Association between Concomitant Use of Hydrochlorothiazide and Adverse Chemotherapy-Related Events among Older Women with Breast Cancer Treated with Cyclophosphamide

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ABSTRACT

Background: The pharmacy reference database, Micromedex, lists concomitant hydrochlorothiazide and cyclophosphamide use as a potential, major drug–drug interaction (DDI), although only one small, single-center study supports this claim. Our objective was to estimate associations between this potential DDI and two adverse chemotherapy-related events, neutropenia-related hospitalizations and treatment regimen discontinuation, among a cohort of women with breast cancer initiating adjuvant chemotherapy containing cyclophosphamide.

Methods: Using linked Surveillance, Epidemiology, and End Results Program (SEER)-Medicare data, we included women 66 years and older with breast cancer diagnosis between 2007 and 2011, who initiated a regimen containing cyclophosphamide. Risk ratios (RR) and 95% confidence intervals for adverse outcomes comparing women exposed versus unexposed to the potential DDI were assessed using modified multivariable Poisson regression adjusting for potential confounders.

Results: In total, 27% of women receiving cyclophosphamide treatment were exposed to concomitant hydrochlorothiazide, of which 11% experienced a neutropenia-related hospitalization and 21% discontinued their chemotherapy regimen prior to completion. Adjusted risks of both adverse events were similar between those exposed and unexposed to the potential DDI [neutropenia-related hospitalization: adjusted RR (aRR) = 0.92 (0.70–1.21); treatment discontinuation: aRR = 1.00 (0.96–1.05)].

Conclusions: Our results do not support an association between concomitant hydrochlorothiazide use and two clinically relevant adverse chemotherapy-related events.

Impact: Our results support reassessing and potentially lowering severity of this potential interaction in drug reference databases.

Introduction

Cyclophosphamide is a preferred agent in breast cancer treatment (1), and hydrochlorothiazide, a drug used to treat hypertension, is one of the most commonly used medications in the United States (2, 3). Pharmacy reference databases such as Micromedex (4) list hydrochlorothiazide and cyclophosphamide as a significant drug–drug interaction (DDI). However, this claim is supported by one study from 1981, including 14 women receiving breast cancer treatment and also taking a thiazide diuretic for hypertension (5). This study found that white blood cell counts, assessed weekly, were notably lower in cycles where women were treated with thiazide diuretics versus cycles where the same women were treated with other blood pressure medications (reserpine or propranolol), raising concerns that thiazide diuretics may enhance the myelosuppressive effects of chemotherapy (5). No studies to date have evaluated clinical outcomes of this potential DDI in a large population of women with breast cancer.

We aimed to estimate associations between concomitant hydrochlorothiazide use and adverse clinical outcomes (neutropenia-related hospitalizations and chemotherapy discontinuation) among older women with breast cancer treated with cyclophosphamide.

Materials and Methods

Study population

Using linked Surveillance, Epidemiology, and End Results Program (SEER)-Medicare data, we identified women aged 66 years and older with an incident, first, primary breast cancer diagnosed between 2007 and 2011 who underwent surgery within 90 days of diagnosis, did not receive neoadjuvant chemotherapy, and initiated adjuvant chemotherapy containing cyclophosphamide within 120 days of surgery. All women had to have continuous Medicare Parts A, B, and D coverage and be alive from 12 months before through 12 months following surgical resection. Only women initiating a cyclophosphamide-containing regimen were included.

Healthcare Common Procedural Coding System codes were used to identify specific intravenously administered chemotherapeutic agents, including cyclophosphamide, docetaxel, doxorubicin, epirubicin, fluorouracil, methotrexate, and paclitaxel. National Drug Codes from Medicare Part D files were used to capture outpatient fills for oral cyclophosphamide and hydrochlorothiazide.

National Comprehensive Cancer Network (NCCN) Guidelines were used to determine recommended regimens and number of

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cycles. Initial treatment regimen was identified using the first combination of chemotherapy agents with claims on the same date or within 3 days. The 3-day window was used to account for slight delays in therapy receipt and administrative processing. Patients were classified on the basis of the first drug combination received; thus, all patients receiving adriamycin/cyclophosphamide (AC) without a concurrent taxane drug were categorized as AC patients regardless of whether taxane was received subsequently. For the oral cyclophosphamide-containing regimen, CMF, cyclophosphamide claims needed to be within 28 + 3 days of the intravenous chemotherapy claim dates. Twenty-eight days was selected on the basis of the cycle length for the regimen.

When there were multiple claim dates, the earliest claim date for any chemotherapy agent in the regimen was assigned as the cycle start date. Patients were assigned to regimen groups based on their first regimen. Cycle count was determined by summing each time the regimen was observed in the 12 months following surgery.

Exposure and outcome

The exposure, concomitant hydrochlorothiazide use, was defined using Medicare Part D files as any overlap in days' supply and initiation of the first cycle of adjuvant chemotherapy (i.e., 1 or more days of overlap). The first outcome, neutropenia-related hospitalization, was defined using International Classification of Diseases, Clinical Modification, 9th Edition (ICD-9) diagnosis codes 284.1X, 288.00, 288.03, or 288.09 present within 6 months of chemotherapy initiation. The secondary outcome, chemotherapy discontinuation, was defined by whether or not individuals completed the recommended number of cycles for their specific regimen based on NCCN Guidelines (1) within 12 months from surgery. Gaps in treatment of over 90 days were also considered treatment discontinuation.

Statistical analysis

Associations between the potential DDI and adverse outcomes were assessed using modified Poisson regression to overcome convergence issues with log binomial regression. Robust error variance estimation was used to compute 95% confidence intervals (6). The following covariates were included for adjustment in the regression model: colony-stimulating factor (CSF) use, age and stage at diagnosis, race, treatment regimen, and Charlson comorbidity score classified as 0, 1, and 2+. Treatment regimens included TC (docetaxel + cyclophosphamide or paclitaxel + cyclophosphamide or paclitaxel + docetaxel + cyclophosphamide); AC (doxorubicin + cyclophosphamide); CMF [cyclophosphamide (oral) + methotrexate + fluorouracil)]; dose-dense AC (doxorubicin + cyclophosphamide + colony stimulating factor); and a grouping of other regimens that were less frequent, including EC (epirubicin + cyclophosphamide), TAC (docetaxel + doxorubicin + cyclophosphamide), and CEF (cyclophosphamide + epirubicin + fluorouracil).

CSF, prescribed to prevent neutropenia, was defined using prescription or administration claims within 7 days of the initial chemotherapy cycle. Effect measure modification by CSF use and age (75+ vs. <75 years) were explored.

This study received Institutional Review Board approval from the University of North Carolina at Chapel Hill.

Results

In total, 2,136 women initiated adjuvant chemotherapy containing cyclophosphamide for stage I–III breast cancer. Overall, 581 women (27%) were concomitantly exposed to hydrochlorothiazide at adjuvant chemotherapy initiation. Patient characteristics were similar among women exposed and unexposed to hydrochlorothiazide (**Table 1**).

Table 1. Patient characteristics of study population by concomitant hydrochlorothiazide exposure.

	HCTZ, *n* (%)	No HCTZ, *n* (%)
Total	581	1,555
Age at diagnosis [mean (SD)]	71.5 (4.5)	71.2 (4.4)
Age category		
66–69 years	236 (40.2)	681 (43.8)
70–74 years	211 (35.7)	539 (34.7)
75–79 years	97 (17.3)	249 (16.0)
80+ years	37 (6.4)	86 (5.5)
Race		
White	455 (78.3)	1,308 (84.1)
Black	87 (15.0)	128 (8.2)
Other	39 (6.7)	119 (7.7)
Stage at diagnosis		
I	133 (22.9)	359 (23.1)
II	328 (56.5)	826 (53.1)
III	120 (20.7)	370 (23.8)
Charlson comorbidity score		
0	333 (57.3)	970 (62.4)
1	164 (28.2)	386 (24.8)
2+	84 (14.5)	199 (12.8)
Regimen[a]		
TC	295 (50.8)	824 (53.0)
AC	54 (9.3)	165 (10.6)
CMF	48 (8.3)	111 (7.1)
DD-AC	148 (25.5)	365 (23.5)
Other	36 (6.2)	90 (5.8)
CSF		
No	193 (33.2)	510 (32.8)
Yes	388 (66.8)	1,045 (67.2)

Abbreviation: HCTZ, hydrochlorothiazide.

[a]Regimens include TC (docetaxel + cyclophosphamide or paclitaxel + cyclophosphamide or paclitaxel + docetaxel + cyclophosphamide); AC (doxorubicin + cyclophosphamide); CMF [cyclophosphamide (oral) + methotrexate + fluorouracil]; dose-dense AC (DD-AC; doxorubicin + cyclophosphamide + CSF); and other, which includes EC (epirubicin + cyclophosphamide), TAC (docetaxel + doxorubicin + cyclophosphamide), and CEF (cyclophosphamide + epirubicin + fluorouracil).

Only 227 (11%) women were hospitalized with a diagnosis code for neutropenia and 447 (21%) discontinued adjuvant chemotherapy before completion (**Table 2**). Overall, exposure to concomitant hydrochlorothiazide was neither associated with neutropenia-related hospitalization [adjusted RR (aRR) = 0.92 (0.70–1.21)] nor chemotherapy discontinuation [aRR = 1.00 (0.96–1.05)]. There was no evidence of effect measure modification by CSF use or age.

Discussion

Using linked SEER-Medicare data, we observed no association between concomitant hydrochlorothiazide and cyclophosphamide use and either neutropenia-related hospitalization or treatment discontinuation. Our study included 2,136 women and is the largest investigation of this potential DDI to date, in contrast to the study by Orr (5), which included only 14 patients. The large sample size increased precision of our estimates and provided the opportunity to investigate effect measure modification in key subgroups.

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Table 2. Associations between concomitant hydrochlorothiazide exposure and adverse chemotherapy-related events.

Outcome/study population	Total *N*	HCTZ exposed		HCTZ unexposed		Crude RR (95% CI)	aRR (95% CI)[a]
		Events	*N* (%)	Events	*N* (%)		
Neutropenia-related hospitalization							
Full study population	2,136	59	581 (10.15%)	168	1,555 (10.80%)	0.94 (0.71–1.24)	0.92 (0.70–1.21)
Age 75+ years	469	15	134 (11.19%)	35	335 (10.45%)	1.07 (0.61–1.90)	1.03 (0.59–1.83)
Age <75 years	1,667	44	447 (9.84%)	133	1,220 (10.90%)	0.90 (0.65–1.25)	0.88 (0.64–1.21)
CSF use	1,433	34	388 (8.76%)	96	1,045 (9.19%)	0.95 (0.66–1.39)	0.90 (0.63–1.30)
No CSF use	703	25	193 (12.95%)	72	510 (14.12%)	0.92 (0.60–1.40)	0.91 (0.60–1.39)
Chemotherapy discontinuation							
Full study population	2,136	123	581 (21.17%)	324	1,555 (20.84%)	1.00 (0.84–1.20)	1.00 (0.96–1.05)
Age 75+ years	469	39	134 (29.10%)	79	335 (23.58%)	0.93 (0.82–1.05)	0.92 (0.82–1.04)
Age <75 years	1,667	84	447 (18.79%)	245	1,220 (20.08%)	1.02 (0.96–1.07)	1.02 (0.97–1.07)
CSF use	1,433	73	388 (18.81%)	205	1,045 (19.62%)	1.01 (0.95–1.07)	1.00 (0.95–1.06)
No CSF use	703	50	193 (25.91%)	119	510 (23.33%)	0.97 (0.88–1.06)	0.99 (0.90–1.08)

Abbreviations: CI, confidence interval; HCTZ, hydrochlorothiazide.
[a]Adjusted for CSF use, age and stage at diagnosis, race, treatment regimen, and Charlson comorbidity score classified as 0, 1, and 2+.

Our study is subject to limitations. First, it is plausible that knowing about the potential DDI, oncologists might recommend discontinuation of hydrochlorothiazide in women planning to take or taking cyclophosphamide, leading to exposure misclassification that could attenuate observed associations. In our study, the proportion of women concomitantly exposed to hydrochlorothiazide (27%) is comparable with that of the general population of adults age 65 and over (2), among whom 20% receive thiazide monotherapy and 11% have combination antihypertensive use, often including hydrochlorothiazide (2). In addition, we found that 92% of patients had >1 hydrochlorothiazide dispensing following chemotherapy initiation, suggesting continued use of hydrochlorothiazide during treatment. Thus, it does not appear as although oncologists are reacting to the potential DDI. Second, body mass index (BMI) is not available in claims data and could potentially lead to attenuation in the observed associations, if women with higher BMI are underdosed and are more likely to use hydrochlorothiazide. Third, our data are also limited by the lack of laboratory data, which could provide more direct measures of the outcome of interest, such as absolute neutrophil count. If patient-reported outcomes were available, it would be interesting to examine levels of fatigue or other signs of neutropenia.

A recent working group (7) with expertise in pharmacology, drug information, informatics, and clinical decision support found there was little high quality evidence to support many DDIs, and that compendia and pharmacy database editors do not have a standard guideline or methodology to identify DDIs. The findings from this study could inform pharmacy reference database DDI updates and we suggest reducing the severity level applied to the potential DDI between hydrochlorothiazide and cyclophosphamide.

Disclosure of Potential Conflicts of Interest

J.L. Lund's spouse is a full-time, paid employee of GlaxoSmithKline. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California Department of Public Health, the NCI, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred. The interpretation and reporting of these data are the sole responsibility of the authors.

Authors' Contributions

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