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RESEARCH ARTICLE

Effect of GSTP1 and ABCC4 gene polymorphisms on response and toxicity of cyclophosphamide-epirubicin-5-fluorouracil-based chemotherapy in Bangladeshi breast cancer patients

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Abstract The most important cytotoxic drug namely, cyclophosphamide used in breast cancer along with epirubicin and 5-fluorouracil, is transported by ABCC transporters and detoxified by glutathione S-transferases (GSTs). The activities of these enzymes and transporters may vary in different population due to the presence of genetic polymorphisms. This study was aimed to evaluate the effects of GSTP1rs1695 and ABCC4rs9561778 polymorphisms on the response and toxicities produced by chemotherapy used in the treatment of Bangladeshi breast cancer patients. A total of 200 and 56 patients with invasive breast cancers were recruited from different public and private hospitals of Bangladesh of which 117 patients received neoadjuvant chemotherapy to examine the response as well as the toxicity, and another 139 patients received adjuvant chemotherapy to evaluate only the toxicity. Genetic polymorphisms of the mentioned genes were detected by using Polymerase Chain Reaction Restriction Fragment Length Polymorphism (PCR RFLP). Patients carrying AG and AG plus GG genotype of GSTP1rs1695 were more likely to have a good response, whereas no association of ABCC4rs9561778 was found with the chemotherapy response. Patients carrying GT and GT plus TT genotypes of ABCC4rs9561778 were found to be associated with anemia, neutropenia, leukopenia, and gastrointestinal toxicities when compared with GG genotype whereas no association was found with thrombocytopenia. GSTP1rs1695 was not associated with any type of toxicities investigated. Our result indicates that GSTP1rs1695 polymorphism was strongly associated with the response of chemotherapy, whereas ABCC4rs9561778 polymorphism was significantly related with chemotherapy-induced toxicities.

Keyword Polymorphisms · Cyclophosphamide · Epirubicin · 5-fluorouracil · Chemotherapy · Breast cancer

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Introduction

Breast cancer is the most frequent cancer of women, and it was estimated about 1.68 million new cases all over the world in 2012 [1] and projected new cancer cases among women in the United States in 2014 was about 0.23 million [2]. Bangladesh is a least developed country where no national cancer registry system is maintained, and the estimated annual new breast cancer cases are 30,000 [3]. Breast cancer is also the most frequent cause of cancer deaths in women [1]. It is considered as a group of diseases and may be treated in several ways depending on the types and degree of spread [4]. The common treatments utilized

for breast cancer incorporate radiotherapy, chemotherapy, hormone therapy, and targeted therapy that may be used before or after surgical resection. Cytotoxic chemotherapy is usually recommended to stop cancer cell growth and division. When this treatment is used before surgery to make the tumor surgically removable by shrinking, it is called neoadjuvant chemotherapy (NACT), whereas when chemotherapy is used after surgery to ensure the long term disease free survival by eliminating the residual cancer cells [5] then it is called adjuvant chemotherapy (ACT). Combined drug therapy is more effective than a single drug in case of breast cancer chemotherapy [6, 7]. Cyclophosphamide is most frequently used in the treatment of breast cancer in combination with anthracyclines and 5-Fluorouracil (CAF) [8]. Cyclophosphamide is a DNA-alkylating agent upon which the efficacy and toxicity of the combined chemotherapy depend [9]. Doxorubicin and epirubicin among the anthracyclines, whereas 5-fluorouracil from the antimetabolites are widely used in combination with cyclophosphamide [10]. Genetic variation in the phase I activation, phase II detoxification enzymes, and ABC membrane transporters play an important role in the efficacy and toxicities of cyclophosphamide epirubicin and 5-fluorourcil (EFC) based chemotherapy. Cyclophosphamide, a prodrug is initially activated and metabolized by phase I metabolizing enzymes and detoxified by Phase II enzyme GSTP1. A nonsynonymous polymorphism in exon 5 of GSTP1 (GSTP1 313A/G, rs1695) in which Ile is replaced by Val produces toxic effect by decreasing the chemotherapy detoxifying ability of this enzyme and improves survival and decreases the rate of relapse [9]. The rs1695 variant of GSTP1 also involves the detoxification of epirubicin and increases the treatment benefit of breast cancer patients [11]. ABCC4, a member of the superfamily of ATP-binding cassette (ABC) transporters is involved in the transportation of cyclophosphamide, and ABCC4 rs9561778 increases the risk of adverse drug reaction of EFC-based chemotherapy [12]. Only few studies had been conducted to evaluate the effect of ABCC4 and GSTP1 polymorphisms on the response and toxicities of CAF/EFC-based chemotherapy, but none of these studies reported the effect of ABCC4 on chemotherapy response. This study was designed for the first time on the Bangladeshi population that is located in the southeast part of the earlier Indian subcontinent where the population have a wide racial admixture and genetic diversity [13–15] to evaluate the effect of rs1695 and rs9561778 on the response and toxicity of CAF/EFC-based adjuvant (ACT) and neoadjuvant chemotherapy (NACT).

Materials and methods

Subject selection

Total two hundred and fifty six Bangladeshi cases with histologically proven invasive breast carcinoma were recruited from different private and public hospitals of Bangladesh from July 2009 to the end of 2013 who received EFC based chemotherapy (139 received ACT and 117 received NACT) and laboratory analysis was conducted in the laboratory of Pharmacogenetics and pharmacokinetics of the Departments of Clinical Pharmacy and Pharmacology, Faculty of Pharmacy, University of Dhaka, Bangladesh. A written informed consent was taken from all patients and ethical approval was taken from the ethical committees of the respective hospitals. Patients were staged according to the classification of tumor-node-metastasis (TNM) staging and the treatment was provided as per standard institutional multimodal protocols.

Response and toxicity evaluation criteria

The effect of GSTP1 and ABCC4 polymorphisms on the response was evaluated in patients (117) receiving only EFC-based NACT, whereas that on toxicities was evaluated in patients (256) receiving both EFC-based NACT (117) and ACT (139). Toxicities of chemotherapy like anemia, neutropenia, leukopenia, thrombocytopenia, and gastrointestinal toxicity were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0) [16]. Treatment responses like complete response, partial response; progressive and stable condition of tumor were estimated according to the Response Evaluation Criteria in Solid Tumors (RECIST) [17]. TNM staging was evaluated according to published method [18].

Genotyping

Blood sample was collected from each patient in sterile tubes containing EDTA-Na_2 and stored at −80 °C until DNA extraction. Genomic DNA was extracted by the method routinely used in our laboratory [13, 19, 20]. PCR-restriction fragment length polymorphism (RFLP) method was used to genotype both the GSTP1rs1695 and ABCC4rs9561778 polymorphisms. PCR products of GSTP1 were digested with BsmAI restriction enzyme (NEB, USA), and that of ABCC4 were digested with HpaII (NEB, USA) at the prescribed conditions of the manufacturer and the digested products were visualized on 2 % agarose gel after ethidium bromide staining.

Statistical analysis

Chi-square (χ^2) test was applied for comparison of different demographic and clinicopathological parameters like age, menstrual status, TNM stages, histology, tumor grade, receptor status between responders and nonresponders; patients showing higher toxicities (grade III and grade IV) and lower toxicities (≤grade II). Response and toxicity variations between the different genotypes of GSTP1 and ABCC4 were evaluated as odds ratio (OR) with 95 % confidence intervals (Cls) and level of significance (p) by using chi-square (χ^2) test

and $P<0.05$ was considered statistically significant. All statistical analyses relevant to this research work were done applying the SPSS software (version 17.0).

Results

Characteristics of patients

There was no significant difference between the patients who responded and those who did not respond to NACT with respect to different demographic and clinicopathological parameters like age, menstrual status, TNM stages, histology, tumor grade, receptor status (HR status, Her-2/neu expression) (Table 1). Similar finding was also observed between the patients who suffered from higher toxicity (grade III+IV) and those who have no or lower toxicity (Grade ≤II) (Table 1).

Treatment outcomes

Among the 117 patients who were treated with NACT, 17 (14.53 %) patients showed complete response and 51 (43.59 %) patients got partial response; 47 (40.17 %) patients exhibited stable conditions and 2 (1.71 %) patients had disease progression according to RECIST criteria. All

Table 1 Comparison of clinicopathological parameters of nonresponders versus responders and patients who suffered from higher and lower toxicity

Characteristics	Nonresponders (49)	Responders (68)	*P* value	Toxicity Grade (III+IV) (116)	Toxicity Grade≤II (140)	*P* value
Age						
<45	8	13	0.924	20	36	0.174
45–55	19	26		43	55	
>55	22	29		53	51	
Menstrual status						
Premenoposal	15	26	0.355	37	53	0.603
Perimenoposal	1	4		5	6	
Postmenoposal	33	38		74	81	
TNM stage (Clinical)						
I	0	0	0.9174	1	2	0.946
II	1	1		3	3	
III	42	60		102	121	
IV	6	7		10	14	
Lymph node status						
No	4	7	0.968	12	12	0.916
N1	23	33		54	64	
N2	17	22		40	49	
N3	5	6		10	15	
Histology						
Ductal	48	67	0.348	114	136	0.707
Lobular	1	0		1	3	
Mixed	0	1		1	1	
Tumor grade						
Grade I	2	1	0.678	5	3	0.550
Grade II	28	40		63	84	
Grade III	19	27		44	55	
Hormone receptor status						
Estrogen receptor (ER)						
Negative	31	35	0.280	64	79	0.935
Positive	18	33		50	61	
Progesterone receptor (PR)						
Negative	34	40	0.330	68	93	0.901
Positive	15	28		41	56	
Her-2/neu status						
Negative	29	40	0.880	68	84	0.955
Positive	20	28		47	57	

patients received the same regimen during chemotherapy and immunohistochemical analysis was used to detect the estrogen receptor, progesterone receptor status and expression of the Her-2/neu proteins. In this study, we found that the patient carrying variant genotypes in GSTP1rs1695 and ABCC4rs9561778 showed better response in comparison to wild genotype of the respective polymorphism. The statistical significant response was obtained in case of the patients carrying AG and AG+GG genotypes of GSTP1rs1695 polymorphism [OR=2.53, 95 % CI=1.13 to 5.69, p=0.025 and OR=2.69, 95 % CI=1.26 to 5.76, p=0.011, respectively] (Table 2), and no significant effect (p>0.05) of ABCC4rs9561778 polymorphism on the response of EFC-based NACT was found.

Treatment toxicity

In the second phase of this study, we evaluated the role of GSTP1rs1695 and ABCC4rs9561778 polymorphisms on the toxicities of EFC-based ACT and NACT. Patients carrying GT and GT+TT genotypes of ABCC4rs9561778 polymorphism significantly increased the risk of different toxicities like anemia [OR=2.10, 95 % CI=1.09 to 4.03, p=0.027 and OR=2.10, 95 % CI=1.18 to 3.74, p=0.012]; neutropenia [OR=2.40, 95 % CI=1.24 to 4.66, p=0.010 and OR=2.44, 95 % CI=1.35 to 4.40, p=0.003]; leukopenia [OR=2.17, 95 % CI=1.09 to 4.33, p=0.028 and OR=2.28, 95 % CI=1.23 to 4.22, p=0.009] and gastrointestinal toxicity [OR=2.54, 95 % CI=1.09 to 5.93, p=0.031; OR=2.62, 95 % CI=1.22 to 5.59, p=0.013] in comparison with GG genotype. No significant relationship was found for these genotypes in case of thrombocytopenia (Table 3). Variant genotypes of GSTP1 increased the risk of EFC induced anemia, neutropenia, leukopenia, gastrointestinal toxicity, and decreased the risk of thrombocytopenia but no relationship was obtained statistically significant.

Discussion

Drug response and toxicity are varied due to the genetic variation in the genes encoding drug-metabolizing enzymes, detoxifying enzymes and transporters [21–23]. This pharmacogenetic study was designed and carried out to analyze the role of detoxifying enzyme GSTP1 and transporter ABCC4 on the response and toxicity of EFC based ACT and NACT in the Bangladeshi breast cancer patients.

In this study, we found that AG (Ile/val) and AG+GG (Ile/val+val/val) genotypes increased the response of EFC-based NACT to 2.53 and 2.69 times, respectively. GSTP1rs1695 polymorphism resulting from the change of amino acid from Ile to Val at codon 105 has lower detoxifying and thermal activity [24]. This reduced detoxification capacity increases the concentration of active drugs and metabolites that finally raises drug response and survival rate. Our findings are supported by some previous studies where they found GSTP1 105Ile/Val and GSTP1 105Val/Val genotypes increased the response of cyclophosphamide-based chemotherapy in breast and other cancers [25–29]. Our findings are partially inconsistent with studies conducted on Brazilian population where a better response with GSTP1 Ile105 [30] and increased death free survival and overall survival with GSTP1 Val105 were found [31]. One Chinese study also claimed that GSTP1*105Ile/Val or 105Ile/Ile had a better response than the GSTP1*105Val/Val, and this finding is also partially inconsistent with our result, whereas another study is consistent with our findings [32]. This may be due to ethnicity difference and greater genetic admixture and diversity in the population of the Indian subcontinent [13–15]. We did not find any statistically significant effect of variant genotypes of GSTP1rs1695 on the EFC-induced toxicities whereas some previous studies found mixed results [5, 22, 32, 33].

ABCC4 gene, a member of the superfamily of ATP-binding cassette (ABC) transporters plays a vital role in bioavailability and disposition of chemotherapeutic agents and their metabolites due to the involvement of ABC protein in

Table 2 Effect of GSTP1 and ABCC4 polymorphisms on the response of chemotherapy

Genetic polymorphisms	Genotype	Responders (CR + PR) (n=68)	Nonresponders (SD + PD) (n=49)	Odds ratio (95 % Cl)	p
GSTP1 rs1695	AA(60):Ile/Ile	28	32	Reference	
	AG(45):Ile/Val	31	14	2.53 (1.13 to 5.69)	0.025
	GG(12):Val/Val	9	3	3.43 (0.84 to 13.93)	0.085
	AG(45) + GG(12) Ile/Val + Val/Val	40	17	2.69 (1.26 to 5.76)	0.011
ABCC4 rs9561778	GG(89)	50	39	Reference	–
	GT(20)	13	7	1.45 (0.53 to 3.98)	0.472
	TT(8)	5	3	1.30 (0.29 to 5.78)	0.730
	GT(20)+TT(8)	18	10	1.40 (0.583 to 3.38)	0.449

CR complete response, *PR* partial response, *SD* static disease, *PD* progressive disease

Table 3 Effect of GSTP1 and ABCC4 polymorphisms on the toxicities induced by chemotherapy

Toxicities		GSTP1				ABCC4			
		AA(131)	AG(98)	GG(27)	AG(98)+GG(27)	GG(193)	GT(46)	TT(17)	GT(46)+TT(17)
Anemia	Grade 3+Grade 4 (115)	56	45	14	59	78	27	10	37
	Grade≤2 (141)	75	53	13	66	115	19	7	26
	Odds ratio (95 % CI)	Reference	1.14 (0.67 to 1.93)	1.44 (0.63 to 3.31)	1.20 (0.73 to 1.96)	Reference	2.10 (1.09 to 4.03)	2.11 (0.77 to 5.77)	2.10 (1.18 to 3.74)
	P Value		0.633	0.388	0.474		0.027	0.147	0.012
Neutropenia	Grade 3+Grade 4 (79)	39	31	9	40	50	21	8	29
	Grade≤2 (177)	92	67	18	85	143	25	9	34
	Odds ratio (95 % CI)	Reference	1.09 (0.62 to 1.92)	1.18 (0.49 to 2.85)	1.11 (0.65 to 1.89)	Reference	2.40 (1.24 to 4.66)	2.54 (0.93 to 6.95)	2.44 (1.35 to 4.40)
	P value		0.762	0.714	0.700		0.010	0.069	0.003
Leukopenia	Grade 3+Grade 4 (65)	31	26	8	34	41	17	7	24
	Grade≤2 (191)	100	72	19	91	152	29	10	39
	Odds ratio (95 % CI)	Reference	1.16 (0.64 to 2.13)	1.36 (0.54 to 3.41)	1.21 (0.69 to 2.12)	Reference	2.17 (1.09 to 4.33)	2.60 (0.93 to 7.23)	2.28 (1.23 to 4.22)
	P value		0.620	0.514	0.516		0.028	0.068	0.009
Thrombocytopenia	Grade 3+Grade 4 (4)	2	1	1	2	2	1	1	2
	Grade≤2 (252)	129	97	26	123	191	45	16	61
	Odds ratio (95 % CI)	Reference	0.66 (0.06 to 7.44)	2.48 (0.22 to 28.38)	1.05 (0.15 to 7.56)	Reference	2.12 (0.19 to 23.92)	5.97 (0.51 to 69.45)	3.13 (0.43 to 22.70)
	P value		0.741	0.465	0.962		0.543	0.154	0.259
Gastrointestinal toxicity	Grade 3+Grade 4 (33)	15	13	5	18	19	10	4	14
	Grade≤2 (223)	116	85	22	107	174	36	13	49
	Odds ratio (95 % CI)	Reference	1.18 (0.53 to 2.62)	1.76 (0.58 to 5.33)	1.30 (0.62 to 2.71)	Reference	2.54 (1.09 to 5.93)	2.82 (0.83 to 9.51)	2.62 (1.22 to 5.59)
	P value		0.679	0.319	0.482		0.031	0.095	0.013

transport of various molecules across extra and intracellular membranes [34]. From the previous studies, it was found that cyclophosphamide and its metabolites are substrates of ABCC4 and expression of mRNA protein of ABCC4 occurs extensively in several excretory organs like the liver, kidney, and intestine [35].

ABCC4 plays a significant role in the urinary excretion and secretion of cyclophosphamide and its metabolites in the systemic circulation from the liver [12, 35]. Moreover, ABCC4 also involves in the cellular extrusion of Phase II detoxification metabolites of glutathione and glucuronide conjugates [36]. Any genetic variation in ABCC4 like rs9561778 where G is replaced by T interrupts the urinary excretion and hepatic efflux of drug and increases the concentration of cyclophosphamide and its metabolites in blood that finally produces the EFC-induced toxicities in the patients [12, 37].

In the present study, we found that GT and TT genotypes of ABCC4 rs9561778 increased the risk of EFC-induced anemia, neutropenia, leukopenia, and gastrointestinal toxicity more than 2 times in comparison to GG genotype that was statistically significant, whereas no statistical significant relationship was obtained in case of thrombocytopenia. This increased adverse drug reactions may be due to failure of genetically altered mRNA of ABCC4 (G→T) in the clearance of drug and their metabolites. According to our knowledge, only one previous study monitored the effect ABCC4 polymorphism on the adverse drug reactions of cyclophosphamide-based chemotherapy that was on Japanese population, and our findings are consistent with that study [12]. Cyclophosphamide-induced thrombocytopenia was reported in several studies that were not conducted with ABCC4, and the relationship was also not statistically significant [38, 39].

Conclusion

Our study has provided information about the role of GSTP1rs1695 and ABCC4rs9561778 polymorphisms in the outcome of NACT as well as the toxic effect of EFC-based ACT and NACT. The findings of this study indicate that the variant rs1695 of GSTP1 gene was associated with chemotherapy response, and the variant rs9561778 of ABCC4 was associated with chemotherapy-induced toxicities like anemia, neutropenia, leukopenia, and gastrointestinal toxicity in this population where no national cancer registry system is till maintained. To ensure the best treatment and to reduce the drug induced toxic reactions of the breast cancer patients in this country, a large-scale study with more patients and many genes is required.

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Conflicts of interest None

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