RELATIONSHIP OF UGT1A AND ABC GENETIC VARIANTS TO TOXICITY AND RESPONSE IN PREOPERATIVE CHEMORADIATION (CRT) WITH CONCURRENT IRINOTECAN FOR LOCALLY ADVANCED RECTAL CANCER (LARC)


1Clinical Oncology, North Wales Cancer Treatment Centre, Rhyl, UK
2Manchester Centre for Genomic Medicine, University of Manchester, Manchester, UK
3Centre for Musculoskeletal Research, The University of Manchester, Manchester, UK
4Clinical Oncology, Clatterbridge Cancer Centre, Wirral, UK
5Clinical Oncology, Royal Preston Hospital, Preston, UK
6Clinical Oncology, Royal Preston Hospital, Preston, UK
7Clinical Oncology, The Christie Hospital NHS Foundation Trust, Manchester, UK
8Clinical Oncology, St Lukes Cancer Centre, Guildford, UK
9Clinical Oncology, Aberdeen Royal Infirmary, Aberdeen, UK
10Radiation Oncology, Clatterbridge Cancer Centre, Wirral, UK
11Statistics, The Christie NHS Foundation Trust, Manchester, UK

Aim: Germline homozygosity for UDP glucuronosyltransferase (UGT)1A1*28 has been associated with increased haematological and gastrointestinal toxicity to irinotecan. The influence of UGT1A and drug transporter gene ABC genetic variants on the toxicity of and response to CRT including concurrent irinotecan has not been studied.

Methods: Blood was collected retrospectively from 96 surviving patients (pts) (71%) of 135 who had undergone surgery in the NWCOG-2 phase I/II trial in which pts with LARC received preoperative CRT (45 Gy in 25 fractions in 5 weeks) using concurrent capecitabine (650mg/m2 bid PO 7 days/week) and irinotecan (weekly at 60mg/m2 IV weeks 1-4). Germline DNA was tested for variants UGT1A1*6, *27, *28, *60 and *93, UGT1A7*3 and 622T > C and UGT1A9*22 using fragment size analysis and Taqman allelic discrimination assay. The ability of these variants, their common haplotypes (inferred with R package haplo.stats) and transporter gene ABCB1 and ABCC2 variants, to predict treatment toxicity and histological response was examined.

Results: Overall commonest grade (gr) 3/4 toxicities were diarrhoea (n = 18), neutropenia (n = 7) and fatigue (n = 7). No association was seen between any individual variants and serious toxicity. Carriage of at least one haplotype III (all reference UGT1A alleles with the exception of UGT1A7*3 (387T > G)) significantly increased the risk of gr 3/4 diarrhoea (OR 6.03, 95% CI 1.79-21.85, p = 0.001). There was no association of ABC variants with serious toxicity. Overall 41 pts (43%) showed an excellent pathological response (EPR: either ypCR or microfoci). Individuals with one or two variant alleles of UGT1A7*3 had a significantly increased EPR rate (TG = 48%, OR 8.89, 95%CI 1.1-414.60, p = 0.04 and GG = 46%, OR 8.28, 95% CI 1.0-391.40, p = 0.04) compared to those with only reference alleles (TT = 9%).

Conclusions: No association was seen between individual UGT1 genotypic variants (including UGT1A1*28) and serious toxicity. However the presence of the UGT1A7*3 variant as part of a haplotype with all other reference alleles significantly increased diarrhoea and as an individual variant increased EPR.

Disclosure: All authors have declared no conflicts of interest.