
THE UNIVERSITY of ADELAIDE
CANCER TREATMENT TOXICITIES GROUP
Integrating the pathogenesis, prediction and prevention of cancer related side effects
JK Coller, S Korver, IA Ball, RJ Gibson, J Tuke, RM Logan, AM Richards, KR Mead, CS Karapetis, DM Keefe and JM Bowen
Incidence of other toxicities in patients with severe gastrointestinal toxicity and relationship to comorbidities following 5-fluorouracil (5-FU) treatment
adelaide.edu.au
seek LIGHT

Faculty Disclosure – J Coller

X	No, nothing to disclose
	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*

Faculty Disclosure – J Bowen

X	No, nothing to disclose
	Yes, please specify:

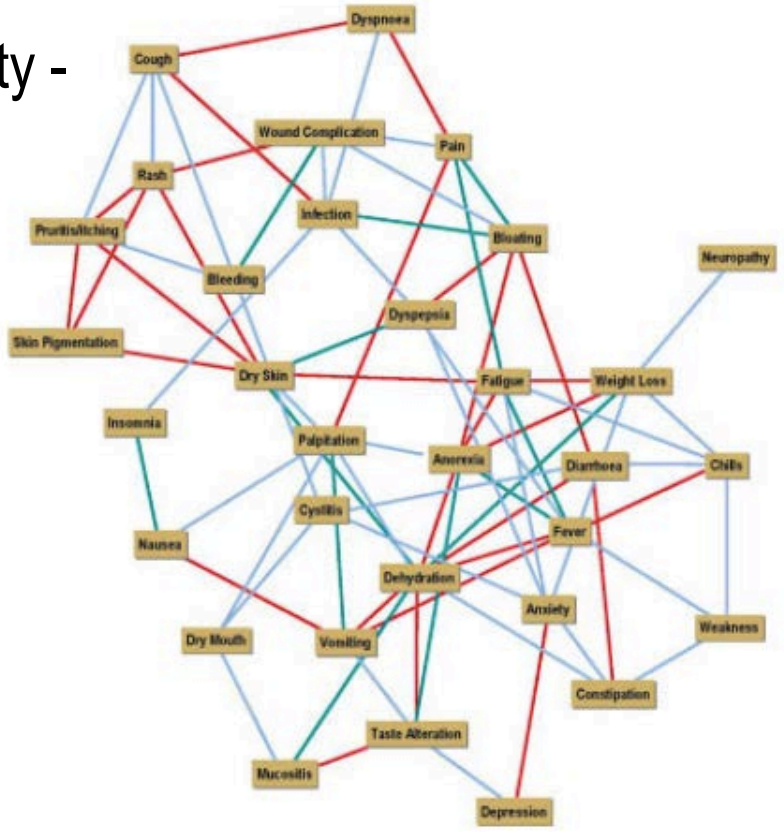
Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*

GI toxicity & other symptom clustering

- 5-FU-based chemotherapy causes GI toxicity - 20-40%[1]
- Groups of symptoms can cluster together[2] - negatively impacts on QOL[3]
- Comorbidities may increase risk of toxicity[4]

Aim

- To investigate the relationship between incidence of other toxicities & comorbidities with severe GI toxicity



From Aprile et al, 2007
Bayesian network of toxicity

[1]Sonis (2004) Nat Rev Cancer 4: 277-284; [2] Aprile *et al* (2007) Cancer 112:284; [3]Keefe *et al* (1997) Clin Sci 92: 385-389. [4]Sarfari *et al* 2016, CA 66:388

Methods

- Retrospective case note review study
  - Eligible patients determined by pharmacy records, 2011-2016
  - Recruited for genetic analysis by mail out invitation and phone interview
  - Multi-site incl. regional hub

- Inclusion/exclusion criteria
  - 5-FU-based chemotherapy for mixed solid tumors
  - No radiotherapy
  - No prior severe neutropenia

Methods

- Data extraction:
  - Demographics, treatment parameters
  - Toxicities (all cycles): GI, neuropathy, pain, skin, cardiotoxicity;
    toxic = Grade ≥ 3 NCI CTCAE[1] v5, chemotherapy reduction or cessation
  - Comorbidities: body surface area, smoking status, alcohol use, type 2 diabetes, cardiovascular disease, arthritis, asthma, GERD, thyroid activity

[1]Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Methods

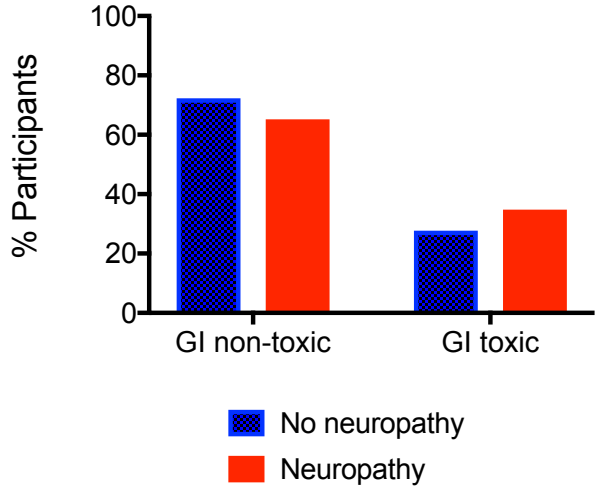
- Data analysis:
  - Differences in demographics, treatment parameters: Chi-square and Mann-Whitney tests with Bonferroni correction
  - Association between GI toxicity & other toxicities: Chi-square tests
  - Relationship between GI toxicity and other comorbidities: multivariate logistic regression

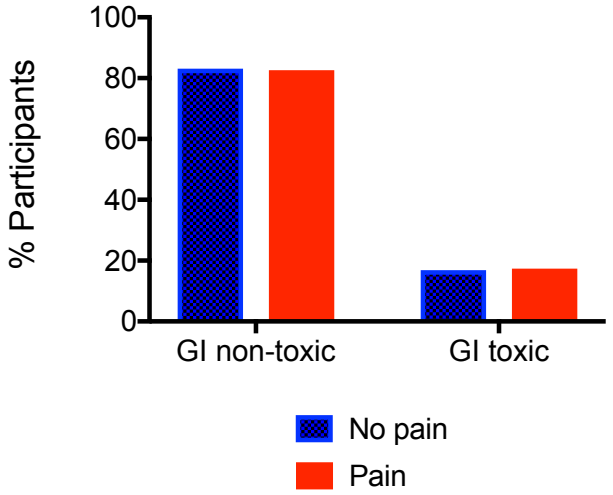
Participant demographics

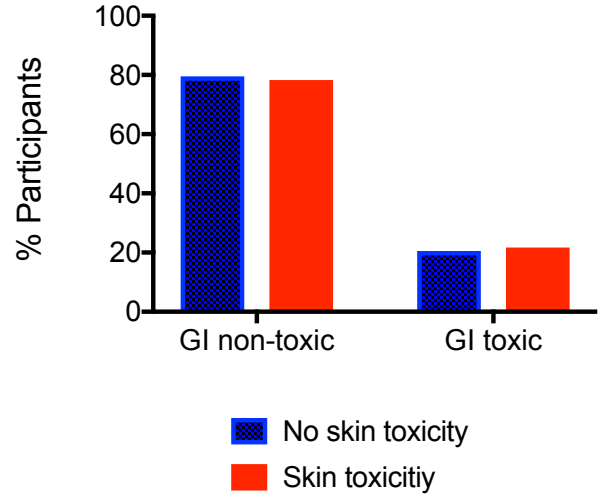
	GI Non-toxic (n = 83, 78%)	GI Toxic (n = 23, 22%)	P value (<0.01 significant*)
Age			
Median (range)	61 (32-86)	68 (28-78)	0.03
Sex (n (%))			
Female	61 (73.5%)	11 (47.8%)	0.02
Male	22 (26.5%)	12 (52.2%)	
Cancer type (n (%))			
Breast	53 (63.9%)	4 (17.4%)	*0.0002*
Colorectal	28 (33.7%)	16 (69.6%)	
Gastric	2 (2.4%)	3 (13%)	
Treatment regimen (n (%))			
Capecitabine[a]	5 (6.0%)	8 (34.8%)	*0.0005*
5-FU	11 (13.3%)	4 (17.4%)	
5-FU combination[b]	67 (80.7%)	11 (47.8%)	
Treatment cycle			
Median (range)	6 (2-30)	8 (3-30)	*0.008*

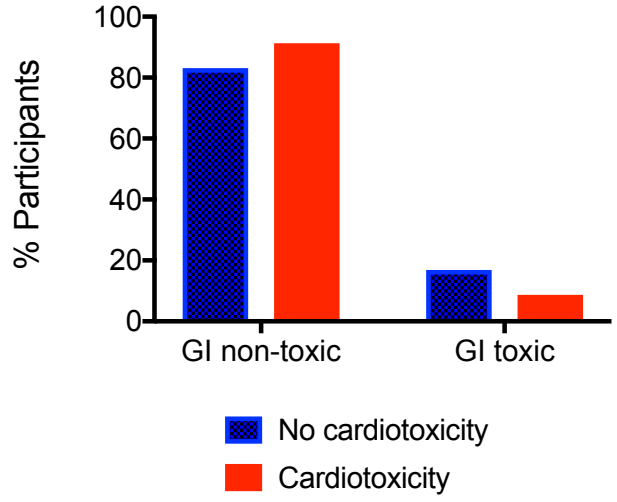
[a] Capecitabine alone or in combination with oxaliplatin or Avastin; [b] 5-FU combination protocols = FOLFOX, FEC, ECF;
*after correction for multiple comparisons

No association between severe GI toxicity & other toxicities









No relationship between severe GI toxicity & comorbidities

	GI Non-toxic	GI Toxic	P value (FDR correction)
BSA	**n = 83**	**n = 23**	
Median (range)	1.87 (1.40 - 2.48)	1.94 (1.41 – 2.20)	0.96
Smoking status	**n = 70**	**n = 18**	
Ex smoker	35 (50.0%)	9 (50.0%)	0.69
Current smoker	13 (18.6%)	1 (5.6%)	
Non-smoker	22 (31.4%)	8 (44.4%)	
Alcohol use	**n = 66**	**n = 17**	
Yes	47 (71.2%)	12 (70.6%)	0.96
No	19 (28.8%)	5 (29.4%)	

No relationship between severe GI toxicity & comorbidities

	GI Non-toxic n (%)	GI Toxic n (%)	P value (FDR correction)
Type 2 Diabetes	**n = 80**	**n = 21**	
Incidence	8 (10)	2 (9.5)	0.96
Cardiovascular Disease	**n = 80**	**n = 20**	
Incidence	27 (33.8)	7 (35.0)	0.96
Arthritis	**n = 79**	**n = 21**	
Incidence	22 (27.8)	5 (23.8)	0.96
Asthma	**n = 79**	**n = 21**	
Incidence	12 (27.8)	4 (19.0)	0.96
GERD	**n = 80**	**n = 21**	
Incidence	15 (18.8)	5 (23.8)	0.96
Altered thyroid activity	**n = 82**	**n = 21**	
Incidence	7 (8.5)	1 (4.8)	0.96

Conclusions

- No evidence for occurrence of severe GI toxicity paired with other severe toxicities
  - *Did not record lower grade toxicity*
- No evidence for impact of comorbidities on risk for severe GI toxicity
  - *Potential bias in patients selected – since some pre-existing comorbidities would be excluded from chemotherapy*
  - *Low numbers in each setting*

➢ study is ongoing to increase recruitment to 200

➢ assess polypharmacy and potential drug interactions

➢ requires prospective analysis

Acknowledgements

University of Adelaide

Imogen Ball
A/Prof Joanne Bowen
Prof Rachel Gibson
Prof Dorothy Keefe
Samatha Korver
Prof Richard Logan
Lorelle Smith

Flinders Medical Centre

Prof Chris Karapetis
Kelly Mead
Alison Richards

Project Funding

Ray and Shirl Norman Cancer Research Trust
Australian Dental Research Foundation

janet.coller@adelaide.edu.au

CANCER TREATMENT TOXICITIES GROUP
Integrating the pathogenesis, prediction and prevention of cancer-related side effects