# The risk factors of toxicity during chemotherapy and radiotherapy in breast cancer patients according to the presence of *BRCA* gene mutation

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**Aim of the study:** Treatment toxicity may decrease the treatment effectiveness due to the need to reduce the dose or increase the interval between cycles. The aim of this study was to distinguish the risk factors for treatment side effects in breast cancer patients and to assess the impact of BRCA1/2 mutations on the treatment toxicity.

**Material and methods:** The analysis was conducted on the medical history of 370 patients who were treated with anthracycline-based chemotherapy between 2006 and 2012 in the Clinical Oncology Department, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Gliwice in Poland (COI). All patients were tested for the presence of BRCA1 and BRCA2 mutations.

**Results:** In the studied group 13% (48) of the patients were BRCA mutation carriers. Neutropaenia after the first cycle of chemotherapy occurred more commonly in mutation carriers compared to non-carriers (29% vs. 10%), $p = 0.0002$. Radiotherapy acute skin toxicity was present in 3% of patients with similar rates in both groups, $p = 0.950$. Toxicity grade 3–4 was present more frequently in patients younger than 70 years ($p = 0.02$) of age, patients with viral hepatitis ($p = 0.045$), hypertension ($p = 0.039$), and cardiovascular disease ($p = 0.044$). Lower WBC count before treatment was observed more frequently in patients with neutropaenia ($p = 0.002$), especially in mutation carriers, $p = 0.0015$.

**Conclusions:** Risk factors for anthracycline-based chemotherapy side effects were: age below 70 years, lower WBC value at baseline, history of infectious diseases, hypertension, and cardiovascular comorbidity. The presence of BRCA mutations may be a risk factor for neutropaenia, but it did not affect radiotherapy toxicity.

**Key words:** BRCA1/2 mutation, breast cancer, chemotherapy, radiotherapy, side effects.

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## Introduction

Complications associated with the use of chemotherapy and radiation therapy may decrease the effectiveness of treatment by the need to reduce the dose or increase of the interval between cycles. This issue was the subject of many studies aiming to identify a subgroup of patients who may be predisposed to particularly severe complications during the treatment. One of the risk factors may be *BRCA* mutations.

*BRCA1* and *BRCA2* mutations cause an impairment of DNA repair, a weakening of the cell cycle checkpoint, a disruption of cell division, and apoptosis. The presence of the above-mentioned gene mutations increases the sensitivity of tumour cells to ionising radiation and DNA damaging cell cytostatics, such as platinum and anthracyclines. *BRCA* gene mutations play an important role in carcinogenesis and may also influence the predisposition to complications of the cancer therapy [1].

The aim of this study was to distinguish the risk factors for side effects of chemotherapy and radiotherapy in patients with breast cancer and to assess the impact of *BRCA1/2* mutations on the toxicity of the treatment.

## Material and methods

This retrospective study was conducted in the Clinical Oncology Department, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch in Poland (COI). The analysis of patients' medical records was performed according to the national legal regulations. The analysis included 370 breast cancer patients treated between the years 2006 and 2012. All patients were women. All were treated and followed up in COI. Inclusion criteria were as follows: breast cancer confirmed by microscopic examination; age above 18 years; performance status ZUBROD 0-1; treatment with anthracycline-based chemotherapy; peripheral blood count, and renal and liver function within normal values; and complete medical documentation.

The data, including the age at onset, menopausal status, disease stage according to TNM classification, surgical procedures, histology, oestrogen and progesterone receptor status, HER2 status, contralateral breast cancer and co-morbidities (diagnosed and treated before chemotherapy), were gathered from hospital records and pathology reports. All patients were tested for the presence of *BRCA1* and *BRCA2* mutations (BRCA1: c.5266dupC, c.6869delAG, c.181T>G, c.4034delA; BRCA2: c.5946delT, c.9403delC). Mutation analysis was carried out by a multiplex allele-specific polymerase chain reaction assay. The most common mutations in Poland are 5382insC, C61G, and 4153delA [2, 3].

All patients received anthracycline-based chemotherapy. The most common regiments were FAC (5-fluorouracil 500 mg/m$^2$, adriamycin 50 mg/m$^2$, cyclophosphamide 500 mg/m$^2$), AC (adriamycin 60 mg/m$^2$, cyclophosphamide 600 mg/m$^2$), AT (adriamycin 50 mg/m$^2$, docetaxel 75 mg/m$^2$), and TAC (docetaxel 75mg/m$^2$, adriamycin 50 mg/m$^2$, cyclophosphamide 500 mg/m$^2$). *BRCA* mutation results did not affect the choice of chemotherapy regiments. All patients (*BRCA* mutation carriers and non-carriers) were treated according to the same protocol and by the same team of physicians. Toxicity was determined on the basis of the toxicity scale CTCAE version 4.0. Toxicity of radiotherapy was evaluated using a scale of severity of early radiotherapy skin reactions according to EORTC.

### Statistical analysis

Statistical analysis was carried out using STATISTICA 7 software. The frequency of appearance of side effects was counted. The qualitative features were presented as the percentage of their occurrence and evaluated with Fisher's exact test and chi-squared test with Yates' correction. Differences were considered as significant if the $p$ value was ≤ 0.05.

## Results

Ninety-four (25%) patients were treated due to metastatic disease and 276 (75%) received adjuvant chemotherapy. In 48 (13%) patients *BRCA1/2* mutations were detected (including 2 patients with *BRCA1* and *BRCA2* and the remaining 46 with *BRCA1*). In the remaining 326 (87%) patients mutations were not found. The number of women with mutations in both genes was too small to warrant separate analysis that would bring statistically valuable results.

Mutation carriers were significantly younger in comparison with patients without detected mutations, $p = 0.03$. The median age of *BRCA1/2* mutation carriers' was 43 years (range from 25 to 74 years) and for non-carriers 50 years (range from 29.5 to 79 years). *BRCA1/2*-associated breast cancer patients were also significantly more often in premenopausal period in comparison with non-carriers (64% vs. 39%), $p = 0.02$. The median age at menarche was 14 years, and this was similar in both groups ($p = 0.559$). The median number of births was significantly lower in patients with the mutation, $p = 0.0001$.

The *BRCA1/2*-associated cancers were significantly more often triple-negative than tumours in sporadic cancers (52% vs. 19%), $p = 0.0001$. They also had significantly more frequently negative steroid receptor status than non-carriers, (71% vs. 47%), $p = 0.012$. HER2 overexpression was significantly more frequently detected in women without mutations in comparison with *BRCA* carriers (33% vs. 6%), $p = 0.0002$. The stage of disease at the time of clinical diagnosis of cancer was significantly more advanced in patients without the mutation, compared to the carriers of *BRCA* mutations (48% vs. 17%), $p = 0.001$. Tumour size (T) was not significantly higher in patients with *BRCA* mutation (47% vs. 37%), $p = 0.192$. However, the lymph nodes occurred more often in patients without *BRCA* mutations (48% vs.19%), $p = 0.0002$. The TNM staging of recruited patients is shown in Table 1. The incidence of the second neoplasm was similar in both groups (10% vs. 7%), $p = 0.322$.

Regardless of the presence of the *BRCA* mutations, patients were treated according to the same protocol and using the same groups of cytostatics. A total of 268 (72%) patients underwent surgery, including 38 patients (81%) with the presence of mutations in *BRCA* genes and 230 (72%) patients without detected mutations. In the remaining 28% of patients surgery was not performed because of the more advanced stage of disease. A breast conserving treatment (BCT) was performed in 10 (21%) mutation carriers and in 60 (17%) patients without mutation, $p = 0.810$. Radiotherapy to the area of the chest wall, and axillary and supraclavicular lymph nodes was given to 30 (64%) mutation carriers and to 191 (60%) non-carriers, $p = 0.409$. Hormone therapy was given to 16 (34%) mutation carriers and to 172 (54%) patients without the mutation, $p = 0.023$. No patient with a *BRCA* mutation received immunotherapy. Thirty-nine (12%) women with no mutations detected were treated with trastuzumab, $p = 0.037$. Most patients received anthracycline-containing chemotherapy in the first-line treatment: 100% of mutation carriers and 98% of patients without mutations.

Chemotherapy side effects grade 1–4 according to CTCAE occurred in 235 (64%) patients, including 58 (16%) patients with grade 3–4 toxicity. The most common grade 3–4 side effects were neutropenia (15%), nausea and vomiting (4%), stomatitis (5%), anaemia (0.5%), and infection (0.8%). Grade 3–4 toxicity was observed more frequently in patients without the mutation, compared with women having *BRCA* mutations (18% vs. 12%), $p = 0.346$. This was especially true for complications of the upper gastrointestinal tract, such as nausea and vomiting, which occurred only in patients without mutations (5% vs. 0), $p = 0.240$. In patients without mutation, anaemia (0.6% vs. 0, $p = 1.00$) and infections (1% vs. 0, $p = 1.00$) were also insignificantly more often observed. In contrast, haematological complications, such as 3-4-degree neutropaenia were significantly more common in mutation carriers, but only after the first course of treatment (29% vs. 10%), $p = 0.0002$. The occurrence of inflammation of the oral mucosa did not differ between both groups (2% vs. 2.2%), $p = 0.988$. There was no diarrhoea or inflammation of veins in grade 3–4 CTCAE. Premature discontinuation of treatment due to side effects was related to 21 (6%) patients, including 3 (6%) mutation carriers and 18 (5%) patients without mutation,

**Table 1.** TNM staging of recruited patients

| TNM | BRCA positive | BRCA negative |
|---|---|---|
| I | 4 (9%) | 59 (18%) |
| IIA | 15 (32%) | 59 (18%) |
| IIB | 24 (51%) | 73 (22%) |
| IIIA | 1 (2%) | 41 (13%) |
| IIIB | 3 (4%) | 64 (20%) |
| IIIC | 0 | 3 (1%) |
| IV | 1 (2%) | 23 (7%) |

$p$ = 1.00. We also analysed the lower WBC count (≤ 4 ×10$^3$/ul) before systemic therapy. There was a significantly higher rate of complications, particularly neutropenia, in patients with a lower value of the WBC, $p$ = 0.002. Patients with *BRCA* mutation more frequently had lower values of WBC before the beginning of the therapy in comparison with patients without the mutation (17% vs. 4%), $p$ = 0.0015. Mutation carriers with a lower WBC count significantly more often experienced neutropaenia in 3–4 degrees in comparison with patients without the mutation (12% vs. 3%), $p$ = 0.003. There was no significant effect of the Hgb < 12 g/dl value on the incidence of treatment side effects. The Hgb lower value prior to treatment was observed more frequently in mutation carriers, in comparison with patients without mutations (30% vs. 11%), $p$ = 0.0005.

Early acute skin side effects of radiation therapy in 3–4 grade were observed in 7 (3%) of all patients: in 6 (4%) without the mutation and 1 (3%) with mutation, $p$ = 0.880. Complications requiring treatment discontinuation were insignificantly more frequently observed in patients without mutations, in comparison with *BRCA* mutation carriers (1% vs. 0%), $p$ = 0.860. Radiotherapy side effects were insignificantly more often detected in patients who received radiation after mastectomy in comparison with patients with breast conserving therapy (10% vs. 6%), $p$ = 0.212.

Risk factors for toxicity were distinguished among all patients, independently of *BRCA* mutation presence. Chemotherapy side effects were observed more frequently in patients under the age of 70 years compared with elderly patients (17% vs. 0), $p$ = 0.02. There was no significant difference between patients with distant metastases and early breast cancer, with respect to adverse events (17% vs. 16%), $p$ = 0.367. There was no association between menopausal status, performance status, use of stimulants and treatment side effects, $p$ = 0.694, $p$ = 0.100, $p$ = 0.367, respectively. All patients were in good performance status (ZUBROD 0-1). Side effects of treatment in 3–4 degrees were significantly more often observed in patients with co-morbidities such as viral hepatitis ($p$ = 0.045), cardiovascular disease ($p$ = 0.044), and hypertension ($p$ = 0.039). Serious complications related to the treatment were insignificantly more often detected in patients with diseases of the urinary tract in their history (5% vs. 2%), $p$ = 0.191.

The presence of risk factors for treatment toxicity was also compared between mutation carriers and non-carriers. Cancers associated with the presence of the mutation were recognised at an earlier age than the tumours of patients without the mutation $p$ = 0.03. Co-morbidities were observed significantly more often in mutation carriers (51% vs. 19%), $p$ = 0.003. This mostly applied to hypertension (27% vs. 9%), $p$ = 0.02 and cardiovascular diseases (30% vs. 11%), $p$ = 0.018. There was no relationship between the presence of other diseases and mutation.

## Discussion

In the present paper the clinical and histopathological characteristics of breast cancer in mutation carriers and non-carriers are presented. Patients with *BRCA* mutation had more frequently triple-negative breast cancer in comparison with patients without mutation. The median age at diagnosis was lower in carriers than in non-carriers, and they were also more likely to be in premenopausal period. Patients without mutations were at a more advanced stage at diagnosis. These results are consistent with previous reports. Previously conducted studies have shown that breast cancer without expression of steroid receptor status (oestrogen and progesterone receptors) was present more often in mutation carriers than in non-carriers [4–6]. In other studies the relationship between the presence of mutations and HER2/neu negative tumours was reported [7, 8].

The lack or inhibition of *BRCA* gene transcription increases the sensitivity of tumour cells to the action of the platinum compounds and anthracyclines [9, 10]. BRCA proteins are involved in the repair of DNA damage induced by ionizing radiation and certain anticancer drugs. Mutations of the gene encoding the above-mentioned proteins can affect the toxicity of systemic therapy and radiotherapy [11, 12]. The analysis evaluating the impact of *BRCA* mutations on the toxicity of chemotherapy conducted by Shanley et al. showed no effect of the presence of mutations on the tolerance of the treatment and the occurrence of complications. The only significant difference was in the neutropaenia, which was observed more rarely in the group of *BRCA2* carriers, in comparison with *BRCA1* carriers and non-carriers. The observed haematological toxicity did not require dose reduction or discontinuation of treatment [13]. In our analysis, grade 3–4 toxicity occurred insignificantly more frequently in patients without the mutation, in comparison with mutation carriers; it mostly applied to complications of the gastrointestinal tract. In contrast, haematological complications, such as neutropaenia in 3–4 degree, were significantly more common in carriers of the mutation but only after the first cycle of chemotherapy. Such significance was not observed in the subsequent cycles of chemotherapy.

Past studies describing complications of radiation therapy did not show significant differences in tolerability and the occurrence of complications between mutation carriers and patients without mutation. It applied to both early and late toxicity [14]. Our results are consistent with previous reports. In addition, complications of radiation therapy were insignificantly more often observed in post-mastectomy patients in comparison with patients with breast conserving therapy.

In the present paper we also analyse the risks factors for chemotherapy-related toxicity, such as age, co-morbid conditions, allergies, disease stage, performance status, and co-morbidity of other cancers with regard to the impact of *BRCA* mutations. Risk factors for complications of treatment were age below 70 years. All patients were in good performance status (Zubrod 0-1). There was a significant effect of co-morbidities such as hypertension and cardiovascular disease on the occurrence of anaemia. Neutropaenia was observed more frequently in patients who had infectious diseases such as hepatitis in their medical history. In patients with a history of urinary tract diseases complications of chemotherapy were observed insig-

nificantly more often, in comparison to patients without those disease (5% vs. 2%), $p = 0.191$. This is most likely due to the effect on the renal excretion of products of the cytostatics metabolism and their effects on the haematopoietic system. There was no correlation between drug or product allergies in history and severity of chemotherapy toxicity.

In several previous studies, older age of the patients was a major risk factor for chemotherapy. It mostly applied to myelosuppression, inflammation of the mucous membranes of the mouth, cardiac, peripheral neuropathy, or neurotoxicity [15, 16]. Physiological changes related to aging, such as reduction of the stem cells, reduced the ability to repair damage (regeneration), a greater loss of protein and fat accumulation, and predisposition to increased therapy toxicity [15, 17]. A prospective study conducted on a group of elderly patients with lymphoma and solid tumours confirmed the importance of age as a risk factor for complications, particularly neutropaenia [18]. In the studied group no patient over 70 years of age developed adverse events (grade 3–4). Elderly patients in worse performance status with the presence of severe co-morbidities were not qualified to anthracycline-based chemotherapy. These patients received less toxic chemotherapy regimens. This may explain the low percentage of side effects in patients over 70 years of age in our study.

The highest percentage of haematological complications has been reported in patients treated with anthracyclines [18]. In the study group, all patients received anthracyclines. Other risk factors, analysed in many works, were co-morbidities. The presence of certain diseases has an effect on the toxicity of the treatment by affecting the organs that are involved in drug metabolism. In addition, drugs used in the treatment of other ailments may interact with cytostatics, increasing their toxicity [15, 19]. Diseases that exert the greatest effect on the toxicity of treatment are as follows: kidney, liver (influence on the metabolism and excretion of drugs) [20, 21], cardiovascular [20], and diabetes (diarrhoea grade 3–4) [22]. It has also been proven that high blood pressure and lung diseases affect the occurrence of neutropaenia and febrile neutropaenia [23]. Other potential risk factors were worse performance status of patients, sex, genetic polymorphisms, laboratory values (Hgb < 12 g/dl, lower value of WBC, platelets), and the type of chemotherapy used [15, 19–21]. The analysis shows the impact of lower leukocyte values before treatment on the occurrence of complications in 3–4 degree. This particularly applied to neutropaenia. There was no effect of Hgb < 12 g/dl on the risk of chemotherapy side effects.

The presence of *BRCA* mutations may predispose to the development of secondary cancers, especially breast or ovarian cancers [24]. In the study group there was no increased incidence of second malignancies. Perhaps such an evaluation will be possible after a longer period of follow-up.

To summarise, risk factors for anthracycline-based chemotherapy side effects were as follows: age below 70 years, lower WBC value at baseline, history of infectious diseases, hypertension, and cardiovascular co-morbidity. The presence of *BRCA* mutations may be considered a risk factor for early neutropaenia. The use of haematopoietic drugs and growth factors compensates for the risk of neutropaenia in both groups of patients. The presence of *BRCA* mutations did not affect the incidence of radiotherapy acute toxicity.

*The authors declare no conflict of interest.*

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