Chemotherapy-Induced Nausea and Vomiting in Asian Women With Breast Cancer Receiving Anthracycline-Based Adjuvant Chemotherapy

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ABSTRACT

Background: Chemotherapy-induced nausea and vomiting (CINV) remain among the most frequently reported distressing side effects associated with anthracycline-based chemotherapy despite significant advances in antiemetic management. The main risk factor for severity of CINV is the emetogenic potential of the chemotherapeutic agents. However, patient-related risk factors have been identified, including genetic makeup. Although studies have noted that ethnicity influences nausea and vomiting in other contexts, there is a paucity of research regarding the impact of ethnicity on CINV. This study was undertaken to evaluate whether Asian women receiving anthracycline-based chemotherapy experience more CINV than non-Asians.

Methods: A retrospective, comparative, correlational chart review was performed to abstract the relevant variables.

Results: Data from a convenience sample of 358 women with breast cancer who received chemotherapy with doxorubicin between 2004 and 2008 at City of Hope in Duarte, California, were evaluated. The sample consisted of Caucasians (45%), Hispanics (27.7%), Asians (19.8%), and African Americans (7.5%). The results indicate that Asian women with breast cancer undergoing anthracycline-based chemotherapy experienced statistically significantly more clinically important CINV than their non-Asian counterparts.

Limitations: The data were collected retrospectively, with a certain population distribution at a specific time.

Conclusion: This study provides interesting preliminary evidence that Asian ethnicity plays a role in the development of severe CINV. When managing chemotherapy toxicities in women with breast cancer, health-care providers should tailor therapy to individual risk profiles. Specifically, consideration of antiemetic therapy should accommodate patient characteristics, such as Asian descent.

Breast cancer is the most common cancer among American women, with an estimated 207 090 new cases and 39 840 breast cancer-related deaths in 2010.[1] Many early-stage breast cancer patients will receive adjuvant chemotherapy following surgical resection, to reduce their risks of recurrence. Currently, anthracycline-based chemotherapy in combination with cyclophosphamide and/or taxane is one of the commonly prescribed adjuvant regimens for early-stage breast cancer and for anthracycline-naive stage IV breast cancer, although taxane-based regimens are increasingly prominent.[2,3] Nausea and vomiting are commonly known adverse effects of anthracycline and cyclophosphamide, occurring in approximately 40%-80% of all patients. Despite the development of drugs such as aprepitant, nausea and vomiting continue to be significant and distressing side effects of adjuvant chemotherapy.[4]

The main risk factor for the severity of chemotherapy-induced nausea and vomiting (CINV) is the emetogenic potential of the chemotherapeutic agents.[5] However, several patient-related risk factors have been identified, such as other medical disorders, alcohol intake, motion sickness, depression, dysfunctional family relationships,

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young age, and genetic makeup.[6-16] A paucity of research exists regarding the impact of ethnicity on CINV.

The purpose of this study was to evaluate a clinical observation that Asian women with breast cancer receiving anthracycline-based chemotherapy experience more CINV than their non-Asian counterparts. The findings of this study, although suggestive rather than definitive, can hopefully be used to motivate the development of ethnicity-specific considerations for CINV counseling and antiemetic regimens for breast cancer patients receiving highly emetogenic chemotherapy regimens.

METHODS

A retrospective chart review was utilized for this study.[17] Data were extracted from the medical records of patients with all stages of breast cancer who were consecutively seen at City of Hope Medical Center for treatment with anthracycline-based regimens. Permission to conduct the study was obtained from the Institutional Review Board (IRB) at City of Hope in accordance with the Health Insurance Portability and Accountability Act.

The study consisted of a chart review of the target population of 358 women with breast cancer who received chemotherapy with doxorubicin and cyclophosphamide plus or minus paclitaxel or docetaxel at City of Hope between 2004 and 2008. Patients were evaluated for CINV prior to each chemotherapy; however, in this study only the data following first chemotherapy and prior to second chemotherapy were collected and analyzed. This time period was chosen to include patients who received aprepitant, which was approved by the Food and Drug Administration in 2004. Included in this population were all women aged 18 years and over, of all races, and with stage I, II, III, and IV breast cancer who were offered anthracycline-based chemotherapy. Excluded were women who presented with other concurrent cancers that may contribute to CINV, such as brain tumors, gastrointestinal cancer, and gynecological cancer.

Procedure

The study patients were selected from the City of Hope registry. The information recorded included the patient's place of birth, race, weight, medical history, history of depression, alcohol intake, marital status or presence of significant others, religion, age, insurance status, education level, CINV, and whether the patient received aprepitant as part of the antiemetic regimen.

Nausea was considered clinically important if an action for treatment modification or future prevention of clinically important CINV was taken. For the purpose of this study, CINV was graded as "clinically important" if other antiemetics were added to the current antiemetic regimen, the patient had a reduction in chemotherapy dose, or the treatment was delayed or discontinued due to CINV only. The measuring instrument may be interpreted differently between physicians, which may skew the grading of CINV; therefore, patients experiencing grades 2, 3, 4, and 5 CINV were grouped together. Patients who received treatment modification related to other reasons, such as severe myelosuppression, were excluded from the study. However, there were no changes in treatment related to other reasons for any of the patients in the study. Any information not already recorded or entered into the medical record at the time of the IRB approval was not utilized for the proposed study.

Statistical Analysis

Prior to analysis, the data were examined for accuracy of data entry and missing values. Univariate descriptive statistics were used to present the demographic data of the patient population. Chi-squared and *t* test analyses were used to determine the relationship between the patient variables and clinically important CINV. Logistic regression was used to determine the predictors of clinically important CINV.[18] Logistic regression was also used to determine odds ratio estimates using a multivariate model of all patient variables. The results were obtained using backward stepwise regression and then reentering each dropped variable in the final model. Statistical software included R (v. 2.12.1, www.r-project.org) and Statistical Package for the Social Sciences, version 17.0 (SPSS, Inc., Chicago, IL).

RESULTS

Data from 358 women were collected and evaluated. The mean age of the patients was 49 years (range 25–72). More than half of the patients (51.4%) were diagnosed with stage II breast cancer, with lower frequencies of stage III (34.1%), stage I (12.6%), and stage IV (2.0%). The majority of patients (70.1%) received treatment that included a combination of doxorubicin (Adriamycin) and cyclophosphamide (AC) chemotherapy given every 2 weeks, dose-dense. Other therapies received by study patients were AC every 3 weeks (19.0%), a combination of AC and docetaxel (8.1%), and weekly AC (2.8%). Patients whose chemotherapy included only AC received subsequent paclitaxel but were evaluated for CINV only during the time they were receiving AC. All patients received growth factors as part of their treatment for prevention of myelosupporession per National Comprehensive Cancer Network guidelines.[19]

The characteristics of the patients are shown in Table 1, with the exception of motion sickness as it was not available in the patient charts.The majority of these patients were Caucasian (45%), with the remainder being Hispanic (27.7%), Asian (19.8%), and African American (7.5%). The Asian group was predominantly comprised of Chinese patients (29.2%) and Taiwanese patients (25.0%), with less frequently Vietnamese, Filipino, Korean, and others (Table 2).

Despite the introduction of the newer antiemetic aprepitant during the study period, 25.7% (92/358) of all consecutive patients with breast cancer receiving treatment with a chemotherapy regimen that included anthracycline experienced severe nausea and/or vomiting. Of the patients who did not receive aprepitant, 36% experienced severe nausea (odds ratio [OR] = 0.51, 95% confidence interval [CI] 0.30–0.87;

Table 1

Sample Characteristics (N = 358)

CHARACTERISTICS	N	PERCENT
Aprepitant		
Present	271	75.7
Absent	87	24.3
Insurance		
Private	214	59.8
State/federal	144	40.2
Stage		
I	45	12.6
II	184	51.4
III	122	34.1
IV	7	2.0
Treatment		
AC every 2 weeks	251	70.1
AC every 3 weeks	68	19.0
AC every week	10	2.8
TAC	29	8.1
Education		
High school or less	223	62.3
More than high school	135	37.7
Age (years)		
≤50	206	57.5
>50	152	42.5
Race		
Caucasian	161	45.0
African American	27	7.5
Asian	71	19.8
Hispanic	99	27.7
Medical history		
Present	87	24.3
Absent	271	75.7
Hypo-/hyperthyroidism	39	10.9
Diabetes	33	9.2
Addison disease	0	0
Liver dysfunction	0	0
Hernia	2	0.6
Parathyroidism	1	0.3
Irritable bowel syndrome	1	0.3
GERD	20	5.6
Pelvic ulcerative disease	0	0
Crohn disease	0	0
Religion		
Christian	278	77.7
Jewish	12	3.4
Buddhist	19	5.3
Muslim	3	0.8
Atheist	1	0.3
Other	45	12.6
Alcohol intake		
None	259	72.3
≤1 drink per day	96	26.8
>1 drink per day	3	0.8
Marital status		
Married	237	66.2
Single	66	18.4
Divorced	36	10.1
Widow	16	4.5
Significant other	3	0.8
History of depression		
No history	319	89.1
History	39	10.9
Severe CINV		
Present	92	25.7
Absent	266	74.3

Abbreviations: AC, doxorubicin (Adriamycin)/cyclophosphamide; CINV, chemotherapy-induced nausea and vomiting; GERD, gastroesophageal reflux disease; TAC, paclitaxel (Taxol)/doxorubicin (Adriamycin)/cyclophosphamide.

$P < .05$). When specifically looking at ethnicity, we found that in non-Asian patients 22.0% (62/286) experienced clinically important CINV vs 40% (29/72) of their Asian counterparts (OR = 2.44, 95% CI 1.40–4.21; $P < .01$). The results of the univariate analysis are presented in Table 3.

No alcohol use was reported in 61/72 (85%) Asians and 198/286 (69%) in non-Asians. This is statistically significant ($P < .01$). However, alcohol (none vs other) did not play a role in CINV in either univariate or multivariate analysis. In fact, 28% of the patients with no CINV reported having consumed alcohol, and 26% of the patients with clinically important CINV reported consuming alcohol. Only 3 patients reported taking more than 1 drink a day, which may have limited the impact of alcohol consumption in this patient population.

In a multivariate model, Asian descent remained a statistically significant independent predictor for clinically important CINV (OR = 2.12, 95% CI 1.18–3.81). In addition, private vs public insurance, younger age (≤50), and gastro-

Table 2

Disribution of Place of Origin for the Asian group

PLACE OF ORIGIN	FREQUENCY	PERCENT
China	21	29.2
Hawaii	1	1.4
Indonesia	2	2.8
Japan	2	2.8
Korea	7	9.7
Philippines	9	12.5
Tailand	1	1.4
Taiwan	18	25.0
Vietnam	11	15.3
Total	72	100

Table 3

Univariate Analysis

PREDICTOR	INCIDENCE OF CINV		OR (UNIVARIATE)	95% CI
Age (years)				
≤50	72/206	(35%)	3.76**	2.19–6.73
>50	19/152	(13%)		
Asian				
Yes	29/72	(40%)	2.44**	1.40–4.21
No	62/286	(22%)		
Chemotherapy				
AC 2 weeks	60/251	(24%)	Baseline	—
AC 3 weeks	19/68	(28%)	1.20	0.661–2.23
AC weekly	6/10	(60%)	4.78*	0.32–19.21
TAC	6/29	(21%)	0.83	0.30–2.02
Depression				
Yes	10/39	(27%)	1.01	0.45–2.11
No	81/319	(25%)		
Diabetes				
Yes	2/33	(6%)	0.17*	0.03–0.58
No	89/325	(27%)		
Education				
>High school	39/135	(29%)	1.34	0.82–2.16
≤High school	52/223	(23%)		
Aprepitant				
Yes	60/271	(22%)	0.51*	0.30–0.87
No	31/87	(36%)		
GERD				
Present	8/20	(40%)	2.05	0.78–5.12
Absent	83/338	(25%)		
Insurance				
Private	69/214	(32%)	2.60**	1.56–4.60
Public	22/144	(15%)		
Marital status				
Married	66/236	(28%)	1.51[a]	0.90–2.58
Divorced	7/36	(19%)		
Single	16/66	(24%)		
Widow	1/17	(6%)		
Other	1/3	(33%)		
Medical history				
Present	18/87	(21%)	0.71	0.39–1.25
None	73/271	(27%)		
Religion				
Christian	65/278	(23%)	0.55*[b]	0.31–0.98
Jewish	2/12	(17%)		
Buddhist	8/19	(42%)		
Atheist	1/1	(100%)		
Muslim	1/3	(33%)		
Other	14/45	(31%)		
Stage				
I–II	65/229	(28%)	1.57	0.94–2.67
III–IV	26/129	(20%)		
Weight				
>70 kg	60/271	(22%)	0.50**	0.31–0.81
≤70 kg	31/87	(36%)		

Table 3

Univariate Analysis (*continued*)

PREDICTOR	INCIDENCE OF CINV		OR (UNIVARIATE)	95% CI
Alcohol				
None	67/259	(25.9%)	0.908	0.550–1.700
≤1 drink/day	24/96	(25.0%)		
>1 drink/day	0/3	(0%)		

Abbreviations: AC, doxorubicin (Adriamycin)/cyclophosphamide; CI, confidence interval; CINV, chemotherapy-induced nausea and vomiting; GERD, gastroesophageal reflux disease; OR, odds ratio; TAC, paclitaxel (Taxol)/doxorubicin (Adriamycin)/cyclophosphamide.

[a] Married vs others.

[b] Judeo-Christian vs others.

* $P < .05$, ** $P < .01$.

esophageal reflux disease (GERD) remained in the multivariate model as predictors of clinically important CINV (see Table 4).Additionally, of the 87 patients who did not receive aprepitant, 23 (26.4%) had state/federal insurance (the remainder had private insurance); and of the 271 patients who received aprepitant, 121 (44.7%) had state/federal insurance, which is a significantly higher proportion ($P < .01$ Fisher's exact test). We also reviewed the effect of body surface area (BSA) on CINV due to the lower BSA of Asian patients compared to non-Asians (1.62 vs 1.85, $P < .001$). We investigated the potential role of dosing, specifically the more frequent use of reduced dosing (based on lower than actual BSA) in non-Asians compared to Asians (31% vs 14%, $P < .01$). However, neither the difference between "actual" and "used" BSA (on a continuous scale) nor dichotomization into "reduced" vs "not reduced" altered the final multivariate model. The remaining variables were not found to be statistically significant predictors of CINV.

DISCUSSION

This study provides provocative evidence that ethnicity may play an important role in the development of clinically important CINV, although there are several limitations that could potentially affect its validity. Since the data were not collected prospectively in a standardized fashion, the charting may potentially have been influenced by physician bias and the percentages reported may be a misrepresentation of the true values. In addition, the grading of clinically important CINV was based on the modification of the treatment due to

Table 4

Multivariate Predictors ($P < .05$)

PREDICTOR	OR	95% CI
Asian	2.12	(1.18–3.81)
Insurance (private)	2.13	(1.23–3.78)
Age ≤50	3.62	(2.05–6.69)
GERD	3.32	(1.15–9.31)

Abbreviations: CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio.

patient report of CINV rather than on the National Cancer Institute's Common Terminology Criteria for Adverse Event toxicity grading guidelines.[20]

Patients in this study were chosen consecutively; thus, there may have been an unequal distribution of patient-related variables. Finally, the patient population consisted only of those patients treated at City of Hope in Duarte, California, with a certain population distribution at a specific time (2004-2008). It is likely that patient populations evaluated elsewhere at a different point in time would possess different characteristics.

The finding that Asian women may be more susceptible to CINV resulting from chemotherapy is in keeping with a number of reported observations. Although the underlying physiological mechanism in different ethnicities has not been fully elucidated, many studies have identified ethnic differences that may alter pharmacokinetics; and there is some evidence suggesting that Asian patients may experience slower drug clearance and increased susceptibility to certain drug toxicities. Several studies have also noted that Asians experience more motion sickness and fluorescein dye–induced nausea and vomiting than non-Asians.[9,10,12,21,22] In addition, early pharmacogenetic findings suggest that genetic polymorphism may affect patients' response to antiemetic therapy following chemotherapy. For example, patients who have been identified as ultrarapid metabolizers of the isoenzyme CYP2D6 have a significantly higher frequency of CINV following administration of odansetron or tropisetron.[7] While the ultrarapid metabolizer does not account for the 20% difference in the severity of nausea and vomiting in Asians, it can explain some of the difference. The prevalence of CYP2D6 poor metabolizers is approximately 7.7% in Caucasian Americans, 1.9%-7.3% in African Americans, 0%-1.2% in Asians, and 2.2%-6.6% in Hispanics.[23] A recent study showed that Chinese appear to be more vulnerable to CINV compared to Indians and Malays in Malaysia.[24] Hence, it is plausible to suggest that careful monitoring for ethnicity-specific adverse events and providing ongoing ethnicity-specific patient education and support will aid health-care professionals in enhancing the quality of life for their Asian patients with breast cancer undergoing treatment with anthracycline.

Clearly, studies that address genetic factors and cultural or social factors are necessary to fully dissect all of the variables that influence the severity of chemotherapy toxicities. In the case of Asian women undergoing chemotherapy for breast cancer, further prospective studies will be necessary to determine whether and how Asian-specific genetic elements influence a propensity toward certain adverse events. Such studies will be challenging to design, however, since genetic factors are difficult to separate from cultural factors that may also influence reactions to therapy. In any case, the results of this study are a start toward an approach to individualized care in which health-care professionals in breast oncology would consider the influence of ethnicity and cultural background in managing the toxicities of chemotherapy.

Patients with private insurance were found to experience more clinically important CINV than those who had state/federal insurance. This may be in part because patients who had state/federal insurance were more likely to get the aprepitant as part of their antiemetic regimen. Traditionally, this has not been the case and may reflect on the current health-care system. Another plausible reason is that patients with private insurance are more likely to be employed and have all of the attendant stresses.

In conclusion, we have presented thought-provoking evidence that Asian women are more subject to CINV during anthracycline-based chemotherapy for breast cancer than are non-Asians. This study has thus revealed ethnic differences in the experience of toxic side effects of chemotherapy during supportive care of cancer patients. These findings are suggestive of the need for more individualized patient care, although additional studies are needed to further elucidate this interesting observation.

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