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Original Research Article

Single nucleotide polymorphisms might influence chemotherapy induced nausea in women with breast cancer

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ABSTRACT

Background: Women receiving FEC (5 fluorouracil, epirubicin and cyclophosphamide) chemotherapy (CT) for breast cancer (BC) often experience side effects such as nausea and vomiting. Individual variations of side effects occur in patients despite similar cancer therapy. The purpose of this study was to investigate a possible genetic background as a predictor for individual variations in nausea induced by CT.
Methods: 114 women were included in the study. All women received adjuvant CT for BC. Self-reported nausea and vomiting was recorded in a structured diary over ten days following treatment. Blood samples were collected before the treatment and used for the detection of 48 single nucleotide polymorphisms (SNPs) in 43 genes. SNPs from each individual woman were analyzed for their relation to the patient-reported frequency and intensity of nausea and vomiting.
Results: Eighty-four percent ($n = 96$) of the women reported acute or delayed nausea or combined nausea and vomiting during the ten days following CT. Three out of the forty-eight SNPs in the following genes: FAS/CD95, RB1/LPAR6 and CCL2 were found to be associated with a risk of nausea.
Conclusion: SNPs in the FAS/CD95, RB1/LPAR6 and CCL2 genes were found to be associated with nausea among women treated with adjuvant FEC for BC. SNPs analysis is fast and cost effective and can be done prior to any cancer therapy. The association between individual SNPs and severe side effects from FEC may contribute to a more personalized care of patients with BC.

Introduction

Nausea and vomiting are significant side effects reported in relation to chemotherapy (CT) despite the development of effective antiemetic drugs. Insufficient control of nausea often results in a decrease in the patients' well-being, quality of life and affects physical activity [1]. Moreover, poorly managed nausea is costly and might impact many aspects of care for patients with cancer [2].

Many studies have focused on factors that can empower CT-induced nausea and vomiting (CINV) (4–6). Women <50 years old and with a history of morning sickness in pregnancy, seems to be more prone to CINV [3], whereas physical activity and high alcohol intake seems to reduce the risk [3–5].

FEC (5 fluorouracil, epirubicin and cyclophosphamide) is a commonly used CT regimen for breast cancer (BC). FEC is considered highly emetogenic and despite the use of antiemetic drugs, acute (within 24 h) or delayed (later than 24 h) CINV is common [6,7].

Specific genetic profiles may influence the tumor response and side effects of CT [8]. Major contributors to individual variations in genetic profiles are single nucleotide polymorphisms (SNPs). A SNP is defined as a variation of one nucleotide in which one allele is present in more than 1% of the studied population [9,10]. SNP is the most common variation in DNA and may result in an altered gene expression, response to external factors and drug metabolism.

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Genetic variation such as SNP could lead to amino acid substitution and alter gene expressions. Even if nausea is complex in nature and probably depending on more than one etiological factor, it is important to evaluate a possible role of SNPs on the frequency and intensity of CINV in women with BC as it could improve the possibility to individualize the antiemetic therapy [11,12]. CINV is complex. Several mechanisms are involved. The complete pathophysiology is not known, and different factors provoking nausea could have different mechanisms. Different pathways have been identified for acute and delayed CINV. Receptors for dopamine, serotonin and substance P have an important role in the mechanism of chemotherapy-induced emesis It is unknown if other receptor also are involved in the pathophysiological mechanisms of chemotherapy-induced emesis [13]. In a previous clinical observational study, heterogeneity was found regarding nausea between women with BC receiving FEC [14]. Despite known predicting factors for CINV, we found no published data that could foretell an individual sensitivity to CT with regards to side effects. It is plausible that this heterogeneity is explained in part by individual genetic alterations. If the genetic alterations could be the basis for choice of antiemetic treatment, both the patients and the health care system would benefit, with the patient receiving better treatment and quality of life and the health care system could use resources more effectively.

The purpose of this study was to investigate a possible association between SNPs and the occurrence of CINV during the first ten days after FEC treatment of women with BC.

Material and methods

Participants

One hundred and seventy-five consecutive women ($\geqslant$18 years old, treated for BC with adjuvant FEC) were asked to participate in the study. Women with insufficient knowledge of the Swedish language, previous treatment with intravenous CT and severe neurological or psychological disorders (clinical diagnosis) were excluded. Out of the remaining 142 women, six dropped out for different reasons. Blood samples were drawn from 136 of the remaining women. Due to technical problems, only 114 blood samples were included (Fig. 1).

The Regional Ethical Review Board in Linköping approved the study (Dnr 2010/331-31, December 2010).

The women included were treated at two different Swedish hospitals of similar size. The patients were treated with same FEC regimens (FEC 100: fluorouracil 500 mg/m^2 iv, epirubicin 100 mg/m^2 iv and cyclophosphamide 500 mg/m^2 iv; FEC 75: fluorouracil 600 mg/m^2 iv, epirubicin 75 mg/m^2 iv and cyclophosphamide 600 mg/m^2 iv and FEC 60: fluorouracil 600 mg/m^2 iv, epirubicin 60 mg/m^2 iv and cyclophosphamide 600 mg/m^2 iv). The first cycle was studied.

Information on previous experiences of nausea and vomiting, smoking and family situation were collected from the patients by a research nurse. Body mass index (BMI) was collected from the electronic health records.

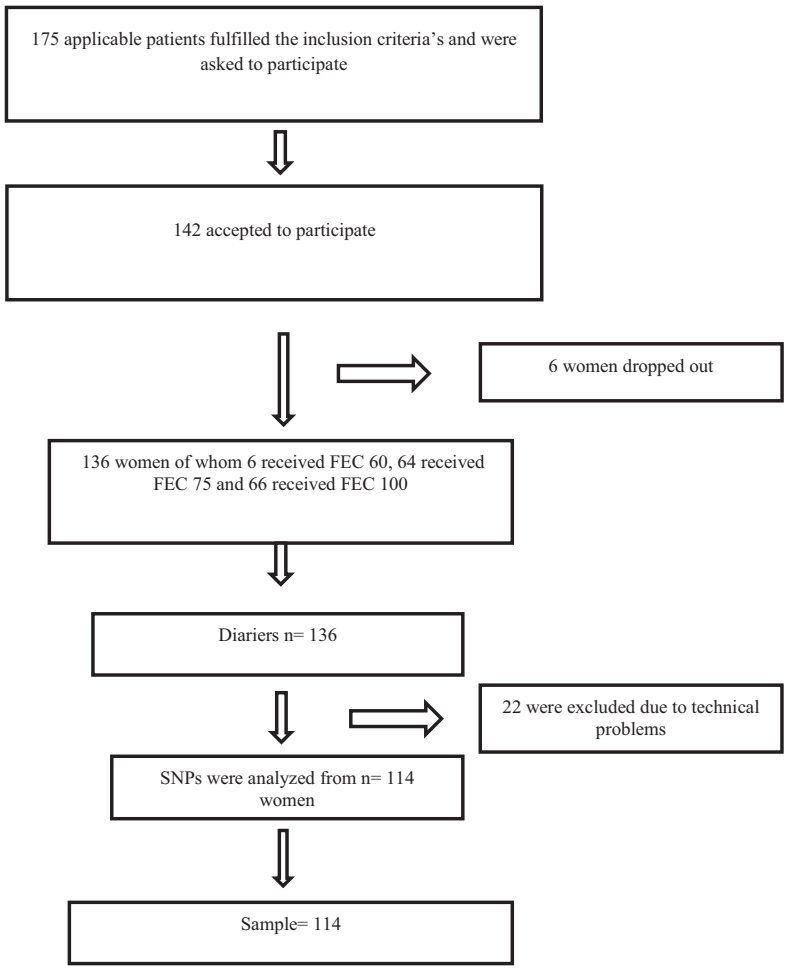

Fig. 1. Inclusion process. FEC = 5 Fluorouracil, Epirubicin and Cyclophosphamide, SNP = single nucleotide polymorphisms.

Procedures

At the first visit at either Department of Oncology, the research nurse informed (verbally and in writing) the women about the study. The women who chose to participate signed the consent form.

Both hospital sites used three different FEC options, depending on performance status, age and tumor type (FEC 60, FEC 75 and FEC 100) (Fig. 1). The antiemetic treatments were standardized in two age groups, ⩽50 years or >50 years (Table 1).

Measurement of nausea, vomiting and well-being

Self-reported CINV and well-being was documented daily during ten days from day 0 (treatment day) in a structured diary distributed to the women on the treatment day.

This diary was developed for and is used in a Swedish National Quality Register on CINV [15]. In the diaries, patients reported the number of vomiting episodes, frequency of nausea and variation of well-being during each day. The intensity of nausea was reported each morning and evening using an ordered categorical (Likert) scale with four response options (none, mild, moderate, and severe nausea). Well-being was also reported each morning and evening using an ordered categorical (Likert) scale with four response options: good, very good, bad or very bad.

The diary also included instructions for the use of prescribed antiemetics for the first five days' post-treatment (Table 1).

Telephone interviews

Ten days after the start of CT, a structured telephone interview was performed by a research nurse. In the interviews, the women were asked if they had experienced nausea or not and if they had experienced any episode of vomiting. If "Yes" (for nausea and/or vomiting), the patients were asked to rate their experience using a Visual analogue scale (VAS) ranging from "0" to "10" (with 0 being no symptom and 10 being worst possible symptom). Likewise, the patients were asked to indicate during which of the ten days after CT they experienced the most intense CINV. The diaries were returned to the research nurse at the start of the next treatment.

Selection and analyses of SNPs

The candidate genes and their SNPs were selected out of those that are commonly known in opioid related nausea, inflammation and toxicity conditions. The hypothesis has being that individual differences in toxicity might in part depend on differences in genes involved in cell cycle progression, cell death process, DNA repair and cell functions. Based on this 48 related SNPs were studied [16–23] (Table 4).

Table 1
Treatment protocol for antiemetic treatment for patients with breast cancer undergoing adjuvant chemotherapy.

Women ⩽50 years and women >50 years	Start of treatment	Treatment day 2–5
NK1 receptor antagonist Aprepitant*	125 mg p.o	80 mg p.o day 2 and day 3
5-HT3 receptor antagonist Ondansetron**	8 mg p.o	8 mg p.o
Cortikosteroid Betametason	8 mg p.o or iv	4 mg day two 2 mg day three 2 mg day four 1 mg day five
Metoclopramid 10 mg (If necessary)		10–20 mg p.o one to three times daily

* Aprepitant use for women ⩽50 years old.
** Ondansetron use for both ⩽50 years old and >50 years old.

Blood samples

Venous blood (30 ml) was drawn from each patient before the start of CT. High molecular weight DNA was extracted from the blood by the MagNa Pure LC2.0 (Roche Diagnostic, Switzerland). The quality and quantity of DNA were determined by Nanodrop and Pico Green ds DNA assay. DNA (250 μg) from each patient was used as the template for SNP analysis. The identification of the SNPs was done by Illumina Golden Gate Genotyping assay at the SNP&SEQ technology platform, Uppsala University, Sweden (http://www.genotyping.se).

Statistics

In the analysis, nausea was dichotomized in nausea (mild, moderate or severe) or no nausea irrespective of day. Descriptive statistics, numbers, medians and percentages were used for the background variables. The genotypes and allele frequencies were quality checked. SNPs where no genotypes were found, not fulfilling Hardy-Weinberg equilibrium (HWE, Chi^2 test, $p < 0.05$) as well as a minor allele frequency (MF) <5%, were discarded from the analysis. The study was designed to find an effect (odds ratio ⩾2.0, with a p-value of 0.05 and power 90%) and a false positive report probability of 3% [16]. Since there were 48 SNPs from 43 candidate genes analyzed, there is a risk of false positive test results. To reduce the number SNP's to analyze, eventual difference in the distribution of alleles where compared between nausea and non-nausea. In the end, there were five remaining SNP's. However, two of these SNP's had zero count of patients in one of the cells in the cross-table and therefore no calculation of Odds-ratio could be performed, rs3088440 in CDKN2A and rs1800610 in TNFα. Also, one of the remaining SNP's rs2854344 in Rb1/LPAR6 had one allele A/A where one was among nausea and one among non-nausea patients. These two patients were recoded as A/G in respective nausea and non-nausea. The three remaining SNP's, rs2530797, rs2234978 and rs2854344 in the genes CCL2, FAS/CD95 and RB1/LPAR6, were used in the final analysis of association to nausea. The statistical software for genetic analysis SAS® Genomics for Windows, ver.9.4 and JMP® Genomics for Windows, ver. 7.0 were used. The Hochberg method was used to correct for multiple testing [24,25].

Results

Out of 175 women, 142 (81%) accepted to participate and signed a consent form. The characteristics of the responding patients are presented in Table 2.

Out of the total number of women asked to participate in the study, blood samples and diaries were collected from 114 (65%), and CINV was reported by 96 (84%) out of these 114 women.

Stratified by age, 33 out of 34 (97%) young women (⩽50 years), and 63 out of 80 (79%) of the older women (>50 years) reported nausea, respectively. The difference was statistically significant (Fisher exact test, $p < 0.01$). A higher proportion of younger women reported acute nausea whereas delayed nausea was reported more frequently among the older women (Table 3, Fisher exact test, $p < 0.01$).

Patient reported data on vomiting was excluded in the analysis, since only 16% of the women experienced vomiting. The number was not sufficient for statistical analysis. An association was found between the day with highest reported VAS scores for nausea and

Table 2
The characteristics of the responding women.

Women	(n = 114)	%
Age (years)		
⩽50	34	30
>50	80	70
Min–max	27–83	
Median	59	
Smoking		
Yes	13	12
No	100	88
BMI		
Min–max	17-45	
Median	28	
Married/cohabiting	85	75
Single	29	25
Comorbidity		
No comorbidity	60	53
Hypertension	24	21
Diabetes	4	3
Rheumatic diseases	9	8
Other disease	17	15

the day reported as worst in terms of well-being (Fig. 2). We found a variation in which day post CT that was associated with the most intense episodes of side effects but the first five days' post CT were most frequently reported (Fig. 2). As this was the first treatment cycle, the antiemetics administered was standardized during the first 4 days. However aprepitant was added to women younger than 50 years (34% n = 39) (Table 1).

SNPS associated to nausea

Three SNPs, rs2530797, rs2234978 and rs2854344 in the genes CCL2, FAS/CD95 and RB1/LPAR6, respectively, were found to be associated with nausea (OR > 2, p < 0.05) (Table 5). No other SNPs were associated with nausea.

Discussion

The most important result from this study is the association of risk for CT induced nausea and individual genetic profiles. Differences in genetic background driving the emetic process could be plausible as the occurrence of CINV is shown to be heterogenous. A majority of the women (84%) in this study experienced nausea after FEC treatment. This is in line with previous studies on adjuvant CT in BC [7,26,27]. Older women experienced less nausea, which also corresponds with results from other investigations. However, we found a difference in time for onset of nausea as younger women more often suffered from acute and older women more often from a delayed nausea. This is in line with our previous study and others [14,28]. Others have found different results. Hilarius (2011) for instance, [6] found that younger women had more delayed nausea than older women. The reason for these differences in the results is difficult to explain. One reason could be different patient populations and/or different antitumor treatments. In our

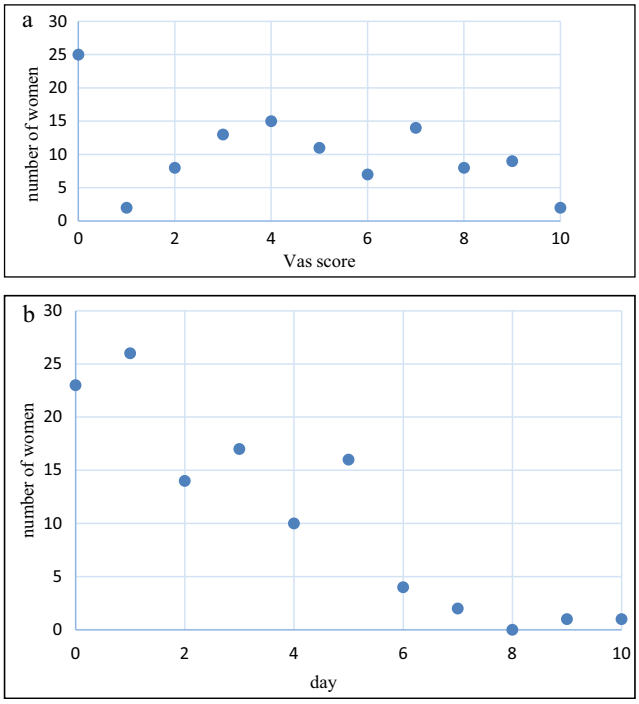

Fig. 2. (a) Reported total VAS-scores for nausea during the first 10 days after start of chemotherapy. (b) Self-reported day for most intense side effects during the first 10 days after start of chemotherapy.

Table 4
Analyzed genes and single nucleotide polymorphism (SNPs).

Gene	SNP	Gene	SNP
IFNg	rs2069705	CCL2	rs2530797
EGFR	rs2293347	XRCC1	rs25487
MGC87042/IL6	rs4719714	CDH13	rs12445758
CYP19A1	rs4646	CDKN2A	rs3088440
TNFa	rs1800629	CCND3	rs3218086
TNFa	rs1800610	GSTP1	rs1695
ABCA1	rs2230806	FAS/CD95	rs2234978
CCL5/Rantes	rs2107538	BRCA2	rs144848
XRCC2	rs2040639	PRKDC/DNAPK	rs1231204
FGFR4	rs2011077	TRPC3/IL2	rs11938795
LIG4/Cyp2D6	rs1805386	PRF1	rs3758562
ATM	rs1801516	PRF1	rs10999426
MTHFR	rs1801133	IL12RB2	rs3790568
CRP	rs1800947	Casp8	rs1045485
MDR/BRCA1	rs1799966	CCL2	rs1024611
CCL4	rs1719153	PPPDE2/Ku70	rs2267437
Rad52	rs11571424	RB1/LPAR6	rs2854344
Casp9	rs1052576	EGF	rs4444903
ABCB1	rs1128503	IL2	rs6822844
IFNg	rs2069718	ABCC5/MRP5	rs7636910
ESR1/EstrogenR	rs2234693	GranzymeB	rs8192917
CCL5	rs2280789	KDM4C/GASC1	rs2296067
MMP2	rs243865	COMT	rs4680
CHRM3	rs10802789	HTR3B	rs1622717

Table 3
Reported distribution of nausea during the first 10 days after start of chemotherapy by age, presented as numbers and percent.

Age	Type of nausea				
	No nausea	Acute nausea	Acute and delayed nausea	Delayed nausea	*P-value (Fishers Exact test)
27–50 (30%) Yrs.	1 (2%)	7 (21%)	22 (65%)	4 (12%)	0.001
51–83 (70%) Yrs.	17 (21%)	6 (8%)	32 (40%)	25 (31%)	
Total 114	18 (16%)	13 (11%)	54 (47%)	29 (25%)	

* The P-values are for the overall four-group.

Table 5
Genes and SNPs associated to nausea and no nausea in the 114 women.

Gene	SNP	Log likelihood ratio *p*-value	OR (95% CI)	SNP (*n* = total women/women experienced nausea)	
FAS/CD95	rs2234978	0.03	A/A vs. A/G 0.5 (0.1–2.6)	A/A	(*n* = 11/9)
			A/A vs. G/G 2.0 (0.3–12.0)	G/G	(*n* = 50/45)
			A/G vs. G/G 3.9 (1.3–11.2)	A/G	(*n* = 53/37)
RB1/LPAR6	rs2854344	0.03	G/G vs. A/G 3.2 (1.2–9.0)	G/G	(*n* = 93/78)
				A/G	(*n* = 21/13)
CCL2	rs2530797	0.01	A/G vs. A/A 3.7 (1.2–11.8)	A/G	(*n* = 44/4)
				A/A	(*n* = 70/19)

study the women's demographics showed a pattern that according to the literature is favorable and should lower the risk of CINV. Most of them were not smokers, most were married or had a partner which is described to be associated with a higher probability of completed treatment [29,30]. Fifty-three per cent did not have any comorbidity. Most of the comorbidity consisted of hypertension (Table 2). Even if 16% of the patients experienced vomiting at least once during the treatment period, this is not regarded as a major problem since it usually happened occasionally [31,32]. Meanwhile, nausea was more persistent. Remarkably, the dosage of FEC did not seem to influence the appearance of nausea. However, only 16% of the women did not experience any nausea, making it impossible to draw any conclusions on the effect of nausea from the subgroups of treatment. Other reason for why some patients' show more nausea than others could be related to emesis pathophysiology. The mechanisms are complex but several substances have been identified [13].

When we linked SNPs with the data from the diaries, we found a trend, however not statistically significant for association to nausea for certain SNPs on day one, three and five post CT (data not shown). When studying the SNPs in relation to nausea during any of the ten days, three SNPs in three out of 43 genes were strongly associated with risk for CINV. It might be that by including more women with BC, other SNPs will be found to associate with CT-induced nausea and also a possible association to acute or delayed nausea.

In the total number of participating women, rs2530797 in CCL2, rs2234978 in FAS/CD95 and rs2854344 in RB1/LPAR6 genes indicated a significant risk for nausea. These three genes have an essential role for the control of cellular homeostasis. CCL2 is a chemokine gene involved in immune-regulatory and inflammatory processes [33]. FAS/CD95 is a death receptor/death ligand system that mediates apoptosis induction to maintain immune homeostasis. In addition, these genes are important in the immune response and elimination of abnormal cells and cancer cells [34]. RB1/LPAR6 is a crucial component of the cell cycle control pathways [35]. Inflammation and cell death could well be associated with nausea even though the mechanism is speculative.

We found no relation between 48 candidate SNPs and the intensity of nausea as measured by VAS (data not shown). A relation between SNP and nausea on certain days did not reach statistically significant levels. This might be due to small sample size.

Previous reports presented that SNPs in the COMT, CHRM3 and HTR3B genes were correlated to nausea in morphine treated patients [21] We tested for SNPs in these genes but found no correlation for CT induced nausea. The difference could possibly be explained by the diverse biological mechanisms of morphine, and CT mediated nausea.

The analysis in this study is based on self-reported data, which gives power to the results. Another advantage is that the genetic techniques are well established. The results indicate a possible genetic impact on the development of nausea, both in the acute and the delayed form, post CT. One weakness though is the fact that only a selected number of possible SNPs were investigated. Exploring the entire genome would possibly identify other interesting SNPs. As the literature does not explore in detail the relation between CINV and genetic background we choose to study the genes previously described to associate to opioid induced nausea as well as genes associated to cell cycle progression, cell death process, DNA repair and cell functions as these might be involved in inflammation and thus toxicity. Thus the results have to be interpreted with great caution [36] and should be validated in other patient groups. The identification of biomarkers for side effects of CT might allow a more personalized care and thus improve both the patients' quality of life and the clinical management.

Conclusions

Chemotherapy induced nausea is a complex experience and an individualized treatment strategy could be possible regarding antiemetic treatments based on SNPs. If proven of clinical value, SNP analysis could be suitable in the clinical practice since it can be done prior to any treatment using fast and cost effective automated techniques.

If the results are confirmed, it could possibly improve and better personalize the antiemetic treatment both in terms of antiemetic drugs as well as other care measures, which at the present time are not totally satisfactory. To validate the findings in this study, further investigation is warranted.

Conflict of interest

The authors declare no conflicts of interest.

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