Editorial

Combination of cetuximab with radio-chemotherapy in patients with esophageal cancer: less is more!

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A main challenge in the treatment of locally advanced esophageal cancer is to improve efficacy while minimizing treatment-related toxicity. Definitive chemoradiotherapy (CRT) is used to treat patients with locally advanced esophageal cancer who are inoperable for medical reasons, in whom complete R0 resection is unlikely or who decline surgery. However, until recently the data available were predominantly for squamous cell esophageal cancer. Molecular targeted drugs are being evaluated in clinical trials for esophageal, gastric, and gastroesophageal junction cancers. EGFR is overexpressed in 60–86% of gastric or gastroesophageal tumors and in 50–70% of esophageal cancers. Preclinical studies have shown that the chimeric monoclonal antibody cetuximab can overcome an important mechanism of radioresistance, and cetuximab was shown to bear radiosensitizing properties (1). These data led to phase I/II trials evaluating the combination of cetuximab with CRT in locally advanced esophageal squamous cell carcinoma (SCC) and adenocarcinomas with encouraging preliminary results (2,3). However, these trials were of small sample size. One study, reported by Ruhstaller included both, adenocarcinomas and SCC and showed, by adding cetuximab to preoperative CRT a significantly increased histopathologic response rate without elevated toxicity and postoperative mortality (2). Another trial, conducted by Chen and coworkers evaluated a regimen of definitive CRT plus cetuximab in 29 patients with SCC, showing a good clinical response and an acceptable safety profile despite high doses of radiotherapy (59.4 Gy) in Chinese patients (3). Moreover, the addition of EGFR inhibitors to radiotherapy significantly improved the results of radiotherapy alone in patients with SCC of the head and neck. In a landmark study by Bonner and coworkers a nearly doubled median overall survival was achieved in patients allocated to the cetuximab-radiotherapy arm (28 to 54 months) (4). In all, there was clear rationale to test the addition of cetuximab to definitive CRT in a randomized trial in patients with cancer of the esophagus.

The SCOPE-1 phase 2/3 trial, included patients scheduled to undergo definitive CRT with both, adenocarcinoma as well as SCC of the esophagus (5). A thorough staging was conducted in most of the patients, including PET in about 85%. Patients were randomized to either receive two cycles of induction chemotherapy (capecitabin + cisplatin; XP) + definitive CRT (based on XP and 50 Gy, i.e., 25×2 Gy) or the same regimen combined with standard doses of cetuximab. Patients were stratified according to center, reason for receiving definitive CRT without surgery, histology, and tumor stage. Primary endpoint of the phase 2 part of this trial was the proportion of patients without treatment failure at week 24. The study was foreseen to proceed to phase 3 provided the phase 2 portion of the trial was positive. Overall survival was the primary endpoint of the phase 3 part. After accrual of a total of 258 patients (73% SCC, 25% adenocarcinoma) the study was stopped for futility because fewer patients were free of treatment failure at the time point 24 weeks in the CRT plus cetuximab group (66.4% *vs.* 73.6% in the standard arm). Likewise, overall survival was shorter in the cetuximab arm (22.1 *vs.* 25.4 months; adjusted HR 1.53; P=0.035).

As expected, the rates of non-haematological grade 3 or 4 toxicities were significantly higher in the cetuximab arm (79% *vs*. 63%; P=0.004). Moreover, the addition of cetuximab to CRT resulted in less protocol treatment being delivered and significantly compared with CRT alone.

These results are in keeping with trials using anti-EGFR therapies in combination with chemotherapy in patients with metastatic gastroesophageal cancer, such as the REAL-3 (6) and the EXPAND (7) studies. Both studies failed to demonstrate a survival advantage in unselected patient populations. In the REAL-3 study, inferior survival was noted with the addition of anti-EGFR therapy (overall survival 8.8 *vs*. 11.3 months; P=0.13), possibly because of using lower doses of chemotherapy in the experimental arm (6). Moreover, the POWER study (ClinicalTrials.gov Identifier NCT01627379), investigating the addition of panitumumab to fluorouracil and cisplatin in metastatic SCC of the esophagus has terminated recruitment prematurely because of futility. Similarly, no benefit of adding anti-EGFR mAbs to CRT protocols were found in patients with cancer of the head& neck and the rectum (8-11).

But what are the reasons for these negative trials? Was SCOPE-1 negative just because cetuximab is ineffective in the treatment of esophageal cancer? Some possible explanations will be discussed in brief.

(I) Toxicity and treatment intensity: an obvious problem in SCOPE-1 was that the addition of cetuximab to CRT led to significantly increased toxicity resulting in a relevant decrease in treatment compliance. Compared to CRT alone, where 90% of patients received four courses of cisplatin and 85% of patients completed all 4 cycles with capecitabine, only 77% of patients treated with cetuximab received all 4 courses of cisplatin and only 69% tolerated the four preplanned cycles of capecitabine. Moreover, only 78% of the cetuximab patients received the assigned radiation dose of 50 Gy compared to 90% in the CRT alone group. Of note, more than twice the number of patients in the cetuximab arm compared to CRT alone did not receive any radiotherapy due to chemotherapy associated side effects (19% *vs.* 8%; P=0.006). Thus, as the data were analyzed according to an intent-to-treat analysis, the inferior overall survival and the higher rates of treatment failure might be also explained with inferior treatment intensity. Due to a limited small sample size in SCOPE-1, a robust subgroup analysis according to tumor histology was not possible;

(II) Interaction of cetuximab with backbone regimen: the REAL-3 study demonstrated that the backbone chemotherapy regimen may significantly affect the efficacy of a particular regimen when combined with a targeted agent (6). The authors of REAL-3 concluded that the capecitabine backbone therapy, as it was also used in the SCOPE-1 and the EXPAND studies and in most patients in the COIN trial (12), might have contributed to dose reductions which might have caused the worse outcome in the cetuximab groups of these trials. Furthermore, two meta-analyses conducted in patients with KRAS wildtype metastatic colorectal cancer concluded that the addition of anti EGFR mABs to capecitabine- (or bolus 5-FU-) regimens did not improve the results of chemotherapy alone (13,14). In contrast, the combination of anti-EGFR antibodies with infusional 5-FU based regimens was associated with significantly improved response rate, progression-free-survival and overall survival. It is still a matter of speculation if this negative interaction between capecitabine and anti-EGFR mAbs are due to pharmacokinetic reasons or just a consequence of overlapping toxicities and consecutive dose reductions;

(III) Lack of valid biomarker/inclusion of unselected patients: another possible explanation is the absence of selection of the right subset of patients likely to respond to cetuximab. Many biomarkers, including high tumor EGFR expression have been shown to be an adverse prognostic factor for esophageal cancer patients and have been suggested as predictive of cetuximab resistance in various tumor entities (15-17). However, in the study by Chen and coworkers, patients with EGFR expressing tumors had a higher rate of complete and better progression-free survival with combined anti-EGFR and radiotherapy (3). The results are in line with preclinical observations, showing that EGFR inhibitors might sensitize tumors to cisplatin or radiation therapy (18). As data are conflicting, selection of patients on the basis of positive EGFR expression might not be a valid option for treatment decision for an additional EGFR antibody therapy. Other biomarkers such as mutations in BRAF, KRAS, PIK3C and the expression of PTEN have been analyzed in an analysis of the REAL3 trial (19). None of the biomarkers predicted resistance to anti-EGFR therapy: Thus, to date, unfortunately no specific biomarker has been validated. With regard to blood and tissue collection in SCOPE-1 (done at baseline and at week 24), no information is provided and correlation analysis have to be awaited.

In summary, SCOPE-1 demonstrated that the addition of cetuximab to CRT in patients undergoing definitive CRT for esophageal cancer was less effective than CRT alone but increased the toxicity burden of the cisplatin/capecitabine/

radiotherapy regimen and therefore had an adverse impact on the delivery of RT. In future trials, tumor biology and the identification of mutations that predict therapeutic response or resistance should be prerequisite to resurrect the development of EGFR inhibition in gastroesophageal cancers. Nevertheless, the authors should be commended for conducting this comparably large trial in a difficult-to-treat tumor entity on the one hand, and for implementing a high level of quality assurance for radiotherapy and patient selection (PET staging in about 85%) resulting in excellent survival data in the standard arm (2-year survival of 56%) on the other hand. Thus, SCOPE-1 is an example that efforts to optimize treatment quality by treating patients in centers or assuring high quality of care nation-wide may occasionally improve treatment results to a greater extent than the implementation of new drugs.

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Footnote

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