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Blood-borne assessment of stromal activation in esophageal adenocarcinoma to guide tocilizumab therapy: A randomized phase II proof-of-concept study

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Background

Production of IL6 by the tumor stroma of esophageal adenocarcinoma (EAC) causes epithelial-to-mesenchymal transition of tumor cells and resistance to chemoradiation (Ebbing *et al.* 2019). Serum ADAM12 protein levels measure stroma activity (Veenstra *et al.* 2018) whilst IL6 and IL6R monitor IL6 inhibition (Nishimoto *et al.* 2008). Here, we aim to demonstrate that targeting stroma with tocilizumab in EAC patients increases efficacy of chemoradiation.

Methods

This was a multicenter, randomized, open label, phase II proof-of-concept trial in 48 patients with resectable EAC. Patients were stratified for serum ADAM12 (cutoff of 203 pg/mL) and randomized for standard of care chemoradiation according to the CROSS regimen or addition of tocilizumab to standard of care, followed by surgery. Tocilizumab 8 mg/kg with a maximum of 800 mg was given intravenously for three cycles. Serum ADAM12, IL6 and IL6R was measured at baseline, during treatment, at resection and three months thereafter. Primary endpoint was histopathological response to chemoradiation according to the Mandard score.

Results

After inclusion of 36 patients, the trial was discontinued due to safety concerns. Perforation of the esophageal wall was observed in 3/20 (15%) of patients in the intervention arm compared to 0/16 (0%) in the control arm. There was no significant difference in Mandard score between treatment arms ($p = 1.000$). Patients treated with tocilizumab had significantly higher serum levels of IL6 and IL6R during treatment ($p < 0.0001$). Baseline ADAM12 was not associated with histopathological response to tocilizumab ($p = 0.672$). There was no difference in serum ADAM12 levels over time between treatment arms.

Conclusions

Addition of tocilizumab to neoadjuvant chemoradiation in patients with EAC is unsafe and should not be considered for clinical practice. Potentially, concurrent inhibition of IL6 impairs wound healing whilst chemoradiation obliviates the tumor in the esophageal wall, increasing the risk for perforation. We plan to investigate this hypothesis with RNA sequencing, immunohistochemistry, cytokine profiling, and flow cytometry of peripheral blood mononuclear cells and tumor biopsies.

Clinical trial identification

NCT04554771.

Legal entity responsible for the study

Amsterdam UMC, location AMC.

Funding

Oncode Institute.

Disclosure

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