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Editorial

Epidermal Growth Factor Inhibitor in Mutated EGFR Non-Small Cell Lung Cancer Patients: Present and Future

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Editorial

In their recent article in Journal of Clinical Oncology Kelly et al [1]. conclude that "Adjuvant erlotinib did not prolong Disease Free Survival (DFS) in patients with EGFR-expressing NSCLC or in the EGFRm-positive subgroup". This international randomized trial, double blind, placebo-controlled study was conducted in patients completely resected stage IB to IIIA NSCLC whose tumours expressed EGFR protein by IHC or EGFR amplification by FISH. The patients were randomized to receive adjuvant erlotinib 150 mg/ daily or placebo for 2 years. Nearly 50% of the patients had adjuvant chemotherapy before being randomized.

Given the increased knowledge about the EGFR mutation sensitivity to Tyrosine Kinase Inhibitors (TKIs), the negative RADIANT's results comes as no surprise to the scientific community. Although the trial didn't meet the primary endpoint, the authors should be prised for trying to address what, at that time, was the burning question:" is a TKI effective in the adjuvant setting in patients with EGFR expression?" We know that the question now would probably be: "Is a TKI effective in the adjuvant setting in EGFR mutated patients"? Novello, in her editorial, highlighted some of the limitations of the trial: the lack of sensitivity for the EGFR expression, the fact that only a subgroup of patients had a genetic test performed, the unbalance in patients' characteristics in this subgroup, the choice of identify DFS instead of the Overall Survival (OS) as primary endpoint.

Is then the RADIANT just another negative trial, or it could represent good lesson for the scientific community? In the trial161 patients had an activating EGFR mutation, 102 patients were randomly assigned to erlotinib and 59 patients to placebo. The median DFS was 46.4 and 28.5 months, with 2-year DFS rates of 75% and 54% for erlotinib and placebo, respectively. This result was not statistically significant despite the unbalance in favor of the erlotinib arm: more patients in the erlotinib arm had stage IB therefore; more patients in the placebo arm had stage IIIA.

Other trials had also raised some concerns on the safety and efficacy of using TKIs in the adjuvant setting [2,3], and Novello [4] highlighted that, in a retrospective study, T790 resistant mutations were more common in cancers that recurred while patients were receiving an adjuvant EGFR TKI than in cancers that recurred after the EGFR TKI was stopped.

The only evidence supporting the use of TKI in the adjuvant setting at the moment is the SELECT trial: a phase II open label trail [5], presented at the ASCO, which showed an encouraging DFS but it has not been fully published yet.

We are all awaiting with great interest the data from the ALCHEMIST study or the ADJUVANT CTONG 1104 and the IMPACT WJCOG6401L. Interesting enough, those trials don't seem to be considering what we might have learnt so far: early stage is (IB) is going to be included; the length of time on Erlotinib is going to be 2 years, despite in the Radiant the median duration treatment was only 11.9 months for the erlotinib arm and the rate of grade ≥3 rush, diarrhoea was significantly higher than in the placebo arm. The 2 years' time on TKIs is extremely debatable and not supported by any evidence so far but purely arbitrary. In a different trial, TASTE [6,7], the erlotinib adjuvant was given up to 1 year and only stages II-IIA were enrolled just to minimize the armful risk of exposing patients to TKIs. Despite the trial being feasible the phase III was never run the TKIs have proven to be more effective than chemotherapy in the metastatic setting , but there is still debatable in the neoadjuvant treatment: the CTONG1103,a Chinese randomized phase III trial of Erlotinib vs cisplatin gemcitabine in EGFR positive stage IIIA, might give the definite answer soon. In neoadjuvant and metastatic setting the comparator against the TKIs has always been the chemotherapy whereas in the adjuvant setting, so far, the nobody has ever compared the adjuvant chemo (4 cycles of platinum based chemo) vs TKIs? Hopefully the CTONG 1104 (NCT01405079), a, multi-center, randomized, open-label, phase III trial that recruited stage II-IIIA (N1-N2) NSCLC patients with the EGFR activating mutation, might answer the question. In the trial the patients were randomized to receive gefitinib for 24 months or vinorelbine plus platinum for four cycles after surgery. The recruiting is complete and the result will be available soon.

A further question arises after the Lux lung data 7 had been presented at the ESMO ASIA meeting 2015, showing better PFS of Afatinib over gefitinib in metastatic lung cancer patients EGFR positive: which TKIs should we be using in neoadjuvant and adjuvant setting?.

In conclusion TKIs in EGFR mutated patients remains standard of care in stage IIIB-IV, and we can now confirm that Afatinib seems to offer a better PFS compared with Gefitinib. On the other hand in neoadjuvant and adjuvant the question is still very open and debatable but hopefully some of the ongoing trials will give us some more robust guide and indication.

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