (median PFS 4.1 versus 2.9 months, HR 0.61, 95% CI, 0.45-0.83, P<0.0001), confirming the potential role of gefitinib in maintenance setting.

In a recent issue of Lancet Oncology, Zhang *et al*. (9) reported the final results of the INFORM (Iressa in NSCLC FOR Maintenance, C-TONG0804) trial, a phase III study of gefitinib versus placebo as maintenance treatment in Chinese patients with molecularly unselected locally advanced or metastatic NSCLC who had achieve disease control after completion of 4 cycles of platinum-based doublet chemotherapy. The study, enrolling 148 patients per arm, met its the primary end-point of PFS. Patients treated with gefitinb had a 58% relative reduction in risk of progression compared with those receiving placebo (4.8 versus 2.6 months; HR 0.42, 95% CI, 0.33-0.55, P<0.0001), while overall survival did not differ between the two groups (median survival 18.7 versus 16.9 months; HR 0.84, 95% CI, 0.62-1.14, P=0.26). Sequential anti-EGFR therapy was also associated with higher disease control rate (72% versus 51%, P=0.0001) and better symptom control. Although tissue collection was not mandatory for study entry, 79 patients (27%) provided tumor tissue for *EGFR* status assessment and activating mutations were found in 30 samples (38%). Compared to ITT population, in *EGFR* mutant patients the improvement in PFS was greater (16.6 versus 2.8 months; HR 0.17, 95% CI, 0.07-0.42, P<0.0001) with a HR quite similar to that observed in SATURN trial, with no evidence of benefit in the *EGFR* wild type population.

How should we interpret the INFORM data in the context of clinical practice? How gefitinib maintenance data compare to erlotinib results? Looking at the PFS curve of SATURN and INFORM, it seems that the outcome of patients included in the INFORM study was better. Clearly the difference in PFS observed between the two studies was largely influenced by the difference in study populations. In fact, the INFORM study was conducted in China, a geographic area with higher incidence of *EGFR* mutations when compared to western countries, while the SATURN included less than 15% of Asiatic patients. Analysis of *EGFR* mutated patients in the two studies showed comparable results: both erlotinib and gefitinib produced a similar PFS benefit, with approximately 90% reduction in the risk of progression. Importantly, in the *EGFR* wild-type population, only erlotinib produced a significant PFS improvement, confirming previous data showing that gefitinib works only in *EGFR* mutated while erlotinib produces some benefit, modest but statistically significant, even in absence of *EGFR* mutations. Probably the most interesting finding comes from survival analysis. In the INFORM study, no survival difference between gefitinib and placebo was detected, while in the SATURN trial, the modest improvement in PFS translated in a significant survival difference favoring erlotinib. Looking at the HR, in both SATURN and INFORM, the reduction in risk of death was similar (HR=0.81 in SATURN and HR=0.83 in INFORM), suggesting a marginal efficacy difference between the two drugs. Moreover, it is not possible to exclude that INFORM failed to meet the overall survival end-point because of the high percentage of patients with *EGFR* mutations (approximately 40%) and therefore because of the confounding effect of post-study therapies including further administration of EGFR-TKIs.

Finally, INFORM data confirmed again that *EGFR* mutations are the best predictor of response to an EGFR-TKI and consequently *EGFR* mutant patients gain the greater benefit when treated early during the course of their disease. Moreover, it is confirmed that Asian patients are a “naturally enriched population” with a higher incidence of hidden *EGFR* mutations: In the INFORM the HR for progression in *EGFR* unknown individuals was 0.40, superimposable to that in the ITT population (HR=0.42) and median survival time reported in both groups as well as response rate after first-line chemotherapy (37%) are aligned with other trials conducted in Eastern countries, even if in a different setting (10,11). Furthermore also in the WJTOG0203 (7), only considering the most favorable subgroup (i.e. adenocarcinoma histology, non-smokers), median survival time was 23.5 and 25.1 months for patients in the chemotherapy arm and gefitinib arm respectively.

In conclusion, INFORM trial demonstrated that maintenance gefitinib is an additional option for metastatic NSCLC harboring an activating *EGFR* mutation. Although the role of maintenance therapy remains debatable, we

should avoid the risk that a patient with mutation cannot receive an EGFR-TKI. Therefore, when not given in front-line setting, we need to INFORM our *EGFR* mutated patients about the opportunity of starting an effective therapy as soon as possible.

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