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

Delmy Oliva a,b,* , Mats Nilsson c, Bengt-Åke Andersson b,d, Lena Sharp e,f, Freddi Lewin a,b, Nongnit Laytragoon-Lewin b,d

a Department of Oncology, Ryhov County Hospital, SE-551 85 Jönköping, Sweden
b Linköpings University, Department of Clinical and Experimental Medicine, Oncology, SE-581 85 Linköping, Sweden
c Futurum – The Academy for Healthcare, Region Jönköping County, SE-551 85 Jönköping, Sweden
d Division of Medical Diagnostics, Region Jönköping County, SE-551 85 Jönköping, Sweden
e Regional Cancer Centre, Stockholm-Gotland, SE-10239 Stockholm, Sweden
f Karolinska Institutet, Department of Learning, Informatics Management and Ethics, SE-171 77 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 26 September 2016
Revised 29 November 2016
Accepted 4 December 2016
Available online 27 December 2016

Keywords:
Single nucleotide polymorphisms
Chemotherapy
Nausea
Breast cancer

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.

© 2016 The Authors. Published by Elsevier Ireland Ltd on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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]. 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.

* Corresponding author at: Department of Oncology, Ryhov County Hospital, SE-551 85 Jönköping, Sweden. Fax: +46 (0)36 12 29 16.
E-mail address: delmy.oliva@rlj.se (D. Oliva).

http://dx.doi.org/10.1016/j.ctro.2016.12.001
2405-6308/© 2016 The Authors. Published by Elsevier Ireland Ltd on behalf of European Society for Radiotherapy and Oncology.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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 receptors 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 (≥ 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/m² iv, epirubicin 100 mg/m² iv and cyclophosphamide 500 mg/m² iv; FEC 75: fluorouracil 600 mg/m² iv, epirubicin 75 mg/m² iv and cyclophosphamide 600 mg/m² iv and FEC 60: fluorouracil 600 mg/m² iv, epirubicin 60 mg/m² iv and cyclophosphamide 600 mg/m² 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.

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).

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, Chi² test, p < 0.05) as well as a minor allele frequency (MF) <5%, were discared 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 SNPs. However, two of these SNPs 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 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 |
| NFK1 receptor antagonist | 125 mg p.o | 80 mg p.o day 2 and day 3 |
| Aprepitant | 8 mg p.o | 8 mg p.o |
| 5-HT3 receptor antagonist | 8 mg p.o | 8 mg p.o |
| Ondansetron | 8 mg p.o or iv | 4 mg day two 2 mg day three |
| Betametason | Metoclopramid 10 mg | 2 mg day four 1 mg day five |
| (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.
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

Table 2
The characteristics of the responding women.

| Age (years) | 27–50 (30%) yrs. | 51–83 (70%) yrs. | Total 114 |
|------------|------------------|------------------|-----------|
| No nausea  | 1 (2%)           | 17 (21%)         | 18 (16%)  |
| Acute nausea | 7 (21%)         | 6 (8%)           | 13 (11%)  |
| Acute and delayed nausea | 22 (65%)     | 32 (40%)         | 54 (47%)  |
| Delayed nausea | 4 (12%)       | 25 (31%)         | 29 (25%)  |

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

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

| Age (years)          | Type of nausea          | P-value (Fishers Exact test) |
|----------------------|-------------------------|------------------------------|
|                      | No nausea               | Acute nausea                | Acute and delayed nausea | Delayed nausea |
| 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%)      |                |

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

| Gene       | SNP       | Gene       | SNP       |
|------------|-----------|------------|-----------|
| IFNg       | rs2069705 | CCL2       | rs2530797 |
| EGFR       | rs2293347 | XRC1       | rs25487   |
| MGC87042/ IL6 | rs4719714 | CDH13      | rs12445758|
| CYP19A1    | rs4646    | Cdkn2a     | rs3088440 |
| TNFa       | rs1806029 | Ccnd3      | rs318086  |
| TNFa       | rs1806010 | Gstp1      | rs1695    |
| ARCA1      | rs2230806 | Fas/Cd95   | rs2234978 |
| CCL5/Rantes| rs2107538 | BrcA2      | rs144848  |
| XRC2       | rs2046039 | Proc/DnApk | rs1231204 |
| Fgfr4      | rs2011077 | Trfc3/J1   | rs11938795|
| Lig4/Cyp2D6 | rs1805386 | Prf1       | rs3758562 |
| Atn        | rs1801516 | Prf1       | rs10999425|
| Mthfr      | rs1801133 | L12R2B     | rs3790568 |
| Crp        | rs1800947 | Casp8      | rs31045485|
| Mdr/BrcA1  | rs1799966 | Ccl2       | rs1024611 |
| Ccl4       | rs1719153 | Ppdp2e/Ku70 | rs2267437 |
| Rad52      | rs11571424 | Bb1/Lpar5  | rs2854344 |
| Casp9      | rs1052576 | Egf        | rs4444903 |
| Abcb1      | rs1128503 | Il2        | rs6822844 |
| Ifng       | rs2069718 | Abcc5/Mrp5  | rs7636010 |
| Esr1/Estrog5 | rs2234693 | GranzymeB  | rs8192917 |
| Ccl5       | rs2280789 | Kdm4c/Gasc1 | rs2296067 |
| Mmp2       | rs243865  | Comt       | rs4680    |
| ChrM3      | rs10802789 | Htr3B  | rs1622717 |

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.
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 delayed nausea.

In the total number of participating women, rs2530797 in CCL2, rs2234978 in FAS/C9D5 and rs2854344 in RB1/LPAR6 genes indicated a significant risk for nausea. These three genes have an essential role for the control of cellular homoeostasis. CCL2 is a chemokine gene involved in immune-regulatory and inflammatory processes [33]. FAS/C9D5 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.

Acknowledgments

We would like to thank Sture Löfgren for valuable input on the text, the staff of the outpatient ward at the Dept. of Oncology, Ryhov County Hospital and Central Hospital Växjö, the staff at Laboratory Medicine and Tomas Axelson for practical help and suggestions. The genotyping was done at the SNP & SEQ technology unit (www.genotyping.se) with support from Uppsala University – Sweden and the Knut & Alice Wallenberg foundation. This investigation was partly supported by Foundation for Clinical Cancer Research in Jönköping and Futurum Academy for Health and Care, Region Jönköping County, Sweden.

References

[1] Salonen P, Kellokumpu-Lehtinen PL, Tarkka MT, Kovisto AM, Kaunonen M. Changes in quality of life in patients with breast cancer. J Clin Nurs 2011;20(1-2):255–66.
[2] Evangelista AL, Santos EM. Cluster of symptoms in women with breast cancer treated with curative intent. Support Care Cancer 2012;20(7):1499–506.
[3] Liau CT, Chu NM, Deuson HE, Lien J, Chen JS. Incidence of chemotherapy-induced nausea and vomiting in Taiwan: physicians’ and nurses’ estimation vs. patients’ reported outcomes. Support Care Cancer 2005;13(5):277–86.
[4] Shih V, Wan HS, Chan A. Clinical predictors of chemotherapy-induced nausea and vomiting in breast cancer patients receiving adjuvant doxorubicin and cyclophosphamide. Ann Pharmacother 2009;43(3):444–52.

[5] Hesketh PJ. Management of nausea and vomiting in cancer and cancer treatment. Canada: Jones and Bartlett Publishers; 2005.

[6] Hilarus DL, Kloege PH, van der Wall E, van den Heuvel JJ, Gundy CM, Aaronson NK. Chemotherapy-induced nausea and vomiting in daily clinical practice: a community hospital-based study. Support Care Cancer 2012;20(1):107–17.

[7] Molassiotis A, Stricker CT, Eaby B, Velders L, Coventry PA. Understanding the concept of chemotherapy-related nausea: the patient experience. Eur J Cancer Care (Engl) 2008;17(5):444–53.

[8] Tang J, Xiong Y, Zhou HH, Chen XP. DNA methylation and personalized medicine. J Clin Pharm Ther 2014.

[9] Shen M, Hung RJ, Brennan P, Malaveille C, Donato F, Placidi D, et al. Polymorphisms of the DNA repair genes XRCC1, XRCC3, XPD, interaction with environmental exposures, and bladder cancer risk in a case-control study in northern Italy. Cancer Epidemiol Biomarkers Prev 2003;12(11 Pt 1):1234–40.

[10] Wang L, Habuchi T, Mitsumori K, Li Z, Kamoto T, Kinoshiba H, et al. Increased risk of prostate cancer associated with AA genotype of cyclin D1 gene A870G polymorphism. Int. J. Cancer 2003;103(1):116–20.

[11] Waldman SA, Terzic A. Managing the innovation supply chain to maximize personalized medicine. Clin Pharmacol Ther 2014;95(2):113–8.

[12] Jorgensenmeier JM, Eder JP, Herbst RS. New strategies in personalized medicine for solid tumors: molecular markers and clinical trial designs. Clin Cancer Res 2014;20(17):4425–35.

[13] Navani RM, Aapro M. Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. N Engl J Med 2016;374(14):1336–67.

[14] Oliva D, Sandgren A, Nilsson M, Lewin F. Variations in the 5-hydroxytryptamine type 3B receptor gene as predictors of chemotherapy-induced nausea and vomiting, and well-being during the first 10 days postchemotherapy in women with breast cancer. Clin J Oncol Nurs 2014;18(2):E32–6.

[15] Börjeson S. Svenska Emesisregistret stärker kvaliteten i behandling av illamående vid kemoterapi. Cancervården 2009;3:27–9.

[16] Tromblay P-B, Kaiser R, Sezer O, Rösler N, Schelzén C, Possinger K, et al. Effect of increase in duration of aprepitant consumption from 3 to 6 days on the prevention of nausea and vomiting in women receiving combination of anthracycline/cyclophosphamide chemotherapy: a randomized, crossover, clinical trial. Adv Biomed Res 2015;4:238.

[17] Kitamura T, Qian BZ, Soong D, Cassetta L, Noy R, Sugano G, et al. CCL2-induced chemokine cascade promotes breast cancer metastasis by enhancing retention of metastasis-associated macrophages. J Exp Med 2015;212(7):1043–59.

[18] Wang L, Wilson SE, Stewart DR, Holloway S, Maltoni M, Caona S, Kamm H, et al. Keeping it in the family: the impact of marital status and next of kin on cancer treatment and survival. Am J Surg 2016;212(4):691–9.

[19] Wang L, Wilson SE, Stewart DR, Holloway S, Maltoni M. Marital status and colon cancer outcomes in US surveillance, epidemiology and end results registries: does marriage affect cancer survival by gender and stage? Cancer Epidemiol Biomarkers Prev 2011;20(5):417–22.

[20] Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. Stat Med 1990;9(7):811–8.

[21] Roscoe JA, Morrow GR, Colagiuri B, Heckler CE, Pudlo BD, Colman L, et al. Insight in the prediction of chemotherapy-induced nausea. Support Care Cancer 2010;18(7):869–76.

[22] Laugsand EA, Børjeson S. Svenska Emesisregistret stärker kvaliteten i behandling av illamående vid kemoterapi. Cancervården 2009;3:27–9.