AB065. First line chemotherapy regimens used in oesophageal adenocarcinoma promote immune dysfunction and enhance a cancer stem-like phenotype: potential implications for chemoimmuno resistance and novel multi-modal treatment regimens

Maria Davern, Noel Edward Donlon, Andrew Sheppard, Anshul Bhardwaj, Narayanasamy Ravi, John Reynolds, Niamh Lynam-Lennon, Stephen Maher, Joanne Lysaght

Trinity Translational Medicine Institute, St James's Hospital Campus, Dublin, Ireland

Background: Chemoresistance is a major clinical challenge facing oesophageal adenocarcinoma (OAC) patients, as 70% don't respond to current treatments. Combining immune checkpoint inhibitors (ICIs) to boost responses is a therapeutic option of emerging interest. ICIs block IC receptors on T cells and ligands on cancer cells, reinvigorating anti-tumour immunity and blocking tumour cell-intrinsic survival signalling, respectively.

Methods: In vitro, OE33 and SKGT4 cells (OAC cells) were used to: (I) assess basal expression of Ics; (II) examine the effect of combination chemotherapeutic regimens, (FLOT:5-fluorouracil, oxaliplatin and docetaxel, MAGIC:epirubicin, cisplatin and 5-fluoruracil and CROSS:paclitaxel, carboplatin) on (I) IC expression (n=3), (II) OAC stemness by assessing aldehyde dehydrogenase (ALDH) and CD54 expression (III) co-expression of ICs on cancer stem cells (CSCs) (n=3).

Results: In vitro, inhibitory IC receptors including PD-1, TIGIT, TIM-3, LAG-3, CD160, PD-L1, PD-L2 and A2aR were identified basally on OAC cells. FLOT, MAGIC and CROSS significantly ($P<0.05$) upregulated ICs. All regimens enhanced a CSC phenotype demonstrated by upregulation of stemness markers ALDH and CD54 *in vitro* on OAC cells. PD-L1, PD-L2, TIM-3 and LAG-3 inhibitory ICs were significantly increased on stem-like OAC cells following FLOT, MAGIC and CROSS treatment *in vitro*.

Conclusions: This data demonstrate the induction of ICs by chemotherapy regimens, an effect potentially promoting immune-resistance. A CSC phenotype is augmented by these treatments. Several studies demonstrate that blocking ICs on cancer cells enhances chemotherapy toxicity. This suggests that combining immunotherapy and chemotherapy as a multi-modal approach could prevent immune dysfunction and limit treatment resistance resulting in improved responses.

Keywords: Chemoresistance; immune checkpoints; oesophageal adenocarcinoma (OAC)

doi: 10.21037/map.2020.AB065

Cite this abstract as: Davern M, Donlon NE, Sheppard A, Bhardwaj A, Ravi N, Reynolds J, Lynam-Lennon N, Maher S, Lysaght J. First line chemotherapy regimens used in oesophageal adenocarcinoma promote immune dysfunction and enhance a cancer stem-like phenotype: potential implications for chemoimmuno resistance and novel multi-modal treatment regimens. Mesentery Peritoneum 2020;4:AB065.