The prevalence of breast cancer, the most common cancer affecting women globally, is increasing every year. The year 2020 saw nearly 2.3 million new cases (65,868 in Indonesia alone) and 0.7 million deaths from breast cancer worldwide. Mortality rates in breast cancer tend to be high, partly because most patients present at advanced stages.

While chemotherapy has improved recovery rates, it also produces adverse reactions such as hematological toxicity. Chemotherapeutic agents such as anthracycline, taxane, cyclophosphamide,
5-Fluorouracil (5-FU), and vinblastine may cause myelosuppression leading to bone marrow suppression, triggering anemia, neutropenia, and thrombocytopenia. When hematological toxicity occurs, the physician may decide to delay the chemotherapy. Such breaks in treatment can cause resurgence of the cancer, increasing the risk of morbidity and mortality.

Anthracycline is one of the most widely used drugs for chemotherapy, often in combination with cyclophosphamide and taxane as adjuvant or neoadjuvant therapy. The combination carries the risk of serious side effects such as cardio, gastrointestinal, and hematological toxicities.

There are large differences between the clinical responses of individual breast cancer patients in chemotherapy induced hematological toxicities. Involvement of genetic factors is suspected, especially because polymorphisms in genes which encode the drug transporters and enzymes that metabolize drugs are known to affect an individual’s responses to chemotherapy.

Several studies have suggested associations between therapeutic response and single nucleotide polymorphism (SNP) in a particular gene, whereas the response and therapeutic efficacy involve multiple pathways and genes. Therefore, it is more reasonable to analyze the genes and SNPs haplotype-wise. The gene ATP-binding cassette B1 (ABCB1) is suggested as promoting drug resistance by encoding P-glycoprotein (P-GP), an efflux transporter for toxins including chemotherapeutic agents. The GSTP1 gene, by contrast, encodes an enzyme that metabolizes certain drugs, including anthracycline and cyclophosphamide.

Polymorphisms of the ABCB1 gene in C1236T (rs1128503) located in exon 12, C3435T (rs1045642) in exon 26, and G2677T (rs2032582) are suggested to be involved in hematological toxicities induced by chemotherapy. However, various studies have yielded mixed results. Some studies in breast cancer patients found no association of ABCB1 C3435T with neutropenia, while others linked ABCB1 polymorphism with hematological toxicities. Another study that investigated the relationship of GSTP1 A313G (rs1695) to chemotherapy also linked GSTP1 polymorphism with hematological toxicities, but a similar study showed no association. These results imply insufficient understanding of the role of gene polymorphism in hematological toxicities in breast cancer patients subjected to chemotherapy, which points to the need for further study. Therefore, this study focuses on analyzing the relationship of GSTP1 and ABCB1 polymorphisms both by single SNP and in haplotype form with the incidence of hematological toxicity in breast cancer patients who received anthracycline-based chemotherapy.

**METHODS**

This was a cohort retrospective study, conducted from September to December 2020 at H. Adam Malik Hospital, Medan, Indonesia. The data pertaining to patients who underwent three cycles of chemotherapy during the study period was collected from their medical records. The study began after receiving the ethical approval from the Medical Ethics Committee of Universitas Sumatera Utara (No.879/KEP/USU/2020).

Our subjects comprised N=138 Indonesian women who met the following inclusion criteria: aged 18–68 years, normal liver and renal function, typical blood test result (blood collected before chemotherapy), and completed three cycles of chemotherapy regimen that contained anthracycline combination. Prospective subjects who fulfilled the criteria were invited to the study. Written informed consent was received from the 138 women who were willing to participate. Excluded were patients who underwent radiotherapy within three weeks before the start of chemotherapy, and those who had pre-existing hematologic disorders, cardiac disease, or history of smoking.

The DNA was isolated from leukocytes via a standard procedure using a commercial genomic DNA kit (Promega, USA). The polymerase chain reaction (PCR) method was applied to amplify the isolation process with GoTaq® Green Master Mix (Promega) was used to amplify ABCB1 C3435T, C1236T and G2677T. The amplifying process for ABCB1 C3435T was as per Syarifah et al., and that for ABCB1 C1236T followed Syarifah et al. The amplifying process for ABCB1 G2677T was conducted using forward primer F5’- TGC AGG CT A T AG GTT CCAGG– 3’ and reverse primer R5’- TTT AGT TTG ACT CAC CTT CCC G – 3’ DNA. The annealing stage was run for 30 seconds at 72 °C extension stage, and then it was followed for 45 seconds at 72 °C, and finally was performed for elongation for 10 minutes at 72 °C in 35 cycles.
The amplifying process for GSTP1 A313G was performed as per Hasni et al.\textsuperscript{10}

SNP ABCB1 C1236T, C3435T, and G2677T analyses were carried out using the PCR-RFLP method. For the SNP \textit{ABCB1} C3435T analysis, the restriction enzyme of Sau3AI was used,\textsuperscript{4} for the SNP \textit{ABCB1} C1236T analysis, 5 μL of amplified PCR product was digested with 1 unit of restriction enzyme HaeIII (Promega), and then incubated at 37 °C for 1 hour.\textsuperscript{15} Restriction enzyme Ban-I (Promega) was used for SNP ABCB1 G2677 analysis, while the PCR-RFLP products were electrophoresed in agarose gel 4%.\textsuperscript{16}

The electrophoresis pattern for ABCB1 C1236T consists of three forms, one band (272 bp) for homozygous CC genotype, two bands (272 bp and 250 bp) for heterozygous CT genotype, and one band (250 bp) for variant homozygous TT genotype. The pattern for \textit{ABCB1} G2677T has two bands (198 dan 26 bp) for homozygous GG, two bands (224 dan 198 bp) for heterozygous GT, and one band (224 bp) for variant homozygous TT. The pattern for \textit{ABCB1} C3435T consists of three forms, CC, CT and TT.\textsuperscript{4,15} The pattern for GSTP1 A313G has two bands (292 and 132 bp) for homozygous AA, four fragments for heterozygous AG (292, 222, 132, and 70 bp), and three fragments for variant homozygous GG (222, 132, and 70 bp).\textsuperscript{10}

Neutropenia and anemia were selected to study the effect of hematological toxicities since these two were the most frequently observed conditions in breast cancer patients treated with chemotherapy at the hospital. In addition, neutropenia and anemia disrupt the treatment schedule by delaying the next cycle of chemotherapy.

Neutropenia and anemia were classified into normal, grade 1 to 5 according to Common Terminology and Criteria of Adverse Events v.5.0 (CTCAE v.5.0), the data pertaining to which was collected from patients’ medical records for three cycles of chemotherapy. Degree of neutropenia (grade 1: < 2500–1500 mm\textsuperscript{3}; grade 2: < 1500–1000 mm\textsuperscript{3}; grade 3: < 1000–500 mm\textsuperscript{3}; grade 4: life-threatening; grade 5: death). Degree of anemia (grade 1: hemoglobin (Hb) 10 g/dL; grade 2: < 10–8 g/dL; grade 3: < 8 g/dL; grade 4: life threatening; grade 5: death).\textsuperscript{17}

The data was analyzed statistically using IBM SPSS. After three cycles of chemotherapy, the trends of neutropenia and anemia were analyzed by using

\begin{table}[h]
\centering
\caption{Characteristics of subjects.}
\begin{tabular}{|l|l|}
\hline
\textbf{Variables} & \textbf{n (\%)} \\
\hline
Age group & \\
28–35 & 4 (2.9) \\
36–43 & 23 (16.7) \\
44–51 & 45 (32.6) \\
52–59 & 45 (32.6) \\
60–68 & 21 (15.2) \\
\hline
Ethnicity & \\
Batak & 68 (49.3) \\
Javanese & 45 (32.6) \\
Acehnese & 16 (11.6) \\
Tionghoa & 1 (0.7) \\
Malay & 5 (3.6) \\
Minangkabau & 3 (2.2) \\
\hline
Occupation & \\
Homemaker & 87 (63.0) \\
Farmer & 6 (4.3) \\
Entrepreneur & 9 (6.5) \\
Teacher & 1 (0.7) \\
Pastor & 1 (0.7) \\
Government employee & 34 (24.6) \\
\hline
Body Mass Index & \\
Underweight & 1 (0.7) \\
Normal & 58 (42.0) \\
Overweight & 58 (42.0) \\
Obese & 21 (15.2) \\
\hline
Staging & \\
Staging IIA & 13 (9.4) \\
Staging IIB & 25 (18.1) \\
Staging IIIA & 8 (5.8) \\
Staging IIIIB & 78 (56.5) \\
Staging IV & 14 (10.1) \\
\hline
Histopathology & \\
infiltrating ductal carcinoma & 13 (9.4) \\
invasive ductal carcinoma & 109 (79.0) \\
invasive lobular carcinoma & 15 (10.9) \\
carcinoma mucinous mammae & 1 (0.7) \\
\hline
Chemotherapy & \textit{Anthracycline (doxorubicin)-paclitaxel} & 71 (51.4) \\
Cyclophosphamide\textit{-anthracycline-5 Fluorouracil} & 67 (48.6) \\
\hline
Neutropenia grading & \\
Normal & 71 (51.4) \\
Grade 1 & 35 (25.4) \\
Grade 2 & 15 (10.9) \\
Grade 3 & 17 (12.3) \\
\hline
Anemia grading & \\
Normal & 40 (29.0) \\
Grade 1 & 80 (58.0) \\
Grade 2 & 16 (11.6) \\
Grade 3 & 2 (1.4) \\
\hline
\end{tabular}
\end{table}
the Friedmann test and the Wilcoxon sign rank test. The association of ABCB1 (each SNP and haplotype) and GSTP1 with graded neutropenia and anemia was assessed by using the Kruskal-Wallis test, and \( p < 0.050 \) was considered statistically significant. The evaluation of deviation between allele and genotype frequency was performed using Hardy-Weinberg Equilibrium (HWE), and \( p > 0.050 \) was considered as no deviation.

**RESULTS**

Among the \( N = 138 \) breast cancer patients who participated in the study, 90 (65.2%) were in the age range = 44–59 years. Nearly half (\( n = 68, 49.3\% \)) were of Batak ethnicity. Most patients (\( n = 87, 63.0\% \)) were homemakers. Most (\( n = 78, 56.5\% \)) had advanced cancer (stage IIIB). The vast majority (\( n = 109, 79.0\% \)) had been diagnosed with invasive ductal carcinoma, and 67 (48.6%) patients had neutropenia (grades 1 to 3), while 98 patients (71.0%) had anemia (grades 1 to 3). More details are in Table 1.

There was a progressive decrease in absolute neutrophils count (ANC) after each cycle of chemotherapy [Table 2]. Based on the data, after the three cycles, the ANC within the patient blood experienced a significant decrease, in which the neutrophil trends accounted for \( p < 0.050 \) (Friedmann test), and for every cycle of chemotherapy the subjects tended to experience a decrease in neutrophils with \( p < 0.050 \) (Wilcoxon signed-rank test).

The changes in anemia in the subjects were also monitored. Table 3 shows progressive mean Hb decline after each cycle of chemotherapy (\( p < 0.050 \)), falling to the lowest level post-third cycle (\( p < 0.050 \)).

The ABCB1 patterns for each SNP and its haplotype, along with the \( GSTP-1 \) gene, can be seen in Table 4. In the \( GSTP-1 \) gene, the most common form of polymorphism was the homozygous wildtype, which was found in 72 (52.2%) patients. The second and third most common forms were for heterozygote wildtype in 55 (39.9%) patients and homozygote variant (GG) in 11 (8.0%) patients. In ABCB1 C3435T, the form of homozygote wildtype was found in 45 (32.6%) patients, whereas the homozygote variant was present in 26 (18.8%) patients. In ABCB1 C1236T, the most common polymorphism was wildtype heterozygote with 89 (64.5%) patients, and the least common form, found in 12 (8.7%) patients, was the wildtype homozygote (CC). Wildtype heterozygote was present in 72 (52.2%) patients who also had ABCB1 G2677T polymorphism. The homozygote variant was present in 19 (13.8%) patients. In the haplotype ABCB1 form, there was a homozygous variant in the three SNPs (TT-TT-TT), found in 10 (7.2%) patients. The homozygote variant of ABCB1 (3SNPs) and \( GSTP-1 \) (1 SNP) genes (TT-TT-TT) was found in only 4 (2.9%) patients. Both these polymorphisms had value of allele distribution frequencies of > 0.050 (\( p > 0.050 \)) which implied no

**Table 2**: Trend of absolute neutrophil count decrease for three cycles of chemotherapy.

| Absolute neutrophil count mm\(^3\) | N  | Mean   | SD    | Minimum | Maximum | \( p\)-value* | \( p\)-value** |
|-----------------------------------|----|--------|-------|---------|---------|---------------|---------------|
| pre chemotherapy                  | 138| 5 644.4| 2 962.5| 1 741   | 23 890  | -             | < 0.001       |
| post chemotherapy cycle 1         | 138| 4 073.9| 2 813.1| 580     | 19 710  | < 0.001       |               |
| post chemotherapy cycle 2         | 138| 3 540.4| 2 430.0| 210     | 19 870  | 0.018         |               |
| post chemotherapy cycle 3         | 138| 3 034.8| 2 049.6| 200     | 9 520   | 0.025         |               |

SD: standard deviation. *Wilcoxon signed-rank test; **Friedmann test.

**Table 3**: Trend of anemia (Hemoglobin level decreasing) for three cycles of chemotherapy.

| Anemia (g/dL) | N  | Mean   | SD    | Minimum | Maximum | \( p\)-value* | \( p\)-value** |
|---------------|----|--------|-------|---------|---------|---------------|---------------|
| pre-chemotherapy| 138| 12.1   | 1.5   | 8.00    | 15.90   | -             | < 0.001       |
| post chemotherapy cycle 1 | 138| 11.6   | 1.4   | 8.40    | 15.10   | < 0.001       |               |
| post chemotherapy cycle 2 | 138| 11.4   | 1.2   | 8.50    | 14.10   | 0.005         |               |
| post chemotherapy cycle 3 | 138| 11.2   | 1.3   | 6.80    | 14.60   | 0.007         |               |

SD: standard deviation. *Wilcoxon sign rank test; **Friedmann test.
deviation of the allele frequencies, based on Hardy-Weinberg Equilibrium (HWE).

The relationships between polymorphisms and the degree of neutropenia were evaluated. Among N = 138 subjects, 71 did not have neutropenia, while the others variously had grade 1 (25.4%), grade 2 (10.9%), and grade 3 (12.3%) neutropenia. The relations of GSTP1 and ABCB1 gene polymorphisms with their SNPs and haplotypes are displayed in the following Table 5. Based on Table 5, there was no significant relationship between GSTP-1, ABCB1 C3435T polymorphisms as well as the relationship of ABCB1 C1236T and ABCB1 G2677T with its haplotype shapes to the incidences of neutropenia (p > 0.050).

The relations between GSTP1 and ABCB1 genes polymorphisms to the incidence of anemia is shown in Table 6, which shows 40 (29.%) patients experienced no anemia. Grade 1 anemia was present in 80 (58.0%) patients, grade 2 in 16 (11.6%) patients, while grade 3 was present only in two (1.4%) patient, which indicated no significant relationships of ABCB1 and GSTP1 polymorphisms in individual SNP and haplotype (p > 0.050).

**DISCUSSION**

Based on our study results, the most dominant ethnicity of the breast cancer patients is Batak. This is to be expected as the hospital is in North Sumatra, which has Batak majority. Most breast cancer cases were detected at advanced stages, similar to the trend reported from the Middle Eastern countries such as Oman.18

Most patients developed neutropenia and anemia after three cycles of chemotherapy. This finding is in accordance with a previous study, which reported that 50% patients experienced neutropenia in varying degrees and 20% had febrile neutropenia after three cycles of chemotherapy.19 Our results appear to partly contradict some previous studies that showed that the risk of developing neutropenia was highest in the first cycle of chemotherapy.20 The trend of neutropenia over three cycles of chemotherapy could also be due to other factors such as poor nutrition and older age (the present study did not analyze this). Hematological toxicity is a common side effect of chemotherapy drugs such as anthracyclines, cyclophosphamide and taxane.21 The chemotherapy drug 5-FU can also cause side effects such as anemia,
**Table 5:** Association of polymorphism GSTP-1 and ABCB1 with neutropenia.

| Gene   | Polymorphism | Normal (n = 71) | Neutropenia | Total (n = 138) | p-value* |
|--------|--------------|----------------|-------------|----------------|----------|
|        |              | n   | %    | n   | %    | n   | %    | n   | %    |       |
| GSTP-1 | AA           | 31  | 43.7 | 23  | 65.7 | 10  | 66.7 | 8   | 47.1 | 72    | 52.1  | 0.277 |
|        | AG           | 33  | 46.5 | 10  | 28.6 | 4   | 26.7 | 8   | 47.1 | 55    | 39.9  |
|        | GG           | 7   | 9.9  | 2   | 5.7  | 1   | 6.7  | 1   | 5.8  | 11    | 8.0   |
| ABCB1  | C3435T       |     |      |     |      |     |      |     |      |       |       |
|        | CC           | 22  | 31.4 | 13  | 37.1 | 5   | 33.3 | 5   | 29.4 | 45    | 32.6  | 0.366 |
|        | CT           | 39  | 54.9 | 14  | 40.0 | 6   | 40.0 | 8   | 47.1 | 67    | 48.6  |
|        | TT           | 10  | 14.1 | 8   | 22.9 | 4   | 26.7 | 4   | 23.5 | 26    | 18.8  |
|        | C1236T       |     |      |     |      |     |      |     |      |       |       |
|        | CC           | 6   | 8.5  | 2   | 5.7  | 3   | 20.0 | 1   | 5.9  | 12    | 8.7   | 0.574 |
|        | CT           | 44  | 62.0 | 27  | 77.1 | 8   | 53.3 | 10  | 58.8 | 89    | 64.5  |
|        | TT           | 21  | 29.5 | 6   | 17.1 | 4   | 26.7 | 6   | 35.3 | 37    | 26.8  |
|        | G2677T       |     |      |     |      |     |      |     |      |       |       |
|        | GG           | 23  | 32.4 | 10  | 28.6 | 6   | 40.0 | 8   | 47.1 | 47    | 34.1  | 0.739 |
|        | GT           | 42  | 59.2 | 19  | 54.3 | 5   | 33.3 | 6   | 35.3 | 72    | 52.2  |
|        | TT           | 6   | 8.5  | 6   | 17.1 | 4   | 26.7 | 3   | 17.6 | 19    | 13.8  |
| ABCB1  | Haplotype    |     |      |     |      |     |      |     |      |       |       |
|        | Non-TT-TT-TT | 67  | 94.4 | 33  | 94.3 | 14  | 93.3 | 14  | 82.4 | 128   | 92.8  | 0.374 |
|        | TT-TT-TT     | 4   | 5.6  | 2   | 5.7  | 1   | 6.7  | 3   | 17.6 | 10    | 7.2   |
| GSTP1 +|              |     |      |     |      |     |      |     |      |       |       |
| ABCB1  | Non variant-variant | 69 | 97.2 | 35  | 100.0 | 15  | 100.0 | 15  | 88.2 | 134   | 97.1  |
|        | (TT-TT-TT)   | 2   | 2.8  | 0   | 0.0  | 0   | 0.0  | 2   | 11.8 | 4     | 2.9   | 0.456 |

*Kruskal-Wallis test.*
Table 6: Association of polymorphism GSTP-1 and ABCB1 with anemia.

| Gene       | Polymorphism | Anemia          | Total (n = 138) | p-value* |
|------------|--------------|-----------------|-----------------|----------|
|            | Normal (n = 40) | Grade 1 (n = 80) | Grade 2 (n = 16) | Grade 3 (n = 2) |
|            | n | % | n | % | n | % | n | % | n | % | n | % |
| GSTP-1     |   |   |   |   |   |   |   |   |   |   |   |   |
| AA         | 22 | 55.0 | 39 | 48.8 | 11 | 68.8 | 0 | 0.0 | 72 | 52.2 |
| AG         | 15 | 37.5 | 33 | 41.3 | 5 | 31.3 | 2 | 100 | 55 | 39.9 |
| GG         | 3  | 27.3 | 8  | 10.0 | 0  | 0.0  | 0 | 0.0 | 11 | 8.0 |
| ABCB1      | C3435T |   |   |   |   |   |   |   |   |   |   |   |
| CC         | 15 | 37.5 | 26 | 32.5 | 4 | 25.0 | 0 | 0.0 | 45 | 32.6 |
| CT         | 16 | 40.0 | 41 | 51.3 | 9 | 56.3 | 1 | 50.0 | 67 | 48.6 |
| TT         | 9  | 22.5 | 13 | 16.3 | 3 | 18.8 | 1 | 50.0 | 26 | 18.8 |
| C1236T     |   |   |   |   |   |   |   |   |   |   |   |   |
| CC         | 3  | 7.5  | 8  | 10.0 | 1 | 6.3  | 0 | 0.0 | 12 | 8.7 |
| CT         | 26 | 65.0 | 54 | 67.5 | 9 | 56.3 | 0 | 0.0 | 89 | 64.5 |
| TT         | 11 | 27.5 | 18 | 22.5 | 6 | 37.5 | 2 | 100 | 37 | 26.8 |
| G2677T     |   |   |   |   |   |   |   |   |   |   |   |   |
| GG         | 16 | 40.0 | 29 | 36.3 | 2 | 12.5 | 0 | 0.0 | 47 | 34.1 |
| GT         | 18 | 45.0 | 41 | 51.3 | 12 | 75.0 | 1 | 50.0 | 72 | 52.2 |
| TT         | 6  | 15.0 | 10 | 12.5 | 2 | 12.5 | 1 | 50.0 | 19 | 13.8 |
| ABCB1      | Haplotype |   |   |   |   |   |   |   |   |   |   |   |
| Non-TT-TT-TT | 39 | 97.5 | 73 | 91.3 | 15 | 93.8 | 1 | 50.0 | 128 | 92.8 |
| TT-TT-TT   | 1  | 2.5  | 7  | 8.8  | 1  | 6.3  | 1 | 50.0 | 10 | 7.2 |
| GSTP1 + ABCB1 | Non variant-variant | 40 | 100.0 | 78 | 97.5 | 15 | 93.8 | 1 | 50.0 | 134 | 97.1 |
|           | Variant (GG)-variant (TT-TT-TT) | 0  | 0.0  | 2  | 2.5  | 1  | 6.2  | 1 | 50.0 | 4  | 2.9 |

*Kruskall-Wallis test*
leukopenia, and thrombocytopenia,22 these being various expressions of myeloid toxicity. The rapid division rates of myeloid cells render them vulnerable targets of cytotoxic drugs.14,23,24

The distribution of allele and genotype of ABCB1 (C1236T, G2677T, and C3435T) among our subjects was in accordance with previous studies and in proportions similar to that of C1236T, G2677T, and C3435T polymorphisms among the Japanese and Chinese populations,5,26 but differed from the polymorphism distribution found in populations in Russia, Serbia, and Germany.27,28 Nevertheless, the polymorphism distribution of ABCB1 between Asian and Caucasian populations did not differ significantly.29 The distribution of GSTP1 in our study is also in accordance with previous studies, in which most patients had the homozygous wildtype (AA) form compared to heterozygous and homozygous mutants.10 We found no significant relationship between ethnicity and ABCB1 and GSTP1 polymorphisms.

In our study, no relation was found between the ABCB1 and GSTP1 polymorphisms, and anemia and neutropenia. Several previous studies also found no relation between ABCB1 and GSTP1 and neutropenia.11,13,28,30 Our results were also similar to those of a previous study conducted on 882 patients involved in the SWOG trial S0221 which showed that none of the SNPs of ABCB1 was associated with hematological toxicity.31 Some previous studies have yielded results at variance with ours, suggesting a lack of association between ABCB1 polymorphism and the incidence of neutropenia and leukopenia (SWOG Trial 2021). Meanwhile Chaturvedi et al.,13 (2013) showed a link between ABCB1 C1236T polymorphism and neutropenia. By contrast, a study has reported that the TT variant in the ABCB1 gene, which is known to be a factor that could lower P-GP expression, and the presence of the variant in ABCB1 (C3435T, C1236T, G2677T) causes more significant changes of P-GP function compared to only one SNP.32 The contradictory explanations for the involvement of ABCB1 C3435T, C1236T, and G2677T polymorphism can cause less functional P-GP.29,33 In this study, most subjects had a non-homozygous variant of haplotype ABCB1 form (92.8%) while the homozygous variant (TT-TT-TT) was only 7.2%. The minority of TT variant in SNP and haplotype of ABCB1 and GSTP1 found in our subjects would affect the result in this study.

Lack of significant relationship between ABCB1 and GSTP1 polymorphisms—either individually (one SNP) or in the form of haplotypes—with hematological toxicity might be due to several factors, such as the small number of subjects, the involvement of other genes in the metabolism of taxane and cyclophosphamide, or administration of filgrastim to treat neutropenia.24 It has also been shown that the inconsistency of the association between ABCB1 polymorphisms and breast cancer treatment outcomes may be due to small sample-sized studies, interethnic variations, and the involvement of other gene polymorphisms involved in metabolic enzyme pathways.34 It is known that there are 16 genes involved in the drug pathway alone, including ABC1, ABCC2, CYP3A5, MAPT, TP53, and XRCC9. In the anthracycline pathway (doxorubicin and epirubicin), several other genes were also involved; for instance, not only ABCB1 as an efflux drug transporter and GSTP1 (which plays a role in drug detoxification), but also genes CBR1, CBR3, AKR1A1, and AKR1C3, which are involved in phase 1 of drug biotransformation.34

Apart from the polymorphisms, the epigenetic factors—the changes in gene expression without altering the nucleotide sequences but rather the DNA methylation, miRNA, and modified histones—affect not only cancer initiation and development but also the chemotherapy response.35 Also to be considered are non-genetic factors relevant to the clinical response to treatment, such as diet and lifestyle, chemotherapy, and inter-drug interactions.24 Healthy food habits, such as microbiota-friendly diet, very low ketogenic diet, and Mediterranean and Japanese diets, may help suppressing the specific reactive oxygen and nitrogen species which affect epigenetic modification. However, their effects on direct hematological toxicity have not been proven yet.36 Obesity, unhealthy diet, smoking, and inadequate physical activity contribute significantly reducing cancer patient survival and clinical response to chemotherapy.37

The present study found all forms of homozygous, heterozygous variants in ABCB1 and GSTP1 genes, but no relationship between ABCB1 and GSTP1 polymorphisms and the incidence of anemia and neutropenia. The existence of a trend of hematological toxicity after chemotherapy administration certainly requires further study with a larger sample size involving the other genetic and non-genetic factors.
to determine the factors linked to hematological toxicity post chemotherapy.

There are limitations in our study that need to be considered in interpreting our results. First, we selected only two genes that affect the pharmacokinetic pathway of anthracycline and cyclophosphamide. However, it is important to consider the multiple SNPs and genes involved and examine the effects on patient outcomes. Second, we did not analyze non-genetic factors such as diet, physical activity, and smoking that could affect clinical response to chemotherapy.

CONCLUSION

The incidence of neutropenia and anemia in breast cancer patients receiving anthracycline-based chemotherapy was found by this study. However, no association was found between ABCB1 and GSTP1 polymorphisms on hematological toxicity.

Disclosure

The authors declared no conflicts of interest. This research is funded by the Research Institute of Universitas Sumatera Utara.

Acknowledgements

We thank the Universitas Sumatera Utara Research institute committee for their tremendous support. We also acknowledge the support received from Dr. Kamal Basri Siregar (surgical oncologist) and Ms. Mardiah Nasution (laboratory technician).

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