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RAPID COMMUNICATION

Biological sex and chemotherapy treatment delays in patients with colorectal cancer

Pinkie Chambers*,a [ID], Anna Dorothea Wagnerb, Ofran Almossawic [ID], Simon Jenkinsond, Gabriel A Brookse [ID] and John Bridgewaterf [ID]

aResearch Department of Practice and Policy, School of Pharmacy, University College London & University College London Hospitals NHS Foundation Trust, London, WC1H 9JP, UK; bDepartment of Oncology, Lausanne University Hospital & University of Lausanne, Lausanne, Switzerland; cPopulation, Policy & Practice Department, UCL Institute of Child Health & Great Ormond Street Hospital for Children NHS Foundation Trust, London, WC1N 1EH, UK; dPharmacy Department, Royal Free London, NHS Foundation Trust, Pond St, London, NW3 2QG, UK; eDartmouth Cancer Center, Lebanon, NH, 03756, USA; fDepartment of Oncology, UCL Cancer Institute & University College London Hospitals NHS Foundation Trust, London, WC1E 6DD, UK

ABSTRACT

Aim: We investigated the association of biological sex with the incidence of inter-cycle treatment delays. **Patients & methods:** This retrospective cohort study included patients receiving first-line chemotherapy. Multivariable logistic regression was used to assess the association between biological sex and a 7-day treatment delay, adjusting for confounders. **Results:** Among 1904 patients, 1106 (58%) were males and 798 (42%) females. 387 patients (20%) had a treatment delay (54% males, 46% females; $p = 0.08$). Sex was associated with treatment delays in multivariable analysis (males vs females OR: 0.73, 95% CI 0.57–0.93). **Conclusion:** The findings are concordant with other studies reporting differences in toxicity profiles of fluorouracil. Further research is required to optimize dosing between males and females.

Plain language summary: Some research has shown that cancer drugs might work differently in men and women. This means that some women might suffer more side effects. When a patient suffers from a side effect, their next treatment is delayed. This is so that they can recover. In our study, we looked at these delays in treatments between men and women. We studied 1904 patients with cancer who had had cancer drug treatment and found that women were around a third more likely to have a delay in the timing of their next dose of treatment. Our work was similar to other research that women might be suffering more side effects than men. We need to do more research to find the best drug dosages for women.

TWEETABLE ABSTRACT

Study showing that females are 30% more likely to have a #chemo delay compared with males. Research is needed to find better dosing for females. @myESMO @PinkieChambers @School_Pharmacy

1. Background

The fundamental differences in the biology between males and females are reported to affect the pharmacokinetics of cancer drug treatments [1]. These differences could impact treatment efficacy and toxicity; however, because women were historically excluded as subjects of investigations in non-reproductive clinical research, the dosing of both sexes is the same [2]. Furthermore, trials that have included women fail to stratify toxicities by sex; despite reports that differences in drug adverse events between males and females are present [1].

Colorectal cancer is the third most common malignant tumor and the second most frequent cause of cancer-related mortality worldwide [3]. Sexual dimorphism has been reported in both the incidence and prognosis of colorectal cancer, where the survival of men is lower than in women [4,5]. Chemotherapy is used in both the curative and palliative settings for patients and the drug, 5-Fluorouracil (5FU), is the backbone of most treatment regimens [6]. The pharmacokinetics of 5FU are reported to be different between males and females [7] and these differences would inevitably influence toxicity of treatments. Differences in toxicity have been reported in retrospective studies of trial patients [8,9] but evidence from real-

world studies is lacking. Additionally, studies exploring the impact of changes in dosing strategy are sparse.

Severe treatment-related toxicity can cause unplanned delays in treatment that lead to reductions in dose intensity, a measure that is known to influence treatment outcomes in colorectal cancer [10]. In this study, we aimed to evaluate the association of biological sex with dose delays between a first and second chemotherapy treatment in a real-world setting.

2. Methods

2.1. Study design & data source

This was a retrospective cohort study using chemotherapy data for patients from four hospitals in England. The outcome of interest was a delay of 7 days or more from the scheduled date of the second cycle of treatment. A 7-day delay to treatment is considered standard when a patient is presenting with toxicity around their next treatment date, allowing the patient to recover [11].

2.2. Patient selection

2.2.1. Eligibility criteria

Data were included for patients aged 18 or over, identified through the chemotherapy electronic patient record systems at each hospital for the period of 1 January 2013 to 1 January 2018. The first chemotherapy treatment date was used as the index date for entry to the cohort during the study period. We included patients with colorectal cancer of any stage receiving first-line chemotherapy. We restricted our inclusion to the following treatments: irinotecan modified de Gramont (FOLFIRI); oxaliplatin modified de Gramont (FOLFOX) and oxaliplatin and capecitabine (OXCAP). We excluded patients who had a gap of over 60 days from the index date suggesting a change of treatment such as surgery or disease-related interruption, which was outside the scope of this research.

2.3. Data extraction

Variables selected for extraction were guided by a systematic review [12,13]. These were extracted and assessed for data quality. Data quality is reported elsewhere [14] and for this study, we did not analyze co-morbidity information due to the type of missingness. Additionally, very few patients had a dose reduction at the first cycle, and therefore this variable was excluded from the analysis. Covariables included were treating hospital, type of chemotherapy, length of treatment cycle prescribed, whether a colony-stimulating factor was prescribed at cycle 1, age of the patient at the start of chemotherapy, patient-reported ethnicity, biological sex, body mass

index (BMI) calculated at the start of chemotherapy and baseline laboratory data. Ethnicity is standardly reported in England by patients and coded in groups [15]. Groupings included the categories 'not available' and 'unknown', which were brought into the analysis. The variable sex was assigned within the patient record from birth. The laboratory data was extracted if recorded within 28 days of the first chemotherapy administration and included baseline absolute neutrophil count (ANC), hemoglobin, bilirubin, and creatinine.

2.3.1. Defining chemotherapy treatment delay

To identify whether treatment had been delayed, we used the cycle length stipulated by the chemotherapy regimen and compared the number of days between the index date and the date of the second cycle with this value. If the administered second cycle date was 7 days or more from the expected date, the patient was recorded to have a treatment delay.

2.4. Statistical analysis

We calculated the incidence of delays between the first and second chemotherapy treatments, in total. Descriptive analysis was performed to understand the distribution of patient demographic characteristics, treating hospital, laboratory characteristics, treatment characteristics, and the outcomes of the delayed second cycle.

Multivariable logistic regression was used to assess the association biological sex of the patient and the occurrence of a dose delay at the second cycle; adjusting for covariables. The variables age and BMI were categorized concordant with other researchers [16,17], using 65 as a threshold for age and a BMI of 30 to indicate obesity.

2.4.1. Missing data

The extent of missing data for included variables was investigated and associations between the outcome and complete variables were assessed and presented. Complete records were used as the dependent variable in a logistic regression.

3. Results

3.1. Patient characteristics

A total of 1904 patients met our inclusion criteria from four hospitals in England, including 1094 males and 789 females. In total, 387 patients (20.3%) had a treatment delay of 7 days or more. The unadjusted incidence of treatment delays by sex was 18.7% in males and 22.1% in females. Table 1 shows additional information about the incidence of treatment delay in demographic and clinical subgroups.

Table 1. Overview of patients with a delay at cycle 2.

Characteristic	Missing	No delay, n = 1504[†]	Delay, n = 379[†]	p-value[‡]
Hospital code	0 (0%)			0.001
1		717 (48%)	221 (58%)	
2		424 (28%)	95 (25%)	
3		287 (19%)	52 (14%)	
4		76 (5.1%)	11 (2.9%)	
Length of cycle (days)	0 (0%)			<0.001
14		1223 (81%)	337 (89%)	
21		281 (19%)	42 (11%)	
GCSF at cycle 1	0 (0%)			0.043
No		1483 (99%)	368 (97%)	
Yes		21 (1.4%)	11 (2.9%)	
Performance status	28 (1.5%)			0.600
0		1274 (86%)	315 (84%)	
1		181 (12%)	50 (13%)	
2		24 (1.6%)	9 (2.4%)	
3		2 (0.1%)	0 (0%)	
4		0 (0%)	0 (0%)	
Sex	0 (0%)			0.077
Male		889 (59%)	205 (54%)	
Female		615 (41%)	174 (46%)	
Ethnicity	0 (0%)			
Asian		45 (3.0%)	9 (2.4%)	
Black		53 (3.5%)	9 (2.4%)	
Chinese		13 (0.9%)	2 (0.5%)	
Mixed		13 (0.9%)	0 (0%)	
Other		81 (5.4%)	24 (6.3%)	
Unknown		55 (3.7%)	12 (3.2%)	
White		1244 (83%)	323 (85%)	
Regimen	0 (0%)			0.002
IRMDG		479 (32%)	152 (40%)	
OXCAP		354 (24%)	64 (17%)	
FOLFOX		671 (45%)	163 (43%)	
Performance status group	0 (0%)			0.570
0		1297 (86%)	320 (84%)	
1		181 (12%)	50 (13%)	
2		26 (1.7%)	9 (2.4%)	
Age	0 (0%)			0.512
≤65 years		952 (63%)	233 (61%)	
>65 years		552 (37%)	146 (39%)	
BMI	0 (0%)			0.830
≤30		1239 (82%)	314 (83%)	
>30		265 (18%)	65 (17%)	

[†]n, (%).
[‡]Pearson's chi-squared test; Fisher's exact test.
FOLFOX: Oxaliplatin modified de gramont; IRMDG: Irinotecan modified de gramont; PS: Performance status.

In the univariable analysis, we noted that hospital, cycle length, and chemotherapy regimen were significantly associated with treatment delay ($p < 0.05$). In the multivariable analysis (Table 2) only hospital and sex were significantly associated with delay. Treatment delay was less likely in male patients, compared with female patients (adjusted OR 0.73; 95% CI: 0.57–0.93).

4. Discussion

In our real-world study of 1904 patients, we found dose delays between the first and second chemotherapy treatments occurred in 20% of patients receiving treatment for colorectal cancer. Furthermore, biological sex was significantly associated with the occurrence of these delays,

with females being more likely to incur a delay, compared with male patients.

There is increasing evidence that optimal chemotherapy dosing may differ by sex for some drugs [1]. Mueller and colleagues reported differences in the elimination of the drug fluorouracil in males and females for colorectal cancer [18] and a further report identified pharmacokinetic differences between the two sexes to be a predictor of toxicity [19]. These differences in pharmacokinetics are likely to explain the association between sex and treatment delays observed in our study.

A further retrospective study [18] examined differences in toxicity in patients recruited to the PETACC-3 trial [20]; finding statistically significant and clinically relevant greater risk of both hematological and non-hematological adverse events in women for all 5FU-

Table 2. Multivariable logistic regression.

Covariate	OR[†]	95% CI[†]	p-value
Sex			
Female	—	—	
Male	0.73	0.57, 0.93	0.010
Hospital code			
1	Ref	Ref	
2	0.84	0.61, 1.16	0.3
3	0.66	0.45, 0.96	0.034
4	0.51	0.21, 1.09	0.10
Regimen			
IRMDG	—	—	
OXCAP	0.85	0.50, 1.40	0.5
FOLFOX	0.85	0.65, 1.11	0.2
Length of cycle (days)			
14	—	—	
21	0.63	0.34, 1.20	0.2
BMI			
$\leq$30	—	—	
>30	0.97	0.71, 1.31	0.9
Age			
$\leq$65 years	—	—	
>65 years	1.13	0.88, 1.45	0.3
Performance status group			
0	—	—	
1	0.99	0.69, 1.40	>0.9
2	1.40	0.60, 3.01	0.4
Ethnicity			
Non-White	—	—	
White	1.05	0.76, 1.46	0.8
Baseline neutrophil count	0.98	0.94, 1.01	0.15
Baseline HB	0.97	0.94, 1.01	0.14
Baseline Cr	1.00	1.00, 1.01	0.028
Baseline Bilirubin	1.00	0.98, 1.01	>0.9

FOLFOX: Oxaliplatin modified de gramont; IRMDG: Irinotecan modified de gramont.
[†]CI: Confidence interval; OR: Odds ratio.

containing regimens. Similar to this work was a study conducted by Kogan and colleagues [21] evaluating the causes of treatment delays in patients with colorectal cancer patients at two hospitals in the USA and finding the majority of delays reported were a resultant effect of neutropenia. In two large studies using retrospective trial data, it was found that women were more likely to suffer from hematological toxicities compared with men [8,9]. Our findings are concordant with these, and more research is required to ensure optimal dosing of male and female patients with colorectal cancer. In fact, on the basis of the observed differences in the pharmacokinetics of 5-FU, optimal doses might be different for male and female patients. Consequently, different doses should be investigated in clinical trials.

Another important area that should be further investigated is the influence of gender on treatment outcomes. Sex and gender are not equivalent concepts. Sex is a biological attribute while gender refers to a chosen sexual identity. Gender, on the other hand, is a concept that varies between societies and can also change throughout a patient's lifetime [4]. Similarly, both sex and gender are seldom taken into account, in either preclinical or clinical research. However, whereas there is a growing body of evidence reporting that sexual dimorphisms in colorectal cancer influence incidence, treatment tolerability, and outcomes there is a dearth of evidence investigating gender differences [5]. Differences that could be attributed to behaviors. Our work only investigated differences in sex assigned at birth due to poor reporting of gender at the time of data extraction and we acknowledge that this is a limitation of this study and an area requiring further research.

There are further limitations of our work including our inability to include variables specific for the cancer type and staging. We were also unable to determine the specific reasons for delays in our cohort of patients. A granular understanding of types of toxicity and severity between males and females would have strengthened our findings. A further limitation was that our study focused on chemotherapy, and we did not examine newer targeted agents. The rationale for this was that chemotherapy continues to be widely used in the colorectal population of patients. Despite these limitations, we believe that the findings of our study will contribute to the growing body of evidence to influence change.

5. Conclusion

In conclusion, and despite these limitations, we believe that the findings of our study will contribute to the growing body of evidence, supporting the investigation of sex-specific dosing strategies for treatment regimens based on 5-FU, as well as other anticancer drugs with sex differences in pharmacokinetics. Our study underlines the need for further research into sex differences in cancer treatments, which could ultimately lead to improved therapeutic outcomes for all patients.

Article highlights

- Increasing evidence supports differences between males and females and treatment effects in those with colorectal cancer.
- There is little known about the association between biological sex and chemotherapy treatment delays in patients with colorectal cancer.
- In this retrospective cohort study including 1904 adults, males were less likely to have a delay between the first and second chemotherapy treatment, compared with females (adjusted OR 0.73; 95% CI: 0.57–0.93). This study supports the need for changing the dosing strategy for males and females.

Author contributions

P Chambers, J Bridgewater, AD Wagner, and GA Brooks designed and conceptualized the study. P Chambers, O Almossawi, and S Jenkinson undertook the data analysis. P Chambers led the drafting of the manuscript. All authors contributed to the drafting and revision of the final manuscript.

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Competing interests disclosures

P Chambers reports research grants from Janssen, Pfizer, Tessaro and Bristol Myers Squibb, and Gilead; outside the submitted work. J Bridgewater reports grants from MSD and Bristol Myers Squibb outside the submitted work; AD Wagner reports grants from Bristol Myers Squibb outside the submitted work. GA Brooks reports institutional research funding from Roche-Genentech, and consulting payments from Glaxo-Smith-Kline (both outside of the submitted work). The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosures

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The data study was based on retrospective datasets; Heath Research Authority (HRA) approvals were required and granted on 24 November 2017 (IRAS 226078). Information governance approvals were granted at each recruited site in accordance with hospital policies.

Data sharing statement

The datasets generated during and analyzed during the current study are available from the corresponding author upon reasonable request.

ORCID

Pinkie Chambers https://orcid.org/0000-0002-6669-9411
Ofran Almossawi https://orcid.org/0000-0001-6900-3590
Gabriel A Brooks https://orcid.org/0000-0003-3984-9995
John Bridgewater https://orcid.org/0000-0001-9186-1604

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