AB064. SOH22ABS053. Strategies to boost immune function in oesophageal adenocarcinoma—hypofractionated radiotherapy may be superior to current CROSS regimen chemo-radiation

Noel Donlon, Maria Davern, Andrew Sheppard, Fiona O'Connell, Tim Nugent, Narayanasamy Ravi, Claire Donohoe, Melissa Conroy, Margaret Dunne, Stephen Maher, Jacintha O'Sullivan, John Reynolds, Joanne Lysaght

Department of Surgery, Trinity Translational Medicine Institute and Trinity St. James's Cancer Institute, St. James's Hospital, Dublin, Ireland

Background: CROSS regimen (41.4 Gy; carboplatin and paclitaxel) is a standard trim-modality treatment for locally advanced oesophageal adenocarcinoma (OAC). The addition of adjuvant immunotherapy targeting PD-L1 may improve outcomes, hence the impact of radiation therapy on the immune tumour microenvironment is of considerable interest. The radiation fraction dose has not been studied in this context, especially hypofractionation, and this study explored immunogenic cell death, specifically damage associated molecular patterns (DAMPs) release, and the impact of immune checkpoint blockade (ICB).

Methods: The ability of CROSS-regimen (3×1.8 Gy) and hypo-fractionation (3×4 Gy) to induce immunogenic tumour cell death was assessed by flow cytometry of DAMPs calreticulin & HMGB-1. Expression of DAMPs were evaluated on OAC tumour and whole blood samples (n=10) pre and post conventional therapies versus hypofractionation. The immunostimulatory effect of conventional CROSS and hypofractionation using post-treatment tumour cell secretome with/without ICB on the cytolytic ability of OAC-donor lymphocytes was interrogated by CCK8-assay.

Results: The expression of calreticulin & HMGB1 was significantly higher on tumour tissue compared to whole blood post chemo(radio)therapy (P<0.01). Hypofractionation increased TNF-α & IFN-γ production by T-cells greater than CROSS fractions *ex vivo* (P<0.01). The post-CROSS and hypofractionated tumour cell secretome enhanced lymphocyte mediated killing of tumour cells (P<0.01), significantly further enhanced with dual ICB (nivolumab & ipilimumab) (P<0.01). Patients who were high expressors of HMGB1 or calreticulin pre-operatively had a significantly (P<0.01) better tumour regression grade (TRG1-2) compared to low expressors.

Conclusions: The current CROSS regimen radiation for OAC is immunogenic, however, hypo-fractionated doses boosted the immune response to OAC, and was synergistic with ICB. This may warrant further exploration in a clinical and translational trial.

Keywords: Chemoradiotherapy; damage associated molecular pattern (DAMP); immunogenicity; oesophageal adenocarcinoma (OAC); oncology

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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