ANTICANCER RESEARCH *43*: 2671-2681 (2023)
doi:10.21873/anticanres.16433

Single Nucleotide Polymorphism Directed Antiemetic Treatment in Women With Breast Cancer Treated With Neo- or Adjuvant Chemotherapy: A Randomised Multicentre Phase II Study. (EudraCT: 2015–000658-39)

DELMY OLIVA[1], BENGT-ÅKE ANDERSSON[2], LEVAR SHAMOUN[3], NONGNIT LEWIN[4], MATS P. NILSSON[5,6], ELSY-BRITT SCHILDT[7], LISA FUST[7], ULRIKA ÅSENLUND[8], GUNILLA SELLERSTAM[9], ELLINOR ELINDER[9], LENA SHARP[10,11] and FREDDI LEWIN[1,2]

[1]*Department of Oncology, Ryhov County Hospital, Jönköping, Sweden;*
[2]*Department of Natural Science and Biomedicine, School of Welfare, Jönköping University, Jönköping, Sweden;*
[3]*Department of Laboratory Medicine and Pathology, Region Jönköping County, Jönköping, Sweden;*
[4]*Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden;*
[5]*Futurum, Academy of Health and Care, Region Jönköping County, Jönköping, Sweden;*
[6]*Department of Medical and Health Sciences, Linköping University, Linköping, Sweden;*
[7]*Department of Oncology, Kalmar County Hospital, Kalmar, Sweden;*
[8]*Trial Unit, Department of Oncology, Gävle County Hospital, Gävle, Sweden;*
[9]*Trial Unit, Department of Oncology, SöderHospital AB, Stockholm, Sweden;*
[10]*Department of Nursing, Umeå University, Umeå, Sweden;*
[11]*Regional Cancer Centre Stockholm-Gotland, Stockholm, Sweden*

Abstract. *Background/Aim: The role of single nucleotide polymorphisms (SNPs) in the frequency and intensity of chemotherapy-induced nausea and vomiting (CINV) in women with breast cancer (BC) is unclear. The primary purpose of this study was to compare/evaluate the effect of SNP-guided antiemetic treatment versus standard CINV treatment. Patients and Methods: A randomised, factorial, phase II multicentre study design was used. Women planned for neoadjuvant or adjuvant chemotherapy with epirubicin, cyclophosphamide and fluorouracil (FEC /EC, with or without fluorouracil) for BC were randomised to SNP-guided antiemetic treatment (based on the results of SNP analyses) versus standard CINV treatment. Blood samples were taken before the treatment was initiated. Patient-reported data on CINV (during 10 days from onset of cancer treatment) and health-related quality of life (HRQoL), were collected before and after the first cancer treatment. Results: A total of 188 women were included. Overall, nausea was reported by 86% (n=129) of the patients during the ten-day period from the start of cancer treatment. The SNP genotype studied varied. In FAS-CD95, the genotypes AG and GG were overrepresented; in RB1-LPAR6, GG was overrepresented, and in CCL2, both AA and GG were overrepresented. We found no statistically significant difference in CINV between SNP-guided antiemetic treatment versus standard CINV treatment. Conclusion: SNP-guided antiemetic treatment could be as effective as standard treatment. SNP-guided antiemetic treatment of CINV is possibly useful in detecting patients with a higher or lower risk for CINV and thus may help in avoiding over-treatment with toxic components. CINV negatively affects the HRQL.*

Correspondence to: Delmy Oliva, RN, Ph.D., Department of Oncology, County Hospital Ryhov, SE-55185 Jönköping, Sweden. Tel: +46 102426909, Fax: +46 102422916, e-mail: delmyoliva@telia.com; delmy.oliva@rjl.se

Key Words: Breast cancer, chemotherapy-induced nausea and vomiting, single nucleotide polymorphism.

Chemotherapy-induced nausea and vomiting (CINV) varies in both incidence and intensity between individuals. The development of antiemetic drugs has been significant over the past 30 years. The most common drug combination for CINV is a combination of NH1 receptor antagonist, 5-HT3 receptor antagonist, and some form of corticosteroids (1). Even though treatment has improved significantly with these treatment protocols, CINV remains a clinical problem (2), negatively affecting many cancer patients' daily lives.

Another issue is the lack of an individual approach, with some patients not experiencing CINV and therefore risking unnecessary antiemetic treatment (3).

Heterogeneity regarding nausea and vomiting has been demonstrated in women with BC treated with the anthracycline Epirubicin and the nitrogen mustard alkylating mediator Cyclophosphamide (EC), sometimes in combination with the antimetabolite 5-Fluorouracil (FEC) (4). Despite previous experience of nausea associated with pregnancy, motion sickness, age, and sex, it is not possible to predict which patients will be prone to CINV (4, 5). Better predictions for CINV could improve the quality of care by enabling individualised treatment, and thereby potentially better outcomes (6). The mechanisms behind different cytostatic drugs vary between the types of drugs used. Cells in the division phase are sensitive to chemotherapy, and cells in the gastrointestinal tract are particularly sensitive to side effects of chemotherapy (7). One hypothesis about the mechanism of CINV is that cell death causes inflammation in the gastrointestinal tract, which in turn could cause nausea (8).

A factor may be genetic variations in DNA, so-called single nucleotide polymorphisms (SNPs) (9). SNPs are defined as variations in nucleotides in which an allele is represented in more than 1% of the studied group. SNPs could have an impact on the ability to bind other components and transcribe the information, suppress cell cycle progression, or induce cell death (10, 11). There is a lack of knowledge concerning the role SNPs could play in the frequency and intensity of CINV in women with breast cancer (BC) (12).

In our previous study, high risk genotypes of three SNPs were identified as potentially associated with CINV. Seventy-five percent of the patients had one or more of a certain SNP genotype but it is unknown how potentiating these can be. The SNPs were localised in genes of importance for inflammation, apoptosis, and cell proliferation (13). Rs2234978 is located in the *FAS* gene, which encodes a receptor that has a central role in programmed cell death. In addition, the gene is important in the immune elimination of irregular cells, such as virus-infected cells and cancer cells (14). Rs2854344 is located in *RB1/LPAR6*. *RB1* or Retinoblastoma-1 encodes a protein that plays an important role in regulating cell dispersion and induces apoptosis or cell death (15). Rs2530797 is located in the *CCL2* gene and encodes a chemo attractive protein, involved in inflammation (16). A possible marker that could identify those individuals who have a lower risk of CINV could prevent over-treatment (17).

One way to counteract CINV is the use of non-pharmacological methods such as acupressure, which has been shown to be a safe and effective complement to pharmacological CINV treatment (18-20). Acupressure is also frequently used to effectively treat pregnancy sickness and motion sickness (21, 22).

The primary purpose of this research was to study whether patients experience equivalent treatment effects using SNP-guided antiemetic treatment compared to receiving standard treatment.

The secondary endpoints were to compare patient-reported acute and delayed CINV (intensity and number of days vomiting) between SNP-guided antiemetic treatments *versus* standard CINV treatment, as well as to estimate the value of a structured anamnesis.

Patients and Methods

Study design. In this randomised, factorial, phase II multicentre study, four hospitals located in different parts of Sweden (with an uptake of 248,000 to 500,000 citizens) participated. Two interventions were studied in the same study, SNP-guided antiemetic treatment *versus* standard treatment and acupressure *versus* placebo acupressure, respectively. Only SNP- guided antiemetic treatment *versus* standard treatment is reported in this paper.

The study was conducted in accordance with the Swedish Medical Products Agency (Läkemedelsverket) and the latest versions of the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use, guidelines for Good Clinical Practice (ICH-GCP) (23) and the Declaration of Helsinki (24). Patient data were managed in accordance with the Swedish Personal Data Act (25).

Inclusion and exclusion. Women treated for BC were included consecutively from the four hospitals during January 2017 to December 2020. The included women were planned for neoadjuvant or adjuvant chemotherapy with FEC/EC treatment, were ≥18 years of age, understood the Swedish language in speech and writing and submitted written informed consent. Exclusion criteria consisted of previous treatment with chemotherapy, verified distant metastases, and contraindications to any of the included study drugs. Only the first treatment they received was included in the study. The time in the study for each patient was 3±4 weeks.

Cancer treatment for all included patients. The cytostatic regimens examined in the study included EC_{60} (Epirubicin 60 mg/m^2 and Cyclophosphamide 600 mg/m^2), FEC_{75} (Fluorouracil 600 mg/m^2, Epirubicin 75 mg/m^2 and Cyclophosphamide 600 mg/m^2), EC_{75} (Epirubicin 75 mg/m^2 and Cyclophosphamide 600 mg/m^2), and EC_{90} (Epirubicin 90 mg/m^2 and Cyclophosphamide 600 mg/m^2).

Randomisation process and informed consent. The women were randomised to either open genetic (information receiving antiemetic therapy based on the results of the SNP analyses) or hidden genetic information (treated according to the standard antiemetic) according to the schedule seen in Table I and Table II. The patients were included at their first visit to the respective oncology outpatient clinic. The research nurse informed them about the study (the purpose and processes involved, its voluntary nature and the option to opt out without further explanation) orally and in writing. After written informed consent was obtained, the clinical information was registered in a case reported form (CRF), including previous experiences of nausea and/or vomiting, motion sickness, and nausea in relation to pregnancy, age, alcohol use, smoking, and body max index (BMI). The tumour TNM classification (26) and the Eastern

Table I. *Treatment schedule for patients with high risk of nausea according to the SNP-genotype.*

High risk	T1, Start of treatment	Day 2-10 after start of treatment
Betamethasone®	12 mg Orally or *iv*	8 mg orally Day 2 4 mg Day 3 to Day 4
Other antiemetic according to the investigator's choice		

iv: Intravenous.

Table II. *Treatment schedule for patients with medium/low risk of nausea.*

Medium risk	T1, Start of treatment	Day 2-10 after start of treatment
Betamethasone®	8 mg orally or *iv*	4 mg orally Day 2 2 mg Day 3 to Day 4
Other antiemetic according to the investigator's choice		

iv: Intravenous.

Cooperative Oncology Group (ECOG/WHO) performance status were included in the CRF (27). Blood samples were collected for analysis after randomisation. At the appointment for the first cancer treatment, the patient received repeated information about the study from the research nurse, who also handed over the patient diary and a quality-of-life questionnaire. The study nurses were not blinded to the study. The results of the randomisation were revealed in connection with electronic randomisation.

Based on randomisation to open or hidden genetic information, each research subject was eligible for one of three different antiemetic treatment options.

Intervention group (open genetic information). Subjects randomised to open genetic information, based on SNP analysis, received treatment according to "high risk" or "intermediate/low risk" as specified in Table I and Table II.

Control group (hidden genetic information). Subjects randomised to hidden genetic information received standard care as shown in Table I. CINV treatment was prescribed according to normal guidelines at the clinics. No study-specific labelling of the drugs was applied. Only drugs included in guidelines for standard antiemetic treatment and which are used in clinical practice were administered.

Data collection. The patients self-managed the CINV drug administration according to the prescription and reported the intake in the patient diary. Compliance was monitored by the patient documenting their drug intake in the diary. Generic preparations were used entirely depending on the purchased brand at the local pharmacy. The dosage and, if needed, additional doses were chosen according to local guidelines for antiemetic treatment.

Risk classification for patients in the intervention group. The patients were classified according to the criteria below for "high" or "medium/low" risk of nausea and received corticosteroid (Betamethasone®) in addition to CINV treatment according to the respective group's treatment schedule described in Table I and Table II. High risk: Presence of at least one of the following SNP genotypes: GG for rs2234978, GG for rs2854344, and AG rs2530797. Medium/low risk: No SNP genotype, described above.

Patient-reported data. The patients were instructed to keep a structured diary. In the diary, for each of the ten days after the administration of the first chemotherapy, they self-reported, morning and evening, the frequency of nausea, vomiting, and their well-being in general. Nausea was categorised as: none, mild, moderate, or severe. Vomiting was stated with yes/no. Well-being was stated in four different categories: very good, good, bad, and very bad. The level of nausea was quantified, using a Visual Analogue Scale (VAS) (28) where 0 was no nausea and 10 worst possible nausea. In addition, health-related quality of life (HRQoL) was measured using the Swedish version of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ C-30 core questionnaire, at baseline (before the start of treatment) and follow-up (ten days after the first treatment). The EORTC QLQ C-30 is a validated instrument, developed to assess HRQoL among cancer patients and has been used in more than 3,000 studies. It consists of five functional scales (physical, emotional, social, and cognitive functioning, and three symptom scales (fatigue, pain, and nausea/vomiting). In addition, EORTC QLQ C-30 includes six single items on the impact of financial difficulties, symptoms, and overall quality of life. Responses are graded into four categories, from 1 - not at all, to 4 - very much. Two of the items on global health are graded from 1 - very poor to 7 - excellent (29). The women completed the questionnaire at home and returned it to the research nurse before the start of the first treatment. The second questionnaire was returned at the start of the second treatment.

DNA extraction and SNP analyses. In the present study, genomic DNA was isolated from blood samples using biorobot EZ1 Advanced XL (Qiagen, Hilden, Germany) with EZ1 DNA Blood 200 μl Kit from the same company. The purity and concentration of the DNA were measured using a Nano Drop spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). The TaqMan SNP genotype assays (Applied Biosystems, Foster City, CA, USA) were

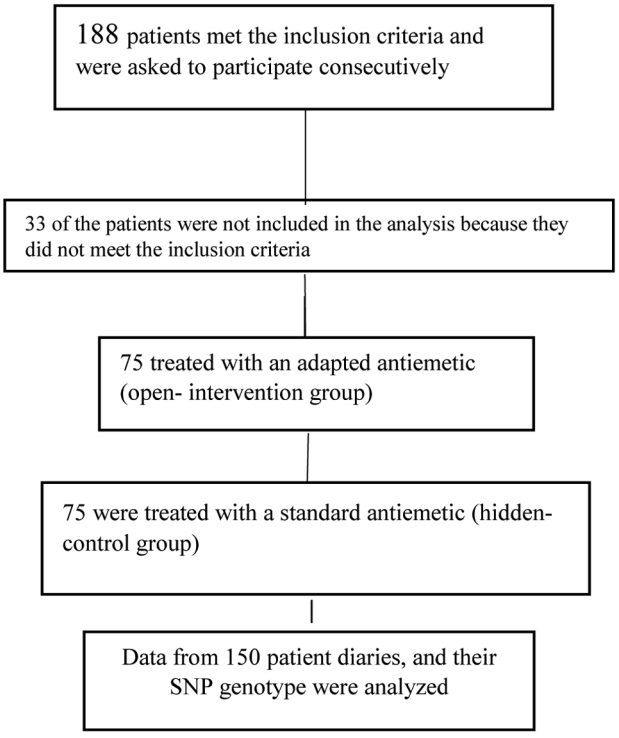

Figure 1. *Flow chart of the inclusion of patients.*

Table III. *Self-reported demographic data from all patients included.*

	Min	Max	Mean
Age	27	83	58
Body Mass Index (BMI)	18	42	27
Smoke	16 (9)	161 (91)	
Current smoker	14		
Previous smoker	2		
Never smoker	161		
Alcohol consumption			
Yes	141 (80)		
No	34 (20)		
Previous experience of pregnancy nausea			
Yes	89 (51)		
No	78 (45)		
Not applicable	9 (5)		
Motion sickness			
Yes	66 (38)		
No	109 (62)		
Occupation			
Working	92 (52)		
On sick leave	15 (8)		
Retired	58 (33)		
Other	11 (7)		
Civil status			
Married	134 (76)		
Single	33 (19)		
Cohabiting	3 (2)		
Widowed	5 (3)		

used for analysis of the SNP genotypes in *FAS/CD95* (rs223478), *RB1/LPAR6* (rs2854344), and *CCL2* (rs2530797) according to the manufacturer's instructions with 7900HT Fast Real-Time PCR System (Applied Biosystems).

For patients randomised to open SNPs, the antiemetic treatment was determined by the test results. The result of the SNP genotype (high risk or medium/low risk) was sent to the research nurse by email (or fax if this was preferred) before 18.00 on the same day as the analysis was conducted. For patients randomised to hidden SNPs (control group) standard antiemetics were administered (Table I).

Statistics. As this is an exploratory phase II trial, when selecting the sample, the percentage of nausea in the medium/high risk group was estimated at 80% and the non–inferiority limit was set at 14% (equivalent to odds ratio=1.18); this was considered clinically relevant. With a significance level of 0.05 and a power of 0.8, 101 included medium/low risk patients were then required per arm (hidden *vs.* open genetic information). When the proportion of intermediate/low risk patients was estimated at 25%, the total number of patients that needed to be included was 404 in each group. Data are presented as numbers, percentages, min and max values, mean and 95% confidence intervals as appropriate. If the subjective grade of nausea was reported to be >5 on the VAS scale, during any of the ten days in the diary, this was categorised as nausea at least once during the period. Fisher's exact test was used to evaluate differences between baseline and follow-up for the different dimensions on the EORTC QLQ C-30 questionnaire.

For differences between exposure and outcome for categorical variables Fisher's exact test was used. A p-value ≤0.05 was considered as a statistically significant result. The results must however always be judged in the light of clinical importance for the patients.

Results

Out of the 188 patients included in the total sample from the four sites, 45 (24%) were excluded due to non-compliance with the betamethasone dose according to randomisation (n=33, 18%) or non-completion of the study (n=12, 6%). Data from 150 (80%) patients (75 in the intervention group and 75 in the control group) were analysed (Figure 1).

The median age was 58 years. Eighty percent (n=141) reported consuming alcohol and 9% (n=16) reported that they were current smokers. Half of the women (n=89, 51%) reported having previous experience of pregnancy nausea, while 38% (n=66) reported previous experience of motion sickness. Demographic data are presented in Table III.

Tumour characteristics. The tumour status is presented in Table IV. Most patients, 134 (77%), were diagnosed with ductal carcinomas, while 25 patients (14%) had lobular carcinomas.

Table IV. *Age, tumour characteristics, stage of disease, and chemotherapy received.*

Characteristics	All patients (N=174)	<60 years old (N=83)	≥60 years old (N=91)	EC60 (N=6)	EC75 (N=37)	EC90 (N=115)	EC100 (N=8)	FEC75 (N=8)
Age (years)								
Median (range)	60	50 (28-59)	67 (60-83)	76 (63-83)	69 (45-78)	56 (28-74)	50 (36-65)	71 (69-75)
Breast tumour type, N (%)								
Ductal	134 (77)	62 (46)	72 (54)	5 (4)	27 (20)	88 (66)	6 (4)	8 (6)
Lobular	25 (14)	14 (56)	11 (44)	1 (4)	4 (16)	19 (76)	1 (4)	0
Other	15 (9)	7 (47)	8 (53)	0	6 (40)	8 (53)	1 (7)	0
Stage of disease, N (%)								
I	7 (4)	2 (29)	5 (71)	0	3 (43)	4 (57)	0	0
IA	34 (20)	14 (41)	20 (59)	0	11 (32)	19 (56)	1 (3)	3 (9)
IB	4 (2)	2 (50)	2 (50)	0	0	3 (75)	0	1 (25)
IIA	63 (36)	35 (56)	28 (44)	3 (5)	9 (14)	43 (68)	6 (10)	2 (3)
IIB	44 (25)	18 (41)	26 (59)	3 (7)	9 (21)	30 (68)	1 (2)	1 (2)
IIIA	13 (8)	7 (54)	6 (46)	0	3 (23)	10 (77)	0	0
IIIB	2 (1)	1 (50)	1 (50)	0	1 (50)	1 (50)	0	0
IIIC	4 (2)	1 (25)	3 (75)	0	1 (25)	2 (50)	0	1 (25)
Other	3 (2)	3 (100)	0	0	0	3 (100)	0	0
Receptor status, N (%)								
ER								
Positive	137 (79)	68 (49.6)	69 (50.4)	5 (4)	28 (20)	91 (66)	8 (6)	5 (4)
Negative	37 (21)	15 (40)	22 (60)	1 (3)	9 (24)	24 (65)	0	3 (8)
PR								
Positive	100 (57)	56 (56)	44 (44)	3 (3)	18 (18)	67 (67)	7 (7)	5 (5)
Negative	74 (43)	27 (36)	47 (64)	3 (4)	19 (26)	48 (65)	1 (1)	3 (4)
HER2								
Positive	28 (16)	11 (39)	17 (61)	1 (4)	5 (18)	20 (71)	0	2 (7)
Negative	146 (84)	72 (49)	74 (51)	5 (3)	32 (22)	95 (65)	8 (6)	6 (4)

CINV. A majority of patients (n=53, 37%) reported day four after chemotherapy as the most intense for CINV. However, 19 (13%) women in the control group, "Hidden", reported in the diary that they experienced mild nausea. In the intervention group, "open genetics", 29 (20%) of the women experienced mild nausea, while three reported moderate nausea and two severe nausea (Table V).

Previous experience of nausea and vomiting.
Pregnancy. In total, 145 patients were analysed for this variable. Of these, 78 patients (54%) reported nausea during their previous pregnancies. Among these, 23 reported CINV in this study (16%). A total of 60 patients (41%) did not experience previous nausea during pregnancy (Table V).

Motion sickness. In total, 144 patients were analysed for this variable. Of these, 55 patients (38%) reported previous experience of motion sickness. Among these, 21 (15%) experienced CINV. A total of 89 patients (62 %) had not experienced previous motion sickness. Among these, 18 patients (12%) reported CINV and 71 patients (49%) did not (Table V).

Age and impact of CINV. We found that younger women (n=31, 36%) reported statistically significantly more nausea (≥ VAS 5, during day 1-10), compared with older women (n=19, 20%), Fisher's exact test, p=0.03) (Table V).

Alcohol consumption and impact of CINV. In total, 175 patients answered the question. Of these, 141 (80%) patients reported using alcohol, and of them, 38 (27%) reported CINV VAS ≥5 during any of the ten days after treatment. In total, 34 of 175 (20%) patients reported not using alcohol; however, 12 patients (7%) reported CINV VAS ≥5 during any of the ten days. No statistically significant influence of alcohol use on CINV was found (Table V).

Distribution of SNP genotype in vomiting and nausea. Vomiting was reported by 13 (8%) of the patients in both studied arms, disregarding the three biomarkers. Nausea was reported by 129 (86%) of the patients during the ten days they reported. Only 21 (14%) of the patients did not report any nausea. The sequence in each SNP studied varied. In *FAS-CD95*, the AG and GG sequencing were overrepresented; in RB1-*LPAR6*, GG was overrepresented and in *CCL2* both AA

Table V. *Chemotherapy-induced nausea and vomiting stratified on randomisation, visual analogue scale (VAS) scoring associated with alcohol consumption, age, pregnancy, and motion sickness.*

Nausea between hidden and open biomarkers (SNP)						
	Hidden (Control group)	Open (Intervention group)	Total	Fisher's Exact test		
Nausea	64	65	129	p=1.0		
No nausea	11	10	21			
Total	75	75	150			
Nausea morning day 4, 143 patients (hidden and open antiemetic)						
	None	Mild	Moderate	Severe	Total	Fisher's Exact test
Hidden	53	19	0	0	72	p=0.009
Open	37	29	3	2	71	
Total	90	48	3	2	143*	
*Missing 38 of the total group.						
Nausea morning day 10, (Hidden and open antiemetic) Sample size=140						
	None	Mild	Moderate	Severe	Total	Fisher's Exact test
Hidden	61	7	2	0	70	p=0.5
Open	57	11	1	1	70	
Total	118	18	3	1	140	
[1]VAS scoring ≥5 and alcohol consumption any day 1-10 after treatment (sample size=175)						
	Nausea	No nausea	Total	Fisher's Exact test		
Alcohol use	38	103	141	p=0.40		
Non-alcohol	12	22	34			
Total	50 (29%)	125 (71%)				
VAS scoring ≥5 and age any day 1-10 after treatment (sample size=181)						
	Nausea	No nausea	Total	Fisher's Exact test		
≤59 years	31	56	87	p=0.03		
≥60 years	19	75	94			
Total	50 (28%)	131 (72%)				
VAS scoring ≥5 and previous experience of nausea in pregnancy any day 1-10 after treatment (sample size=145)						
	Nausea	No nausea	Total	Fisher's Exact test		
Pregnancy nausea	23	55	78	0.24		
No pregnancy nausea	12	48	60			
Never pregnant	4	3	7			
Total	35 (27%)	103 (73%)				
VAS scoring ≥5 and previous experience of motion sickness any day 1-10 after treatment (sample size=144)						
	Nausea	No nausea	Total	Fisher's Exact test		
Motion sickness	21	34	55	0.02		
No motion sickness	18	71	89			
Total	39 (27%)	105 (73%)				

SNP: Single nucleotide polymorphism; [1]patient's own measurement of nausea.

Table VI. *Chemotherapy-induced nausea and vomiting stratified based on the genotype of the three analysed SNPs.*

Vomiting, any day			Nausea, any day		
SNP genotype	Yes	No	SNP genotype	Yes	No
FAS-CD95-genotype rs2234978					
AA	1	10	AA	12	1
AG	8	65	AG	58	14
GG	4	66	GG	59	6
Total	13	141		129	21
RB1-LPAR6 genotype rs2854344					
AG	1	24	AG	24	3
GG	12	117	GG	105	18
Total	13	141		129	21
CCL2 genotype rs2530797					
AA	4	59	AA	52	12
AG	6	72	AG	59	9
GG	3	10	GG	18	0
Total	13	141		129	21

SNP: Single nucleotide polymorphism.

and GG were overrepresented (Table VI). To illustrate how the patients perceived nausea in relation to SNP, the evening of day one is presented in Table VII.

HRQoL based on the EORTC QLQ C-30 questionnaire. We found statistically differences between baseline and follow-up for the following scales: Global health status, p-value=0.002; Physical functioning, p=0.0009; Role functioning, p=0.0001; Cognitive functioning, p=0.002; Social functioning, p=0.0006. The symptoms in the questionnaire were likewise affected at follow-up. Fatigue, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties are not presented in a Table. Only nausea and vomiting, which indicated a p=0.0001, are presented since CINV was the main study objective (Table VIII).

Table VII. *Nausea stratified based on SNP genotype of the three analysed SNPs, on the evening of day 1 according to the diary.*

SNP GENOTYPE	None	Mild	Moderate	Severe	Total
FAS-CD95-genotype rs2234978					
AA	7	3	2	1	13
AG	41	26	6	4	77
GG	35	29	9	7	80
					170*
RB1_LPAR6 genotype rs2854344					
AG	17	7	1	4	29
GG	66	51	16	8	141
					170
CCL2 genotype rs2530797					
AA	37	25	3	6	71
AG	42	28	9	4	83
GG	4	5	5	2	16
					170

*Missing 11 patients where the analysis failed. SNP: Single nucleotide polymorphism.

Discussion

In this phase II randomised multicentre study, we found that nausea was unpredictable, whether the antiemetic was adjusted or not. A clear majority (86%) of the studied patients experienced some CINV despite the usage of the recommended combination of antiemetics, in accordance with international guidelines (30, 31). The hypothesis was that no difference in nausea would be found between standard antiemetic treatment and adjusted antiemetic treatment based on genetic biomarkers (SNPs). No known biomarkers exist to predict the patient's risk of nausea at the moment. Regarding the primary endpoint, *i.e.*, that SNP-guided antiemetic treatment would have the same effect as standard maximum antiemetic treatment, we previously observed that many patients were over-treated, with various side effects as a result. We therefore decided to adapt the

Table VIII. *Health-related quality of life at baseline and follow-up measured by European Organisation for Research and Treatment for Cancer Quality of life Questionnaire core 30 (EORTC QLQ C-30).*

	QoL n (%)	PF	RF	EF	CF	SF	CINV	
Baseline/Range								
0-33.3	9 (6)	5 (3)	25 (18)	16 (11)	5 (3)	11 (8)	116 (81%)	No nausea
42-66.7	61 (42)	19 (13)	38 (26)	58 (40)	24 (17)	44 (30)	28 (19%)	Nausea
75-100	74 (52)	120 (84)	81 (56)	70 (49)	115 (80)	89 (62)		
Follow-up/Range								
0-33.3	22(15)	14 (10)	52 (36)	13 (11)	11 (8)	26 (18)	66 (46%)	No nausea
42-66.7	81 (56)	38 (26)	45 (31)	50 (40)	45 (31)	60 (41)	79 (54%)	Nausea
75-100	42 (29)	93 (64)	48 (33)	61 (49)	89 (61)	59 (41)		
Difference between baseline and follow-up using Fisher's exact test	p=0.002	p=0.0009	p=0.0001	p=1.000	p=0.002	p=0.0006	p=0.0001	

n: Number of frequencies; QoL: Global health status; PF: physical functioning; RF: role functioning; EF: emotional functioning; CF: cognitive functioning; SF: social functioning; CINV: chemotherapy induced-nausea and vomiting.

steroid part of the treatment, which is known to cause unwanted side effects (32, 33), for the patients that lacked the SNPs previously found to be associated with an increased risk for CINV. Otherwise, it is known that CINV can occur regardless of the antiemetic that the patient receives (34, 35). It is known that CINV is a complicated symptom that needs to be addressed both medically and non-medically for better results (30, 36). The physiological causes of nausea are challenging to understand in BC patients, though it is known that some cytostatic medications harm cells in the intestinal wall (31, 37).

As a secondary goal we compared the value of a structured anamnesis to SNP-guided antiemetic treatment, since many claim that in addition to the pathophysiological cause of CINV, there are other factors such as age, sex, alcohol consumption, and anxiety that are strong factors in the emergence of CINV (38-41). No statistically significant differences were found when the results were compared between themselves. Among patients younger than 60 years, as we used in this study, the intensity of nausea was higher than that for patients aged 60 or older, indicated by 5 or more according to the VAS scale. This difference is in line with other studies (37, 42). Alcohol use did not seem to affect the risk of CINV. However, the number of patients in the non-drinking group was too small to allow any conclusion that could be compared to the results in other studies (43, 44). CINV associated with the SNPs used as biomarkers in this study has been shown to have a good association with the number of patients who have these polymorphisms and moderate to severe nausea. The SNPs localised in the genes *FAS-CD95, RB1-LPAR6,* and *CCL2*, and their genotypes found in our previous study (13) may be used for identifying patients who would experience nausea.

Based on HRQoL, only emotional functioning did not change between baseline and follow-up. The other four functioning scales of the questionnaire: physical, role, cognitive, and social functioning, were dramatically changed, which means that the patients' HRQoL was affected during the time of treatment. The symptoms of fatigue, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties were also affected somehow, which implies that the quality of life of these women had been affected (data not shown). Nausea and vomiting were reported at baseline by 28 (19%) of the patients, and at follow-up 79 (54%) of the patients reported CINV. These findings are in accordance with other studies where reduced HRQoL was identified in association with chemotherapy, even if it was not the same questionnaire that was used (45-47).

One of the main limitations of this study was the relatively small study sample. The inclusion started at the beginning of 2017. Various problems encountered, for example new oncological treatment modalities were introduced for BC patients, and the COVID-19 pandemic occurred (which stopped the inclusion prematurely, as the lab staff were unable to devote time to research). When the study was designed, it was thought, based on the power calculation, that 880 patients would be needed to obtain statistical power to show equality between the two arms ±14%. However, although this number of patients was not achieved, the results indicate that the hypothesis is valid even if not conclusive. Just to clarify, the results presented in some tables include all the patients and in others only those affected and reported in a specific situation. Some patients did not fill everything in the questionnaires or in the diary and therefore the number of answers will be different for the different variables we asked about.

The use of biomarkers is still not well studied regarding predicting CINV, and no other study has found the same

biomarkers we found. We still conclude that the SNPs in this study indicated the usefulness in relation to the presence of CINV. However, the results must be confirmed in larger randomised studies. It is possible that a structured anamnesis regarding previous experience of nausea could be a complement to SNP-guided treatment, in identifying patients who would benefit from a lower intensity of antiemetic treatment, since some patients with a history of previous pregnancy-related nausea and or motion sickness experienced CINV in this study. However, the age of the women had a significant impact on CINV, regardless of previous experience or SNP.

Conclusion

The results indicate that SNP-guided antiemetic treatment could be as effective as standard treatment. SNP-guided antiemetic treatment of CINV is possibly useful in detecting patients with a higher or lower risk for CINV, thereby avoiding over-treatment with toxic components in the antiemetic treatment. CINV negatively affects the HRQL of the patients. More research is needed, including larger samples, to further establish the possible impact of SNP-guided antiemetic therapy. This therapy needs to be addressed both medically and non-medically for better results.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Delmy Oliva performed writing – original draf and conceptualization, project administration, visualization, conceptualization, methodology, validation. Bent-Åke Anderson, Levar Shamoun and Nongnit Lewin, validation and investigation. Mats P. Nilsson, validation, formal analysis. Elsy-Britt Schildt, Lisa Fust, Gunilla Sellerstam, Ellinor Elinder and Ulrica Åsenlund, contribution with patient recruiting-resources. Lena Sharp, writing – review and editing. Freddi Lewin, supervision, funding acquisition, conceptualization, methodology.

Acknowledgements

The Authors would like to thank the nurses and physicians at the Department of Oncology and the staff at the clinical trial unit from all the centres participating for the help with the inclusion and collection of questionnaires. The Authors also thank all the participating patients for making this study possible. Special thanks go to Karin Skoglund and Forum Östergötland for the legal support.

Funding

This investigation was partly supported by the Foundation for Clinical Cancer Research in Jönköping and Futurum Academy for Health and Care, Region Jönköping County and the Medical Research Council of Southeast Sweden, FORSS.

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Received March 8, 2023
Revised March 24, 2023
Accepted March 27, 2023