European Journal of Cancer 102 (2018) 31–39

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Pharmacogenetic analyses of 2183 patients with advanced colorectal cancer; potential role for common dihydropyrimidine dehydrogenase variants in toxicity to chemotherapy

Ayman Madi [a,1], David Fisher [b], Timothy S. Maughan [a,2], James P. Colley [a], Angela M. Meade [b], Julie Maynard [a], Vikki Humphreys [a], Harpreet Wasan [c], Richard A. Adams [a], Shelley Idziaszczyk [a], Rebecca Harris [a,3], Richard S. Kaplan [b], Jeremy P. Cheadle [a,*]

[a] *Division of Cancer and Genetics, School of Medicine, Cardiff University, Heath Park, Cardiff, CF14 4XN, UK*
[b] *MRC Clinical Trials Unit, Aviation House, 125 Kingsway, London, WC2B 6NH, UK*
[c] *Imperial College Healthcare NHS Trust, Hammersmith Hospital, Du Cane Road, London, W12 0HS, UK*

Received 27 April 2018; received in revised form 29 June 2018; accepted 8 July 2018

KEYWORDS
Pharmacogenetics;
Toxicity;
Colorectal cancer;
DPYD;
Dihydropyrimidine dehydrogenase;
Chemotherapy

Abstract ***Background:*** Inherited genetic variants may influence response to, and side-effects from, chemotherapy. We sought to generate a comprehensive inherited pharmacogenetic profile for oxaliplatin and 5FU/capecitabine therapy in advanced colorectal cancer (aCRC).
Methods: We analysed more than 200 potentially functional, common, inherited variants in genes within the 5FU, capecitabine, oxaliplatin and DNA repair pathways, together with four rare dihydropyrimidine dehydrogenase (*DPYD*) variants, in 2183 aCRC patients treated with oxaliplatin-fluoropyrimidine chemotherapy with, or without, cetuximab (from MRC COIN and COIN-B trials). Primary end-points were response, any toxicity and peripheral neuropathy. We had >85% power to detect odds ratios (ORs) = 1.3 for variants with minor allele frequencies >20%.
Results: Variants in DNA repair genes (Asn279Ser in *EXO1* and Arg399Gln in *XRCC1*) were most associated with response (OR 1.9, 95% confidence interval [CI] 1.2–2.9, $P = 0.004$, and

* *Corresponding author.*
E-mail address: cheadlejp@cardiff.ac.uk (J.P. Cheadle).
[1] The Clatterbridge Cancer Centre NHS Foundation Trust, Clatterbridge Road, Bebington, Wirral CH63 4JY and Department of Molecular and Clinical Cancer Medicine, Institute of Translational Medicine, University of Liverpool, Crown Street, Liverpool L69 3BX, UK.
[2] CRUK/MRC Oxford Institute for Radiation Oncology, University of Oxford, Roosevelt Drive, Oxford OX3 7DQ, UK.
[3] Institute of Medical Genetics, University Hospital of Wales, Cardiff, CF14 4XW, UK.

https://doi.org/10.1016/j.ejca.2018.07.009

OR 0.7, 95% CI 0.5–0.9, $P = 0.003$, respectively). Common variants in *DPYD* (Cys29Arg and Val732Ile) were most associated with toxicity (OR 0.8, 95% CI 0.7–1.0, $P = 0.008$, and OR 1.6, 95% CI 1.1–2.1, $P = 0.006$, respectively). Two rare *DPYD* variants were associated with increased toxicity (Asp949Val with neutropenia, nausea and vomiting, diarrhoea and infection; IVS14+1G>A with lethargy, diarrhoea, stomatitis, hand-foot syndrome and infection; all ORs > 3). Asp317His in *DCLRE1A* was most associated with peripheral neuropathy (OR 1.3, 95% CI 1.1–1.6, $P = 0.003$). No common variant associations remained significant after Bonferroni correction.

Conclusions: DNA repair genes may play a significant role in the pharmacogenetics of aCRC. Our data suggest that both common and rare *DPYD* variants may be associated with toxicity to fluoropyrimidine-based chemotherapy.

1. Introduction

Genetic factors affect response to, and side-effects from, chemotherapy and biological therapies used in the treatment of advanced colorectal cancer (aCRC). For example, somatic mutations in *KRAS* and *NRAS* in the epidermal growth factor receptor (EGFR) signalling pathway predict a lack of response to anti-EGFR monoclonal antibodies [1,2]. Germline changes in drug metabolism, transport and target genes have also been implicated in altering response [3,4]. Although several large studies have attempted to identify inherited predictive biomarkers, including the analysis of ten variants in 1188 CRC patients [5,6], 1456 5FU pathway tagging variants in 968 patients [7] and 34 variants in 520 patients [8], none have comprehensively analysed all the pharmacological pathways. Indeed, the vast majority of studies performed to date have used small cohorts of patients, and most findings have not been validated in independent analyses.

We have previously sought predictive biomarkers for cetuximab response and side-effects by analysing 54 common, inherited EGFR pathway variants in 815 aCRC patients from the COIN [9,10] and COIN-B [11] trials that received cetuximab together with oxaliplatin-fluoropyrimidine chemotherapy [12]. Although we identified five potential biomarkers for response and four for skin rash, none remained significant after correction for multiple testing [12]. Here, we sought predictive biomarkers for oxaliplatin-fluoropyrimidine chemotherapy by analysing more than 200 potentially functional common inherited variants in 2183 COIN and COIN-B patients treated with oxaliplatin-fluoropyrimidine chemotherapy with, or without, cetuximab.

2. Methods

2.1. Patients and treatments

All patients had metastatic or locally advanced colorectal adenocarcinoma and received no previous chemotherapy for advanced disease. All patients gave fully informed consent for this study (approved by REC [04/MRE06/60]). COIN patients were randomised 1:1:1 to receive continuous oxaliplatin and fluoropyrimidine chemotherapy (arm A), continuous chemotherapy + cetuximab (arm B) or intermittent chemotherapy (arm C) (ISRCTN27286448) [9,10]. COIN-B patients were randomised 1:1 to receive intermittent chemotherapy and cetuximab (arm D) or intermittent chemotherapy and continuous cetuximab (arm E) (ISRCTN3837568) [11]. For the first 12 weeks, at which point the primary pharmacogenetic analyses were carried out, treatments were identical in all patients apart from the choice of fluoropyrimidine (n = 834, 38% received infusional 5FU with oxaliplatin [OxMdG] and n = 1349, 62% received capecitabine with oxaliplatin [Xelox]) together with the randomisation of ±cetuximab (n = 815, 37% received cetuximab) (Supplementary Table 1).

2.2. Selection of potential pharmacogenetic variants

Potentially functional variants were sought in 62 genes identified from literature reviews as likely to play a role in the metabolic pathways associated with the agents used in COIN and COIN-B—5FU and capecitabine (28 genes) and oxaliplatin (34 genes). Variants were considered potentially functional if there was previously reported clinical or biological evidence for an effect on response or side-effects, if they were non-synonymous or if they occurred in the promoter region. We also sought similar variants in 155 DNA repair genes that were likely to play a role in repairing the damage caused by these agents. Variants were mined from dbSNP (v.129, http://www.ncbi.nlm.nih.gov/SNP/) and from exome resequencing germline data [13], and those with a minor allele frequency (MAF) > 5% (Caucasian population) were considered for genotyping.

2.3. Genotyping

Most variants were single nucleotide polymorphisms (SNPs) genotyped using a custom Illumina GoldenGate