Is there a future for EGFR Targeted Agents in Esophageal Cancer?

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Funding: None to declare

Conflict of Interest: None to declare

In the current issue of the Annals, authors report the results of the SAKK phase III trial, adding the anti-EGFR agent cetuximab to preoperative chemoradiotherapy in esophageal squamous cell and adenocarcinoma¹. The authors observe an improvement in local tumor control for use of cetuximab with reduced local tumor recurrence, which translated into non-significant differences in progression free and overall survival. The trial is relatively small and underpowered and pools together patients with squamous cell and adenocarcinoma. The reduction in local tumor recurrence occurred despite no difference in the achievement of either an R0 resection or a pathologic complete response at surgery. Despite these negative observations, the improved local control with cetuximab is somehow attributed to an enhancement of a radiotherapy effect. The authors do not comment on the pathologic T and N stages achieved with or without the addition of cetuximab. Fewer patients on the control arm had transthoracic resection, which potentially could have increased the risk of local tumor recurrence. There also was less toxicity observed on the arm receiving cetuximab, arguing that these patients potentially had a better baseline functional status. Although the treatment arms appear balanced in pre-treatment characteristics, these two factors could have influenced the ultimate survival outcome in a small trial.

The results from the SAKK trial¹ need to be put in context of a sea of negative results for the use of EGFR-targeted agents in esophagogastric cancer. The RTOG 0436² and SCOPE-1³ trials looked at cetuximab combined with non-operative chemoradiotherapy in over 600 patients with esophageal squamous cell and adenocarcinoma. The RTOG trial, using a comparable chemotherapy backbone to the SAKK trial, showed no difference in overall survival for the addition of cetuximab. No difference in clinical complete response or local tumor progression was seen, irrespective of histology. The SCOPE-1 trial indicated actual inferior overall survival for the addition of cetuximab, likely due to compromised delivery of chemoradiotherapy because of greater treatment related toxicity. Observations from these two trials argue against any putative beneficial effect on radiation therapy for cetuximab, given the failure to impact on local tumor control. Furthermore, in metastatic disease, EGFR-targeted agents have failed to improve outcome. The EXPAND⁴ and REAL-3⁵ trials, treating over 1400 patients with esophagogastric adenocarcinoma, showed no survival benefit for adding an EGFR-targeted antibody to chemotherapy in metastatic disease. The REAL-3 trial reported a significantly inferior survival with the
addition of an EGFR agent. Lastly, in late line therapy, the use of the EGFR-targeted tyrosine kinase inhibitor gefitinib failed to improved survival in 450 patients with metastatic adenocarcinoma or squamous cell cancer, compared to supportive care alone.\textsuperscript{6} Although a recent publication indicated that EGFR copy number might be a predictive biomarker for benefit from gefitinib, the benefit achieved was marginal despite being statistically significant.\textsuperscript{7} Most would argue that a survival difference of a few weeks is of little clinical significance.

EGFR-targeted agents have also failed in other chemoradiotherapy settings. Cetuximab added to chemoradiotherapy in rectal cancer did not improve outcome in pilot trials.\textsuperscript{8,9} In head and neck cancer, although cetuximab improved the efficacy of radiotherapy alone, it failed to enhance any effect when added to combined chemoradiotherapy.\textsuperscript{10} Given the consistent and negative results for EGFR-targeted therapy in esophagogastric cancer, outside of a biomarker driven clinical trial, it is not justifiable to move these agents forward. In this context, the SAKK trial has to be viewed as an outlier. At the end of the day, the absolute number of patients achieving either a local control benefit (6 of 188 adenocarcinoma and 8 of 109 squamous cancer patients) or a survival benefit (8 of 188 adenocarcinoma and 9 of 109 squamous cancer patients) was quite small.

What lies ahead in the future to improve outcome in the chemoradiotherapy management of esophageal squamous cell and adenocarcinoma? We now know from genomic profiling that these are biologically quite distinct diseases.\textsuperscript{11} Esophageal adenocarcinoma comprises largely genomically unstable cancers with the common presence of p53 mutation and frequent amplification of receptor associated kinase pathways, led by HER2. Squamous cancers are genomically distinct and appear to resemble more squamous cancers of the head and neck. Unfortunately, using identified potential biomarkers to design treatment strategies to date has achieved limited success, with failure of agents targeting the EGFR and MET pathways, and mixed results with HER2-targeted agents. We await results of RTOG 1010, which added trastuzumab to preoperative chemoradiotherapy in HER2 positive esophageal and gastroesophageal junction cancers. It is likely, however, that targeting one pathway or one mutation with a novel agent will not improve outcome. We need to understand networks and interactions of pathways leading to cross talk and potential targeted therapy resistance.

PET scan response during induction chemotherapy, prior to chemoradiotherapy, may guide chemotherapy selection during subsequent radiotherapy: CALGB trial 80803,\textsuperscript{12} using a PET-directed strategy, led to an enhancement of pathologic complete response, but final results of this study are still pending. Immune checkpoint inhibitors, which appear to have a modest signal of activity in esophageal cancer, are also under evaluation in the adjuvant setting, and in pilot trials combining these agents with chemoradiotherapy.

References

1. Ruhstaller T, Thuss-Patience P, Hayoz S et al. Neo-adjuvant chemotherapy followed by chemoradiation and surgery with and without cetuximab in patients with resectable esophageal cancer:


