Perspective

EGFR IHC score for selection of cetuximab treatment: ready for clinical practice?

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The discovery of activating epidermal growth factor receptor (EGFR) mutations and the anaplastic lymphoma kinase gene rearrangement led to significantly improved outcomes with EGFR-tyrosine kinase inhibitors (TKIs) and crizotinib, respectively. These results have revolutionized treatment algorithms in non-small cell lung cancer (NSCLC), which are now, - at least in part-, biomarker-guided. The advantage of this approach is obvious, allowing active treatments to be offered to a selected group of patients who are more likely to benefit. At the same time, the toxicity of an inactive drug can be spared to patients who are lacking the target. Unfortunately, many novel targeted agents continue to be tested in patient populations not selected for the molecular target in question. As a consequence, trial results show only limited if any benefit at all. The FLEX study tried to enrich advanced NSCLC patients for individuals whose tumours had at least 1% of the cells expressing the epdidermal growth factor receptor (EGFR) measured with immunohistochemstry (IHC), in accordance to the initial trials in colorectal cancer (1-3). A total of 1,125 patients were randomized to receive first line cisplatin/vinorelbine plus or minus cetuximab. Although, overall survival (OS) was significantly improved by the addition of cetuximab (HR 0.87, 95% CI 0.76-1.0, P=0.044), the benefit was considered to be of modest clinical relevance, and the drug failed to get approval from regulatory authorities.

The current analysis of this study is an attempt to identify a predictive biomarker for cetuximab (4). The authors used an IHC score (H-score), which took into account the percentage of cells (0-100%) as well as each staining intensity category (0-3+). Both variables were used to compute a score ranging from 0 and 300. Starting at a score of 150 a trend towards an increased response rate with treatment with cetuximab was observed and significance was reached at a value of 200, dividing the patients into an H-score EGFR high (31% of the population) and low group. In the H-score high group the effect of the addition of cetuximab was greater than in the whole study population [median OS: 9.6 *vs.* 12.0 months (HR 0.73, 95% CI 0.58-0.93), P=0.01]. Conversely, no benefit was observed in the low group (HR 0.99, 95% CI 0.84-1.16, P=0.88).

We agree with the authors, that these findings are important, particularly in view of previous studies analyzing K-RAS mutation status, EGFR protein expression, EGFR gene copy number by FISH and EGFR mutational status which were all not predictive for a benefit from cetuximab in this setting (5). Is this unplanned post-hoc analysis solid enough to change the current practice concerning the use of cetuximab in NSCLC? On the positive side it is important to note that the original FLEX analysis was positive for its primary endpoint, OS. Thus this study does not try to convert a negative result by statistical over-analysis, but rather it represents an honest attempt to identify the best sub-population of patients in which to use cetuximab. The method with which the H-score was identified is scientifically meaningful, since the cutoff was determined with a marker of biological efficacy: objective response. In addition samples of almost all patients in the FLEX study (96%) were available for determination of the H-score. The high versus low expressers did not seem to represent prognostically different subgroups, even tough intriguingly the high expressers had a higher proportion of

squamous cell histology. Nonetheless, several caveats need to be mentioned: Although the assessment of the EGFR expression status was prespecified in the protocol, the score was performed retrospectively and the analysis presented here was post hoc. The H-score seems reproducible among pathologists after specific training; however validation of these findings seems essential. Another retrospective analysis of a second phase III study analyzed the same score in a smaller cohort of patients and also predicted for a better response rate and a trend towards better survival in the H-score high group with the cetuximab-containing regimen (6). A prospective validation of the score in the large ongoing phase III study (SWOG 0819) which compares carboplatin, paclitaxel and bevacizumab, plus or minus cetuximab is eagerly awaited. It is also of interest that similarly to the overall FLEX study, no increase in PFS was observed with the addition of cetuximab in the H-score high group. This finding, once again remains somewhat unexplained. Lastly, one should keep in mind, that only a minority of NSCLC patients (25%) fall in the H-score high group. It would be important to learn the number of patients in the H-score high group whose tumors harbor an EGFR mutation, since these patients would be normally treated with a TKI and reduce the number of patients qualifying for cetuximab even more. The slightly higher proportion with squamous cell carcinoma could be suggestive of an obvious patient group: Cetuximab is clearly highly active in squamous cell cancer of the head and neck (7) and TKIs have little efficacy in squamous cell NSCLC.

In summary, the current analysis of the FLEX study is a small but important step forward towards personalized treatment. If these results are confirmed, a subgroup of H-score high patients who derive an increased benefit from the addition of cetuximab to chemotherapy can be treated accordingly. Equally, an even larger group of NSCLC patients who does not benefit and in whom cetuximab should be withheld will be identified.

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