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Toxicity of (neo)adjuvant chemotherapy for *BRCA1*- and *BRCA2*-associated breast cancer

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Abstract Treatment with (neo)adjuvant chemotherapy for breast cancer, as currently given, causes cell damage by induction of double-strand DNA breaks. Because BRCA1 and BRCA2 proteins play a role in the repair of DNA damage, the efficacy of (neo)adjuvant chemotherapy may be increased in *BRCA1/2*-associated breast cancer patients. As a downside, acute chemotherapy-related toxicity may also be increased. We selected all female patients who were treated at the Erasmus MC Cancer Institute, with (neo)adjuvant chemotherapy for primary or locoregional recurrence of breast cancer (PBC/LR) between January 1, 2004 and December 31, 2014. The primary outcome was the relative total dose intensity (RTDI), calculated for anthracyclines and taxanes separately. Secondary outcomes were the occurrence of febrile neutropenia, delay in chemotherapy administration, and switch to another chemotherapy regimen due to toxicity. In total, 701 patients treated for PBC/LR were eligible for data analyses, among which 85 *BRCA1/2* mutation carriers ($n = 67$ *BRCA1* and $n = 18$ *BRCA2*). The mean RTDI for anthracyclines was not significantly different between both groups (98.7 % in the *BRCA1/2*, 96.6 % in the sporadic group, $p = 0.27$). Also the mean RTDI for taxanes was not significantly different between the groups (93.6 % in the *BRCA1/2*-associated, 90.0 % in the sporadic group, $p = 0.12$). Linear regression analysis revealed no significant effect of *BRCA1/2* mutation carriership on the RTDIs. No significant differences were found in the percentages of patients presenting with febrile neutropenia, having a delay in chemotherapy administration or switching to an altered chemotherapy regimen. Additionally, the odds ratios showed no significant effect of *BRCA1/2* mutation carriership on the secondary outcome variables. (Neo)adjuvant chemotherapy-related toxicity was not different between *BRCA1/2*-associated and sporadic breast cancer patients suggesting that the DNA damage repair mechanism of non-cancer cells with only one normal copy of either the *BRCA1* or *BRCA2* gene is sufficiently functional to handle acute chemotherapy-associated toxicity.

Keywords Chemotherapy · *BRCA* mutation · Toxicity · Breast cancer · Dose intensity

Introduction

Carriers of a germline *BRCA1* or *BRCA2* (*BRCA1/2*) mutation face an increased lifetime risk of developing breast cancer, estimated to range from 47 to 66 % for *BRCA1* mutation carriers and from 40 to 57 % for *BRCA2* mutation carriers [1, 2].

Carriers of a germline *BRCA1/2* mutation, by definition, have one allele with a mutation in the *BRCA1/2* gene, while the gene on the other allele is intact. In normal cells, it seems that enough BRCA1 or BRCA2 protein is present for adequate functioning of cells in the various tissues of these women. However, *BRCA1/2*-associated breast cancers often have lost the wild-type allele through somatic alterations during tumor development. As a consequence, there

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is no functional BRCA1 or BRCA2 protein in these tumor cells. Since BRCA1 and BRCA2 proteins are essential in the repair of double-strand DNA breaks (DSBs) by homologous recombination [3, 4], treatments which cause DSBs might be more effective in BRCA1/2-associated than in sporadic breast cancer patients, which tumor cells mostly have an intact homologous recombination repair system. The platinum derivates carboplatin and cisplatin, both strong inducers of DSBs, indeed showed higher efficacy in BRCA1/2-associated compared to sporadic breast cancer patients [5–7]. Although less pronounced, anthracyclines are also known to induce indirect DSBs by inhibiting topoisomerases, causing DNA interstrand cross-links and the generation of free radicals [8]. Accordingly, several clinical studies have shown increased sensitivity for anthracycline-containing chemotherapy in BRCA1/2 mutation carriers [9–11].

An important question is whether acute toxicity due to (neo)adjuvant chemotherapy is different in BRCA1/2 mutation carriers treated for breast cancer when compared with sporadic breast cancer patients. Since (neo)adjuvant chemotherapy induces massive DNA damage also in normal cells, one might argue that the amount of functional BRCA1 or BRCA2 protein in mutation carriers is too low to repair all the DNA damage created, compared to sporadic breast cancer patients, resulting in more toxicity. Thus far two studies investigated the acute toxicity of (neo)adjuvant chemotherapy in BRCA1/2-associated, compared to sporadic breast cancer patients, with inconsistent results [12, 13]. In the retrospective study of Shanley et al., comparing 62 BRCA1/2 mutation carriers with breast cancer to 62 matched sporadic breast cancer cases, a large proportion of patients (80/124; 65 %) was treated with older chemotherapy regimens without anthracyclines, while no patient was treated with taxanes. In BRCA2 mutation carriers, less hematologic toxicity and dose alterations were observed compared to both BRCA1-associated and sporadic breast cancer patients, while no differences were seen for BRCA1-associated versus sporadic patients [12]. In the study by Huszno et al., comparing 41 BRCA1/2-associated with 229 breast cancer patients without a BRCA1/2 mutation, all patients were treated with an anthracycline-based regimen and also patients treated with taxanes were included [13]. It was found that the proportion of patients with neutropenia at the planned start date of the second chemotherapy cycle was significantly higher in breast cancer patients with a BRCA1/2 mutation compared to patients without a BRCA1/2 mutation. Twelve patients (4.5 %), all in the group of patients without a BRCA1/2 mutation, required early termination of treatment due to chemotherapy toxicity, mostly because of grade 3-4 neutropenia. Nausea and vomiting were seen more often in patients without a BRCA1/2 mutation. There were no differences in the other investigated variables (anemia, diarrhea, and mucositis).

Nowadays, standard (neo)adjuvant chemotherapy regimens for breast cancer contain both anthracycline (either epirubicin or doxorubicin) and taxanes (either paclitaxel or docetaxel). In view of the sparse available data on toxicity of taxanes and currently used chemotherapy regimens in BRCA1/2 mutation carriers, we performed a larger single-center retrospective cohort study to examine potential differences in (neo)adjuvant chemotherapy-associated toxicity between BRCA1/2-associated and sporadic breast cancer patients.

Patients and methods

Patient population

For this retrospective cohort study, we selected from the hospital pharmacy prescription registry all female patients who were treated at the Erasmus MC Cancer Institute, Rotterdam, The Netherlands, with adjuvant or neoadjuvant chemotherapy for primary breast cancer or local/locoregional recurrence (PBC/LR). Further eligibility criteria concerned: chemotherapy regimen consisting of anthracyclines and/or taxanes and chemotherapy treatment started between January 1, 2004 and December 31, 2014. Patients who were previously treated with chemotherapy for either breast or another invasive cancer were not excluded, but subgroup analyses were performed with the exclusion of these patients, since pre-treated patient might have increased hematologic toxicity. Patients treated with (neo)adjuvant chemotherapy twice in the time period of the study were included for both episodes of chemotherapy treatment. Eleven PBC/LRs were excluded because of missing data concerning chemotherapy administration, leaving a total of 704 PBC/LRs (in 701 patients) eligible for the primary analysis (Fig. 1).

For eligible patients, data on tumor characteristics (type of histology, differentiation grade, estrogen receptor status, progesterone receptor status, HER2 status and stage) and treatment details (surgery, radiotherapy, and/or chemotherapy) were retrieved. We also collected specific data on chemotherapy treatment (treatment regimen, dosing, delays, alterations, and complications). Data on mutation status were collected from the institutional database of the family cancer clinic. Patients not tested for a BRCA1/2 mutation were considered as sporadic breast cancer patients.

Chemotherapy regimens

During the time period of the study, the chemotherapy regimens were not different for BRCA1/2 mutation carriers
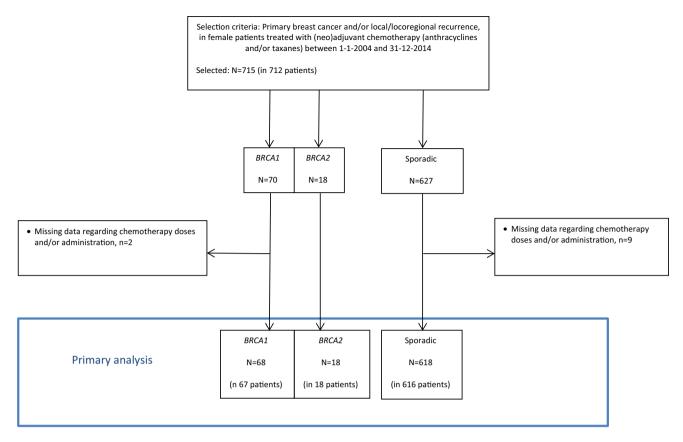
Fig. 1 Study population

and sporadic patients. Patients were treated with systemic therapy based on the national guidelines. For patients with HER2-negative breast cancer, the standard regimens at start of the study contained anthracyclines but no taxanes. From July 2008 till the end of the study, standard regimen for node-positive patients included taxanes (3-weekly docetaxel), while for node-negative patients, taxanes (3-weekly docetaxel) were included in the standard regimen from October 2011 onwards. Patients with HER2-positive breast cancer were treated with anthracyclines and no taxanes till August 2006. Trastuzumab was added to this regimen from September 2005 onwards. From August 2006 till the end of the study, the standard regimen contained anthracyclines and taxanes (weekly paclitaxel) in combination with trastuzumab.

Some patients were treated with other schemes because of participation in a clinical trial, prior chemotherapy treatment, or comorbidities. Standard G-CSF (granulocyte colony-stimulating factor) prophylaxis was only used for six cycles of TAC (docetaxel, doxorubicin, and cyclophosphamide) and dose-dense regimens (AC, doxorubicin/cyclophosphamide, given every 2 weeks). In case of febrile neutropenia or persisting neutropenia at planned start of next chemotherapy cycle, G-CSF was added to the next treatment cycle. In case of febrile neutropenia or

persisting neutropenia at planned start of next chemotherapy cycle in patients treated with G-CSF, dose reduction was considered. Furthermore, dose reduction and/or dose delay were considered based on the severity of hematological and non-hematological toxicities.

Toxicity outcomes

Primary outcome was the relative total dose intensity (RTDI), a measure of delivered (actual) total dose intensity (ATDI; i.e. administered dose over the total time course of treatment), relative to the planned total dose intensity (PTDI). The RTDI, therefore, expresses the effect of reductions, delays, as well as premature discontinuations of a treatment. The RTDI was calculated separately for anthracyclines and taxanes.

RTDI was calculated based on an adaptation of the formula described by Loibl et al. [14], and defined as the ratio of the ATDI and the PTDI, expressed as a percentage:

$$\text{RTDI }(\%) = \frac{\text{ATDI}}{\text{PTDI}} \times 100\%$$

The ATDI was defined as the actual total dose intensity over the real treatment duration, expressed as percentage/day. In case of permanent treatment discontinuation,

the remaining cycles were calculated with the planned
length and zero dose:

$$\text{ATDI}(\%\,\text{day}) = \frac{\text{Sum of }\%\text{ of delivered dose per cycle}}{\text{Duration of therapy (days)}}$$

The PTDI was defined as the planned total dose intensity
over the entire treatment duration, expressed as %/day:

$$\text{PTDI }(\%/\text{day}) =$$
$$\frac{100\,\%\ \times\ \text{Number of planned treatment cycles}}{\text{Planned duration of therapy (days)}}$$

The secondary outcomes were the occurrence of one or
more episodes of febrile neutropenia, of one or more delays
in chemotherapy administration (either due to anthracy-
cline-related toxicity or taxane-related toxicity) and of
switch to another chemotherapy regimen.

Statistical analyses

We evaluated characteristics of patients, tumors and
chemotherapy regimens, as well as outcome variables by
comparing patients with proven BRCA1/2-associated breast
cancer (BRCA1/2 group) with those with sporadic breast
cancer (sporadic group). For categorical variables, Pear-
son's Chi square test was used to test for significant dif-
ferences between the two groups, and the two-sample
Wilcoxon rank-sum (Mann–Whitney) test was used for
differences between continuous variables.

To quantify the effect of carrying a BRCA1/2 gene
mutation on the RTDI of anthracyclines and taxanes, we
performed univariate linear regression analyses. To esti-
mate the effect of mutation carriership on the other end-
points (i.e. a delay in administration of chemotherapy,
febrile neutropenia, and an alteration of the chemotherapy
scheme due to toxicity), we used logistic regression
models to obtain odds ratios (ORs) and accompanying
95 % confidence intervals (CIs), using treatments for
PBC/LRs in sporadic patients as the reference group. To
adjust for other variables, we fitted multivariate regres-
sion models. We considered age at start of chemotherapy,
previous chemotherapy, radiotherapy before chemother-
apy, neoadjuvant chemotherapy, and number of admin-
istered chemotherapy cycles as potential confounders. We
incorporated a variable in a regression model if (1) there
was a significant difference in the median or in the dis-
tribution of the respective variable between the BRCA1/2-
associated and the sporadic group and (2)—for linear
regression models—univariate analysis of the respective
variable showed a significant association with the out-
come, or—for logistic regression models—the likelihood
ratio test showed that the model including the respective
variable was significantly different from the model with-
out the variable.

All p values were two-sided, and a significance level
α = 0.05 was used. Analyses were performed with
STATA (version 13.1; StataCorp, College Station, TX,
USA).

Results

In total, 701 patients were eligible for data analyses, of
whom one BRCA1 mutation carrier and two sporadic
patients were treated with two separate episodes of
(neo)adjuvant chemotherapy for a PBC/LR during the
study period. Tables 1 and 2 depict the patient and tumor
characteristics, and the treatment features, respectively. 85
patients (12 %) were BRCA1/2 mutation carriers (n = 67
BRCA1 and n = 18 BRCA2). The median age at start of
chemotherapy was significantly lower in the BRCA1/2
group compared to the sporadic group (38 years [range
21–64] vs. 51 years [range 23–77], respectively,
p < 0.001). PBC/LRs in BRCA1/2 mutation carriers more
often showed high differentiation grade (Bloom/Richard-
son grade 3), triple-negative tumors and negative lymph
node status compared to PBC/LRs in sporadic patients. For
a total of 492 PBC/LRs (70 %), treatment with both
anthracycline- and taxane-containing chemotherapy was
applied, while chemotherapy consisted of anthracyclines
with no taxanes for 193 PBC/LRs (27 %) and for 19 PBC/
LRs (3 %) of taxanes with no anthracyclines. In the
BRCA1/2 group, more patients were previously treated
with chemotherapy for breast cancer or for another inva-
sive malignancy (13 vs. 5 % in the sporadic group,
p = 0.004; Table 2).

Primary outcome

The mean RTDI for anthracyclines was high, without sig-
nificant differences between the BRCA1/2 and the sporadic
groups (98.7 and 96.6 %, respectively, p = 0.27; Table 3).
The mean RTDI for taxanes was slightly lower than for
anthracyclines, but again without significant differences
between the two groups (93.6 % in the BRCA1/2 group and
90.0 % in the sporadic group, p = 0.12; Table 3). As
illustrated in Fig. 2, BRCA1/2 mutation carriers showed
less variability in the RTDI than sporadic patients. As
shown in Table 4, the linear regression models revealed no
significant effect of BRCA1/2 mutation carriership on the
RTDIs.

Secondary outcomes

As shown in Table 3, no significant differences between
the BRCA1/2-associated and sporadic groups were found
in the percentage of patients presenting with febrile

Table 1 Patient and tumor characteristics

	BRCA1/2 mutation carriers (n = 85)	Sporadic patients (n = 616)	p value
Year of birth, median (range)	1971 (1942–1990)	1957 (1936–1987)	<0.001
Year of birth, n (%)			
1930–1939	0 (0)	8 (1)	<0.001
1940–1949	4 (5)	130 (21)	
1950–1959	15 (18)	205 (33)	
1960–1969	18 (21)	188 (31)	
1970–1979	30 (35)	66 (11)	
1980–1989	17 (20)	19 (3)	
1990–1999	1 (1)	0 (0)	
Ethnicity, n (%)			
East Asian	0 (0)	17 (3)	0.33
Black	6 (7)	36 (6)	
White	79 (93)	557 (90)	
Other	0 (0)	6 (1)	
BRCA mutation, n (%)			
BRCA1	67 (79)	–	–
BRCA2	18 (21)	–	–

	PBC/LRs in BRCA1/2 mutation carriers (n = 86)	PBC/LRs in sporadic patients (n = 618)	
Age at start chemotherapy, median (range)	38 (21–64)	51 (23–77)	<0.001
Age at start chemotherapy, n (%)			
20–29 years	12 (14)	15 (2)	<0.001
30–39 years	34 (40)	61 (10)	
40–49 years	23 (27)	179 (29)	
50–59 years	12 (14)	221 (36)	
60–69 years	5 (6)	136 (22)	
70–79 years	0 (0)	6 (1)	
Body surface area (m^2), median (range)	1.8 (1.4–2.3)	1.8 (1.4–2.6)	0.41
Histologic subtype, n (%)			
Ductal	74 (88)	521 (86)	0.005
Lobular	1 (1)	58 (10)	
Other	9 (11)	30 (5)	
Unknown	2	9	
Histologic grade (Bloom/Richardson), n (%)			
1	4 (5)	48 (8)	<0.001
2	13 (16)	265 (46)	
3	64 (79)	269 (46)	
Unknown	5	36	
Receptor status, n (%)			
Triple-negative	51 (60)	101 (17)	<0.001
Estrogen receptor positive	32 (37)	466 (75)	<0.001
HER2-positive	4 (5)	135 (22)	<0.001
Lymph node status, n (%)			
N0	55 (65)	228 (38)	<0.001
N1	21 (25)	254 (43)	
N2	4 (5)	78 (13)	
N3	4(5)	37 (6)	
Unknown	2	21	

PBC/LR Primary breast cancer or local/locoregional recurrence

Table 2 Features of (neo)adjuvant chemotherapy and other treatments

	PBC/LRs in *BRCA1/2* mutation carriers ($n = 86$)	PBC/LRs in sporadic patients ($n = 618$)	*p* value
Planned chemotherapy regimen, *n* (%)			
Containing both anthracyclines and taxanes	49 (57)	443 (72)	<0.001
3 × FE100C/3 × D	46 (53)	290 (47)	
4 × AC/12 × P	1 (1)	103 (17)	
6 × TAC	1 (1)	40 (6)	
Other	1 (1)	10 (2)	
Containing anthracyclines and no taxanes	30 (35)	163 (26)	
5 × FE90C	19 (22)	86 (14)	
6 × FE90C	7 (8)	60 (10)	
4 × AC	1 (1)	13 (2)	
Other	3 (3)	4 (1)	
Containing taxanes and no anthracyclines	7 (8)	12 (2)	
Dose-dense regimens, *n* (%)	3 (3)	1 (0.2)	<0.001
Regimens with standard G-CSF prophylaxis, *n* (%)	4 (5)	41 (7)	0.48
Regimens with weekly chemotherapy, *n* (%)	1 (1)	104 (17)	<0.001
Number of 3-weekly chemotherapy cycles, median (range)	6 (3–10)	6 (1–8)	0.14
Previous chemotherapy, *n* (%)	11 (13)	31 (5)	<0.01
Adjuvant radiotherapy before chemotherapy, *n* (%)	2 (2)	87 (14)	<0.01
Neoadjuvant chemotherapy, *n* (%)	10 (12)	81 (13)	0.70

PBC/LR primary breast cancer or local/locoregional recurrence, *3 × FE100C/3 × D* three cycles of 3-weekly fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2, followed by three cycles of docetaxel 100 mg/m^2, *4 × AC/12 × P* four cycles of 3-weekly doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, followed by 12 cycles of weekly paclitaxel 80 mg/m^2, *6 × TAC* six cycles of 3 weekly docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2, *5 × FE90C* five cycles of 3-weekly fluorouracil 500 mg/m^2, epirubicin 90 mg/m^2 and cyclophosphamide 500 mg/m^2, *6 × FE90C* six cycles of 3-weekly fluorouracil 500 mg/m^2, epirubicin 90 mg/m^2 and cyclophosphamide 500 mg/m^2, *4 × AC* four cycles of 3-weekly doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, *G-CSF* granulocyte colony-stimulating factor

Table 3 Primary and secondary outcome variables

	PBC/LRs in *BRCA1/2* mutation carriers ($n = 86$)	PBC/LRs in sporadic patients ($n = 618$)	p value
Mean relative total dose intensity, % (SD)			
Anthracyclines	98.7 (3.7)	96.6 (10.5)	0.27
Taxanes	93.6 (17.6)	90.0 (19.9)	0.12
Febrile neutropenia, *n* (%)	18 (21)	107 (17)	0.42
Delay of chemotherapy administration, *n* (%)			
Because of anthracyclines	12 (15)	90 (15)	0.97
Because of taxanes	2 (4)	46 (10)	0.13
Alteration of chemotherapy scheme, *n* (%)	8 (9)	65 (11)	0.73

PBC/LR Primary breast cancer or local/locoregional recurrence, *SD* standard deviation

neutropenia (21 and 17 %, respectively, $p = 0.42$), having a delay in chemotherapy administration due to chemotherapy toxicity (for anthracyclines: 15 % in both groups, $p = 0.97$; for taxanes: 4 % in the *BRCA1/2*-associated, and 10 % in the sporadic group, $p = 0.13$) or switching to an altered chemotherapy regimen due to chemotherapy toxicity (9 % in the *BRCA1/2*-associated and 11 % in the sporadic group, $p = 0.73$). Additionally,
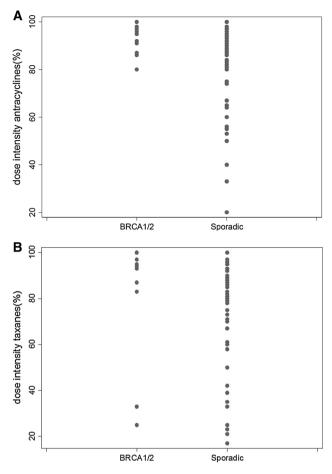
Fig. 2 Relative total dose intensity (%) for **a** anthracyclines and **b** taxanes, separately for *BRCA1/2*-associated and sporadic breast cancer patients

the ORs yielded by logistic regression showed no significant effect of *BRCA1/2* mutation carriership on the secondary outcome variables (Table 5).

Subgroup analyses

To exclude effect modification by differences in treatment regimens between the two groups on the outcome variables, we performed analyses with exclusion of certain chemotherapy regimens. Exclusion of the patients being treated with regimens administered with standard G-CSF prophylaxis ($n = 4$ treated with dose-dense regimens; $n = 41$ treated with TAC), with regimens consisting of weekly chemotherapy administration ($n = 105$) or with regimens containing taxanes with no anthracyclines ($n = 19$) did not significantly influence the results of both primary and secondary outcome variables (data not shown). Febrile neutropenia was then found in 25 % of the *BRCA1/2*-associated and in 20 % of the sporadic group, $p = 0.57$.

Excluding the patients who were previously treated with adjuvant chemotherapy for breast cancer or for another invasive cancer ($n = 42$) also did not significantly influence the results of both primary and secondary outcome variables (data not shown). When taking the *BRCA1/2*-associated and the sporadic group together, the RTDI was not significantly different between patients previously versus not previously treated with chemotherapy (for anthracyclines RTDI: 96.8 % in both groups, $p = 0.80$; for taxanes RTDI: 95.8 vs. 90.1 %, $p = 0.20$).

Discussion

In this single-center retrospective cohort study, we found no differences in RTDI of (neo)adjuvant chemotherapy (both for anthracyclines and taxanes) between *BRCA1/2*-associated and sporadic breast cancer patients. Furthermore, we found no differences in the occurrence of febrile neutropenia, in delay of chemotherapy administration or in alteration

	Univariate model		Multivariate model	
	Coefficient (SE)	*p* value	Coefficient (SE)	*p* value
Mean RTDI anthracyclines (%)				
BRCA1/2 versus sporadic	1.69 (1.08)	0.12	Not applicable[c]	
Age at start chemotherapy	−0.05 (0.03)	0.12		
Previous chemotherapy[a]	−1.09 (1.84)	0.55		
Radiotherapy before chemotherapy[b]	−1.16 (1.00)	0.25		
Mean RTDI taxanes (%)				
BRCA1/2 versus sporadic	3.94 (2.98)	0.19	3.33 (2.97)	0.26
Age at start chemotherapy	−0.10 (0.08)	0.22	–	–
Previous chemotherapy[a]	6.71 (4.17)	0.11	–	–
Radiotherapy before chemotherapy[b]	−6.77 (2.75)	0.01	−6.50 (2.76)	0.02

Table 4 Linear regression analyses for mean relative total dose intensity

RTDI Relative total dose intensity, *SE* standard error

[a] Versus no previous chemotherapy

[b] Versus no radiotherapy before chemotherapy

[c] None of the variables were associated with the outcome variable

Table 5 Logistic regression analyses for secondary outcome variables

	Univariate model odds ratio (95 % CI)	Multivariate model odds ratio (95 % CI)
Febrile neutropenia	1.27 (0.71–2.27)	1.11 (0.59–2.07)[a]
Delay of chemotherapy administration		
Because of anthracyclines	0.99 (0.50–1.97)	Not applicable[b]
Because of taxanes	0.36 (0.08–1.54)	Not applicable[b]
Alteration of chemotherapy scheme	0.80 (0.33–1.93)	Not applicable[b]

Sporadic breast cancer patients as references versus breast cancer patients with a *BRCA1/2* mutation

CI confidence interval

[a] Adjusted for age at start chemotherapy. The other variables did not meet the criteria for incorporation in the multivariate model

[b] No variables did meet the criteria for incorporation in the multivariate model as described in the methods section

of the chemotherapy regimen due to toxicity between the two groups. Our observations on the absence of increased acute toxicity due to (neo)adjuvant chemotherapy in *BRCA1/2* mutation carriers, compared to sporadic breast cancer patients, suggest that the DNA damage repair mechanism of non-cancer cells with only one normal copy of either the *BRCA1* or *BRCA2* gene is sufficiently functional to handle acute chemotherapy-associated toxicity.

Our results have to be interpreted in the light of the two previously published studies on chemotherapy-associated toxicity in *BRCA1/2* mutation carriers. Huszno et al. found more neutropenia at the planned date of the second chemotherapy cycle in *BRCA1/2*-associated ($n = 41$) than in sporadic breast cancer patients ($n = 229$) [13]. It is unclear what the clinical relevance of this finding is, since they did not mention the proportion of patients needing dose reductions, experiencing delay in chemotherapy administration and febrile neutropenia. We choose to use more clinically relevant outcome measures such as dose intensity which is likely to be associated with efficacy [15] and febrile neutropenia that might have consequences for the subsequent cycle. The data of the study of Shanley et al., not finding increased chemotherapy-associated toxicity in *BRCA1/2*-associated ($n = 62$) compared to sporadic breast cancer patients ($n = 62$) [12], are hardly comparable to our study observations, since a large part of their patients were treated with older chemotherapy regimens.

To the best of our knowledge, our study is the largest published on this topic so far. We did not find any differences in clinically relevant toxicity measures after treatment with anthracyclines and/or taxanes between *BRCA1/2*-associated and sporadic breast cancer patients. In both previous studies, as well as in our study, age at the start of chemotherapy was significantly lower in the *BRCA1/2* group than in the sporadic group. Although increased risk of myelosuppression at increased age of administration has been previously reported [16], in our study no difference

was seen in mean RTDI comparing *BRCA1/2* mutation carriers aged >50 years to BRCA1/2 mutation carriers younger than 50 years (data not shown).

In the *BRCA1/2* group more patients were previously treated with adjuvant chemotherapy than in the sporadic group, mainly for an earlier primary breast cancer. Since there is a maximum cumulative dose for anthracyclines, a relevant proportion of these patients did receive a non-anthracycline-containing regimen. One might expect increased toxicity when patients are treated for a second time with chemotherapy. Leaving out all pre-treated patients, however, did not influence the results, and comparing previously treated patients with non-previously treated patients (irrespective of *BRCA1/2* mutation status) showed no significant differences in the RTDI, suggesting that previous treatment with chemotherapy does not increase acute chemotherapy-related toxicity.

In the *BRCA1/2*-associated group, fewer patients were treated with weekly chemotherapy regimens and with regimens containing standard G-CSF prophylaxis. However, exclusion of patients treated with these regimens did not significantly influence the results. The percentage of patients presenting with febrile neutropenia in the sporadic group increased in the subgroup analyses, compared to the percentage found in the primary analysis, which might be explained by the fact that in the sporadic group a larger proportion of patients were treated with regimens containing standard G-CSF prophylaxis.

We are aware of a number of shortcomings to be mentioned. Despite the fact that our study is the largest published on this topic with inclusion of 86 PBC/LRs in *BRCA1/2*-associated patients, being 12 % of the total study group, this number is still quite low. The numbers were too small to perform useful analyses for *BRCA1* and *BRCA2* mutation carriers separately, which would be of interest since BRCA1 and BRCA2 proteins have different roles in the DNA repair mechanism and the cell cycle. Nevertheless, it is unlikely that a clinically relevant difference will

be found with higher numbers of patients, since the RTDI, especially for anthracycline is very high. In contrast to the study of Huszno et al., not all our patients were tested for a *BRCA1/2* mutation, but we expect, if any, only a small proportion of *BRCA1/2* mutation carriers in the sporadic subgroup, since at our institution (and in The Netherlands) patients are already tested with a low suspicion of *BRCA1/2* mutation carriership. Further, in the current study, we did not include non-hematologic toxicity as an outcome, since it is well known that these outcome variables are more prone to inter-observer variability and are less clinically relevant when they do not lead to dose delay or dose reduction [17]. For the same reason, we did not include hematologic laboratory values measured at planned start of a new cycle, since these are only relevant when they lead to dose reduction, delay in chemotherapy administration, or alteration of chemotherapy regimen. It could have been of scientific interest to compare neutrophil *nadir* levels between *BRCA1/2* mutation carriers and sporadic patients. Unfortunately, due to the retrospective nature of our data, these data are lacking.

Recent data showed increased efficacy of platinum derivates in patients with triple-negative breast cancer and/or a *BRCA1/2* mutation, leading to incorporation of carboplatin in standard (neo)adjuvant chemotherapy regimens in this population [5–7]. These studies did not report on differences in toxicity between *BRCA1/2* mutation carriers and sporadic breast cancer patients. In our study, the number of patients treated with carboplatin was very low and no conclusions can be drawn hereon. Poly ADP-ribose polymerase (PARP) inhibitors are an important new class of targeted anti-cancer drugs which induce DSBs in tumors with homologous recombination deficiency due to, for example, a mutation in one of the *BRCA* genes. Recently, the first PARP inhibitor has been approved for the treatment of *BRCA1/2*-associated ovarian cancer, while trials in early and metastatic breast cancer are ongoing. Lederman et al. compared toxicity of the PARP inhibitor olaparib in *BRCA1/2* mutation carriers and sporadic patients with ovarian cancer and found no differences in toxicity [18]. Both platinum derivates and PARP inhibitors have a much higher capacity to induce DSBs, compared to anthracyclines. Therefore, further research on the toxicity of these regimens in *BRCA1/2* mutation carriers compared to sporadic patients is warranted, especially since these drugs will be increasingly used in the treatment of *BRCA1/2*-associated breast cancer.

Conclusion

In conclusion, there seems no clinically relevant difference in toxicity of anthracycline- and taxane- containing (neo)adjuvant chemotherapy regimens for *BRCA1/2*-associated

compared to sporadic breast cancer patients, which suggests that the DNA damage repair mechanism of non-cancer cells with only one normal copy of either the *BRCA1* or *BRCA2* gene is sufficiently functional to handle acute chemotherapy-associated toxicity.

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