Published in final edited form as:

Support Care Cancer. 2018 August ; 26(8): 2911–2918. doi:10.1007/s00520-018-4120-6.

Prediction of Chemotherapy-Induced Nausea and Vomiting from Patient-Reported and Genetic Risk Factors

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Abstract

Purpose: Chemotherapy-induced nausea and vomiting (CINV) is common among cancer patients. Early identification of patients at risk for CINV may help to personalize anti-emetic therapies. To date, few studies have examined the combined contributions of patient-reported and genetic risk factors to CINV. The goal of this study was to evaluate these risk factors.

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Conflict of Interest

Disclosures of potential conflicts of interest: Dr. Li is a consultant for Novartis. Dr. Jim is a consultant for RedHill Biopharma. This work was performed while Dr. Jacobsen was at the Moffitt Cancer Center and does not represent the views of the National Cancer Institute.

Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

This manuscript describes original work and is not under consideration by any other journal. We have adhered to the journals submission requirements. We have full control of all primary data and we agree to allow the journal to review the data if requested. All authors approve the manuscript and its submission.

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Methods: Prior to their first chemotherapy infusion, participants completed demographic and risk factor questionnaires and provided a blood sample to measure genetic variants in *ABCB1* (rs1045642) and *HTR3B* (rs45460698) as well as *CYP2D6* activity score. The M.D. Anderson Symptom Inventory was completed at 24 hours and 5 days post-infusion to assess the severity of acute and delayed CINV, respectively.

Results: Participants were 88 patients (55% female, $M=60$ years). A total of 23% experienced acute nausea and 55% delayed nausea. Younger age, history of pregnancy-related nausea, fewer hours slept the night prior to infusion, and variation in *ABCB1* were associated with more severe acute nausea; advanced stage cancer and receipt of highly emetogenic chemotherapy were associated with more severe delayed nausea (p values <0.05). In multivariable analyses, *ABCB1* added an additional 5% predictive value beyond the 13% variance explained by patient-reported risk factors.

Conclusions: The current study identified patient-reported and genetic factors that may place patients at risk for acute nausea despite receipt of guideline consistent anti-emetic prophylaxis. Additional studies examining other genetic variants are needed, as well as the development of risk prediction models including both patient-reported and genetic risk factors.

Keywords

Chemotherapy; neoplasms; nausea; vomiting; risk factors; genetic variation

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common and feared side effects of cancer treatment [1, 2]. Despite use of modern prophylactic anti-emetic regimens according to international guidelines [3], up to 33% of patients treated with highly- or moderately-emetogenic chemotherapy experience one or more episodes of emesis and up to 62% experience nausea [4–6]. Patients experiencing CINV may be less likely to complete their prescribed chemotherapy regimen due to the significant impact of CINV on quality of life and activities of daily living [7, 8]. Consequently, CINV is a significant clinical problem.

CINV can be separated into acute (occurring in the first 24 hours of chemotherapy) and delayed (occurring between day 2 to day 5) nausea and vomiting. Documented patient-reported risk factors for acute and delayed CINV include younger age, female gender, greater anxiety, history of motion sickness, history of morning sickness during pregnancy, non-habitual alcohol consumption, non-smoking status, less sleep the night before chemotherapy, and previous chemotherapy [9–12]. A series of recent studies have analyzed demographic, clinical, and patient-reported risk factors to develop and validate predictive indices of acute and delayed CINV [10–12]. Each index yields a dichotomous risk score (high/low) intended to be used in routine clinical practice to tailor anti-emetic therapy [11]. Nevertheless, since these indices were developed, new research has been published suggesting that genetic variation may also predict CINV [13–15].

Several studies have shown that variation in genes involved in transport and metabolism of anti-emetic drugs are associated with inter-individual differences in response to these agents [13, 16–19]. For example, 5-hydroxytryptamine type 3 receptor antagonists (5HT₃-RA) are one of the most commonly prescribed classes of anti-emetic drugs in oncology and HTR3

genes code for its therapeutic target [20]. Data suggest that variations in *HTR3A*, *HTR3B*, *HTR3C* and *HTR3D* genes are associated with the efficacy of 5HT₃-RA in cancer patients; of these, the most evidence exists for *HTR3B* [14, 21, 22]. Similarly, variants in a gene coding for 5HT₃-RAs drug transporter ATP-binding cassette B1 protein (*ABCB1*) have been shown to be associated with acute nausea and vomiting, particularly in the first 24 hours of chemotherapy [15, 18]. Additionally, as a majority of the anti-emetic drugs (including 5HT₃-RA and dopamine antagonists) are metabolized by the cytochrome P 450 (CYP) D6 system in the liver; variation in *CYP2D6* can result in large variations in their metabolism and may ultimately affect the overall drug response [13]. For example, *CYP2D6* ultrarapid metabolizers, who have additional functional copies of alleles, tend to report greater CINV when treated with ondansetron and tropisetron [23]. Nevertheless, the abovementioned genes have never been examined in the context of patient-reported risk factors. Doing so could lead to earlier identification of patients at risk of CINV who may benefit from stronger anti-emetic prophylaxis such as netupitant-palonosetron plus dexamethasone or the addition of alprazolam, lorazepam, olanzapine, or metoclopramide to their anti-emetic regimen [24].

The goal of the current study was to examine the independent contributions of genetic variants over and above recognized demographic, clinical, and patient-reported risk factors. In addition to the demographic, clinical, and patient-reported risk factors identified in previous research, we investigated variation in three genes previously found to be associated with CINV: *HTR3B*, *ABCB1*, and *CYP2D6*. We hypothesized that demographic, clinical, and patient-reported risk factors and genetic variants would demonstrate significant associations with CINV in univariate analyses. We also hypothesized that genetic variants would contribute significant variance in CINV over and above that contributed by demographic, clinical, and patient-reported risk factors.

Methods

Participants

Eligible patients were: a) 18 years of age, b) capable of speaking and reading English or Spanish, c) diagnosed with cancer, d) chemotherapy naïve, e) scheduled to receive highly- or moderately-emetogenic intravenous standard-dose chemotherapy as defined by the 2011 American Society of Clinical Oncology (ASCO) anti emesis guidelines [25] at Moffitt Cancer Center, and f) able to provide informed consent. All patients who participated in the study signed an IRB-approved written informed consent document.

Procedures

Participants were recruited between April 2014 and April 2015. Potential participants were identified using the existing computerized appointment system and in consultation with the medical team. Participants were recruited prior to their first chemotherapy infusion. Following informed consent, participants were asked to complete a baseline sociodemographic questionnaire and provide a blood sample to assess genetic variants. On the morning of the first infusion, participants completed a measure of self-reported risk factors. They also completed self-report measures of nausea and vomiting at 24 hours post-

infusion (i.e., acute) and 5 days post-infusion (i.e., delayed). Electronic email or call reminders were sent to ensure timely completion.

Measures

Demographic and Clinical Characteristics.—Demographic variables assessed via self-report included age, gender, race, ethnicity, education, marital status, annual household income, and history of smoking and alcohol use. Medical comorbidities were assessed at recruitment using a self-report version of the Charlson Comorbidity Index [26]. Participants were asked to list any non-prescription medications and supplements that they were taking over the study period. Clinical variables collected via medical record review included date of diagnosis, cancer type, disease stage, date of on-study chemotherapy infusions, chemotherapy regimen, prescribed anti-emetic drugs, and changes in anti-emetic regimens between the first and second infusion.

Patient-Reported Risk Factors.—Variables assessed were selected based on previous literature [9–12]. They included hours of sleep the night before the first infusion, extent of the meal before the first infusion (i.e., liquids only, light meal or snack, full meal), history of nausea and vomiting (i.e., due to pregnancy, motion sickness, and anxiety), recent surgery, expectancies regarding post-chemotherapy nausea and vomiting, and current anxiety.

Acute and Delayed Nausea and Vomiting.—The MD Anderson Symptom Inventory (MDASI)[27] was used to assess the severity of patient-reported CINV. Items used in the current analyses were “your nausea at its worst” and “your vomiting at its worst” keyed to “the last 24 hours” for acute CINV and “24 or more hours after chemotherapy” for delayed CINV. Items are evaluated on an 11-point Likert scale (0=not present, 10=as bad as you can imagine). Additional items asked what patients did about their CINV (e.g., ate less than usual, took anti-emetic medication, went to a hospital or urgent care facility, received intravenous fluids); these items were selected based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3 [28]. Responses were used by research staff to rate acute and delayed nausea and vomiting according to the CTCAE.

Blood Collection and Analysis.—Blood was collected in 10 ml EDTA tubes, inverted 10 times, chilled, and sent to the Moffitt Tissue Core for DNA purification. DNA was extracted using the AutoPure system (Autogen, Holliston, MA). DNA quantity and quality was assessed using the Qubit fluorometer (Thermo Fisher Scientific, Waltham, MA) and the Agilent TapeStation (Agilent Genomics, Santa Clara, CA). Samples were centrifuged and plasma aliquoted into multiple 1.2 mL cryovials and frozen at –80 degrees Celsius. Genotyping was conducted by Cancer Genetics Inc. (Rutherford, NJ). Variants genotyped included rs1045642 in *ABCB1*, rs45460698 in *HTR3B*, and *CYP2D6* *2, *3, *4, *5, *6, *7, *9, *10, *17, *21, *29, and *41. *CYP2D6* results were used to categorize patients into phenotypes (i.e., poor, intermediate, extensive, and ultrarapid metabolizers) [29]. A continuous activity score was also assigned with higher scores indicating more rapid metabolism [30].

Statistical Analysis

Participants' demographic and clinical characteristics were summarized using descriptive statistics. Spearman correlations, chi-squares, and Kruskal Wallis tests were used to examine univariate relationships among demographic, clinical, patient-reported and genetic variables and outcomes. Variables examined included age, gender, cancer stage, comorbidities, chemotherapy emetogenicity (i.e., highly versus moderately emetogenic), alcohol use, hours of sleep the night before the first infusion, extent of the meal before the first infusion (i.e., liquids only, light meal or snack, full meal), history of nausea and vomiting (i.e., due to pregnancy, motion sickness, and anxiety), recent surgery, expectancies (i.e., regarding post-chemotherapy nausea and vomiting), and current anxiety. Primary outcomes were patient ratings of severity of acute and delayed CINV. Secondary outcomes were CTCAE grade of acute and delayed CINV (i.e., grade 2 versus < grade 2) and change in anti-emetic regimen from the first to second infusion. Risk factors correlated with outcomes at $p < 0.05$ were entered as independent variables in multivariable hierarchical multiple regression analyses to determine their combined contributions. Demographic, clinical, and patient-reported risk factors were entered into the first step and genetic risk factors were entered into the second step. All statistical analyses were performed using SAS 9.4 (Cary, NC).

Results

Patient Characteristics

A total of 120 eligible patients who were approached signed consent (90%). Of these, 107 (89%) completed the study, genotyping was conducted on 93 patients, and 88 patients had complete self-report and genetic data. Therefore, 88 patients were included in the current analyses. Demographic and clinical characteristics of the sample are shown in Table I. Patients were a mean age of 60 years (SD=10). The majority of patients were female (55%); white (93%), non-Hispanic (97%) and had an annual household income of at least \$40,000 per year (60%). Most patients were diagnosed with gastrointestinal (34%), thoracic (27%) or breast malignancies (26%); had advanced stage disease (74%); and received highly-emetogenic chemotherapy regimens (65%). Prescribed anti-emetic medications are shown in Table II. Nearly all participants received palonosetron (99%) and dexamethasone (98%). Additional commonly used anti-emetics included prochlorperazine (88%), ondansetron (46%), and fosaprepitant (34%). Patient-reported and genetic risk factors for CINV are summarized in Table III. Most participants could be characterized as CYP2D6 intermediate or extensive metabolizers, 77% of participants had at least one copy of the variant ABCB1 allele at rs1045642, and 31% had the variant deletion at rs1045642.

Rates of CINV

Mean self-reported CINV severity and CTCAE ratings are displayed in Table IV. A total 12% of patients experienced CTCAE grade 2 or above acute nausea and 30% experienced delayed nausea. Vomiting of any CTCAE grade was experienced by 3% in the acute period and 11% in the delayed period. Anti-emetic regimen was switched in 14% of patients.

Associations among Demographic, Clinical, Patient-Reported, and Genetic Variables and CINV

In the univariate analyses examining demographic, clinical, and patient-reported risk factors for CINV, patient-reported severity of acute nausea was associated with younger age ($r=-0.32$, $p<0.01$) and fewer hours of sleep the night before chemotherapy ($r=-0.34$, $p<0.01$). CTCAE grade of acute nausea was associated with younger age ($r=-0.24$, $p=0.02$), fewer hours of sleep the night before chemotherapy ($r=0.29$, $p<0.01$), and history of nausea and vomiting due to morning sickness ($r=0.22$, $p=0.04$). No risk factors were associated with acute vomiting (p values >0.05). Patient-reported severity of delayed nausea was associated with younger age ($r=-0.29$, $p<0.01$) and receipt of highly emetogenic chemotherapy ($r=-0.25$, $p=0.02$). Severity of CTCAE grade of delayed nausea was associated with advanced stage cancer ($r=-0.22$, $p=0.04$) and receipt of highly emetogenic chemotherapy ($r=-0.24$, $p=0.02$). No risk factors were associated with delayed vomiting (p values >0.05).

In the univariate analyses examining genetic risk factors, variation in *ABCB1* (rs1045642) was associated with acute nausea, with heterozygotes reporting more severe acute nausea (A/G: mean=1.91, SD=2.83) than individuals with homozygous wild type (G/G: mean=0.80, SD=2.31) and homozygous variant (A/A: mean=0.62, SD=1.96) genotypes (Kruskal Wallis, $p=0.04$) (see Figure I). *ABCB1* variation was not associated with delayed CINV (p values >0.05). There were no associations between variation in *HTR3B* (rs45460698), *CYP2D6* phenotype, or *CYP2D6* activity score and acute or delayed CINV (p values >0.05).

Because only patient-reported acute nausea was associated with both patient-reported and genetic risk factors, multivariable analysis focused on this outcome. Results are shown in Table V. Demographic, clinical, and patient-reported risk factors accounted for 13% of variance in acute nausea ($p=0.03$); *ABCB1* genotype added an additional 5% of variance ($p=0.10$).

Discussion

The goal of the current study was to evaluate the combined contributions of demographic, clinical, patient-reported, and genetic risk factors towards predicting acute and delayed CINV. Results show that incorporation of genetic factors to CINV risk assessment indices based on patient related factors has the potential to improve prediction. Despite recent advances in anti-emetic therapy, CINV remains a significant cause of morbidity in cancer patients [7, 31]. Our study showed a suboptimal control of nausea post chemotherapy despite guideline-consistent anti-emetic prescribing, with 12% patients reporting moderate to severe nausea in the acute setting and 30% in the delayed setting [25]. Nevertheless, control of vomiting was high, with 1% of patients experiencing CTACE grade 2 or above acute vomiting and 5% delayed vomiting.

Control of nausea was related to patients' sociodemographic, clinical, patient-reported, and genetic characteristics. Consistent with previous studies [9–12], we found in univariate analyses that younger age and fewer hours of sleep prior to chemotherapy was significantly related to development of acute nausea. Advanced stage malignancy and receipt of highly emetogenic chemotherapy were found to be significantly related to development of delayed

nausea. Univariate analyses also indicated that variation in *ABCB1* at rs1045642 was significantly associated with development of acute nausea. While these findings are consistent with previous literature [15, 18], it is not clear why heterozygotes would experience greater nausea than homozygotes. It may be that this variant is in high linkage disequilibrium with a functional variant. Despite frequent use of anti-emetic agents metabolized by *CYP2D6*, we did not observe an association of activity score or phenotype with CINV. Lack of a relationship may be due to the fact that majority of our participants were extensive metabolizers (94%), as a result of which our study sample was not adequately powered to evaluate the CYP2D6 phenotype as a potential CINV risk factor. Similarly, we did not observe any association between variation in the *HTR3B* gene and the risk of CINV, perhaps due to our relatively small sample size.

Over the years, there has been development of several risk assessment indices for prediction of CINV based on patient-reported risk factors and the emetogenic potential of chemotherapeutic regimens [11, 12, 32]. In a randomized control study, Clemons et al [33] evaluated the control of CINV in breast cancer patients and found significant improvement in both acute and delayed CINV when patients were given a tailored anti emetic medication regimen based on an established risk based model. We found that demographic, clinical, patient-reported, and genetic factors accounted for a combined 18% of the variance in acute nausea, with genetic factors accounting for 5%. Our data suggest that existing algorithms may be improved by including genetic information. Relatively few candidate gene studies have been conducted to date; additional, larger studies such as genome-wide association studies (GWAS) are needed to provide a more comprehensive examination of genetic risk factors for CINV. The falling cost of genotyping, in combination with CLIA-certified genotyping available to providers and consumers, suggests that genotype-based antiemetic prescribing is likely to become increasingly practical.

Our study is one of the first to look at the combination of patient-reported and genetic risk factors to identify risk of CINV in cancer patients. Strengths of the study include a clinically important research question; longitudinal, prospective design; a sample that was heterogeneous in terms of diagnosis and stage; well-validated measures of CINV; and appropriate statistical analyses. Limitations of the study should also be noted. Our sample of 88 patients was relatively small and the incidence of some outcomes, such as vomiting, was low. Therefore the study may have lacked statistical power to detect more subtle effects of patient-reported and genetic risk factors on CINV. Additionally, our sample was relatively homogeneous in terms of race and ethnicity; additional studies are needed to determine whether findings can be generalized to other racial and ethnic groups.

In conclusion, the current study suggests that patient-reported and genetic risk factors may improve early identification of patients at risk of CINV. Additional studies are needed to confirm our results and systematically investigate the role of additional genetic variants (i.e., GWAS) to select appropriate genetic risk factors for tailored anti-emetic prescribing in clinical practice. Future research will be targeted towards establishing additional genetic variants responsible for inter individual variability in CINV risk, development and dissemination of risk prediction models, and evaluating the cost effectiveness of risk-based anti-emetic prescribing. Additional research should also focus on pharmacogenetics studies

of anti-emetic metabolism. Improved nausea risk prediction and management would be highly impactful for the 650,000 cancer patients who receive outpatient chemotherapy in the U.S. each year.[34]

Acknowledgements:

Funding was provided by the Moffitt Cancer Center Team Science Award (PIs: Jim, McLeod). This work has been supported in part by the Survey Methods Core and the Tissue Core Facilities at the H. Lee Moffitt Cancer Center & Research Institute, an NCI designated Comprehensive Cancer Center (P30 CA076292).

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Figure I.
Ratings of acute nausea by ABCB1 genotype.

Table I.

Sample Demographic and Clinical Characteristics (N=88)

Age: mean (SD)	60 (10)
Gender: n (%) female	48 (55%)
Race: n (%) white	82 (93%)
Ethnicity: n (%) non-Hispanic	85 (97%)
Marital status: n (%) married	60 (68%)
Education: n (%) completed college	32 (36%)
Annual household income: n (%) more than \$40,000	41 (60%)
Cancer type: n (%)	
Breast	23 (26%)
Thoracic	24 (27%)
Gastrointestinal	30 (34%)
Head/neck	5 (6%)
Other	6 (7%)
Stage	
I	4 (4%)
II	14 (16%)
III	34 (39%)
IV	31 (35%)
Missing	5 (6%)
Time since diagnosis: mean (range) days	107 (6-3579)
Chemotherapy regimen	
Moderately emetogenic	31 (35%)
Highly emetogenic	57 (65%)
Charlson Comorbidity Index: mean (SD)	2.93 (1.28)

Table II.

Frequency of Prescribed Anti Emetic Medications: n(%)

	HEC (n=31)	MEC (n=57)	All (N=88)
Dexamethasone	30 (97%)	56 (98%)	86 (98%)
Diphenhydramine	0 (0%)	19 (33%)	19 (21%)
Dronabinol	1 (3%)	0 (0%)	1 (1%)
Fosaprepitant	30 (97%)	0 (0%)	30 (34%)
Lorazepam	13 (42%)	7 (12%)	20 (23%)
Methylprednisolone	0 (0%)	11 (19%)	11 (12%)
Metoclopramide	2 (3%)	0 (0%)	2 (2%)
Ondansetron	21 (68%)	20 (35%)	41 (46%)
Palonosetron	31 (100%)	56 (98%)	87 (99%)
Prochlorperazine	27 (87%)	47 (82%)	74 (88%)
Promethazine	1 (3%)	0 (0%)	1 (1%)

HEC: highly-emetogenic chemotherapy, MEC: moderately-emetogenic chemotherapy

Table III.**Patient-Reported and Genetic Characteristics of the Sample**

Hours slept: mean (SD)	6.01 (1.86)
Last meal: n (%)	
Liquids only	5 (6%)
Light meal or snack	50 (57%)
Full meal	33 (37%)
NV due to morning sickness	
None (including men)	65 (74%)
Nausea only	10 (11%)
Nausea and vomiting	13 (15%)
NV due to motion sickness	
None	63 (72%)
Nausea only	13 (15%)
Nausea and vomiting	12 (13%)
NV due to anxiety	
None	79 (90%)
Nausea only	7 (8%)
Nausea and vomiting	2 (2%)
Expectations about nausea	
I am certain I will not have this	2 (2%)
I might not have this	17 (20%)
I am unsure	43 (49%)
I might have this	24 (27%)
I am certain I will have this	2 (2%)
Expectations about vomiting	
I am certain I will not have this	7 (8%)
I might not have this	17 (19%)
I am unsure	48 (55%)
I might have this	16 (18%)
I am certain I will have this	0 (0%)
Current anxiety: mean (SD)	4.02 (2.26)
<i>CYP2D6</i> phenotype	
Poor metabolizer	1(1%)
Intermediate metabolizer	3(4%)
Extensive metabolizer	82(94%)
Ultra rapid metabolizer	1(1%)
<i>CYP2D6</i> activity score: mean (SD)	1.37(0.50)
<i>ABCB1</i> rs1045642 (A is variant)	
A/A	21(24%)

A/G	47(53%)
G/G	20(23%)
<i>HTR3B</i> rs45460698	
AAG/-	27 (31%)
AAG/AAG	61 (69%)

NV: nausea or vomiting

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Table IV:**Severity and Incidence of Chemotherapy-Induced Nausea and Vomiting**

MDASI acute nausea: mean (SD)		1.35 (2.58)
MDASI acute vomiting: mean (SD)		0.17 (1.10)
MDASI delayed nausea: mean (SD)		2.38 (2.97)
MDASI delayed vomiting: mean (SD)		0.79 (2.28)
CTCAE acute nausea grade: n (%)		
	0	60 (68%)
	1	17 (20%)
	2	9 (10%)
	3	2 (2%)
CTCAE acute vomiting grade: n (%)		
	0	85 (97%)
	1	2 (2%)
	2	1 (1%)
	3	0 (0%)
CTCAE delayed nausea grade: n (%)		
	0	38 (43%)
	1	24 (27%)
	2	24(27%)
	3	2 (3%)
CTCAE delayed vomiting grade: n (%)		
	0	78 (89%)
	1	5 (6%)
	2	2 (2%)
	3	3 (3%)
Change in anti-emetic regimen: n (%) yes		12 (14%)

MDASI: M.D. Anderson Symptom Inventory, CTCAE: Common Terminology Criteria for Adverse Events v. 4.0.3.

Table V:

Multivariable Analysis for Variables Predicting Patient Reported Acute Nausea (MDASI)

Variables	β	SE	<i>p</i>	Change in R ²	Total R ²
Step 1: Demographic, clinical, and patient-reported factors			<.01	0.13	0.13
Age	−0.05	0.03	0.05		
Hours slept	−0.32	0.15	0.04		
Step 2: Genetic factors				0.05	0.18
<i>ABCB1</i> heterozygote	−0.35	0.76	0.65		
<i>ABCB1</i> recessive	0.91	0.67	0.17		