Samantha Korver, JM Bowen, IA White, J Tuke, RJ Gibson, RM Logan, A Richards, K Mead, CS Karapetis, DM Keefe & JK Coller

Personalized Supportive Care for Patients Receiving 5-FU:
Interim analysis of multivariate SNP risk prediction for severe GI toxicity
## Faculty Disclosure

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<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
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5-Fluorouracil (5-FU) induces GI Toxicity

- 5-FU = Antimetabolite that inhibits thymidylate synthase
- Breast, upper GI and colorectal solid tumors
- 20 - 40% of patients experience toxicity
- Severe toxicity (grade ≥ 3);
  - Treatment delays and dose reductions
  - 2° consequences (pain, dehydration)
  - financial burden
  - ↓ quality of life

Pathophysiology of GI toxicity


MASCC/ISOO Annual Meeting 2018
The Problem

Q: Why does ‘Patient B’ suffer GI toxicity and not ‘Patient A’?

A: ????

We need a predictor for severe GI toxicity risk

Personalization of supportive care to reduce GI toxicity severity

‘Patient A’

Demographics
Mid 40’s | Female | Healthy BMI
Non-smokers | No medical history

Diagnosis
Left Breast Cancer
Grade 3 | 5-FU-based regimen

Chemotherapy side effects
- Fatigue
- Grade 1 nausea

‘Patient B’

Chemotherapy side effects
- Fatigue
- Grade 3 diarrhea
- Grade 2 mucositis

Hospitalisation
In 34 patients, severe GI toxicity risk model\textsuperscript{1}
- TLR2 and TNF
- Colorectal and gastric cancer types
- ROC AUC 87%

SPiT Validation (SPiT-V) Study

Pilot study → Validation!!

Aim: To investigate the association between SNPs of the TIR domain innate immune signaling pathway and severe GI toxicity following 5-FU-based treatment

Methods

- Retrospective study; multi-site state-wide
- 5-FU-based therapy
- Clinical case notes = demographics, treatment and toxicity data
- Genomic DNA = genotype analysis

SPiT-V Study – Participant Demographics

- n = 114

- Two toxicity groups:
  - No/mild (≤ 2)
  - Severe (≥ 3, treatment cessation or reduction)

- Cancer type and treatment protocol significant (P < 0.02)

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<th>No/mild (n = 90)</th>
<th>Severe (n = 24)</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>Sex (n (%))</strong></td>
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<tr>
<td>Female</td>
<td>63 (71%)</td>
<td>11 (46%)</td>
<td>0.03</td>
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<tr>
<td>Male</td>
<td>27 (29%)</td>
<td>13 (54%)</td>
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<tr>
<td><strong>Cancer Type (n (%))</strong></td>
<td></td>
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<tr>
<td>Breast</td>
<td>55 (62%)</td>
<td>5 (21%)</td>
<td>0.001*</td>
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<td>Colorectal</td>
<td>32 (35%)</td>
<td>16 (66%)</td>
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<tr>
<td>Upper GI</td>
<td>3 (3%)</td>
<td>3 (13%)</td>
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<tr>
<td><strong>Hospital (n (%))</strong></td>
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<tr>
<td>Royal Adelaide Hospital</td>
<td>31 (35%)</td>
<td>7 (29%)</td>
<td>0.81</td>
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<tr>
<td>Flinders Medical Centre</td>
<td>59 (65%)</td>
<td>17 (71%)</td>
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<tr>
<td><strong>Treatment Protocol (n (%))</strong></td>
<td></td>
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<tr>
<td>5-FU monotherapy</td>
<td>10 (11%)</td>
<td>10 (42%)</td>
<td>&lt;0.0001**</td>
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<td>5-FU in combination</td>
<td>73 (82%)</td>
<td>6 (25%)</td>
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<tr>
<td>Capecitabine</td>
<td>7 (7%)</td>
<td>8 (33%)</td>
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<tr>
<td><strong>Age</strong></td>
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<td>Median (range)</td>
<td>61 (32 – 86)</td>
<td>68 (28 – 78)</td>
<td>0.03</td>
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SPiT-V Study – Building the Predictive Risk Model

Covariates
- Sex
- Age
- Hospital
- Cancer type
- Treatment protocol
- Number of treatment cycles

SNPs
- IL1B, IL12, IL6, TNF, IL10, TGF, ICE (CASP1), IL6R, TLR2, TLR4, MD2, MYD88, BDNF, CRP

Each predictor is added individually to the model

Improves model (ANOVA)

Does not improve model (ANOVA)
SPiT-V Study – Interim Predictive Risk Model

Predictive severe GI toxicity risk model

- $n = 105$
- $IL1B$ rs16944 and rs1143634
- Colorectal and gastric cancer types
- ROC AUC 82%
To create a predictive platform that will allow the personalization of supportive care measures during chemotherapy treatment.

Future Directions
- Complete validation study: Reach target sample size of 150 and complete analysis, but promising so far; TIR pathway identified
- Investigate how these SNPs influence cytokine secretion; genotype/phenotype relationship

Project Funding
- Ray and Shirl Norman Cancer Research Trust Grant
- Australian Dental Research Foundation

Scholarships
- Research Training Program Scholarship
- Doctor Chun Chung Wong and Madam So Sau Lam Memorial Postgraduate Cancer Research Scholarship
- Adelaide Medical School Research Travel Award

Acknowledgments

University of Adelaide
Imogen Ball
A/Prof Joanne Bowen
Dr Janet Coller
Prof Rachel Gibson
Prof Dorothy Keefe
Prof Richard Logan
Lorelle Smith

Flinders Medical Centre
Prof Chris Karapetis
Kelly Mead
Alison Richards