Original Article

Differences in symptom occurrence, severity, and distress ratings between patients with gastrointestinal cancers who received chemotherapy alone or chemotherapy with targeted therapy

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Background: Approximately 28% of patients with gastrointestinal (GI) cancers will receive targeted therapy (TT) because of the associated increases in survival. Only four studies have examined the symptom experience of these patients. To date, no studies have evaluated for differences in symptom occurrence, severity, and distress between patients who received chemotherapy (CTX) alone (n=304) or CTX with TT (n=93).

Methods: Patients completed self-report questionnaires, approximately one week after they received CTX. A modified version of the Memorial Symptom Assessment Scale (MSAS) was used to obtain data on symptom occurrence, severity, and distress. Binary logistic regression analyses were used to test for differences in symptom occurrence rates between the two treatment groups. Ordinal logistic regression analyses were used to test for differences in severity and distress ratings between the two treatment groups.

Results: Patients who received CTX with TT were significantly younger (P=0.009); were diagnosed with cancer longer (P=0.004); had a higher number of prior treatments (P=0.024); had metastatic disease, specifically to the liver (P<0.001); had a diagnosis of anal, colon, rectum, or colorectal cancer (CRC) (P<0.001); and were positive for detection of B-Raf proto-oncogene, serine/threonine kinase (BRAF) and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations (both P<0.001). In addition, CTX treatment regimens were significantly different between the two groups (P<0.001). After controlling for significant covariates, patients who received TT reported lower occurrence rates for lack of energy, cough, feeling drowsy, and difficulty sleeping (all, P<0.05). Patients who received TT reported lower severity scores for dry mouth (P=0.034) and change in the way food tastes (P=0.035). However, they reported higher severity scores for "I don't look like myself" (P=0.026). No differences in symptom distress scores were found between the two treatment groups.

Conclusions: This study is the first to evaluate for differences in the symptom experience of GI cancer patients who received CTX alone or CTX with TT using a multidimensional symptom assessment scale. While between group differences in patients' symptom experiences were identified, both treatment groups warrant ongoing assessments to optimally manage their symptoms.

Keywords: Gastrointestinal cancer; symptoms; chemotherapy (CTX); targeted therapy (TT)

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Introduction

Gastrointestinal (GI) cancers include the esophagus, stomach, small intestine, large intestine (colon), gall bladder, liver, pancreas, rectum, and anus. While the mortality rates for colon and rectal cancers have decreased over the past two decades, other GI cancers (e.g., pancreas) that do not have reliable screening methods have not seen similar effects (1). The American Cancer Society estimates that 304,930 new cases of GI cancers will be diagnosed in 2016 and approximately half of these patients will die from their disease (1).

Historically, chemotherapy (CTX) was one of the standard treatments for GI cancers (2-8). These agents are administered to reduce tumor burden, decrease tumor-related symptoms, improve patients' well-being, and prolong survival (9-12). However, these agents are inherently toxic and destroy rapidly dividing cancer cells, which results in significant symptoms (3,13). Therefore, ongoing assessments of patients with GI cancers are critical because unrelieved symptoms may alter their CTX regimen, as well as have negative effects on their functional status and quality of life (QOL) (14).

Today, patients with GI cancers are treated with surgery, radiation therapy, CTX, and/or targeted therapy (TT) depending on the stage of their disease at the time of diagnosis (15-18). Because TT was developed to act on well-defined targets or biological pathways, initial evidence suggested that patients tolerated targeted therapies better than traditional CTX (19). In addition, survival rates increased in patients with GI cancers who received TT (20). However, more recent evidence suggests that these targeted therapies result in unique toxicities (e.g., skin changes) (21).

To date, the majority of symptom management research has evaluated patients who were heterogeneous with respect to their cancer diagnoses. Most studies that evaluated the symptom experience of patients with GI cancers were done within the context of randomized clinical trials (RCTs) for new CTX regimens. The evaluation of symptoms within the context of these RCTs is limited because most studies used the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) (22-26). Only four studies used valid and reliable symptom assessment instruments to evaluate various dimensions of the symptom experience (i.e., occurrence, severity, distress) in patients with GI cancers receiving CTX (27-30).

In the first study (28), data from the Cancer Care Outcomes Research and Surveillance (CanCORS) study (i.e., a demographically representative national database) were used to describe the prevalence and severity of symptoms in patients who were four to 6 months post diagnosis of lung cancer or colorectal cancer (CRC). Of the 5,422 patients who completed the symptom survey, 93.5% reported at least one symptom in the four weeks before the survey. In addition, 51% reported at least one symptom as moderate or severe. Patients with CRC reported significantly fewer symptoms than patient with lung cancer. In addition, patients who were most recently diagnosed with lung cancer and CRC were more likely to report a significantly higher number of symptoms regardless of the stage of their disease. While this study's sample was large and representative, comparisons were not made between CRC patients who received CTX with or without TT.

In the second study (29), multiple dimensions of the symptom experience (i.e., occurrence, severity, and distress) associated with the second or third cycle of CTX for CRC were evaluated. On average, these patients (n=104) reported 10.3 (±7.7) symptoms. The five most common symptoms were numbness/tingling in the hands/feet (64%), lack of energy (62%), feeling drowsy (49%), nausea (45%), and shortness of breath (43%). Using the Memorial Symptom Assessment Scale (MSAS), these patients reported higher scores for frequency than for either severity or distress. Again, this study did not evaluate for differences in the symptom experience of CRC patients who received CTX with or without TT.

In a study that evaluated multiple symptoms using the MSAS, as well as psychological distress, social support, and QOL in newly diagnosed patients with GI cancers (n=146) (27), the most common symptoms were fatigue (63%), pain (42.1%), weight loss (41.1%), dry mouth (38.4%), and lack of appetite (35.6%). These patients' mean anxiety score was 40.5 (±11.2) and 27.4% of the patients were categorized as clinically depressed. While, multiple dimensions of the symptom experience were evaluated, comparisons were not made between GI patients who received CTX with or without TT.

Only one retrospective, cohort study evaluated the symptom experience of patients with GI cancers on targeted therapies (30). In this study, differences in the symptom burden of patients with CRC who received second-line treatments that contained bevacizumab or cetuximab with or without CTX were evaluated. Regardless of treatment group, fatigue was the most common symptom (67%) that occurred at moderate to severe levels. However, compared to bevacizumab, cetuximab produced a significantly higher

rate of moderate to severe dry skin (P<0.0001), itching (P=0.0028), and rash (P<0.0001). Of note, compared to the bevacizumab group, patients who received only CTX had a higher rate of moderate to severe nausea (P=0.0485) and tended to report a higher rate of physical pain (P=0.0564). In this study, the Patient Care Monitor Instrument was used to evaluate the severity of 80 symptoms (86 for women), using a 0 to 10 scale. While 80 to 86 symptoms were evaluated, detailed information on the severity and distress of these symptoms were not reported.

Current evidence suggests that approximately 28% of patients with GI cancers will receive TT because of the associated increases in survival (31). Given the paucity of research on the symptom experience of these patients, the purpose of this study was to evaluate for differences in symptom occurrence rates, as well as in severity and distress ratings, in the week following the administration of CTX, between patients with GI cancers who received CTX alone or CTX with TT. We hypothesized that patients who received CTX with TT would report lower symptom occurrence rates, as well as lower severity and distress ratings.

Methods

Patients and settings

This study is part of a larger descriptive, longitudinal study of the symptom experience of oncology outpatients who received CTX (32,33). Eligible patients were ≥18 years of age; had a diagnosis of breast, GI, lung, or gynecological cancer; had received CTX within the preceding four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and provided informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veterans Affairs hospital, and four community based oncology programs.

A total of 2,234 patients were approached and 1,343 consented to participate (60.1% response rate) in the larger study. The major reason for refusal was being overwhelmed with their cancer treatment. For this study, only patients with GI cancers were included (n=404).

Study procedures

The study was approved by the Committee on Human Research at the University of California at San Francisco and by the Institutional Review Board at each of the study sites. A research staff member in the infusion unit approached eligible patients and discussed participation in the study. Written informed consent was obtained from all patients. Based on the length of the CTX cycle, GI cancer patients completed questionnaires in their homes, a total of six times over two cycles of CTX, namely: before CTX administration (i.e., recovery from previous CTX cycle, Times 1 and 4), approximately one week after CTX administration (i.e., acute symptoms, Times 2 and 5), and approximately two weeks after CTX administration (i.e., potential nadir, Times 3 and 6). For this study, symptom data from the Time 2 assessment were analyzed.

Instruments

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. Functional status was assessed using the Karnofsky Performance Status (KPS) scale, which is widely used in patients with cancer and has well established validity and reliability. Patients rated their functional status using the KPS scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms) (34).

Self-Administered Comorbidity Questionnaire (SCQ) consists of 13 common medical conditions simplified into language that can be understood without prior medical knowledge (35). Patients indicated if they had the condition; if they received treatment for it (proxy for disease severity); and if it limited their activity (indication of functional limitations). For each condition, patients can receive a maximum of 3 points. The total SCQ score ranges from 0 to 39. The SCQ has well established validity and reliability (35).

Alcohol Use Disorders Identification Test (AUDIT) is a 10-item questionnaire that assesses alcohol consumption, alcohol dependence, and the consequences of alcohol abuse in the last 12 months. The AUDIT gives a total score that ranges between 0 and 40. Scores of ≥8 are defined as hazardous use and scores of ≥16 are defined as use of alcohol that is likely to be harmful to health (36,37). The AUDIT has well established validity and reliability (38-40). In this study, its Cronbach's alpha was 0.63.

A modified version of the MSAS was used to evaluate the occurrence, severity, and distress of 38 symptoms commonly associated with cancer and its treatment. In addition to the original 32 MSAS symptoms, the following six symptoms were assessed: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, and weight gain. The MSAS is a self-report questionnaire

designed to measure the multidimensional experience of symptoms. Patients were asked to indicate whether they experienced each symptom within the past week (i.e., symptom occurrence). If they experienced the symptom, they were asked to rate its severity and distress. Severity was rated using a 4-point Likert scale (i.e., 1= slight, 2= moderate, 3= severe, 4= very severe). Distress was rated using a 5-point Likert scale (i.e., 0= not at all, 1= mild, 2= moderate, 3= severe, 4= very severe) (41). The validity and reliability of the MSAS are well established (41-43).

Data analysis

Data were analyzed using SPSS Version 22 (IBM, Armonk, NY, USA) and Stata Version 14 (StataCorp LP, College Station, TX). Descriptive statistics as means and standard deviations (SD) for quantitative variables and frequencies and percentages for categorical variables were calculated for all study variables. Patients were dichotomized into individuals who received CTX alone or CTX with TT. Independent sample t-tests, Mann-Whitney U tests, and Chi-Square analyses were used to evaluate for differences in demographic and clinical characteristics between the two treatment groups.

Binary logistic regression analyses were performed to test for differences in symptom occurrence rates between the two treatment groups. Ordinal logistic regression analyses were used to test for differences in severity and distress ratings between the two treatment groups (44). Because some of the symptoms had a low occurrence rate, regression analyses were performed only when ≥60 responses were available. Additionally, symptom severity and distress ratings were not analyzed if <15 responses were available in the upper two categories. Because the severity and distress ratings were ordinal and most were highly skewed, analyses for these items were carried out with ordinal logistic regression and estimation was carried out with a nonparametric bootstrap, with 1,000 repetitions for each analysis, to obtain bias-corrected confidence intervals (CI) for the predictors. For each bootstrapped regression, likelihood ratio deviance tests were used to determine whether a set of six covariates that differed between the treatment groups (i.e., age, time since cancer diagnosis, number of metastatic sites including lymph node involvement, number of prior cancer treatments, GI cancer diagnosis, CTX treatment regimen) improved the fit of the model over the single treatment predictor. Significance was evaluated using bias-corrected bootstrapped CIs. A P value of <0.05 was considered statistically significant.

Results

Differences in demographic characteristics between patients who received CTX with or without TT

Of the 404 patients with GI cancers who consented to participate, 397 patients (94%) completed the MSAS. Of these 397 patients, 23.4% (n=93) received CTX with TT and 76.6% (n=304) received only CTX. As shown in *Table 1*, except for age, no differences were found in any demographic characteristics between patients who received CTX alone or CTX with TT. Patients who received CTX with TT were significantly younger (P=0.009).

Differences in clinical characteristics between patients who received CTX with or without TT

As shown in *Table 1*, compared to patients who received CTX alone, patients who received CTX with TT were diagnosed with cancer longer (P=0.004) and had a higher number of prior treatments (P=0.024). In addition, a higher percentage of patients on CTX with TT had metastatic disease, specifically to the liver (P<0.001), had a diagnoses of anal, colon, rectum or CRC (P<0.001), and were positive for detection of B-Raf proto-oncogene, serine/threonine kinase (BRAF) and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations (both P<0.001).

The percentages of patients who received the most common CTX regimens differed between the two groups (P=0.002). In patients who received CTX alone, the most common CTX regimens were: leucovorin/5-fluorouracil/irinotecan (FOLFIRI), leucovorin/5-fluorouracil/oxaliplatin (FOLFOX), capecitabine and oxaliplatin (CapeOX), gemcitabine and paclitaxel, and leucovorin/5-fluorouracil/irinotecan/oxaliplatin (FOLFIRINOX). In patients who received targeted therapies, the most common CTX regimens were: FOLFIRI, FOLFOX, FOLFIRINOX, and CapeOX. The most common targeted therapies were: bevacizumab (80.4%), cetuximab (12.4%), panitumumab (6.2%), and transtuzumab (1.0%).

Differences in symptom occurrence rates and total number of symptoms between patients who received CTX with or without TT

The occurrence rates for the top ten symptoms are listed

Table 1 Differences in demographic and clinical characteristics between patients who received CTX alone or CTX with TT

Characteristic	Mean (SD)		Statistics
	NT [1], 76.6% (n=304)	TT [2], 23.4% (n=93)	
Age (years)	58.80 (11.92)	55.16 (11.17)	t=2.61; P=0.009
Education (years)	16.11 (3.14)	15.81 (2.74)	t=0.82; P=0.416
Body mass index (kg/m^2)	25.63 (5.25)	26.26 (5.30)	t=–1.01; P=0.311
KPS score, (n%)	80.61 (12.71)	80.91 (12.00)	t=–0.19; P=0.848
AUDIT score, (n%)	3.28 (2.64)	3.51 (3.76)	t=–0.41; P=0.683
Number of comorbidities, (n%)	2.31 (1.41)	2.40 (1.12)	t=–0.53; P=0.594
SCQ score, (n%)	5.31 (3.03)	5.54 (2.61)	t=–0.66; P=0.512
Time since cancer diagnosis (years)	1.25 (2.77)	2.01 (3.02)	U; P=0.004
Time since diagnosis (median)	0.39	0.69	
Number of prior cancer treatments, (n%)	1.31 (1.20)	1.66 (1.57)	t=–2.26; P=0.024
Number of metastatic sites including lymph node involvement, (n%)	1.23 (1.02)	2.24 (1.07)	t=–8.27; P<0.001
Number of metastatic sites excluding lymph node involvement, (n%)	0.76 (0.91)	1.56 (0.89)	t=–7.50; P<0.001
Gender, (n%)			FE; P=1.000
Female	45.4 (138.0)	45.2 (42.0)	
Male	54.6 (166.0)	54.8 (51.0)	
Ethnicity, (n%)			X^2=1.04; P=0.791
White	67.6 (200.0)	68.5 (61.0)	
Black	10.1 (30.0)	6.7 (6.0)	
Asian or pacific islander	11.5 (34.0)	12.4 (11.0)	
Hispanic mixed or other	10.8 (32.0)	12.4 (11.0)	
Married or living together (% yes)	67.1 (202.0)	68.5 (63.0)	FE; P=0.899
Lives alone (% yes)	18.3 (55.0)	20.7 (19.0)	FE; P=0.648
Child care responsibilities (% yes)	20.6 (61.0)	20.0 (18.0)	FE; P=1.000
Care of adult responsibilities (% yes)	5.8 (16.0)	11.9 (10.0)	FE; P=0.087
Currently employed (% yes)	33.4 (100.0)	34.1 (31.0)	FE; P=0.900
Income, (n%)			U; P=0.231
<$30,000	20.3 (55.0)	21.2 (18.0)	
$30,000 to <$70,000	18.5 (50.0)	22.4 (19.0)	
$70,000 to <$100,000	15.9 (43.0)	21.2 (18.0)	
≥$100,000	45.4 (123.0)	35.3 (30.0)	
Specific comorbidities (% yes)			
Heart disease	4.6 (11.0)	4.5 (2.0)	FE; P=1.000
High blood pressure	35.7 (86.0)	38.6 (17.0)	FE; P=0.735
Lung disease	6.6 (16.0)	2.3 (1.0)	FE; P=0.486
Diabetes	14.1 (34.0)	13.6 (6.0)	FE; P=1.000
Ulcer or stomach disease	5.0 (12.0)	6.8 (3.0)	FE; P=0.711
Kidney disease	1.7 (4.0)	0.0 (0.0)	FE; P=1.000
Liver disease	10.4 (25.0)	22.7 (10.0)	FE; P=0.041
Anemia or blood disease	9.1 (22.0)	6.8 (3.0)	FE; P=0.777
Depression	15.4 (37.0)	25.0 (11.0)	FE; P=0.127

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Mean (SD)		Statistics
	NT [1], 76.6% (n=304)	TT [2], 23.4% (n=93)	
Osteoarthritis	10.4 (25.0)	2.3 (1.0)	FE; P=0.148
Back pain	21.6 (52.0)	25.0 (11.0)	FE; P=0.693
Rheumatoid arthritis	2.5 (6.0)	2.3 (1.0)	FE; P=1.000
Exercise on a regular basis (% yes)	65.8 (198.0)	68.5 (63.0)	FE; P=0.706
Cancer diagnosis, (n%)			X^2=41.00; P<0.001
Colon/Rectum/Anal pancreatic/Liver/Gall bladder	54.8 (165.0)	91.4 (85.0)	
Esophageal/Gastric/Small intestine/Other	45.2 (136.0)	8.6 (8.0)	
Type of prior cancer treatment, (n%)			X^2=3.67; P=0.299
No prior treatment	28.9 (86.0)	30.3 (27.0)	
Only surgery, CTX, or RT	40.3 (120.0)	31.5 (28.0)	
Surgery & CTX, or surgery & RT, or CTX & RT	19.8 (59.0)	28.1 (25.0)	
Surgery & CTX & RT	11.1 (33.0)	10.1 (9.0)	
Genetic testing (% yes)			
BRAF detected	1.3 (4.0)	5.4 (5.0)	X^2=17.13; P<0.001
KRAS detected	9.6 (29.0)	22.8 (21.0)	X^2=53.69; P<0.001
Metastatic sites, (n%)			X^2=66.33; P<0.001
No metastasis	24.1 (73.0)	3.2 (3.0)	1>2
Only lymph node metastasis	24.4 (74.0)	4.3 (4.0)	1>2
Only metastatic disease in other sites	28.4 (86.0)	29.0 (27.0)	NS
Metastatic disease in lymph nodes and other sites	23.1 (70.0)	63.4 (59.0)	1<2
Metastasis location (% yes)			
Bone	4.8 (11.0)	7.8 (7.0)	FE; P=0.290
Brain	1.3 (3.0)	2.2 (2.0)	FE; P=0.622
Liver	42.9 (99.0)	78.9 (71.0)	FE; P<0.001
Lung	16.9 (39.0)	26.7 (24.0)	FE; P=0.060
Lymph	62.6 (144.0)	70.0 (63.0)	FE; P=0.243
Peritoneum	16.0 (37.0)	17.8 (16.0)	FE; P=0.739
Skin/Scalp	0.4 (1.0)	1.1 (1.0)	FE; P=0.483
Viscera	5.6 (13.0)	2.2 (2.0)	FE; P=0.249
Other	11.7 (27.0)	24.4 (22.0)	FE; P=0.006
CTX treatment regimen, (n%)			X^2=14.58; P=0.002
FOLFIRI	11.2 (34.0)	23.7 (22.0)	1<2
FOLFOX	43.4 (132.0)	44.1 (41.0)	NS
FOLFIRINOX	13.2 (40.0)	3.2 (3.0)	1>2
Other	32.2 (98.0)	29.0 (27.0)	NS

AUDIT, Alcohol Use Disorders Identification Test; BRAF, B-RAF proto-oncogene, serine/threonine kinase; CapeOx, capecitabine and oxaliplatin; CTX, chemotherapy; FE, Fisher's exact test; FOLFIRI, leucovorin/5-fluorouracil/irinotecan; FOLFIRINOX, leucovorin/5-fluorouracil/irinotecan/oxaliplatin; FOLFOX, leucovorin/5-fluorouracil/oxaliplatin; kg, kilograms; KRAS, Kristen rat sarcoma viral oncogene homolog; m^2, meter squared; NS, not significant; RT, radiation therapy; SCQ, Self-Administered Comorbidity Questionnaire; SD, standard deviation; U, Mann Whitney U test; KPS, Karnofsky Performance Status; TT, targeted therapy; NT, no targeted therapy.

Table 2 Differences between patients who received CTX alone or CTX with TT in rankings of symptoms with the highest occurrence rates

Rank	NT	% of patients	TT	% of patients
1	Lack of energy	83.3	Lack of energy	72.1
2	Numbness or tingling in hands or feet	68.1	Numbness or tingling in hands or feet	65.1
3	Feeling drowsy	64.2	Pain	57.0
4	Difficulty sleeping	63.2	Nausea	52.3
5	Nausea	60.4	Difficulty sleeping	50.0
6	Pain	55.2	Changes in the way food tastes	48.8
7	Change in the way food tastes	50.3	Lack of appetite	47.7
8	Lack of appetite	49.3	Difficulty concentrating	47.7
9	Difficulty concentrating	46.5	Feeling drowsy	45.3
10	Hair loss	43.4	Changes in skin	43.0

Additional six symptoms not included on the original MSAS: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, weight gain. MSAS, Memorial Symptom Assessment Scale; TT, targeted therapy; NT, no targeted therapy.

in *Table 2*. No differences were found in the total number of symptoms reported between patients who received CTX with ($\bar{x}$=11.50±6.9) or without ($\bar{x}$=12.75±6.8; t=1.501, P=0.134) TT. The five symptoms with the highest occurrence rates in patients who received CTX with TT were: lack of energy (72.1%), numbness/tingling in hands or feet (65.1%), pain (57.0%), nausea (52.3%), and difficulty sleeping (50.0%). Except for pain, four of these symptoms were in the top five symptoms reported by the patients who received CTX alone.

In the bivariate analyses (*Table 3*), patients who received CTX with TT reported lower occurrence rates for lack of energy, cough, feeling drowsy, and difficulty sleeping (all, P<0.05). In the multivariable analyses that adjusted for age, time since cancer diagnosis, number of metastatic sites including lymph node involvement, number of prior cancer treatments, GI cancer diagnosis, and CTX treatment regimens, patients who received CTX with TT reported significantly lower occurrence rates for lack of energy (P<0.05), cough (P<0.01), feeling drowsy (P<0.05), and difficulty sleeping (P<0.05).

Differences in symptom severity scores between patients who received CTX with or without TT

The ten symptoms with the highest mean severity scores are listed in *Table 4*. For patients who received CTX with TT, the five symptoms with the highest severity scores were: swelling of arms and legs, "I don't look like myself", problems with urination, changes in skin, and problems with sexual interest or activity. For patients who received CTX alone, the five symptoms with the highest severity scores were: problems with sexual interest or activity, change in the way food tastes, lack of energy, diarrhea, and lack of appetite.

In the bivariate analyses (*Table 5*), patients who received CTX with TT reported a lower severity score for change in the way food tastes (P=0.023). However, these patients reported significantly higher severity scores for "I don't look like myself" (P=0.005), and changes in skin (P=0.019). In the multivariable analyses, the severity scores for dry mouth (P=0.034), and change in the way food tastes (P=0.035) were significantly lower in patients who received CTX with TT. In addition, these patients were more likely to report higher severity scores for "I don't look like myself" (P=0.026).

Differences in symptom distress scores between patients who received CTX with or without TT

The ten symptoms with the highest distress scores are listed in *Table 6*. For patients who received CTX with TT, the five symptoms with the highest distress scores were: problems with urination, "I don't look like myself", hair loss, constipation, and vomiting. For patients who received CTX alone, the five symptoms with the highest distress scores were: problems with sexual interest or activity, lack of energy, change in the way food tastes, pain, and diarrhea.

In the bivariate analyses (*Table 7*), patients who received

Table 3 Differences in symptom occurrence rates between patients who received CTX alone (n=304) or CTX with TT (n=93)

Symptom	Occurrence rates (%) by treatment group		Unadjusted values TT		Adjusted values TT[+]	
	NT	TT	Odds ratio	CI	Odds ratio	CI
Difficulty concentrating	46.5	47.7	1.056	0.652–1.712	1.015	0.580–1.775
Pain	55.2	57.0	1.080	0.664–1.756	0.792	0.449–1.398
Lack of energy	83.3	72.1	0.510	0.290–0.898*	0.443	0.224–0.875*
Cough	26.0	15.1	0.507	0.266–0.969*	0.346	0.165–0.724**
Feeling nervous	24.7	19.8	0.743	0.410–1.346	0.494	0.248–0.987
Dry mouth	43.1	31.4	0.611	0.366–1.021	0.688	0.385–1.231
Nausea	60.4	52.3	0.711	0.437–1.154	0.724	0.408–1.285
Feeling drowsy	64.2	45.3	0.463	0.284–0.754**	0.539	0.309–0.942*
Numbness/tingling in hands/feet	68.1	65.1	0.862	0.518–1.433	1.108	0.597–2.055
Difficulty sleeping	63.2	50.0	0.592	0.364–0.963*	0.522	0.293–0.931*
Feeling bloated	26.4	22.1	0.794	0.447–1.409	0.710	0.367–1.371
Problems with urination	17.7	10.5	0.536	0.252–1.140	0.553	0.236–1.295
Vomiting	15.3	17.4	1.157	0.608–2.201	1.207	0.572–2.546
Shortness of breath	15.3	12.8	—	—	—	—
Diarrhea	34.7	43.0	1.419	0.868–2.319	1.723	0.968–3.067
Feeling sad	34.4	39.5	1.248	0.759–2.050	1.053	0.593–1.871
Sweats	20.5	17.4	0.809	0.433–1.514	0.817	0.395–1.691
Worrying	39.9	36.0	0.858	0.520–1.415	0.785	0.441–1.399
Problems with sexual interest	23.3	22.1	0.979	0.548–1.750	0.936	0.474–1.846
Itching	17.7	19.8	1.158	0.628–2.136	1.456	0.709–2.990
Lack of appetite	49.3	47.7	0.944	0.582–1.529	1.023	0.588–1.781
Dizziness	29.2	24.4	0.800	0.459–1.393	0.701	0.373–1.317
Difficulty swallowing	19.1	22.1	1.213	0.673–2.187	1.409	0.708–2.807
Feeling irritable	37.5	31.4	0.750	0.448–1.255	0.640	0.351–1.168
Mouth sores	21.5	19.8	0.905	0.496–1.651	0.803	0.400–1.609
Change in the way food tastes	50.3	48.8	0.935	0.577–1.514	0.857	0.493–1.491
Weight loss	28.1	30.2	1.091	0.644–1.849	1.594	0.853–2.980
Hair loss	43.4	39.5	0.861	0.527–1.408	0.892	0.504–1.579
Constipation	42.4	38.4	0.844	0.515–1.383	0.649	0.366–1.150
Swelling of arms or legs	5.9	3.5	—	—	—	—
I don't look like myself	25.3	24.4	0.974	0.556–1.706	1.119	0.581–2.156
Changes in skin	34.0	43.0	1.487	0.908–2.433	1.316	0.744–2.331
Hot flashes	15.6	14.0	—	—	—	—
Chest tightness	10.8	5.8	—	—	—	—
Difficulty breathing	12.2	9.3	—	—	—	—
Abdominal cramps	33.0	24.4	0.656	0.379–1.138	0.590	0.311–1.120
Increased appetite	19.1	15.1	0.745	0.385–1.440	0.768	0.361–1.634
Weight gain	18.4	11.6	0.604	0.292–1.247	0.450	0.199–1.019

Analyses were done only when ≥60 responses were available. Additional six symptoms not included on the original MSAS are: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, and weight gain. *, P<0.05, **, P<0.01; [+], covariates in the regression analyses included: age, time since cancer diagnosis, number of metastatic sites including lymph node involvement, number of prior cancer treatments, GI cancer diagnosis, CTX treatment regimen. CI, confidence interval; MSAS, Memorial Symptom Assessment Scale; TT, targeted therapy; NT, no targeted therapy; GI, gastrointestinal.

Table 4 Differences between patients who received CTX alone or CTX with TT in rankings of symptoms with the highest severity scores

Rank	NT	Mean score[a]	TT	Mean score[a]
1	Problems with sexual interest or activity	2.49	Swelling of arms and legs	3.00
2	Change in the way food tastes	2.22	I don't look like myself	2.53
3	Lack of energy	2.16	Problems with urination	2.25
4	Diarrhea	2.04	Changes in skin	2.22
5	Lack of appetite	2.04	Problems with sexual interest or activity	2.17
6	Numbness or tingling in hands or feet	2.02	Lack of energy	2.15
7	Swelling	2.00	Difficulty sleeping	2.05
8	Feeling bloated	2.00	Constipation	2.03
9	Difficulty sleeping	1.96	Diarrhea	2.03
10	Constipation	1.94	Pain	2.00

Additional six symptoms not included on the original MSAS: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, and weight gain. [a], severity ratings = slight [1], moderate [2], severe [3], very severe [4]. MSAS, Memorial Symptom Assessment Scale; TT, targeted therapy; NT, no targeted therapy.

CTX with TT reported significantly higher distress ratings for: worrying (P=0.044), feeling irritable (P=0.035), and "I don't look like myself" (P=0.010). In the multivariable analyses, none of these between group differences remained significant.

Discussion

This study is the first to report on differences in multiple dimensions of the symptom experience in patients with GI cancers who received CTX with or without TT. Like the current literature, which reports conflicting evidence on the side effects associated with TT (45), our *a priori* hypothesis was only partially supported. Depending on the dimension evaluated, some symptoms were better and some were worse in patients on TT. Of note, in all of the multivariate analyses, neither GI cancer diagnosis nor CTX treatment regimen was a significant predictor of any symptoms' occurrence, severity or distress.

Symptom occurrence

While fatigue is the most common symptom reported by oncology patients receiving CTX (46), compared to previous reports of newly diagnosed patients with GI cancers (63%) (27), and CRC patients receiving CTX (62.0%) (29), the overall occurrence rate for fatigue (i.e., lack of energy) in our study regardless of treatment group was higher (80.7%). This difference may be related to differences in age, GI cancer diagnoses, and/or presence of metastatic disease. However, compared to patients who received CTX alone, patients on TT had a 55.7% decrease in the odds of reporting fatigue.

In terms of the overall occurrence rates for feeling drowsy and difficulty sleeping, our findings are similar to those of Pettersson and colleagues who reported occurrence rates of 49.0% and 46.0%, respectively for these two symptoms (29). Again, when differences in the occurrence rates for both of these symptoms were evaluated, patients in our study on TT had a 46.1% and 47.8% decrease in the odds of reporting feeling drowsy and difficulty sleeping, respectively. These differences in rates for all three symptoms remained significant after controlling for age, time since cancer diagnosis, number of metastatic sites, number of prior cancer treatments, GI cancer diagnosis, and CTX regimen.

While the exact reasons for the decreased occurrence rates for fatigue, feeling drowsy, and difficulty sleeping in patients on targeted therapies are not known, a number of potential explanations warrant consideration. First, while it is possible that specific CTX regimens and/or administration schedules could result in different occurrence rates for fatigue, no evidence was found to support this hypothesis, after we controlled for CTX regimen in the multivariate analyses. In addition, in a recent meta-analysis that evaluated the effects of doublet versus single cytotoxic

Table 5 Differences in severity ratings between patients who received CTX alone (n=304) or CTX with TT (n=93)

Symptom	Samplesize	Rx group	Mean score	Severity ratings† (%)				Unadjusted values TT			Adjusted values TT+		
				1	2	3	4	OR	CI	P value	OR	CI	P value
Difficulty concentrating	129	NT	1.58	48.1	45.7	6.2	0.0	—	—	—	—	—	—
	41	TT	1.44	61.0	34.1	4.9	0.0						
Pain	155	NT	1.91	29.7	54.2	11.6	4.5	1.246	0.669–2.321	0.448	1.151	0.501–2.647	0.740
	45	TT	2.00	24.4	57.8	11.1	6.7						
Lack of energy	233	NT	2.16	15.5	55.8	25.8	3.0	1.006	0.528–1.916	0.986	1.038	0.486–2.215	0.924
	59	TT	2.15	22.0	44.1	30.5	3.4						
Cough	71	NT	1.45	60.6	33.8	5.6	0.0	—	—	—	—	—	—
	13	TT	1.31	69.2	30.8	0.0	0.0						
Feeling nervous	69	NT	1.61	44.9	49.3	5.8	0.0	—	—	—	—	—	—
	15	TT	1.80	46.7	26.7	26.7	0.0						
Dry mouth	116	NT	1.84	35.3	49.1	11.2	4.3	0.457	0.195–1.069	0.071	0.268	0.079–0.907	0.034
	26	TT	1.54	53.8	38.5	7.7	0.0						
Nausea	163	NT	1.83	36.2	49.7	9.2	4.9	—	—	—	—	—	—
	41	TT	1.90	34.1	46.3	14.6	4.9						
Feeling drowsy	169	NT	1.84	31.4	56.2	9.5	3.0	—	—	—	—	—	—
	38	TT	1.76	34.2	55.3	10.5	0.0						
Numbness/tingling in hands/feet	185	NT	2.02	27.6	46.5	22.2	3.8	0.689	0.384–1.236	0.212	0.582	0.298–1.139	0.114
	53	TT	1.87	35.8	45.3	15.1	3.8						
Difficulty sleeping	177	NT	1.96	27.7	52.5	15.8	4.0	1.256	0.653–2.415	0.494	1.021	0.433–2.404	0.963
	40	TT	2.05	22.5	55.0	17.5	5.0						
Feeling bloated	73	NT	2.00	26.0	54.8	12.3	6.8	0.635	0.212–1.906	0.418	0.501	0.123–2.040	0.335
	18	TT	1.78	38.9	44.4	16.7	0.0						
Problems with urination	49	NT	1.63	49.0	42.9	4.1	4.1	—	—	—	—	—	—
	8	TT	2.25	12.5	62.5	12.5	12.5						
Vomiting	42	NT	1.83	38.1	47.6	7.1	7.1	—	—	—	—	—	—
	13	TT	1.85	30.8	53.8	15.4	0.0						
Shortness of breath	43	NT	1.49	55.8	39.5	4.7	0.0	—	—	—	—	—	—
	11	TT	2.00	27.3	54.5	9.1	9.1						
Diarrhea	95	NT	2.04	28.4	45.3	20.0	6.3	1.078	0.573–2.028	0.815	1.169	0.497–2.751	0.721
	37	TT	2.03	18.9	59.5	21.6	0.0						
Feeling sad	94	NT	1.69	41.5	50.0	6.4	2.1	—	—	—	—	—	—
	33	TT	1.70	39.4	51.5	9.1	0.0						
Sweats	58	NT	1.59	50.0	43.1	5.2	1.7	—	—	—	—	—	—
	13	TT	2.00	30.8	46.2	15.4	7.7						
Worrying	111	NT	1.77	36.9	51.4	9.9	1.8	1.981	0.925–4.242	0.078	2.414	0.885–6.585	0.085
	29	TT	2.00	17.2	69.0	10.3	3.4						
Problems with sexual interest	65	NT	2.49	10.8	44.6	29.2	15.4	0.540	0.149–1.955	0.348	0.184	0.033–1.015	0.052
	18	TT	2.17	33.3	27.8	27.8	11.1						
Itching	49	NT	1.65	44.9	44.9	10.2	0.0						
	17	TT	2.00	23.5	52.9	23.5	0.0						

Table 5 (*continued*)

Table 5 (*continued*)

Symptom	Samplesize	Rx group	Mean score	Severity ratings† (%)				Unadjusted values TT			Adjusted values TT+		
				1	2	3	4	OR	CI	P value	OR	CI	P value
Lack of appetite	135	NT	2.04	23.7	53.3	18.5	4.4	0.758	0.378–1.518	0.434	0.890	0.399–1.984	0.776
	39	TT	1.92	30.8	48.7	17.9	2.6						
Dizziness	82	NT	1.41	64.6	30.5	3.7	1.2	—	—	—	—	—	—
	20	TT	1.80	50.0	30.0	10.0	10.0						
Difficulty swallowing	53	NT	1.81	41.5	41.5	11.3	5.7	—	—	—	—	—	—
	19	TT	1.47	57.9	36.8	5.3	0.0						
Feeling irritable	104	NT	1.68	43.3	47.1	7.7	1.9	—	—	—	—	—	—
	26	TT	1.77	30.8	65.4	0.0	3.8						
Mouth sores	60	NT	1.77	40.0	48.3	6.7	5.0	—	—	—	—	—	—
	16	TT	1.63	50.0	37.5	12.5	0.0						
Change in way food tastes	139	NT	2.22	20.1	50.4	17.3	12.2	0.443	0.220–0.894	0.023	0.410	0.178–0.941	0.035
	40	TT	1.83	37.5	45.0	15.0	2.5						
Weight loss	79	NT	1.68	46.8	40.5	10.1	2.5	—	—	—	—	—	—
	24	TT	1.63	50.0	41.7	4.2	4.2						
Hair loss	118	NT	1.75	40.7	46.6	10.2	2.5	1.049	0.412–2.672	0.919	1.518	0.562–4.101	0.410
	32	TT	1.91	46.9	31.3	6.3	15.6						
Constipation	119	NT	1.94	30.3	48.7	17.6	3.4	1.239	0.522–2.940	0.627	1.209	0.463–3.349	0.716
	31	TT	2.03	32.3	35.5	29.0	3.2						
Swelling of arms or legs	16	NT	2.00	31.3	43.8	18.8	6.3	—	—	—	—	—	—
	2	TT	3.00	0.0	0.0	100.0	0.0						
I don't look like myself	70	NT	1.86	41.4	37.1	15.7	5.7	4.183	1.547–11.313	0.005	5.643	1.228–25.923	0.026
	19	TT	2.53	10.5	42.1	31.6	15.8						
Changes in skin	94	NT	1.81	39.4	43.6	13.8	3.2	2.574	1.171–5.659	0.019	2.473	0.929–6.586	0.070
	36	TT	2.22	19.4	50.0	19.4	11.1						
Hot flashes	42	NT	1.81	42.9	40.5	9.5	7.1	—	—	—	—	—	—
	12	TT	1.75	33.3	58.3	8.3	0.0						
Chest tightness	29	NT	1.52	58.6	34.5	3.4	3.4	—	—	—	—	—	—
	5	TT	1.60	40.0	60.0	0.0	0.0						
Difficulty breathing	30	NT	1.47	60.0	33.3	6.7	0.0	—	—	—	—	—	—
	8	TT	1.88	37.5	37.5	25.0	0.0						
Abdominal cramps	88	NT	1.91	29.5	53.4	13.6	3.4	0.627	0.229–1.717	0.364	0.448	0.127–1.577	0.211
	21	TT	1.76	42.9	42.9	9.5	4.8						
Increased appetite	51	NT	1.71	37.3	54.9	7.8	0.0	—	—	—	—	—	—
	13	TT	1.77	23.1	76.9	0.0	0.0						
Weight gain	49	NT	1.43	65.3	28.6	4.1	2.0	—	—	—	—	—	—
	9	TT	1.56	44.4	55.6	0.0	0.0						

Additional six symptoms not included on the original MSAS are: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, and weight gain. Symptom severity data were not analyzed if <15 responses were available in the upper two categories. †, severity ratings = slight [1], moderate [2], severe [3], very severe [4]; +, covariates in the regression analyses included: age, time since cancer diagnosis, number of metastatic sites including lymph node involvement, number of prior cancer treatments, GI cancer diagnosis, CTX treatment regimen. CI, confidence interval; NT, no targeted therapy; OR, odds ratio; Rx, treatment, TT, targeted therapy; MSAS, Memorial Symptom Assessment Scale; GI, gastrointestinal.

Table 6 Differences between patients who received CTX alone or CTX with TT in rankings of symptoms with the highest distress scores

Rank	NT	Mean score[a]	TT	Mean score[a]
1	Problems with sexual interest or activity	2.09	Problems with urination	2.67
2	Lack of energy	1.88	I don't look like myself	2.53
3	Changes in the way food tastes	1.83	Hair loss	2.06
4	Pain	1.78	Constipation	2.03
5	Diarrhea	1.78	Vomiting	2.00
6	Feeling bloated	1.73	Swelling	2.00
7	Nausea	1.69	Worrying	1.97
8	Difficulty sleeping	1.67	Lack of energy	1.91
9	Numbness or tingling in hands or feet	1.66	Shortness of breath	1.91
10	Hair loss	1.62	Feeling nervous	1.88

Additional six symptoms not included on the original MSAS: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, weight gain. [a], distress ratings = not at all [0], a little bit [1], somewhat [2], quite a bit [3], very much [4]. MSAS, Memorial Symptom Assessment Scale; TT, targeted therapy; NT, no targeted therapy.

agent treatment for non-small cell lung cancer (47), no between group differences in fatigue occurrence rates were found. Finally, fatigue, feeling drowsy, and sleep disturbance were reported in previous studies to be part of a symptom cluster (48,49). Given that all three symptoms had higher occurrence rates in the patients who received only CTX suggests that when these three symptoms do occur they may interact with each other and result in a higher symptom burden.

The occurrence of cough in our study was similar to previous reports that ranged from 15.8% (27) to 28.0% (29). Of note, while the overall occurrence rate for cough was relatively low in our study (i.e., 23.5%), patients on TT had a 65.4% decrease in the odds of reporting cough. While the occurrence of comorbid lung disease or lung metastasis was similar in both treatment groups, the occurrence rate for esophageal cancer was higher in the CTX alone group (6.6%) compared to the TT group (3.5%). Given that esophageal cancer is associated with gastro-esophageal reflux disease (GERD) and chronic cough is a common symptom in patients with GERD (50), the differential occurrence rates for cough may be partially explained by the different rates of esophageal cancer in the two treatment groups.

Symptom severity

None of the symptoms that had significant between group differences in occurrence rates had differences in severity scores. However, the severity scores for dry mouth and change in the way food tastes were significantly lower in the TT group. For the total sample, mean severity scores for dry mouth (i.e., 1.79) and change in the way food tastes (i.e., 2.12) were similar to those reported by Yan and colleagues (i.e., 1.66 and 2.29, respectively) (27). However, when treatment group differences in the severity rates for both of these symptoms were evaluated, patients on TT were 73.2% and 59.0% less likely to report a higher severity score for dry mouth and change in the way food tastes, respectively.

Consistent with previous studies (51,52), patients receiving CTX experience significant changes in the way food tastes and dry mouth, that peak after the administration of CTX. In addition, in another study (53), the severity of these two symptoms were moderately correlated ($r=0.425$, $P\leq0.01$). However, no studies were identified that evaluated the severity of these two symptoms in patients on TT. Most of the previous studies of TT used the CTCAE scoring criteria, which only evaluates "mucositis/stomatitis" (54,55). In both treatment groups, the severity scores for taste changes and dry mouth were in the moderate range. Because these two symptoms can interfere with food and fluid intake, both groups of patients warrant ongoing assessments to evaluate for and manage nutritional deficits (56).

While patients on TT reported lower severity scores for change in the way food tastes and dry mouth, these patients reported a higher severity score for "I don't look like myself". Patients on targeted therapies were 5.6 times more

Table 7 Differences in DISTRESS ratings between patients who received CTX alone (n=304) or CTX with TT (n=93)

Symptom	Sample size	Rx group	Mean score	Distress ratings† (%)				Unadjusted values TT			Adjusted values TT+		
				0	1	2	3+4	OR	CI	P value	OR	CI	P value
Difficulty concentrating	130	NT	1.45	12.3	49.2	23.8	14.6	0.857	0.422–1.742	0.671	0.854	0.333–2.193	0.743
	41	TT	1.37	14.6	51.2	19.5	14.6						
Pain	154	NT	1.78	7.8	38.3	27.9	25.9	1.232	0.651–2.333	0.522	1.135	0.506–2.550	0.758
	44	TT	1.86	11.4	27.3	29.5	31.8						
Lack of energy	227	NT	1.88	11.9	26.9	30.8	30.4	1.093	0.648–1.844	0.738	0.965	0.496–1.878	0.916
	58	TT	1.91	10.3	25.9	32.8	31.0						
Cough	70	NT	1.03	28.6	48.6	15.7	7.1	—	—	—	—	—	—
	13	TT	1.00	46.2	15.4	30.8	7.7						
Feeling nervous	70	NT	1.44	11.4	51.4	21.4	15.8	2.284	0.634–8.234	0.207	2.503	0.424–14.794	0.311
	16	TT	1.88	18.8	18.8	25.0	37.6						
Dry mouth	118	NT	1.18	28.8	41.5	16.9	12.7	0.781	0.352–1.733	0.543	0.455	0.153–1.353	0.157
	26	TT	1.00	34.6	38.5	19.2	7.7						
Nausea	164	NT	1.69	9.1	37.8	33.5	19.5	1.188	0.601–2.348	0.621	1.139	0.529–2.452	0.739
	43	TT	1.77	14.0	27.9	32.6	25.6						
Feeling drowsy	175	NT	1.21	26.3	39.4	23.4	10.9	1.183	0.628–2.228	0.604	0.956	0.468–1.956	0.902
	39	TT	1.31	23.1	38.5	28.2	10.2						
Numbness/tingling in hands/feet	189	NT	1.66	14.3	36.5	26.5	22.7	0.814	0.459–1.441	0.479	0.754	0.407–1.397	0.369
	55	TT	1.53	18.2	38.2	21.8	21.9						
Difficulty sleeping	176	NT	1.67	11.9	38.6	26.1	23.3	1.414	0.737–2.716	0.297	1.012	0.426–2.406	0.979
	40	TT	1.85	15.0	20.0	37.5	27.5						
Feeling bloated	74	NT	1.73	12.2	33.8	32.4	21.7	0.710	0.264–1.907	0.497	0.432	0.100–1.870	0.262
	18	TT	1.56	11.1	50.0	22.2	16.6						
Problems with urination	49	NT	1.39	26.5	28.6	30.6	14.3	—	—	—	—	—	—
	9	TT	2.67	0.0	11.1	33.3	55.5						
Vomiting	42	NT	1.60	14.3	38.1	33.3	14.3	—	—	—	—	—	—
	13	TT	2.00	7.7	30.8	30.8	30.8						
Shortness of breath	44	NT	1.32	13.6	52.3	22.7	11.4	—	—	—	—	—	—
	11	TT	1.91	0.0	45.5	36.4	18.2						
Diarrhea	98	NT	1.78	15.3	29.6	27.6	27.5	0.776	0.395–1.484	0.429	0.802	0.295–2.183	0.666
	37	TT	1.59	16.2	35.1	27.0	21.6						
Feeling sad	94	NT	1.49	14.9	40.4	31.9	12.8	1.527	0.746–3.127	0.247	1.936	0.718–5.218	0.192
	32	TT	1.69	6.3	37.5	40.6	15.6						
Sweats	58	NT	1.14	27.6	43.1	19.0	10.3	—	—	—	—	—	—
	12	TT	1.67	16.7	41.7	8.3	33.3						
Worrying	111	NT	1.54	10.8	46.8	26.1	16.2	2.114	1.020–4.382	0.044	2.133	0.782–5.816	0.139
	29	TT	1.97	0.0	41.4	27.6	31.0						
Problems with sexual interest	65	NT	2.09	9.2	26.2	27.7	36.9	0.713	0.268–1.899	0.499	0.592	0.116–3.027	0.529
	18	TT	1.78	16.7	27.8	16.7	38.9						
Itching	49	NT	1.49	18.4	36.7	26.5	18.4	—	—	—	—	—	—
	17	TT	1.59	11.8	41.2	29.4	17.7						

Table 7 (*continued*)

Table 7 (*continued*)

Symptom	Sample size	Rx group	Mean score	Distress ratings† (%)				Unadjusted values TT			Adjusted values TT+		
				0	1	2	3+4	OR	CI	P value	OR	CI	P value
Lack of appetite	137	NT	1.53	21.2	28.5	31.4	19.0	0.858	0.466–1.582	0.625	0.915	0.463–1.809	0.798
	39	TT	1.46	20.5	35.9	28.2	15.4						
Dizziness	83	NT	1.20	15.7	57.8	18.1	8.4	—	—	—	—	—	—
	20	TT	1.75	15.0	30.0	35.0	20.0						
Difficulty swallowing	53	NT	1.51	17.0	39.6	26.4	16.9	—	—	—	—	—	—
	18	TT	1.56	11.1	38.9	33.3	16.7						
Feeling irritable	105	NT	1.37	13.3	51.4	22.9	12.4	2.201	1.055–4.589	0.035	1.677	0.619–4.546	0.310
	25	TT	1.76	0.0	48.0	32.0	20.0						
Mouth sores	61	NT	1.49	14.8	45.9	21.3	18.1	—	—	—	—	—	—
	14	TT	1.36	14.3	50.0	21.4	14.3						
Change in way food tastes	140	NT	1.83	15.0	28.6	27.1	29.2	0.721	0.397–1.309	0.282	0.679	0.318–1.452	0.318
	39	TT	1.59	12.8	43.6	20.5	23.0						
Weight loss	79	NT	1.44	25.3	30.4	22.8	21.5	0.804	0.287–2.251	0.678	0.801	0.213–3.003	0.742
	22	TT	1.36	36.4	22.7	18.2	22.7						
Hair loss	117	NT	1.62	19.7	30.8	24.8	24.7	1.788	0.783–4.081	0.168	2.364	0.895–6.240	0.082
	31	TT	2.06	12.9	32.3	16.1	38.7						
Constipation	120	NT	1.58	15.8	37.5	26.7	20.0	1.918	0.803–4.581	0.143	1.721	0.611–4.850	0.304
	30	TT	2.03	13.3	26.7	26.7	33.3						
Swelling of arms or legs	16	NT	1.50	31.3	12.5	31.3	25.0	—	—	—	—	—	—
	2	TT	2.00	0.0	50.0	0.0	50.0						
I don't look like myself	71	NT	1.62	15.5	38.0	23.9	22.6	4.238	1.405–12.787	0.010	5.939	0.992–35.557	0.051
	19	TT	2.53	5.3	21.1	15.8	57.9						
Changes in skin	94	NT	1.52	19.1	37.2	24.5	19.1	1.640	0.773–3.478	0.197	1.617	0.611–4.276	0.333
	36	TT	1.86	16.7	27.8	25.0	30.6						
Hot flashes	41	NT	1.29	29.3	39.0	17.1	14.6	—	—	—	—	—	—
	12	TT	1.50	16.7	50.0	8.3	25.0						
Chest tightness	31	NT	1.26	22.6	41.9	22.6	12.9	—	—	—	—	—	—
	5	TT	1.40	20.0	60.0	0.0	20.0						
Difficulty breathing	33	NT	1.18	27.3	39.4	21.2	12.1	—	—	—	—	—	—
	8	TT	1.88	12.5	37.5	12.5	37.5						
Abdominal cramps	90	NT	1.60	10.0	40.0	33.3	16.6	0.619	0.195–1.965	0.416	0.451	0.124–1.636	0.226
	21	TT	1.48	19.0	47.6	9.5	23.8						
Increased appetite	54	NT	0.76	55.6	20.4	18.5	5.6	—	—	—	—	—	—
	13	TT	0.38	61.5	38.5	0.0	0.0						
Weight gain	51	NT	1.00	54.9	17.6	7.8	19.6	—	—	—	—	—	—
	9	TT	0.56	66.7	11.1	22.2	0.0						

Additional six symptoms not included on the original MSAS are: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, and weight gain. Symptom distress data were not analyzed if <15 responses were available in the upper two categories. †, distress ratings = not at all [0], a little bit [1], somewhat [2], quite a bit [3], very much [4], +, covariates in the regression analyses included: age, time since cancer diagnosis, number of metastatic sites including lymph node involvement, number of prior cancer treatments, GI cancer diagnosis, CTX treatment regimen. CI, confidence interval; NT, no targeted therapy; OR, odds ratio; Rx, treatment, TT, targeted therapy; MSAS, Memorial Symptom Assessment Scale; GI, gastrointestinal.

likely to report a higher severity score for the symptom "I don't look like myself". While the hair loss associated with CTX can impact a patient's body image (57), the between group differences in this symptom may be directly related to the skin toxicities associated with TT. In one study (58), 41% of patients with advanced CRC treated with TT reported psychological distress caused by a rash. When asked how the rash affected their willingness to go out into public, 25% of the patients answered "somewhat" and 22% answered "very much". Additional research is warranted using a symptom assessment scale that evaluates specific skin toxicities to determine their impact on the body image of patients who receive targeted therapies.

Symptom distress

While in the bivariate analyses, patients on CTX with targeted therapies reported higher distress scores for worrying, feeling irritable, and "I don't look like myself", these differences did not remain significant in the multivariable analyses. Only one study was found that reported mean MSAS distress scores in a sample of Chinese patients receiving treatment for GI cancers (27). The five symptoms with the highest distress scores were sleep disturbance (2.06), change in the way food tastes (1.93), hair loss (1.92), lack of energy (1.82), and shortness of breath (1.79). In our study, except for shortness of breath, patients who received CTX alone reported that the same symptoms were the most distressing and the distress scores were comparable. However, in the patients in our study who received TT, only three of the five most distressing symptoms were similar to those reported by Yan and colleagues (27) (i.e., hair loss, lack of energy, shortness of breath). In fact, the two most distressing symptoms reported by patients on TT (i.e., problems with urination, "I don't look like myself") were not listed in the top ten most distressing symptoms by patients who received only CTX in the study by Yan and colleagues (27).

Consistent with previous studies (27,29), in both treatment groups in our study, the symptoms with the highest distress scores did not have the highest occurrences rates or severity scores. An evaluation of symptom distress is important because unrelieved distress can interfere with patients' willingness to obtain or continue treatment, which can impact overall survival. Our findings suggest that clinicians need to assess multiple dimensions of the symptom experience in patients with GI cancers and attempt to manage the most common, severe, and distressing symptoms.

Conclusions

While significant between groups differences in patients' symptom experiences were identified, patients in both treatment groups reported an average of 12.5 symptoms during the week following CTX administration. This finding is consistent with previous reports that found that patients who received CTX for CRC (29) and patients with advanced cancer (59) reported between 10.3 and 11.7 symptoms. Therefore, both groups of patients warrant ongoing assessments to optimally manage their unrelieved symptoms.

Several study limitations need to be acknowledged. Information on the cumulative doses of CTX and TT received by these patients prior to enrollment were not collected. Because the multidimensional symptom instrument utilized in the study was not developed to evaluate symptoms experienced by patients receiving TT, additional symptoms that are specific to TT (e.g., pruritis associated with rash, xerosis, pain associated with paronychia) (60) warrant evaluation in future studies. In addition, the varied distribution of GI cancer diagnoses and CTX regimens makes it difficult to distinguish specific symptoms associated with these characteristics. Finally, while the total sample was large, the number of patients on TT was relatively small. Therefore, differences in the symptom burden associated with specific targeted therapies could not be evaluated. Additional differences may emerge in future studies with a larger sample of patients on CTX with TT.

Findings from this study provide new information regarding symptoms experienced by GI cancer patients receiving CTX with and without TT. Clinicians can use this information to better assess and manage symptoms in both treatment groups. Future studies need to evaluate for differences between these two treatment groups in changes over time in occurrence, severity, and distress of these symptoms. These findings will allow for the development and testing of more tailored symptom management interventions.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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