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DELETION OF GSTM1 ASSOCIATED WITH BETTER PATHOLOGICAL RESPONSE IN LOCALLY ADVANCED BREAST CANCER PATIENTS OF SOUTH INDIAN POPULATION

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ABSTRACT:

Studies have emphasized the significance of genotyping GSTP1 and detecting deletions of GSTM1 and GSTT1 genes in predicting the response of breast cancer patients to anthracycline and taxane-based treatment regimens. Nevertheless, there are discrepancies in the data due to the substantial influence of interethnic differences on the prediction of chemotherapeutic response. This study examined the impact of GSTM1 and GSTT1 gene deletions, as well as GSTP1 polymorphism, on the response and toxicity of South Indian patients with locally advanced breast cancer who were undergoing anthracycline-based neoadjuvant chemotherapy. We conducted a prospective study from January 2015 to December 2018. We enrolled 170 patients who had been diagnosed with locally advanced breast cancer and were undergoing treatment with anthracycline-based therapy. The frequencies of the homozygous wild-type variant AA, the heterozygous variant AG, and the mutant homozygous variant GG were 44%, 41%, and 15%, respectively. Out of the 152 patients, 48 successfully attained a pathologic response. Patients with the GSTM1 null variant had a complete pathologic response, whereas those with the GSTM1 gene did not. Additionally, we have noticed a pattern in the susceptibility to neutropenia among patients who had null variants of GSTM1. In our study, South Indian breast cancer patients with the GSTM1 deletion experienced better complete pathological responses.

Keywords: Breast Cancer, GSTT1, GSTM1, GSTP1, Pathological Response, Neutropenia, Chemotherapy Induced Toxicity.

1. INTRODUCTION

Breast cancer is the predominant form of cancer in women. In 2012, there were 1.67 million cases of breast cancer globally, making up 25% of all cancer cases. It has the top position among emerging nations in terms of cancer fatalities, behind lung cancer (Ferlay et al., 2012). In India, breast cancer constitutes 5-8% of the total cancer cases, and its prevalence is steadily rising annually. Urban Indian women have the highest incidence of this type of cancer, whereas rural women have the second highest incidence (Anonymous 2001). India has an annual incidence rate of around 100,000 new cases, with a yearly increase of up to 5% (Mehrotra, 2022). Approximately 50% of women who have preoperative cytotoxic therapy do not exhibit a positive response to the treatment (Ellis et al., 1998a,1998b). Therefore, the identification of genetic markers that may accurately predict patient responses would enhance survival rates and mitigate the harmful consequences of cytotoxic therapy. Anthracycline is a commonly recommended cytotoxic drug for breast cancer and is a key component of most treatment plans (Bonadonna, et al., 1998) Reactive oxygen species (ROS) primarily contribute to the anticancer effects of anthracycline by inducing DNA damage and disrupting the mitochondrial membrane. As a result, the apoptotic cascade is triggered (Ambrosone, et al., 2005). Glutathione-s-transferases (GSTs), enzymes responsible for eliminating reactive oxygen species (ROS), may influence apoptotic processes (Bewick, 2008; Sau et al., 2010). The GSTP1, GSTM1, and GSTT1 enzymes have important functions in the conjugation and detoxification of xenobiotics, including chemotherapeutic drugs. Scientists have identified three operational variations in the GST gene, specifically responsible for encoding GSTM1, GSTT1, and GSTP1. Null variants of GSTM1 and GSTT1, along with a polymorphic version of GSTP1 that leads to decreased or absent enzyme activity, have been linked to a positive response in some types of cancer (Srivastava, et al 1999). Studies have demonstrated that substituting a single nucleotide from 313A to G in GSTP1 decreases the enzyme's metabolic activity (Srivastava, et al., 1999). A study conducted on breast cancer patients found a correlation between a mutation in the GSTP1 gene and enhanced survival rates following chemotherapy treatment (Sweeney, et al., 2000). Scientists have investigated the potential of GSTM1 and GSTT1 polymorphisms to serve as predictors of a tumor's response to neoadjuvant chemotherapy (Lizard-Nacol, et al., 1999; Iwao-Koizumi, et al., 2005) Several studies have documented the impact of GSTM1 and GSTT1 null alleles on the responsiveness and toxicity of specific types of cancer, such as breast cancer (Mossallam, et al., 2006; Goekkurt, et al., 2006 and Valladares et al., 2006). An effective reaction to neoadjuvant chemotherapy serves as an indicator of enhanced survival. By identifying the factors that influence the response and tailoring the medication to individual patients, we can achieve more effective management of the disease. The response to treatment was significantly influenced by interethnic variation. There is a variation in the frequency of GSTM1 and GSTT1 between the South Indians and other groups (Syamala, et al., 2008; Chen, 1996). It is hypothesized that variations in the GSTM1, GSTT1, and GSTP1 genes may influence the therapeutic response of breast cancer patients from South India. Hence, our objective was to investigate the impact of variations in GSTM1, GSTT1, and GSTP1 on the response of breast cancer patients to anthracycline-based neoadjuvant chemotherapy.

2. MATERIALS AND METHODS

Study population: We enrolled patients from January 2015 to December 2018, after obtaining consent from the institutional ethical committee at the outpatient department of medical oncology at Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry. This study encompassed all recently diagnosed patients with locally advanced breast cancer who had neoadjuvant chemotherapy using anthracycline and taxane-based regimens. We

specifically eliminated patients who had metastases, male breast cancer, contraindications for chemotherapy, or known allergies to iodine-based contrast materials. We conducted fine needle aspiration cytology and a core needle biopsy to verify the diagnosis of breast cancer. We verbally communicated the details of their medical condition and the prescribed medications to the patients. The study encompassed all patients who willingly granted informed permission. All the human procedures were by the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

Treatment protocol and endpoints

The staging of locally advanced breast cancer was directed by the American Joint Committee on Cancer (AJCC) recommendations, which also determined the treatment plan and objectives. This study enrolled patients with stage IIB (T3 N0M0), stage IIIA, and stage IIIB. The patients were treated with FEC (5-fluorouracil 500 mg/m2, epirubicin 100 mg/m2, or cyclophosphamide 500 mg/m2) for 3 cycles administered once every 3 weeks. This was followed by docetaxel 75 mg/m2 for 4 cycles administered once every 3 weeks. Alternatively, patients received AC (doxorubicin 60 mg/m2 or cyclophosphamide 600 mg/m2) for 4 cycles once every 3 weeks, followed by docetaxel 100 mg/m2 once every 3 weeks. Duration of 21 days. Patients administered with docetaxel at a dosage of 100 mg/m2 were given primary GCSF prophylaxis, whereas other patients were given secondary GCSF only if needed. Patients had a breast MRI scan prior to the initial round of treatment and again after completing the entire course of chemotherapy. We evaluated the tumor response using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, based on an MRI scan. Following the surgical procedure, a pathological complete response (pCR) was determined by the absence of any signs of tumor cells in both the breast and axillary lymph nodes in the removed tissue samples. We assessed the toxicity evaluations using the CTCAE standards, which utilize the common nomenclature for adverse events v3.0.

DNA extraction and genotyping

We obtained a 5 ml blood sample from the patients using tubes that contained ethylenediaminetetraacetic acid (EDTA) to extract DNA. We subjected the blood to a centrifugal force of 3000 g, and removed the plasma supernatant. We isolated the leukocytes and obtained DNA by employing the phenol-chloroform technique. The DNA was quantified using a photometer (Eppendorf AG 22331, Germany). The genotyping of GSTM1 null and GSTT1 null genotypes was conducted using multiplex polymerase chain reaction (PCR). For the albumin gene, the forward and reverse primers used were F = 5' GCC CTC TGC TAA CAA GTC CTA C 3' and R = 5' GCC CTA AAA AGA AAA TCG CCA ATC 3'. For GSTM1, the primers used were GSTM1-F = 5GAA CTC CCT GAA AAG CTA AAG C 3' and R = 5' GTT GGG CTC AAA TAT ACG GTG G 3'; and for GSTT1, the primers used were GSTT1 F = 5' TTC CTT ACT GGT CCT CAC ATC TC 3' and R = 5' TCA CCG GAT CAT GGC CAG CA 3'. The albumin gene was used as an internal positive control. The amplified DNA fragments were separated using 1% agarose gel electrophoresis. The DNA segments of GSTT1, Albumin, and GSTM1 were amplified and measured to be 480 bp, 380 bp, and 215 bp in length, respectively. The lack of 215 bp and 480 bp DNA segments signifies the presence of GSTM1 null and GSTT1 null genotypes, respectively. We performed genotyping of GSTP1 using real-time PCR on a 7300 Applied Biosystems instrument from Life Technologies Corporation, USA. We used TaqMan SNP genotyping assays with the assay ID C____3237198_20. We employed version 1.4 of the 7300 sequence detection software (SDS) to perform allelic discrimination.

Statistical analysis
The chi-square test was employed to examine the observed genotype frequencies for Hardy-Weinberg equilibrium. We analyzed to examine the connections between polymorphic variants of GST genotypes and clinicopathological characteristics, as well as the response to neoadjuvant chemotherapy. To determine the relative risk and 95% confidence intervals (CIs), we utilized the 2-tailed Fisher exact test. The data was subjected to statistical analysis using GraphPad InStat 10.2.2 (GraphPad Software Inc., San Diego, CA, USA). A significance level of $P < 0.05$ was used.

3. RESULTS

Patient and tumor characteristics
A total of 176 patients with locally advanced breast cancer were included in the study, spanning from January 2015 to August 2017. The primary emphasis of the investigation was on the features of their tumors. Exclusion was applied to six of these cases. Three patients exhibited metastases, while three others experienced organ failure. The analysis comprised a total of 170 patients, with the exclusion of these six cases. The patients had a median age of 50 years, with a range of 23 to 60. Table 1 presents a concise overview of the clinicopathological features observed in different genotypes.

Evaluation of primary pathological and tumor response
The pathological response of a total of 152 patients was examined. Out of the total number of patients in the study group, 48 of them successfully obtained a pathological complete response (pCR), whereas the rest of the patients did not reach pCR. We evaluated the responses of 145 individuals utilizing the RECIST criteria. A total of 25 patients were deemed ineligible for MRI scans. Out of the total number of patients, 31% achieved a complete response (CR), 60% achieved a partial response (PR), and 9% did not respond at all.

Genotyping and association with response
There were no significant differences in the genotype frequencies of GSTM1, GSTT1, and GSTP1 between individuals who responded to the treatment and those who did not. We evaluated the pathogenic response and its correlation with GST genotypes. Patients who had the null GSTM1 genotype experienced a complete pathological response that was 1.78 times higher than patients with the GSTM1 genotype, as shown in Table 2. None of the other genotypes had any impact on either the clinical or pathological response.

Genotype Influence on Toxicity
We monitored the patients till they finished the neoadjuvant chemotherapy to evaluate the impact of their genetic makeup on the occurrence of adverse effects. In instances of severe toxicity, we have agreed to postpone treatment for a maximum of 2 weeks. We evaluated the occurrence of blood-related toxicity, the use of additional GCSF prophylaxis, and the decrease of dosage for grades 3 and 4 toxicity. Additionally, we assessed the occurrence of non-blood-related toxicity, the need for dosage reduction, and the possibility of changing the chemotherapy regimen for these same grades. Neutropenia, a prevalent manifestation of hematological toxicity, constituted 48.17%. Among the non-hematological toxicities, alopecia was reported in all patients, whereas leucopenia and anemia accounted for 31.7% and 9.1% respectively. Additional undesirable medication responses that were documented include myalgia (57.3%), nausea (45.1%), vomiting (52.8%), diarrhea (34.14%), mucositis (49.0%), and hand-foot syndrome (30.4%). During the administration of docetaxel chemotherapy, we noted adverse effects including febrile neutropenia, hand-foot syndrome, and myalgia. Four

patients who had febrile neutropenia, grade 3 and 4 mucositis, or diarrhea died due to toxic effects. Out of the total number of patients, 16 experienced a delay in receiving chemotherapy, whereas 21 patients were administered supplementary GCSF prophylaxis. The influence of the GST genotype on several toxicities was examined, and it was found that individuals with GSTM1 null genotypes showed a tendency towards an increased risk of neutropenia ($p = 0.06$) compared to patients with GSTM1 genes. No negative effects were observed in the other genotypes. (Table 3)

4. DISCUSSION

Breast cancer exhibits a high degree of responsiveness to chemotherapy, while the extent of its therapeutic advantages varies considerably. The utilization of preoperative systemic chemotherapy in locally advanced breast cancer has proven advantageous for patients as it allows for the surgical treatment of tumors that were previously deemed inoperable. Preoperative chemotherapy has been established as a viable treatment for patients with locally advanced breast cancer (Ragaz, et al., 2005; Chia, et al., 2008). Patients receiving chemotherapy exhibited significant heterogeneity in their responses. Identifying the people who truly benefit from chemotherapy is a tough task due to the heterogeneity of breast cancer, which consists of several subtypes. However, it is worth noting that chemotherapy does enhance disease-free survival and overall survival. It is necessary to identify pharmacogenetic indicators due to the significant differences in how individuals respond to and tolerate anticancer drugs. The glutathione-S-transferase enzyme has attracted considerable attention due to its role in drug detoxification and its capacity to regulate apoptosis by blocking the JNK signaling pathway (Sau et al., 2010). Research has demonstrated that genetic variations in GSTP1, GSTM1, and GSTT1 have a significant influence in determining an individual's vulnerability to cancer (Helzlsouer et al., 1998). Furthermore, certain variations in GST genes can impact the efficacy of cytotoxic treatment (Hayes, et al., 1995). The reaction can be influenced by lower enzyme activity caused by the loss of the GSTT1 and GSTM1 genes, as indicated by certain studies. Individuals with a null genotype exhibit a reduced ability to metabolize the byproducts of many medications, cancer-causing substances, and specific chemicals. The diminished ability to eliminate microorganisms has heightened vulnerability to the formation of specific types of cancer, such as breast cancer (Bosch, et al., 2006). Patients with the null genotype exhibit a diminished capacity to metabolize medications due to the involvement of GST enzymes in drug detoxification. Consequently, these patients are more prone to experiencing a favorable response and improved survival rates. Multiple studies have demonstrated the significance of GSTP1 expression in determining treatment resistance and unfavorable prognosis, particularly in patients with breast cancer (Arun, et al., 2010). The GSTP1 313A→G mutation, often known as Ile105Val, has been found to decrease enzyme activity (Yang, et al., 2005; Kadouri, et al., 2008). Given the significant impact of interethnic differences on the response, we postulated that the GSTT1, GSTM1, and GSTP1 polymorphisms had an influence on the response of the breast cancer population in South India. The occurrence of GSTM1 and GSTT1-null genotypes differs among different ethnic communities. Several investigations conducted in India have found prevalence rates between 17.6% and 18.4% for the GSTT1 null genotypes and between 22% and 33% for the GSTM1 null genotypes (Mishra, et al., 2004; Vettriselvi, et al., 2006). The study found that the null genotypes GSTM1 and GSTT1 were prevalent in 46% and 24% of the population, respectively. The prevalence of GSTT1 in the South Indian population was also found to be the same. The prevalence of the GSTM1 null variation in the South Indian population was 22% higher compared to the typical frequency of the GSTM1 null variant (Syamala, et al., 2008). The increasing prevalence of this variant allele may be attributed to the high susceptibility of breast

cancer patients to develop the disease. The reason for this is that GSTM1 null variants have been associated with increased vulnerability to illness in multiple investigations. We conducted a comparison of clinical and pathological features, including menopausal state, stage, node involvement, tumor grade, estrogen receptor status, progesterone receptor status, and HER2 receptor status, across individuals with different genotypes of GSTT1, GSTM1, and GSTP1. Patients with the null variant genotype and those with the GSTM1 genotype had distinct differences in their node status. No other clinicopathological features were found to be associated with other genotypes. A study reported a correlation between those who possessed the GSTM1 null mutation and a higher likelihood of having stage 3 malignancies and ER-negative tumors (Duggan, et al., 2013). Our investigation revealed that those who did not possess the GSTM1 gene were 1.7 times more like to attain a pathological reaction. The reaction was not linked to other GSTT1 and GSTP1 genotypes. Several studies have investigated the association between polymorphisms in the GSTT1, GSTM1, and GSTP1 genes and both a favorable prognosis and the efficacy of chemotherapy (Oliveira, et al., 2014; Tulsyan, et al., 2013). A study reported (Bai, et al., 2012) that GSTM1 and GSTP1 had a role in the prognosis of breast cancer patients. In this investigation, we found that the GSTM1 genotype was linked to a favorable pathological response. Some studies reported that variations in the GSTP1 gene may be used to forecast how breast cancer patients respond to chemotherapy (Romero, et al., 2012; Ge, et al., 2013). A further investigation indicated that the presence of the GSTP1 G allele was linked to a favorable response to the treatment (Ji, et al., 2012) The GSTP1 genotype did not show any association with response in our investigation. However, a few studies (Mishra, et al., 2011; Franco, et al., 2012) also reported a lack of association between GSTP1, GSTM1, and GSTT1 gene polymorphisms and the prognosis of breast cancer patients. GSTM1 had a distinct reduction or alteration in its expression and was associated with an improved response to anthracycline and taxane-based treatment plans (Zhang, et al., 2019). These findings indicate that the GSTM1 gene influences the treatment response of breast cancer patients. In our study individuals with GSTM1 null genotypes had a higher likelihood of developing neutropenia, however, the association was not statistically significant ($p = 0.06$). The results of our investigation were consistent with the findings of the Lucknow study (Mishra, et al., 2011). GSTP1 c.313A>GG mutation is a separate risk factor for neutropenia in breast cancer patients who are undergoing anthracycline-based treatment (Zeng, et al., 2022). This contradicts the results of our investigation. This could be attributed to variations in ethnicity and treatment protocols. Our findings revealed that patients with null versions of GSTM1 had a 1.78-fold higher chance of achieving a full pathological response. Furthermore, we have noticed a consistent pattern in the likelihood of neutropenia in these individuals, suggesting that the absence of the GSTM1 gene variant plays a significant role in both the responsiveness to treatment and the occurrence of adverse effects in breast cancer patients from southern India.

Table 1. Clinicopathological characteristics of patients across GST genotypes.

	Total n=170	GSTT1 n=170			GSTM1 n=170			GSTP1 n=170		
	n	+	-	pvalue	+	-	pvalue	AA+AG	GG	pvalue
Menopausal status										0.127
Premenopausal	62	46	16	0.712	33	29	0.874	49	13	
Postmenopausal	108	83	25		59	49		95	13	

Tumor Grade										0.08
Grade 1	20	13	7	0.266	9	11	0.475	14	6	
Grade 2/3	150	116	34		83	67		130	20	
Tumor size										
T3	107	85	22	0.194	59	48	0.752	92	15	0.474
T4	63	44	19		33	30		52	11	
Lymph node										
0	44	32	12	0.682	30	14	0.03	39	5	0.474
1 to 3	126	97	29		62	64		105	21	
Stage										
II	39	29	10	0.832	25	14	0.201	35	4	0.448
III	131	100	31		67	64		109	22	
ER status										
Negative	89	69	20	0.719	47	42	0.759	77	12	0.528
Positive	81	60	21		45	36		67	14	
PR status										
Negative	108	80	28	0.577	59	49	0.8726	93	15	0.513
Positive	62	49	15		32	29		51	11	
HER2										
Negative	69	57	12	0.102	36	33	0.7543	55	14	0.192
Positive	101	72	29		56	45		89	12	

Table 2. Association of Deletions of GSTT1, GSTM1,GSTP1 polymorphism and pathological response.

Genotype	**Pathological response n (%)**		**p-value RR(95%C.i)**
	Complete response n=48	**Partial response n=104**	
GSTT1 NULL	13 (27)	24 (23)	0.2950
+VE	35 (73)	80 (77)	1.33 (0.8070 to 2.223)
GSTM1 NULL	29 (60.4)	41 (39.42)	0.02
+VE	19 (39.6)	63 (60.58)	1.78 (1.103-2.897)
GSTP1 3435	20	46	
AA	23	39	
AG	5	19	
GG			
AA	21 (43.75)	46 (44.23)	0.8607
AG+GG	28 (66.25)	58 (55.77)	0.9307 (0.5783-1.498)

Table 3. Association of Deletions of GSTT1, GSTM1, and GSTP1 genotypes with toxicity.

Genotype	**Toxicity n=164**		**p-value RR (95%C.I.)**
	No toxicity (n=85)	Any grade neutropenia (n=79)	
	59 (84.70)	62 (62.0)	0.2158

GSTT1 +ve Null	26 (15.30)	17 (38.0)	0.86 0.66 to 1.119
GSTM1 +ve Null	48 (84.70) 37 (15.30)	33 (62.0) 46 (38.0)	0.06 1.32 0.9882 to 1.808
GSTP1 313 AA AG GG	31 42 12	40 26 13	
AA+AG	73 (43.75)	66 (44.23)	0.82 1.09 0.7525 to 1.788
GG	12 (66.25)	13 (55.77)	

5. CONCLUSION

In the present study, our results showed that patients harboring null variants of GSTM1 were 1.78 times more likely to achieve a complete pathological response and there is a trend observed for the risk of neutropenia in patients harboring null variants of GSTM1 suggesting the role of GSTM1 null variant in both response and toxicity in south Indian breast cancer patients

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