Overactive Bladder Symptoms in Cancer Patients Undergoing Chemotherapy

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Objectives: To determine if chemotherapy contributes to the development of overactive bladder (OAB) in female cancer patients.

Methods: A prospective, longitudinal study was conducted from 2017 to 2023 at Mount Auburn Hospital to assess the effects of chemotherapy on the development of OAB. Sixty-five female patients diagnosed with nonmetastatic breast cancer, lung cancer, or lymphoma were asked to complete 5 validated questionnaires regarding bladder symptoms just before starting chemotherapy and again at 6 weeks, 3 months, 6 months, and 12 months.

Results: Fifty-eight patients completed the study. Overall, we detected no significant increase in OAB symptoms at any time point relative to baseline. However, an analysis of the data according to different chemotherapy regimens revealed that patients being treated with human epidermal growth factor receptor-2 (HER2) monoclonal antibodies, either trastuzumab alone or in combination with pertuzumab, had significantly higher scores on the questionnaires after the start of chemotherapy. When the HER2-treatment group was further subdivided, we found that patients receiving both monoclonal antibodies, trastuzumab, and pertuzumab, reported more significant urinary tract discomfort and changes in quality of life, particularly at the 6-month and 12-month time points.

Conclusions: We conclude from our study that women receiving both trastuzumab and pertuzumab for HER2-positive breast cancer may experience an increase in OAB symptoms during the course of their treatment.

Key Words: chemotherapy, HER2, overactive bladder, breast

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Approximately, 17% of American woman report symptoms of overactive bladder (OAB), a clinical diagnosis that involves bothersome feelings of urinary urgency and leakage without signs of infection or neurological damage.[1–3] OAB has both a physical component involving incontinence and a quality-of-life (QOL) component.[4] Incontinence is often triggered by physical stress, such as coughing or walking, as well as urge-type triggers, such as hand washing or cold weather. Incontinence can also be associated with discomfort, including irritation, pain, and feelings of obstruction. QOL issues stem from concerns of annoyance or embarrassment of OAB symptoms during physical recreation, long trips, social activities, or while asleep. Age is also a factor in the development of OAB, and in women this typically coincides with menopause.[4–6] Epidemiologic research reveals that OAB sufferers avoid discussing symptoms with their providers, leading to undertreatment in the general population.[2]

Urogynecologists at our institution noted an increase in the number of patients complaining of new-onset OAB after starting chemotherapy, prompting us to question whether cytotoxic chemotherapy contributes to the development of OAB symptoms. In order to eliminate the possible effects of oncological surgery in the pelvis, we focused on women with a recent diagnosis of nonmetastatic breast, lung, or lymphoma who were about to start chemotherapy. We aimed to determine the incidence of new-onset or worsening OAB symptoms after the initiation of cytotoxic chemotherapy and followed these symptoms over a period of 12 months.

METHODS

This is a prospective longitudinal cohort study of cancer patients undergoing chemotherapy at Mount Auburn Hospital (MAH) from 2017 to 2023, approved by the MAH institutional review board. Women diagnosed with nonmetastatic breast cancer, lung cancer, or lymphoma and presenting for cytotoxic chemotherapy were eligible. Participants completed 5 validated questionnaires regarding bladder symptoms upon starting chemotherapy, including: the Medical, Epidemiologic, and Social Aspects of Aging (MESA) questionnaire, the Urogenital Distress Inventory Short Form (UDI-6), the Incontinence Impact Questionnaire-Short Form (IIQ-7), 2 parts of the Overactive Bladder Questionnaire Short Form (OAB-q SF), and the Patient Global Impression of Severity (PGI-S). Patients completed these questionnaires again at 6 weeks, 3 months, 6 months, and 12 months.

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Raw data available upon request, sent to the corresponding author.

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Interpretation of Questionnaires and Statistics

MESA SUI 1-9 and MESA UUI 10-15

The MESA questionnaire consists of 2 separate parts. Responses are scored from 0 to 3, increasing with frequency of symptoms. The first 9 questions address stress urinary incontinence (SUI) and the last 6 address urge urinary incontinence (UUI).[7]

UDI-6 and IIQ-7

The UDI-6 consists of 6 questions examining 3 aspects of urinary distress, including irritative symptoms, obstructive/discomfort, and stress symptoms. Responses are scored from 0 to 3, increasing with symptom intensity. The IIQ-7 consists of 7 questions examining incontinence impact on QOL, including questions about activity, travel, social relationships, and emotional health.[8,9] Responses are scored from 0 to 3, increasing with negative impact on QOL.

OAB-q SF SB and OAB-q SF HRQOL

The OAB-q short form (OAB-q SF) includes 2 subscales. The OAB-q SF Symptom Bother (OAB-q SF SB) comprises 6 questions directed at discomfort and nocturia. Responses are scored 1 to 6, increasing with symptom bother. The OAB-q SF Health-Related Quality of Life (OAB-q SF HRQOL) comprises 13 questions directed at the impact of OAB on QOL, with questions directed towards topics such as relationships with family, interference with physical activity, embarrassment about symptoms, and the ability to get a good night's sleep. Responses are scored 1 to 6, increasing with frequency of negative impact on QOL. These 2 scores are reported separately.[10,11]

PGI-S

The PGI-S questionnaire asks a single question: "how is your urinary tract condition now?" The answers are scaled as 1 = normal, 2 = mild, 3 = moderate, and 4 = severe.[12]

Statistical Analyses

Continuous data are summarized using the median and interquartile range (IQR). Group comparisons were performed using the Kruskal-Wallis test, and longitudinal paired data between baseline and other time points were compared using the Wilcoxon signed-rank test. Subgroup analysis was conducted for the human epidermal growth factor receptor-2 (HER2) treatment subgroup. A 2-tailed $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Stata software (v18.1, StataCorp LLC, College Station, TX).

RESULTS

Of the 70 patients eligible for inclusion in the study, 65 consented. One patient was removed from the study due to an adverse reaction to chemotherapy, 1 was ineligible, 2 withdrew consent, and 2 were lost to follow-up. Fifty-nine patients completed the study, but the baseline data of 1 patient was incomplete, and therefore, excluded from the analysis. The median age of the remaining 58 patients was 57. The majority of patients had breast cancer (87.9%), while 8.6% had lymphoma, and 3.4% had lung cancer (Table 1). Participants received 1 of 4 general courses of chemotherapy (Table 2). Cyclophosphamide was the most commonly used agent, with 68% of participants treated with this cytotoxic compound.

TABLE 1. Patient Demographics

Variable	Patients (N = 58)
Age in years	
Median (IQR)	57 (49–66)
Full range	31–83
Race	
White	51/58 (87.9%)
Black	3/58 (5.2%)
Asian	2/58 (3.4%)
Other/unknown	2/58 (3.4%)
Cancer diagnosis	
Breast	51/58 (87.9%)
Lymphoma	5/58 (8.6%)
Lung	2/58 (3.4%)

IQR indicates interquartile range; N, number.

For the whole cohort, no change in OAB symptoms was detected over time when compared with baseline; however, the PGI-S data revealed mild and moderate OAB symptoms at several time points (Table 3). As PGI-S results strongly correlated with the results from other questionnaires (Table 4), an analysis was performed to determine if the drug regimen had any impact on OAB symptoms.

No increases or changes in OAB complaints were observed from patients undergoing the doxorubicin, cyclophosphamide/paclitaxel (DC/P), or the docetaxel and cyclophosphamide (DC) regimens. As fewer than 10 patients were treated for lung or lymphoma cancer, statistical analyses focused on this subgroup with their varied treatment regimens were not possible. However, we did determine that patients specifically undergoing HER2 therapy complained of increased OAB symptoms (Table 5). Age was not a significant factor and was comparable among the treatment groups (Table 2). Relative to baseline, the HER2-treatment group reported incontinence at 6 weeks and 3 months on the MESA SUI, urinary distress at 6 weeks on the UDI-6, plus QOL issues at 3 months on the IIQ-7 and at 6 weeks and 6 months on the OAB sf QOL questionnaires.

We next addressed whether patients receiving both the HER2 treatments, trastuzumab and pertuzumab, versus trastuzumab alone were equally affected. The patients treated with both antibodies (HER2-treatment subgroup) reported more OAB symptoms than those receiving just trastuzumab, with statistically significant findings on the OAB-q SF HRQOL questionnaires at 12 months and on the OAB-q SF SB at 6 weeks, 6 months, and 12 months (Table 6).

Interestingly, the individual questionnaires revealed that the most common patient's complaints were increased nocturia and bother associated with needing to use the bathroom at night (data not shown).

CONCLUSION

Our findings implicate the inhibition of HER2 receptor function through monoclonal antibodies as a trigger for OAB symptoms in oncology patients. The results of our study both support and expand upon a previous finding that links anti-HER2 monoclonal antibodies to OAB.[13] We were able to rule out age and taxanes as contributing factors. We were also able to rule out cyclophosphamides, the long-term use of which is associated with kidney and bladder irritation;[14] however, the short 8-week course

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TABLE 2. Drug Regimens

Regimen	n	Median age in years (IQR) and full range	Drugs at the time of questionnaire administration			
			6 wk	3 mo	6 mo	12 mo
DC/P	20	53 (49–58) 32–77	Doxorubicin/ cyclophosphamide	Paclitaxel		
DC	17	54 (47–66) 40–69	Docetaxel/ cyclophosphamide			
HER2	16	56 (49–56) 31–76	Trastuzumab +/− pertuzumab	Trastuzumab +/− pertuzumab	Trastuzumab,+/− pertuzumab	Trastuzumab
Non-breast	7	75 (66–79) 64–83	Non-breast regimen	Non-breast regimen		

Regimens: DC/P: doxorubicin and cyclophosphamide given every 2 weeks ×4 cycles followed by paclitaxel; DC: docetaxel and cyclophosphamide; HER2: human epidermal growth factor receptor-2 monoclonal antibodies trastuzumab and/or pertuzumab; non-breast: varied regimens for lung and lymphoma cancer, some using cyclophosphamide along with cisplatin or vinblastine and others using the monoclonal antibody rituximab.

IQR indicates interquartile range; mo, months; n, number; wk, weeks.

TABLE 3. Summary Data from All Questionnaires at Baseline and Clinical Follow-Up Time Points

Questionnaire	Baseline	6 wk	3 mo	6 mo	12 mo
MESA SUI	14.8 (3.7–22.2)	14.8 (7.4–25.9)	14.8 (7.4–33.3)	11.1 (7.4–22.2)	11.1 (3.7–18.5)
MESA UUI	5.6 (0–16.7)	11.1 (0–22.2)	11.1 (0–16.7)	5.6 (0–16.7)	5.6 (0–22.2)
UDI -6	11.1 (5.6–22.2)	11.1 (5.6–22.2)	16.7 (5.6–27.8)	11.1 (5.6–22.2)	16.7 (0–22.2)
IIQ-7	0 (0–0)	0 (0–4.8)	0 (0–4.8)	0 (0–0)	0 (0–4.8)
OAB-q SF SB	27.8 (22.3–33.4)	27.8 (22.3–39)	30.6 (20.9–44.5)	25.1 (22.3–33.4)	30.6 (22.3–41.8)
OAB-q SF HRQOL	20.6 (19.3–25.7)	23.1 (18–30.8)	20.6 (18–28.3)	21.8 (18–27)	21.8 (18–33.4)
PGI-S					
Normal	48/57 (84.2%)	36/55 (65.5%)	35/55 (63.6%)	44/55 (80%)	33/51 (64.7%)
Mild	6/57 (10.5%)	12/55 (21.8%)	13/55 (23.6%)	6/55 (10.9%)	14/51 (27.5%)
Moderate	2/57 (3.5%)	7/55 (12.7%)	7/55 (12.7%)	5/55 (9.1%)	4/51 (7.8%)
Severe	1/57 (1.8%)	0/55 (0%)	0/55 (0%)	0/55 (0%)	0/51 (0%)

Data are presented as median (IQR), except for the PGI-S for which data are presented as number of responses/total number of responses and (percentages) for each time point.

Note: A high score for OAB-q SF HRQOL reflects a poor quality of life.

IIQ-7 indicates incontinence impact questionnaire-7; IQR, interquartile range; MESA SUI, medical, epidemiologic, and social aspects of aging stress urinary incontinence; MESA UUI, medical, epidemiologic, and social aspects of aging urgency urinary incontinence; mo, months OAB-q SF HRQOL, overactive bladder questionnaire short form health-related quality of life; OAB-q SF SB, overactive bladder questionnaire short form symptom bother; PGI-S, patient global impression of severity; UDI-6, urogenital distress inventory-6; wk, weeks.

TABLE 4. Comparison of PGI-S With the Other Questionnaires

Questionnaire	PGI-S				
	Normal (n = 196 responses)	Mild (n = 51 responses)	Moderate (n = 25 responses)	Severe (n = 1 response)	*P*
MESA SUI	11.1 (3.7–18.5)	19 (7.4–33)	37 (14.8–48.1)	48.1	< 0.001*
MESA UUI	0 (0–11.1)	16.7 (0–33)	33.3 (16.7–38.9)	11.1	< 0.001*
UDI -6	11.1 (0–16.7)	22.2 (16.7–27.8)	33.3 (22.2–44.4)	61.1	< 0.001*
IIQ-7	0 (0–0)	4.8 (0–14.3)	9.5 (4.8–38.1)	4.8	< 0.001*
OAB-q SF SB	22.3 (19.5–30.6)	39 (30.6–44.5)	61.2 (55.7–64)	69.6	< 0.001*
OAB-q SF HRQOL	19.3 (18–23.1)	27 (21.8–33.4)	45 (34.7–56.5)	71.9	< 0.001*

*Statistically significant.

Data are presented as median change from baseline (IQR).

P-values were calculated using the Kruskal-Wallis test for comparing change between independent PGI-S groups.

A high score for OAB-q SF HRQOL reflects a poor quality of life.

IIQ-7 indicates incontinence impact questionnaire-7; IQR, interquartile range; MESA SUI, medical, epidemiologic, and social aspects of aging stress urinary incontinence; MESA UUI, medical, epidemiologic, and social aspects of aging urgency urinary incontinence; n, number; OAB-q SF HRQOL, overactive bladder questionnaire short form health-related quality of life; OAB-q SF SB, overactive bladder questionnaire short form symptom bother; PGI-S, patient global impression of severity; UDI-6, urogenital distress inventory-6.

TABLE 5. Changes in Questionnaire Scores Relative to Baseline for the HER2-Treatment Group

Change from baseline to time point	MESA SUI	MESA UUI	UDI -6	IIQ-7	OAB-q SF SB	OAB-q SF HRQOL
6 wk	**3.7 (0–22.2)**	0 (0–16.7)	**5.6 (5.6–22.2)**	0 (0–14.3)	2.8 (−2.8-22.3)	**1.3 (0–6.4)**
	P*=0.039	*P* =0.335	***P* =0.016***	*P* =0.081	*P* =0.053	***P* =0.036***
3 mo	**14.8 (0–26)**	5.6 (0–16.7)	5.6 (0–16.7)	**0 (0–14.3)**	5.6 (−2.8–11.1)	0 (−1.3–7.7)
	P*=0.011	*P* =0.052	*P* =0.103	***P*=0.043***	*P* =0.073	*P* =0.199
6 mo	3.7 (−4–11.1)	5.6 (0–5.6)	5.6 (−5.6–16.7)	0 (0–0)	2.8 (0–13.9)	**2.6 (0–6.4)**
	P =0.28	*P* =0.067	*P* =0.161	*P* =0.268	*P* =0.059	***P*=0.016***
12 mo	0 (−4–7.4)	5.6 (0–11.1)	0 (−5.6–11.1)	0 (0–0)	8.4 (−2.8–16.7)	2.6 (−1.3–7.7)
	P =0.575	*P* =0.199	*P* =0.528	*P* =0.502	*P* =0.059	*P* =0.08

*Bold values are statistically significant.
Data are presented as median change from baseline (IQR).
P-values were calculated using the Wilcoxon signed-rank test for paired data.
A high score for OAB-q SF HRQOL reflects a poor quality of life.
There is no systematic change following chemo initiation (baseline to each follow-up time point) in the questionnaire scores/scales.
HER2 indicates human epidermal growth factor receptor-2; IIQ-7, incontinence impact questionnaire-7; IQR, interquartile range; MESA SUI, medical, epidemiologic, and social aspects of aging stress urinary incontinence; MESA UUI, medical, epidemiologic, and social aspects of aging urgency urinary incontinence; mo, months; OAB-q SF HRQOL, overactive bladder questionnaire short form health-related quality of life; OAB-q SF SB, overactive bladder questionnaire short form symptom bother; UDI-6, urogenital distress inventory-6; wk, weeks.

that our patients completed would be unlikely to cause such a response.

In our HER2 treatment group, very few of our patients responded that they suffered from frequent symptoms or suffered a great deal from their bladder discomfort. Significant findings mostly fell in the moderate category. Besides a general reluctance to discuss bladder symptoms with health care providers, the relative discomfort of OAB symptoms may not have registered as greatly in comparison with chemotherapeutic side effects, coupled with the anxiety of a cancer diagnosis. In addition, cancer treatment may have altered lifestyle to such an extent that any changes in activity or enjoyment levels from OAB discomfort may have been undetectable.

Analysis of the trastuzumab and pertuzumab subgroup led to more significant OAB findings than trastuzumab alone. Trastuzumab administration continued throughout the course of the year, while treatment with pertuzumab ended by 6 months in all but 2 cases, where treatment lasted the entire year. We therefore expected that removing data from those treated with trastuzumab alone would reveal more significant complaints at the beginning of the year, yet it revealed bladder dysfunction at all time points, including at 1 year. As trastuzumab and pertuzumab target and bind different regions of the HER2 receptor to more effectively inhibit its activity,[15] this combination could have a greater and potentially longer-lasting impact on bladder function. Another possibility is that the HER2 monoclonal antibodies are working in conjunction with estrogen modifiers, such as tamoxifen or anastrozole, drugs commonly prescribed to prevent recurrence in estrogen receptor-positive breast cancer. In a study authored by Cheng and de Groat, it was shown that the risk of developing OAB increases in breast cancer survivors under the age of 40 who undergo estrogen deprivation therapy.[16] As 70% of the trastuzumab and pertuzumab HER2 subgroup also received estrogen antagonists for the last 6 months of the study, it is conceivable that this drug combination could be responsible for the bladder discomfort reported at 1 year.

Although monoclonal antibodies, such as trastuzumab and pertuzumab, are not cytotoxic, the bladder epithelium

TABLE 6. Changes in Questionnaire Scores Relative to Baseline for the HER2-treatment Subgroup

Change from baseline to	MESA SUI	MESA UUI	UDI -6	IIQ-7	OAB-q SF SB	OAB-q SF HRQOL
6 wk	**11.1 (0-22.2)**	0 (−5–22.2)	**8.3 (5.6–27.8)**	0 (0-14.3)	**8.4 (0–30.6)**	**3.2 (0–6.4)**
	[***P*=0.011***]	[*P* =0.436]	[***P*=0.016***]	[*P* =0.125]	[***P*=0.041***]	[***P*=0.018***]
3 mo	**20.4 (7.4–25.9)**	8.3 (0–33.3)	11.1 (0–16.7)	**2.4 (0-19)**	7 (2.8-36.2)	2.6 (0-15.4)
	[***P*=0.006***]	[*P* =0.177]	[*P* =0.102]	[***P*=0.028***]	[*P* =0.074]	[*P* =0.09]
6 mo	3.7 (−3.7–7.4)	5.6 (0–16.7)	2.8 (−5.6–16.7)	0 (0-0)	**2.8 (0–13.9)**	**4.5 (1.3–6.4)**
	[*P* =0.241]	[*P* =0.123]	[*P* =0.237]	[*P* =0.158]	[***P*=0.04***]	[***P*=0.008***]
12 mo	5.6 (−3.7–11.1)	6.3 (0–16.7)	2.8 (−5.6–16.7)	0 (0-0)	**11.1 (5.6–19.5)**	**6.4 (0–14.1)**
	[*P* =0.185]	[*P* =0.329]	[*P* =0.357]	[*P* =0.158]	[***P*=0.036***]	[***P*=0.025***]

*Statistically significant (values bolded).
Data are presented as median change from baseline (IQR).
P-values were calculated using the Wilcoxon signed-rank test for paired data.
A high score for OAB-q SF HRQOL reflects a poor quality of life.
HER2 indicates human epidermal growth factor receptor-2; IIQ-7, incontinence impact questionnaire-7; IQR, interquartile range; MESA SUI, medical, epidemiologic, and social aspects of aging stress urinary incontinence; MESA UUI, medical, epidemiologic, and social aspects of aging urgency urinary incontinence; mo, months; OAB-q SF HRQOL, overactive bladder questionnaire short form health-related quality of life; OAB-q SF SB, overactive bladder questionnaire short form symptom bother; UDI-6, urogenital distress inventory-6; wk, weeks.

expresses epidermal growth factor receptors (EGFR).[17] Likewise, estrogen receptors are found not only in the reproductive tract but also in the bladder and urethra.[18] Both classes of receptors regulate cellular processes that translate into healthy bladder function. EGFR present on the human bladder uroepithelium help regulate cell division, potassium channels and stretch exocytosis.[19,20] Changes in estrogen levels impact periurethral blood vessel development in women[21] and prostaglandin levels in the rabbit urinary bladder.[22] In bilateral ovariectomized mice, lower estrogen levels were linked to an increase in bladder collagen III, overproduction of which is thought to reduce bladder compliance.[23] Furthermore, lower estrogen levels resulted in an increase in the number of mechanosensitive channels in the bladder that function to increase voiding frequency.[23] The expression of these mechanosensitive channels is also regulated by circadian rhythms, a finding that possibly connects reduced estrogen levels with nocturia.[24] Together, this evidence suggests that inhibition of these important regulatory activities by HER2 monoclonal antibodies and estrogen inhibitors could translate into the onset of OAB.

In conclusion, we found that breast cancer patients treated with both HER2-receptor monoclonal antibodies, trastuzumab and pertuzumab experienced a mild to moderate increase in OAB symptoms. A larger study focused on HER2-positive breast cancer patients may detect time-dependent trends in the development of OAB symptoms and reveal whether symptoms subside following treatment. Such a finding would allow practitioners to reassure patients that their urinary tract discomfort will likely resolve after completion of therapy.

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