ABSTRACT

Background. Docetaxel is a highly effective treatment of a wide range of malignancies but is often associated with peripheral neuropathy. The genetic variability of genes involved in the transportation or metabolism of docetaxel may be responsible for the variation in docetaxel-induced peripheral neuropathy (DIPN). The main purpose of this study was to investigate the impact of genetic variants in \textit{GSTP1} and \textit{ABCB1} on DIPN.

Material and methods. DNA was extracted from whole blood from 150 patients with early-stage breast cancer who had received adjuvant docetaxel from February 2011 to May 2012. Two polymorphisms in \textit{GSTP1} and three in \textit{ABCB1} were selected for the primary analysis, and a host of other candidate genes was explored and compared between 75 patients with clinician-reported DIPN grade 2 and 75 patients without DIPN.

Results. Patients with the genetic variants \textit{GSTP1} rs1138272 C/T or T/T (114Ala/114Val or 114Val/114Val) genotype had an adjusted odds ratio of 3.82; 95\% confidence interval 1.34–11.09 of developing DIPN. This result was confirmed in both analysis of cumulated docetaxel dose and haplotype analysis. None of the explorative genes investigated were significantly correlated with DIPN. Patients with a BMI \geq 30 were five-fold more likely to have DIPN than patients with BMI < 25.

Conclusion. We found that \textit{GSTP1} Ala114Val polymorphism is associated with occurrence of DIPN. This supports the theory that oxidative stress is involved in DIPN pathophysiology. If confirmed, this may be helpful in the risk assessment of DIPN and perhaps help to achieve better management of neurotoxicity.

Docetaxel is a highly effective treatment of a wide range of malignancies. In early breast cancer, it significantly improves recurrence-free survival and overall survival [1]. However, the use of docetaxel, as well as other taxanes, is often associated with debilitating sensory peripheral neuropathy. The frequency of docetaxel-induced peripheral neuropathy (DIPN), grades 3–4, lies between 0\% and 17\% [2]. We recently showed that 35\% of patients with early breast cancer reported grades 2–4 (grades 3–4, 11\%) DIPN during treatment, which led to dose reduction in up to 25\% of treatment cycles [3]. The necessity of dose reduction has been confirmed by others [4].

The variability of DIPN has been attributed to differences in treatment schedules and cumulated dose, concurrent administration of other neurotoxic chemotherapy, preexisting neuropathy [2,3], large observed inter-individual difference in pharmacokinetics of docetaxel [5], and genetic variability [6–8]. However, no clear pattern has emerged, and currently there is no method for predicting which patients are at high risk of DIPN before treatment.

The genetic variability of genes involved in the transportation or metabolism of docetaxel could explain some of the variation in the exposure of the nerve fibers to docetaxel. Therefore, there is a need for
identification and validation of single nucleotide polymorphisms (SNPs) that are strongly associated with the risk of developing DIPN, allowing oncologists to predict the toxicity before starting chemotherapy. Two pharmacogenetic studies suggest that SNPs in GSTP1 and ABCB1 are associated with DIPN [6,7], but these studies are like other SNP studies of DIPN characterized by a small number of subjects, heterogeneous range of cancers, pretreated patients, or patients receiving concomitant neurotoxic chemotherapy [6–12].

The primary aim of this study was to test whether known alleles of GSTP1 and ABCB1 are associated with DIPN in patients with early-stage breast cancer who were not pretreated or receiving concomitant neurotoxic chemotherapy. The secondary aim was to explore associations of a host of variants in several other candidate genes and DIPN.

Patients and method

Patients

In this case-control study of the influence of genetic factors on DIPN, we compared genetic variation among patients who developed DIPN grade ≥ 2 with patients who received the same treatment but did not develop DIPN. We recruited patients who received chemotherapy with docetaxel as adjuvant treatment for early-stage breast cancer in the Department of Oncology, Odense University Hospital, Odense, Denmark, consecutively from February 2011 until May 2012. Eligibility criteria included Western European origin, chemotherapy naïve at breast cancer diagnosis, at least one cycle of docetaxel received, information available on presence or absence of DIPN, and no major neurological disease or symptoms prior to start of docetaxel. The patients received either three cycles of epirubicin (90 mg/m²) and cyclophosphamide (600 mg/m²) followed by three cycles of docetaxel (100 mg/m²) every third week, or six cycles of cyclophosphamide (600 mg/m²) and docetaxel (75 mg/m²) every third week. Information on diabetes (yes/no) and alcohol consumption (0, 1–7, or ≥ 8 units per week) was recorded for each patient at time of inclusion. All patients provided written informed consent; the trial was performed in accordance with the Helsinki II Declaration and was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20100131) in Denmark.

Neuropathy

Sensory DIPN using National Cancer Institute, Common Toxicity Criteria (NCI CTCAE) version 2.0 is routinely recorded for all patients by the oncologists at the department. In cases with missing data, the investigator extracted the information from patient medical records. All DIPN assessments were blind to patient genotype. The primary endpoint of the study was grade ≥ 2 DIPN.

DNA extraction and genotyping

DNA was extracted from an aliquot of venous blood using the Maxwell 16 Blood DNA Purification Kit (Promega Corporation, Madison, WI, USA). SNPs in GSTP1, ABCB1, NAT2, ERCC1, ATP7A, CYP3A5, SLC10A2, SLC10A3, and CHST3 were genotyped using predesigned TaqMan SNP genotyping assays on a StepOne Plus real-time instrument (Applied Biosystems, Foster City, CA, USA) in accordance with the manufacturer’s protocol. TUBB2A (rs909964, rs909965, rs9501929, rs3734492, and rs13219681) and CYP3A4 (rs2740574) SNPs were genotyped by Sanger Sequencing. For sequencing, TUBB2A and CYP3A4 promoter regions were amplified by PCR using specific primers (Supplementary Table I, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.969846). PCR products were sequenced in both directions on an ABI 3730xl DNA Analyzer (Applied Biosystems) using the BigDye Terminator v 3.1 Cycle sequencing kit (Applied Biosystems). Nested PCR of the CYP3A4 promoter region is as described in Lepper et al. [13] except that Taq DNA polymerase (Sigma-Aldrich, St. Louis, MO, USA) was used and the final volume of the second PCR was 10 μl. The Verbatim High Fidelity PCR Kit (Thermo Fisher Scientific, Waltham, MA, USA) was used for nested PCR of the TUBB2A promoter region in accordance with the manufacturer’s protocol. Assay numbers and sequences of primers used for genotyping are listed in Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.969846. Genotyping was performed by laboratory personnel blinded for the study endpoint.

Selection of candidate genes and SNPs

Selection of candidate genes was based on a review of the literature. Genes and SNPs with a previous association with DIPN were given priority. Nineteen SNPs in 10 genes were picked for analysis. To meet the issue of multiple testing, the candidate genes were split, a priori, into two groups: one for primary analysis and one for explorative analysis. The five SNPs in GSTP1 (rs1695 and rs1138272) and ABCB1 (rs2032582, rs1128503, and rs1045642) selected for the primary analysis have previously been association with DIPN [6,7] and are all non-synonymous (i.e. amino-acid changing) with demonstrated effect on function, except rs1128503 [14]. SNPs for the explorative analysis were selected based on previously reported association with either peripheral neuropathy after paclitaxel or with other neurologically symp-
toms (e.g. dizziness, syncope, or hallucinations) after docetaxel [15]. Two additional SNPs in two docetaxel metabolizing genes were included [5,12].

Statistics

Fisher’s exact test was used to evaluate the association between genotypes and DIPN and p < 0.05 was used to indicate statistical significance for the primary analysis. The p-values calculated in the explorative analyses were calculated without correction for multiple testing and should be interpreted accordingly. Differences in patient characteristics for the group with DIPN versus no DIPN were analyzed using Wilcoxon rank-sum test and χ²-test for continuous and categorical variables, respectively. The covariates for the multivariate logistic regression were determined on the basis of prior studies focusing on the risk factors associated with DIPN [3,16] and other suspected variables and were as follows: age (<55 vs. ≥55), BMI (<25, 25–29, 30 ≥30), type of breast surgery (mastectomy vs. breast conserving surgery), tumor size (<2 cm vs. ≥2 cm), number of positive lymph nodes (0 vs. ≥1), alcohol consumption (0 vs. ≥1), diabetes mellitus (yes vs. no), regimen (D100 vs. D75), and cumulated dose of docetaxel (<300 vs. ≥300). If the p-value of the unadjusted odds ratio (OR) was below 0.05, the variable was included in the multivariate logistic regression analyses. For completeness, time-to-event analysis was also employed, in which time was defined as cumulated dose of docetaxel and an event was defined as the first incidence of DIPN ≥2. For patients not experiencing any event, the total docetaxel drug exposure was used. Since approximately two thirds of the patients in the trial were included after treatment, these data were extracted from the charts. Time-to-neuropathy data was unavailable for three patients. Cox regression was used to test the association between each SNP and DIPN. BMI, lymph node status and regimen were included as covariates. GSTP1 (2 SNPs) and ABCB1 (3 SNPs) haplotypes were analyzed in the same way and haplotypes were estimated separately for GSTP1 and ABCB1 using PHASE software program, version 2.1 [17]. The program was run 10 times with default settings; all calls for both genes were consistent. Stata version 11.2 (StataCorp, College Station, TX, USA) was used to perform statistics calculation.

Results

Patients

One hundred and sixty-five patients were invited to participate. Forty-six patients were included during treatment and 104 patients were included after completion of treatment, three of whom declined. Twelve patients were excluded before genotyping because they did not fulfill the inclusion criteria (nine patients because of prior chemotherapy, one received paclitaxel, one with symptoms mimicking neuropathy, and one patient of Asian origin). We included 75 patients with sensory DIPN and 75 patients without sensory DIPN. Time since last treatment with docetaxel until inclusion in this study was median 7.5 months (range 0–56.5). The clinical characteristics of patients with and without DIPN were similar except for more patients in the DIPN group having a BMI ≥30 than in the group without DIPN (25% vs. 8%, p = 0.008), and more patients in the DIPN group being lymph node positive (75% vs. 51%, p = 0.002) (Table I). In all, 75 (50%) patients had grade ≥2 DIPN, including 46 patients with grade 2, 19 patients with grade 3, and 10 patients with grade 4.

Genotyping

All SNPs were in Hardy-Weinberg equilibrium. Table II gives an overview of the frequency of genotypes in the primary analyses, and Table III gives an overview of the frequency of the genotypes in the exploratory analysis. SNP genotyping of TUBB2A was unavailable in three patients (see Table III).

Primary analysis (GSTP1 and ABCB1)

GSTP1 rs1138272/Ala114Val carrier status was significantly associated with DIPN. Patients with DIPN were almost three times more likely to harbor the T allele (C/T or T/T) than patients without PN [19 of 75 (25%) vs. 7 of 75 (9%)]. After adjustment for the effect of other variables in a multivariate analysis (Table IV), rs1138272 retained its significance (adjusted OR, 3.85; 95% CI 1.34–11.09). Other significant associations were seen for a high BMI, ≥30 versus <25 (reference) (adjusted OR, 4.80 95% CI 1.60–14.41), having no positive lymph nodes, ≥1 versus none (reference), (adjusted OR=0.35; 95% CI 0.18–0.86) and cumulated dose of docetaxel <300 (reference) versus ≥300 mg/m² (adjusted OR=0.17; 95% CI 0.07–0.42). Diabetes (p=0.13), alcohol consumption (p=0.72), and docetaxel schedule (p=0.72) were not significant in the univariate logistic regression analysis and therefore not included in the multivariate logistic regression analysis.

The association of GSTP1 rs1138272/Ala114Val was confirmed in the time-to-neuropathy analysis where GSTP1 rs1138272/Ala114Val was significant associated with DIPN, hazard ratio (HR) 1.90 (95% CI 1.11–3.26; p = 0.02), when adjusting for regimen, numbers of positive lymph nodes, and BMI (see Supplementary Table II, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.969846).
For the \( ABCB1 \) rs1128503 SNP more patients without DIPN were carrying CC (36% vs. 27% in the group with DIPN, Table II). This SNP was borderline significant in the univariate logistic regression with OR = 1.31 (CI 95% 0.63–2.74) for patients carrying C/T versus C/C (reference) and OR = 2.43 (CI 95% 0.93–6.38) for patients carrying T/T, \( p = 0.08 \). In the time-to-neuropathy analysis this SNP also appeared as borderline significant with a HR = 1.26 (95% CI 0.72–2.21) for patients carrying C/T versus C/C (reference) and HR = 1.92 (95% CI 0.99–3.69) for patients carrying T/T, \( p = 0.06 \).

No other SNP in the primary analysis was found to be associated with DIPN neither in the univariate logistic regression nor in the time-to-neuropathy analysis (Supplementary Table II, to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.969846).

### Haplotypes

Analyses of estimated \( GSTP1 \) and \( ABCB1 \) haplotypes and association with DIPN were carried out as a supplement. Generally the results confirmed the associations already described. Table V shows the frequency of haplotypes depending on DIPN status. Data was analyzed with time-to-neuropathy. More patients had haplotype \( GSTP1*A/GSTP1*C \) in the DIPN group compared to the no DIPN group, HR = 2.10 (95% CI 1.08–4.07). None of the

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**Table I. Characteristics of 150 Danish patients with early-stage breast cancer according to docetaxel-induced peripheral neuropathy (DIPN) (grades 2–4) N = 75, or no DIPN (grades 0–1) N = 75.**

|                        | All        | Patients with DIPN (grades 2–4) | Patients without DIPN (grades 0–1) | p-Value |
|------------------------|------------|---------------------------------|------------------------------------|---------|
| Number of patients     | 150        | 75                              | 75                                 | 0.59*   |
| Age, years             | Median 53  | 54                              | 52                                 |         |
|                        | range 29–74| 29–70                           | 36–74                              |         |
|                        | SD 8.36    | 8.54                            | 8.24                               |         |
| BMI                    | < 25       | 77                              | 51                                 | 0.008†  |
|                        | 25–29      | 48                              | 32                                 |         |
|                        | ≥ 30       | 25                              | 17                                 |         |
| Menopausal status      | Pre        | 60                              | 40                                 | 0.10†   |
|                        | Post       | 90                              | 60                                 |         |
| Surgery                | Mastectomy | 37                              | 25                                 | 0.34†   |
|                        | BCS‡       | 113                             | 75                                 |         |
| Tumor size             | < 2 cm     | 89                              | 59                                 | 0.14†   |
|                        | ≥ 2 cm     | 61                              | 41                                 |         |
| Histology**            | Ductal     | 129                             | 86                                 | 0.95†   |
|                        | Lobular    | 11                              | 7                                  |         |
|                        | Other      | 10                              | 7                                  |         |
| Tumor grade**          | I          | 20                              | 13                                 | 0.79†   |
|                        | II         | 66                              | 44                                 |         |
|                        | III        | 54                              | 36                                 |         |
|                        | Unknown    | 10                              | 7                                  |         |
| Estrogen receptor status| ER         | 103                             | 69                                 | 0.45†   |
|                        | ER 0%      | 46                              | 31                                 |         |
|                        | Unknown    | 1                               | 1                                  |         |
| Human epidermal growth factor receptor 2 (HER2) | Positive | 40                              | 27                                 | 0.44†   |
|                        | Negative   | 109                             | 73                                 |         |
|                        | Unknown    | 4                               | 1                                  |         |
| Number of positive lymph nodes | None | 94                              | 63                                 | 0.002†  |
|                        | ≥ 1        | 56                              | 37                                 |         |
| Alcohol consumption (units/week) | 0 | 24                              | 16                                 | 0.48†   |
|                        | 1–14       | 118                             | 79                                 |         |
|                        | >14        | 8                               | 5                                  |         |
| Diabetes               | yes        | 144                             | 96                                 | 0.10†   |
|                        | no         | 6                               | 4                                  |         |
| Performance status (ECOG) | 0 | 120                             | 80                                 | 0.45†   |
|                        | 1          | 9                               | 6                                  |         |
|                        | Unknown    | 21                              | 14                                 |         |
| Regimen ††             | D100       | 108                             | 72                                 | 0.72†   |
|                        | D75        | 42                              | 28                                 |         |

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*Wilcoxon rank sum test; † \( \chi^2 \)-test; ‡ Breast conserving surgery, **Only ductal and lobular carcinomas are graded – the rest were recorded as unknown, ††D100 = 3 cycles of epirubicin (90 mg/m²) and cyclophosphamide (600 mg/m²) followed by 3 cycles of docetaxel (100 mg/m²), D75 = six cycles of cyclophosphamide (600 mg/m²) and docetaxel (75 mg/m²).
haplotypes of ABCB1 were associated with DIPN in this study (Table V).

**Exploratory analysis**

No associations were found for the SNPs in the exploratory analysis and DIPN (Table III).

**Discussion**

This study evaluated the influence of polymorphisms in ABCB1 and GSTP1 on DIPN in a homogenous population of chemotherapy naïve, Western European females treated for early breast cancer. We found that patients with DIPN more often carried GSTP1 rs1138272 C/T or T/T (114Ala/114Val or 114Val/114Val). In contrast none of the SNPs tested in ABCB1, TUBB2A, NAT2, ERCC1, ATP7A, CYP3A5, CYP3A4, CHST3, SLCO1B3, or SLC10A2 were found to be linked to DIPN.

The role of polymorphisms in GSTP1 for DIPN has been studied previously. Mir et al. found that patients with rs1695 (105Ile/105Ile) had a higher risk of DIPN [7]. In the very comprehensive retrospective SCOTROC1 trial with 539 patients treated with docetaxel, Marsh et al. found the same association with rs1695 (105Ile/105Ile) with a p-value of 0.018; however, after correcting for multiple testing, the association was not significant [8]. No association was found for the 454 patients treated with paclitaxel. Others have reported an association between rs1695 (105Ile/105Ile) and oxaliplatin-induced neuropathy, but a recent meta-analysis could not confirm this association [18].

In contrast to our results Marsh et al. and Mir et al. did not find an association of GSTP1 rs1138272/Ala114Val with DIPN [7,8]. This discrepancy may be due to differences in trial setups. Hence, Mir et al. included 58 patients (including 10 patients with DIPN) in their study, and therefore their study may not have had sufficient statistical power. Marsh et al. included 539 patients (including 57 patients with DIPN), but these patients were treated concomitantly with carboplatin, which could account for some of the difference between our results and theirs because carboplatin is also known to be neurotoxic. Furthermore, a debate has been raised concerning the power and interpretation of p-values in the SCOTROC study [19].

Exactly how GSTP1 is linked to DIPN is unknown. However, the fact that GSTP1 encodes an enzyme that plays an important role in the inactivation of various toxic compounds, e.g. metabolites after oxidative stress, offers a plausible link [20]. Polymorphisms in the gene encoding GSTP1 have been associated with alterations in enzyme activity [14], and studies have shown that that expression and catalytic activity of GSTP1 were related to resistance to docetaxel treatment in vitro and in vivo [21]. A recent study of paclitaxel-induced neuropathy in rats showed that paclitaxel was associated with an accumulation of atypical mitochondria in sensory neuron cell bodies and peripheral nerves and a two-fold increase in the production of mitochondrial reactive oxygen species (ROS) [22]. Hence, it could be speculated that if the inactivation of oxidative stress is hampered because of reduced enzyme activ-
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Table III. Frequency of TUBB2A, NAT2, ERCC1, ATP7A, CYP3A5, CYP3A4, CHST3, SLC01B3 and SLC10A2 genotypes among patients with docetaxel-induced peripheral neuropathy (DIPN) (grades 2–4) N = 75 and patients without neuropathy N = 75 (grades 0–1).

| Table III | Frequency of genotype | Explorative analysis | TUBB2A* | NAT2 | ERCC1 | ATP7A | CYP3A5 | CYP3A4 | CHST3 | SLC01B3 | SLC10A2 |
|-----------|----------------------|----------------------|---------|------|-------|-------|--------|--------|-------|--------|--------|
|           | Frequency of genotype | All (N = 150) | Frequency of genotype | + DIPN (N = 75) | Frequency of genotype | - DIPN (N = 75) | Fishers exact test |
| Explorative analysis | rs number | Geno-typ | N | % | N | % | N | % |
| TUBB2A* | 909964 | C/C | 8 | 5 | 4 | 5 | 4 | 5 | 0.96 |
| | 909965 | T/T | 59 | 40 | 29 | 39 | 30 | 41 |
| | 909965 | A/A | 81 | 55 | 42 | 57 | 39 | 53 | 0.93 |
| | 909965 | A/G | 58 | 39 | 28 | 38 | 30 | 41 |
| | 909965 | G/G | 8 | 5 | 4 | 5 | 4 | 5 |
| | 9501929 | A/A | 131 | 89 | 65 | 88 | 66 | 90 | 0.59 |
| | 9501929 | A/G | 15 | 10 | 9 | 12 | 6 | 8 |
| | 9501929 | G/G | 8 | 5 | 4 | 5 | 4 | 5 |
| | 3734492 | A/G | 2 | 2 | 1 | 1 | 0 | 1 |
| | 3734492 | G/G | 144 | 96 | 73 | 99 | 71 | 97 |
| | 13219681 | A/G | 16 | 11 | 9 | 12 | 7 | 10 | 0.79 |
| | 13219681 | G/G | 131 | 89 | 65 | 88 | 66 | 90 |
| | 1799931 | A/G | 4 | 3 | 2 | 3 | 2 | 3 |
| | 1799931 | G/G | 146 | 97 | 73 | 97 | 73 | 97 |
| | 3212986 | A/A | 6 | 4 | 3 | 4 | 3 | 4 | 0.91 |
| | 3212986 | A/C | 53 | 35 | 25 | 33 | 28 | 37 |
| | 3212986 | C/C | 91 | 61 | 47 | 63 | 44 | 59 |
| | 2272921 | C/C | 5 | 3 | 2 | 3 | 3 | 4 |
| | 2272921 | C/G | 55 | 37 | 25 | 33 | 30 | 40 |
| | 2272921 | G/G | 90 | 60 | 48 | 64 | 42 | 56 |
| | 776746 | A/A | 2 | 1 | 1 | 1 | 1 | 1 | 0.74 |
| | 776746 | A/G | 122 | 84 | 65 | 87 | 61 | 81 |
| | 776746 | G/G | 126 | 84 | 65 | 87 | 61 | 81 |
| | 2740574 | A/G | 136 | 91 | 68 | 91 | 68 | 91 | 1.00 |
| | 2740574 | G/G | 13 | 9 | 7 | 9 | 6 | 8 |
| | 4148950 | A/A | 34 | 23 | 20 | 27 | 14 | 19 | 0.40 |
| | 4148950 | A/G | 65 | 43 | 29 | 39 | 36 | 48 |
| | 4148950 | G/G | 51 | 34 | 26 | 35 | 25 | 33 |
| | 1871450 | A/A | 34 | 23 | 20 | 27 | 14 | 19 | 0.40 |
| | 1871450 | A/G | 65 | 43 | 29 | 39 | 36 | 48 |
| | 1871450 | G/G | 51 | 34 | 26 | 35 | 25 | 33 |
| | 11045585 | A/A | 110 | 73 | 52 | 69 | 58 | 77 | 0.24 |
| | 11045585 | A/G | 36 | 24 | 22 | 29 | 14 | 19 |
| | 11045585 | G/G | 4 | 3 | 1 | 1 | 3 | 4 |
| | rs2301159 | C/C | 93 | 62 | 45 | 60 | 48 | 64 | 0.78 |
| | rs2301159 | T/T | 7 | 5 | 3 | 4 | 4 | 5 |

*three patients were not genotyped in TUBB2A.
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Table IV. Odds ratio of neuropathy (grades 2+) after docetaxel treatment among patients with early-stage breast cancer in Denmark.

|                                     | Univariate logistic regression | Multiple logistic regression† |
|---|---|---|
|   | OR (95%CI) | p    | OR (95% CI) | p    |
| BMI |   |     |   |   |
| <25 | 1.0 | 0.006 | 1.0 | 0.02 |
| 25–29 | 1.61 (0.78–3.34) | 0.006 | 1.29 (0.56–2.97) | 0.02 |
| ≥30 | 4.70 (1.69–13.09) | 0.003 | 4.80 (1.60–14.41) | 0.001 |
| Number of positive lymph nodes |   |     |   |   |
| None | 1.0 | <0.0001 | 1.0 | 0.001 |
| ≥1 | 0.35 (0.17–0.69) | 0.003 | 0.39 (0.18–0.86) | 0.001 |
| Cumulative dose of docetaxel mg/m² |   |     |   |   |
| 75–299 | 1.0 | 0.0001 | 1.0 | 0.0001 |
| 300–450 | 0.19 (0.08–0.45) | 0.01 | 0.17 (0.07–0.42) | 0.01 |
| Glutathione S-transferases pi 1 (GSTP1) rs1138272 |   |     |   |   |
| C/C | 3.30 (1.29–8.40) | 0.01 | 3.85 (1.34–11.09) | 0.01 |
| C/T |   |     |   |   |

*Two patients with T/T genotype are calculated as C/T;
† Adjusted for BMI, number of positive lymph nodes, cumulated dose of docetaxel and rs1138272.

[25], but the opposite is true for docetaxel, where the half-life is longer in the obese [25], resulting in greater exposure to the drug. The association with no positive lymph nodes and a higher risk of DIPN was also observed in a recent prospective randomized study by our group [3]. There is no obvious explanation for the association, but at least it indicates that axillary dissection in node positive patients does not increase the risk of DIPN. One explanation for the association of DIPN with low-dose docetaxel is that the dose of the drug is reduced in patients who develop DIPN during treatment, and hence the lower odds of a patient receiving a higher dose of docetaxel.

The strengths of the present study are that it is a case-control study that has included the largest number of patients with DIPN published until now. Due to the nature of a case-control study, our study can only be hypothesis generating, and the results should be confirmed either in a prospectively trial or in several other, well-conducted retrospective trials with the same methodology. However, we included 75 patients with DIPN who had a very homogeneous background, supporting the fact that the findings of this study are genetic.

In conclusion, we demonstrated that the occurrence of grade ≥2 DIPN was significantly more frequent in patients carrying GSTP1 rs1138272 C/T or T/T (one allele of 114Val). This finding supports the theory of a role of oxidative stress in DIPN pathophysiology, and, if confirmed, can play a role in risk assessment of DIPN and perhaps also lead to better management of neurotoxicity.

Acknowledgments

We wish to acknowledge the work and invaluable assistance of laboratory technicians Susanne Hill-

Table V. Frequency of haplotypes and association with docetaxel-induced peripheral neuropathy in an unadjusted time-to-neuropathy analysis, N = 147.

| Haplotypes | Nucleotide by phase | With DIPN (%) N = 72 | Without DIPN (%) N = 75 | Unadjusted time-to-neuropathy HR | 95% CI | P |
|------------|---------------------|---------------------|------------------------|---------------------------------|-------|---|
| GSTP1*A/GSTP1*A | AC/AC | 29 (40) | 32 (43) | Ref (1.0) |       |   |
| GSTP1*A/GSTP1*B | AC/GC | 20 (28) | 30 (40) | 0.79 | 0.44–1.39 | 0.4 |
| GSTP1*A/GSTP1*C | AC/GT | 13 (18) | 2 (3) | 2.10 | 1.08–4.07 | 0.03 |
| GSTP1*B/GSTP1*B | GC/GC | 5 (7) | 6 (8) | † |       |   |
| GSTP1*B/GSTP1*C | GC/GT | 4 (6) | 4 (5) | † |       |   |
| GSTP1*C/GSTP1*C | GT/GT | 1 (1) | 1 (1) | † |       |   |
| ABCBI (rs104542, rs2032582, rs1128503) | Wt/Wt | 12 (17) | 15 (20) | Ref. (1.0) |       |   |
| Wt/Full var | GGC/GGC | 23 (32) | 25 (33) | 1.05 | 0.52–2.12 | 0.9 |
| Full var/ Full var | TTT/TTT | 15 (21) | 10 (13) | 1.74 | 0.81–3.72 | 0.2 |
| Other | *** | 22 (31) | 25 (33) |       |       |   |

Wt, wildtype; var, variant; Ref, reference.

GSTP1*A; 105 Ile → 114 Ala, GSTP1*B; 105Val → 114 Ala, GSTP1*C; 105 Val → 114 Val.

Data were only available for 147 patients in the time-to-neuropathy analysis

† not included because of limited number of patients.
brandt, the Department of Clinical Biochemistry and Pharmacology, University of Southern Denmark, and the clinical staff at the Department of Oncology, Odense University Hospital, Denmark. This study was supported financially by “KreftFonden” and “Aase og Ejnar Danielsens Fond”.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References
[1] Early Breast Cancer Trials’ Collaborative G, Petri R, Davies C, Godwin J, Gray R, Pan HC, et al. Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379:432–44.
[2] Lee JJ, Swain SM. Peripheral neuropathy induced by microtubule-stabilizing agents. J Clin Oncol 2006;24:1633–42.
[3] Eckhoff L, Knoop AS, Jensen MB, Ejlertsen B, Ewertz M. Risk of docetaxel-induced peripheral neuropathy among 1,725 Danish patients with early stage breast cancer. Breast Cancer Res Treat 2013;142:109–18.
[4] Hershman DL, Weiner LH, Wang A, Kranwinkel G, Brafman L, Fuentes D, et al. Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. Breast Cancer Res Treat 2011;125:767–74.
[5] Baker SD, Verweij J, Cusatis GA, van Schaik RH, Marsh S, Orwick SJ, et al. Pharmacogenetic pathway analysis of docetaxel elimination. Clin Pharmacol Ther 2009;85:155–63.
[6] Sissung TM, Baum CE, Deeken JF, Price DK, Aragon-Ching J, Steinberg SM, et al. Abcb1 genetic variation influences the toxicity and clinical outcome of patients with androgen-independent prostate cancer treated with docetaxel. Clin Cancer Res 2008;14:5453–9.
[7] Mir O, Alexandre J, Tran A, Durand JP, Pons G, Treluyer JM, et al. Relationship between gstp1 ile105val polymorphism and docetaxel-induced peripheral neuropathy: Clinical evidence of a role of oxidative stress in taxane toxicity. Ann Oncol 2009;20:736–40.
[8] Marsh S, Paul J, King CR, Gifford G, McLeod HL, Brown R. Pharmacogenetic assessment of toxicity and outcome after platinum plus taxane chemotherapy in ovarian cancer: The Scottish randomised trial in ovarian cancer. J Clin Oncol 2007;25:4528–35.
[9] Boongatanont S, Brown R, Ward T, Heighway J, Ashcroft L, Morris J, Thatcher N. Glutathione-s-transferase p1 isozyme polymorphisms, platinum-based chemotherapy, and non-small cell lung cancer. J Thorac Oncol 2006;1:679–83.
[10] Rizzo R, Spaggiari F, Indelli M, Lelli G, Baricordi OR, Rimessi P, et al. Association of cyp1b1 with hypersensitivity induced by taxane therapy in breast cancer patients. Breast Cancer Res Treat 2010;124:593–8.

Supplementary material available online
Supplementary Table I and II to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.969846.