Perspective

Is there a third line option after chemotherapy and TKI failure in advanced non-small cell lung cancer?

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The EGFR gene is a major therapeutic target in advanced Non-small cell lung cancer (NSCLC). Two reversible tyrosine kinase inhibitors, Erlotinib and Gefitinib, have been validated and registered for the treatment of NSCLC. Gefitinib has a label that is limited to NSCLC carrying mutations in the kinase domain of the EGFR gene, while the label of Erlotinib also includes second line treatment of patients with undefined EGFR status in their tumor, based on an early randomized study that showed a small benefit in such unselected population (1). Today there is a strong evidence based consensus that the best first-line treatment for patients carrying sensitizing mutations in the EGFR gene in their tumor, is with reversible EGFR TKI inhibitors Erlotinib or Gefitinib. These treatments yield impressive and durable responses, prolonged progression free survival (PFS) and improved quality of life when compared to first-line chemotherapy, with an acceptable tolerance profile due to a significant lesser toxicity than first-line chemotherapy (2,3). If the diagnosis of a mutation was missed in the first-line, these patients should be offered these treatments in second-line, as early as possible. There is also a growing consensus and data supporting that these treatments should not be used in patients with a wild-type EGFR in their tumor (4,5).

Unfortunately all patients ultimately develop resistance to EGFR TKI and become eligible for standard chemotherapy. The resistance mechanisms so far identified at baseline or at progression of the disease are: the outgrowth of a subclone of cancer cells with a T790M secondary resistance mutation, activation of the MET pathway, Pi3kinase and other downstream mutations, heterogeneity in EGFR mutation status in multifocal disease or outgrowth of a small cell lung cancer (6-9).

Upon progression, second-line chemotherapy leads to an appreciable, albeit lesser, response rate in this population. When however ultimately also chemotherapy fails, these patients are confronted with a high unmet medical need for which several strategies are being explored (6).

Afatinib, a covalent EGFR/HER2/HER4 inhibitor ("pan-HER" inhibitor), has higher potency in inhibiting EGFR in preclinical testing (10), has the potential to interfere more effectively with HER heterodimerisation signals (11) and is able to block EGFR carrying the T790M mutation, albeit at much higher concentration than what is needed to inhibit EGFR sensitizing mutations only (12).

In the LUX-Lung 1 study (13), afatinib was compared with placebo (double blind 2:1 randomization in favor of active drug), with all 585 patients also getting concomitant supportive care. The trial was open to patients with advanced lung adenocarcinoma who had previously received at least one line of prior chemotherapy, and had not progressed for at least 12 weeks on another EGFR inhibitor, either gefitinib or erlotinib. This is a true third-line setting. The patient selection criteria strongly enriched for an EGFR TKI sensitive population carrying sensitizing mutations in EGFR (which was confirmed in a retrospective mutation analysis on a fraction of the patients). Most patients were never-smokers, the majority (62%) of East-Asian ethnicity; almost half had been pretreated for 48 weeks or more with a first-line TKI and 46% had experienced a prior objective remission on TKI. The study failed to meet its primary endpoint of improved overall survival (OS). There was even a numerical trend for inferior OS with afatinib compared to placebo: the median OS was 10.8 months (95%

CI, 10.0-12.0 months) in the afatinib group and 12.0 months (95% CI ,10.2-14.3 months) in the placebo group (hazard ratio 1.08, 95% CI, 0.86-1.35; P=0.74). The median overall survival (OS) in both arms of the study was better than anticipated by the authors in a more general population of lung cancer such as included in the BR 21 study (1), but this can be attributed to the strong selection of patients in the current study. The response rate was low (7%). Median PFS was longer in the afatinib group (3.3 months, 95% CI, 2.79-4.40 months) than it was in the placebo group (1.1 months, , 95% CI, 0.95-1.68 months; hazard ratio 0.38, 95% CI, 0.31-0.48, P<0.0001) and afatinib treated patients had decreased lung cancer related symptoms. On the other hand, afatinib came with significant toxicity: diarrhea (87% all grades), rash (78% all grades), stomatitis, nail changes (mainly paronychia), diminished appetite, and less commonly epistaxis and pruritus. As a consequence, 36% of the patients needed a dose reduction although only 5% discontinued treatment because of these toxicities. Drug-related serious adverse events (SAE's) occurred in 39 (10%) patients in the afatinib group with two possibly treatment-related deaths.

It should also be noted that the placebo treated patients might have experienced a shortened PFS, simply because they were weaned from TKI upon inclusion in the study. It is becoming evident that even in disease progression under TKI treatment, the TKI retain some activity and stopping the treatment might lead to an accelerated disease progression or "flare" (14). For such patients there are now several options: continue the TKI (Erlotinib or Gefitinib) with local therapy of focal progressive disease sites, switching to chemotherapy or even continuation of the EGFR TKI with chemotherapy, which might be superior to chemotherapy alone (15). Subsequent progression might even be temporarily responsive to a rechallenge or cross-over with a reversible TKI (e.g., Erlotinib if Gefitinib was given in the first line).

The main conclusion of the Lux-Lung 1 study is that afatinib is not a solution for patients with advanced NSCLC failing prior EGFR TKI and at least one line of chemotherapy. In fact, the low response rate, the significant toxicity and the OS data argue against using afatinib in such a third line setting.

In contrast, Afatinib is a valuable drug in the first line treatment of adenocarcinoma of the lung carrying EGFR mutations and was recently shown to be strongly superior over doublet chemotherapy with cisplatinum and pemetrexed in that population with an impressive PFS of 11.1 months, and even 13.6 months with the common exon 19/21 mutations, and improved symptom control compared to chemotherapy (16). The OS data are not yet available. Dacomitinib, a drug with a similar profile, is in an earlier stage of development and also has a long PFS in phase 2 (17). Whether these two pan HER inhibitors will have an increased therapeutic ratio in the first-line setting compared to the first generation TKI's Erlotinib and Gefitinib remains to be determined. Cross trial comparisons suggest that the PFS might be longer with the pan HER inhibitors, but at the expense of increased toxicity.

Afatinib is also the first targeted drug that has shown activity in lung cancer patients with HER2 mutations in their tumor, a mutation that is tenfold less prevalent than EGFR mutations (18).

So, is there a third-line option after chemotherapy and TKI failure in advanced non-small cell lung cancer? The answer today is negative. For the patients that have a baseline or an acquired true resistance to currently available EGFR TKI's, we need the exploration of better strategies to overcome or prevent such resistance. Possible strategies are the concomitant inhibition of c-MET, the development of effective inhibitors of T790M and other specific mechanisms of resistance (e.g., Pi3kinase mutations) and the discovery of additional, currently unknown, driver mutations that cooperate with EGFR mutations in the pathogenesis of the disease that subsequently could be examined for (combined) therapeutic targeting.

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