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Original Article

Polymorphisms in GSTM1 gene influences the chemotherapy response and treatment outcome in breast cancer patients

Xia Wang, Ruiming Zhang, Xiping Zhang, Wanmin Wu, Junwen Bai

Department of General Surgery, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China

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Abstract: GST enzymes detoxify chemotherapeutic drugs or their metabolites by catalyzing the reduction of these compounds by conjugating with glutathione. We performed a case-control study to assess the role of *GSTM1*, *GSTT1* and *GSTP1* rs1695 polymorphisms in the response to chemotherapy and treatment outcome of breast cancer in a Chinese population. A total of 268 patients with histologically confirmed breast cancer were consecutively recruited between March 2010 and March 2015. Up to the March 2015, patients were followed up for 3.4-60 months with the median follow-up time of 52.23 months. The genotypes of *GSTM1*, *GSTT1* and *GSTP1* were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The *GSTM1* null genotype was associated with a better response to chemotherapy when compared with the present genotype, and the adjusted OR (95% CI) was (OR=2.61, 95% CI=1.46-4.75). In the Cox proportional hazards model, the null genotype significant decreased risk of death from all causes in patients with breast cancer, and the adjusted HR (95% CI) was 0.49 (0.25-0.96). No significant association was observed between *GSTT1* and *GSTP1* polymorphisms and response to chemotherapy and overall survival of breast cancer. In conclusion, our study reported that the *GSTM1* null genotype was correlated with good response to chemotherapy and improved the overall survival of breast cancer.

Keywords: *GSTM1*, *GSTT1*, *GSTP1*, polymorphism, breast cancer, prognosis

Introduction

Breast cancer is the most common cancer in women worldwide [1]. It is estimated that more than one million patients annually suffered from breast cancer over the past years, and this cancer is the second leading cause of death among women [2]. The breast cancer is characterized by aggressive local invasion, early metastasis, and low sensitivity to chemotherapy [3, 4]. The rate of long-term survival in patients with advanced breast cancer remains very low, despite the advances of modern treatments such as radiotherapy and chemotherapy is improved [5]. Thus, understanding the mechanisms underlying breast cancer and increasing the sensitivity to chemotherapy is urgent in breast cancer treatment. An increasing number of studies have predicted the role of drug-metabolizing enzymes (DME) in determining inter-individual variations in therapeutic response [6-8].

The human glutathione S-transferase (GST) family, a superfamily of dimeric phase II metabolic enzymes, plays an important role in the cellular defense system [9]. GST enzymes detoxify chemotherapeutic drugs or their metabolites by catalyzing the reduction of these compounds by conjugating with glutathione. The GST family consists of six dimeric isoenzymes: GST alpha (α), mu (μ), pi (π), theta (τ), zeta (ζ), and omega (ω). Allelic deletions in the *GSTM1* and *GSTT1* genotypes result in protein polymorphisms, and complete deletion of both alleles (null-type) is associated with reduced enzyme activity [9]. The rs1695 of *GSTP1* results in an amino acid change at codon 105 (Ile/Val), which is correlated with lower substrate-specific catalytic activity. Recently, several studies reported the association between GSTs gene polymorphisms and response to chemotherapy in breast cancer, but the results are inconclusive [6-8, 10-12]. In our study, we performed a case-control study to assess the

role of *GSTM1*, *GSTT1* and *GSTP1* rs1695 polymorphisms in the response to chemotherapy and treatment outcome of breast cancer in a Chinese population.

Material and methods

Patients

A total of 268 patients with histologically confirmed breast cancer were consecutively recruited from the Affiliated Hospital of Inner Mongolia Medical University between March 2010 and March 2015. The diagnosis of breast cancer was confirmed in all patients by pathological examination. All the breast cancer patients did not receive chemotherapy or any other treatment before enrolling into the present study. Patients who had any serious concomitant systemic disorders inability to receive chemotherapy or concurrent chemo-radiotherapy or had other diseases which could influence the evaluation of results were excluded from this study.

Patients received docetaxel 35 mg/m^2 intravenous on days 1 and 8, thiotepa 60-65 mg/m^2, intravenous on day1, Cycles were repeated every 21 days until disease progression or unacceptable toxicity occurred with maximum of 6 cycles. Premedication consisted of oral dexamethasone 7.5 mg twice daily beginning on the day before docetaxel infusion and continuing for a total of 3 days.

Tumor responses were evaluated by contrasted computed tomography scan and/or magnetic resonance imaging every two cycles to document complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST criteria) version 1.0. Response was determined over 4 weeks later. Overall survival (OS) was calculated from the date of chemotherapy to the date of death or last clinical follow-up. Each participant signed a written consent form prior to enrolling into this study. The study was approved by the Affiliated Hospital of Inner Mongolia Medical University, and the study was carried out in accordance with Declaration of Helsinki.

Patients were followed up through attending clinics or telephone manners. Up to the March 2015, patients were followed up for 3.4-60 months with the median follow-up time of 52.23 months.

Genotyping

Five ml peripheral blood sample was obtained from each subject, and the samples were stored in -20°C until use. Genomic DNA was isolated from peripheral blood lymphocytes using Qiagen blood mini kit (Qiagen, Germany) according to the manufacturer's instruction. The genotypes of *GSTM1*, *GSTT1* and *GSTP1* were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The primers sequences of *GSTM1* were as follows: *GSTM1*: 5'-CTGCCCTACTTGATTGATGGG-3' and 5'-CTGGATTGTAGCAGATCATGC-3'. For *GSTT1*, the primers were 5'-TTCCTTACTGGTCCTCACATCTC-3' and 5'-TCACCGGATCATGGCCAGCA-3'. The β-globin locus was used as an internal control to avoid false-negative readings for *GSTM1* and *GSTT1*. The primers for β-globin locus were 5'-GAAGAGCCAAGGACAGGTAC-3' and 5'-CAACTTCATCCACGTTCACC-3'. The forward and reverse primers for *GSTP1* were 5'-GAAGAGCCAAGGACAGGTAC-3' and 5'-CAACTTCATCCACGTTCACC-3', respectively. The 25 μL PCR mixture included 100 ng of DNA, 12.5 pmol of each primer, 0.2 mmol/L of dNTPs, 2 mmol/L of $MgCl_2$ and 1 U of Taq DNA polymerase. The PCR reaction was started with a denaturation at 94°C for 5 min, 35 cycles of amplification with denaturation at 94°C for 45 sec, annealing at 62°C for 45 sec, and extension at 72°C for 45 sec, and followed by a final extension step of 5 min at 72°C. The product lengths were 215 bp, 480 bp and 268 bp for *GSTM1*, *GSTT1* and β-globin locus. The restriction enzyme for *GSTP1* was *Bsm*AI. The product length for *GSTP1* Ile/Ile was 176 bp, the lengths were 91 bp and 85 bp for *GSTP1* Val/Val, and the lengths were 176 bp, 91 bp and 85 bp for *GSTP1* Val/Val.

Statistical analysis

Continuous and categorical variables were presented using mean ± SD and frequency (N) of subjects (%). Association between *GSTM1*, *GSTT1* and *GSTP1* polymorphisms and response to chemotherapy in breast cancer was calculated using multiple logistic regression analysis, and the results were expressed using the odds ratio (OR) and 95% confidence intervals (95% CI). The correlation between *GSTM1*,

Table 1. Demographic and clinical characteristics of included subjects

Characteristics	Number of breast cancer patients N=268	%
Mean age, years	55.85±7.40	
<50	114	42.54
≥50	154	57.46
Menopausal status		
Premenopausal	112	41.79
Postmenopausal	156	58.21
Tumor size, cm		
<2.0	65	24.25
2.1-4.0	139	51.87
>4.0	64	23.88
TNM stage		
I-II	179	66.79
III-IV	89	33.21
Estrogen receptor (ER) status		
Negative	149	55.60
Positive	119	44.40
Progesterone receptor (PR) status		
Negative	111	41.42
Positive	157	58.58
Response to chemotherapy		
CR+PR	180	67.16
SD+PD	88	32.84
Death		
Yes	58	21.64
No	210	78.36

GSTT1 and *GSTP1* polymorphisms and overall survival of breast cancer was assessed using the Cox proportional hazards regression analysis. The results were illustrated using the hazard ratio (HR) and 95% CI. The survival curves were plotted by the Kaplan-Meier method, and the impact of the SNPs on overall survival of breast cancer was assessed using the log-rank test. Statistical different between groups was defined as *P* value less than 0.05. SPSS statistical package software, version 17.0 (SPSS Inc, Chicago, IL, USA) was taken to perform statistical analysis.

Results

The demographic and clinical characteristics of the breast cancer patients are described in **Table 1**. The mean age of included patients was 55.85±7.40 years. Of the included 268 breast cancer patients, 112 (41.79%) were premenopausal, 156 (58.21%) were postmenopausal, 65 (24.25%) had tumor size <2.0 cm, 139 (51.87%) had tumor size of 2.1-4.0 cm, 64 (23.88%) had tumor size >4.0 cm, 179 (66.79%) showed I-II TNM stage, 89 (33.21%) showed III-IV stage, 149 (55.60%) showed negative ER status, 119 (44.40%) showed positive ER status, 111 (41.42%) showed negative PR status, and 157 (58.58%) showed positive PR status. At the end of the follow up, 180 (67.16%) patients showed CR+PR to chemotherapy, 88 (32.84%) showed SD+PD to chemotherapy, and 58 (21.64%) died from all causes.

By chi-square test, we found significant difference in the *GSTM1* genotype distributions between CR+PR and SD+PD groups (χ^2=11.91, *P*=0.001). No significant difference was found in the *GSTP1* (χ^2=0.37, *P*=0.83) and *GSTT1* (χ^2=0.89, *P*=0.35) genotype distributions between CR+PR and SD+PD groups. After adjustment for clinical variables, the *GSTM1* null genotype was associated with a better response to chemotherapy when compared with the present genotype, and the adjusted OR (95% CI) was (OR=2.61, 95% CI=1.46-4.75). However, we did not find a significant association between *GSTP1* and *GSTT1* gene polymorphisms and tumor response to chemotherapy (**Table 2**).

Until March 2015, a total of 268 patients with breast cancer died from all causes, and the five-year survival rate was 21.64%. We did not find significant association between the *GSTP1* and *GSTT1* gene polymorphisms and survival time of breast cancer patients (**Figures 1** and **2**). The *GSTM1* null genotype was associated with longer overall survival of breast cancer patients when compared with the present genotype (For null vs. present genotypes: 54.79 months vs. 50.42 months, *P* for Log-rank test =0.02) (**Figure 3**, **Table 3**). In the Cox proportional hazards model, the null genotype significant decreased risk of death from all causes in patients with breast cancer, and the adjusted HR (95% CI) was 0.49 (0.25-0.96). No significant association was observed between *GSTT1* and *GSTP1* polymorphisms and overall survival of breast cancer.

Table 2. Association between *GSTP1*, *GSTT1* deletion and *GSTM1* deletion and tumor response to chemotherapy

Genotype		Patients N=268	%	Tumor response				OR (95% CI)[1]	*P* value
				CR+PR N=180	%	SD+PD N=88	%		
GSTP1	Ile/Ile	102	38.06	73	40.56	29	32.95	1.0 (Ref.)	-
	Ile/Val	112	42.50	74	41.11	38	43.18	0.77 (0.41-1.44)	0.39
	Val/Val	54	19.44	33	18.33	21	23.86	0.62 (0.29-1.33)	0.18
Allele	Ile	316	58.96	220	122.22	96	109.09	1.0 (Ref.)	-
	Val	220	41.04	140	77.78	80	90.91	0.76 (0.53-1.12)	0.15
GSTT1	Present	120	44.78	77	42.78	43	48.86	1.0 (Ref.)	-
	Null	148	55.22	103	57.22	45	51.14	1.28 (0.74-2.20)	0.35
GSTM1	Present	155	57.84	91	50.56	64	72.73	1.0 (Ref.)	-
	Null	113	42.16	89	49.44	24	27.27	2.61 (1.46-4.75)	<0.001

[1]Adjusted for age, menopausal status, tumor size, TNM stage, ER status and PR status.

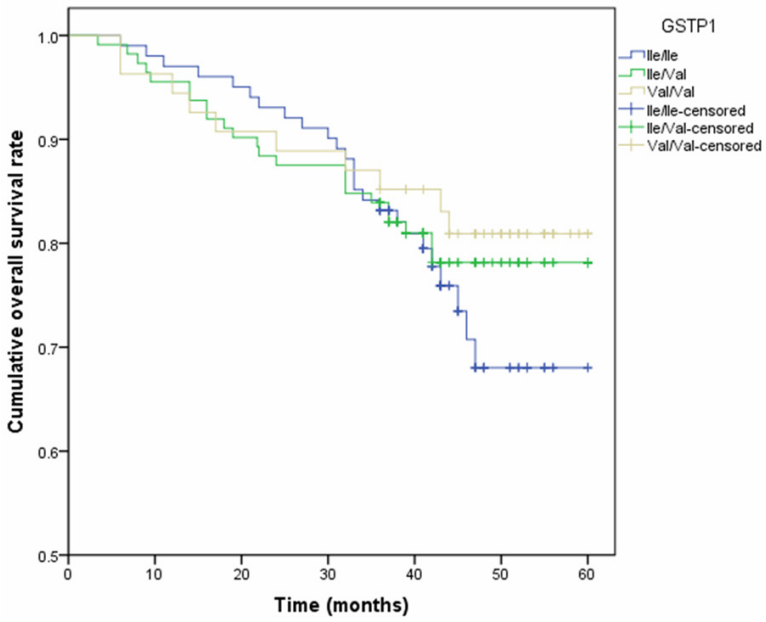

Figure 1. Kaplan-Meier survival curves by *GSTP1* polymorphism in patients with breast cancer.

Discussion

Increasing evidences have reported that the genetic polymorphisms play an important role in the efficacy of chemotherapy treatment in cancer patients, which contribute to the drug-metabolizing enzymes, drug transporters and drug targets [13]. Individualized chemotherapy treatment is regarded to improve the response to chemotherapy and promote the survival of cancer patients. Therefore, identification of the molecular factors for predicting the treatment efficacy of chemotherapy could effectively improve the treatment outcome of cancer patients.

In the present study, we investigated the impact of *GSTP1*, *GSTM1* and *GSTT1* polymorphisms on the treatment outcome of breast cancer in a sample of Chinese population. Our findings showed a significant association between *GSTM1* polymorphism and response to chemotherapy and overall survival of breast cancer, and the *GSTM1* null genotype decreased the risk of poor response to chemotherapy and death from all causes in comparison with the present genotype. While no significant association was found between *GSTP1* and *GSTT1* polymorphisms and response to chemotherapy and survival of breast cancer.

The GST super-family belongs to the phase II group of enzymes. Previous studies have indicated that the GST enzymes contribute to the metabolism of several kinds of xenobiotics and chemotherapeutic agents [14, 15]. Many previous epidemiologic studies have reported that the glutathione S-transferases may have in determining the efficacy of chemotherapy

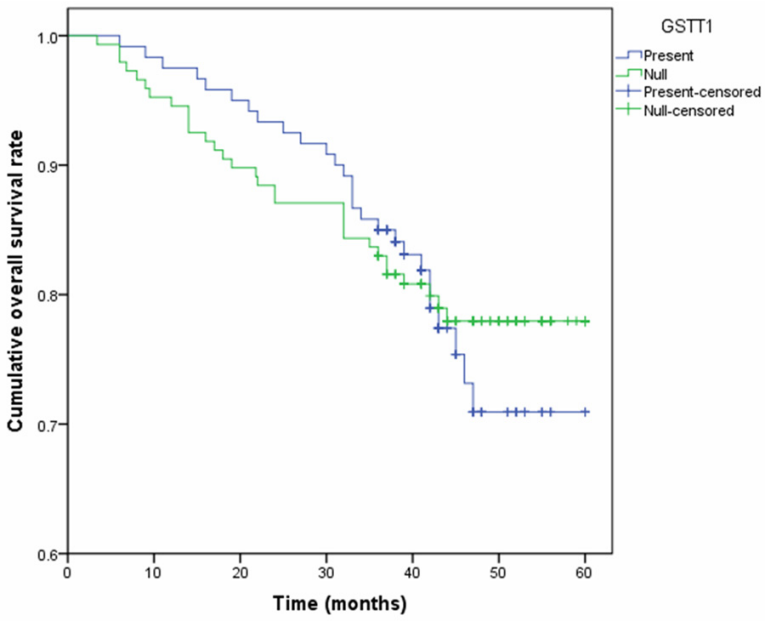

Figure 2. Kaplan-Meier survival curves by *GSTT1* polymorphism in patients with breast cancer.

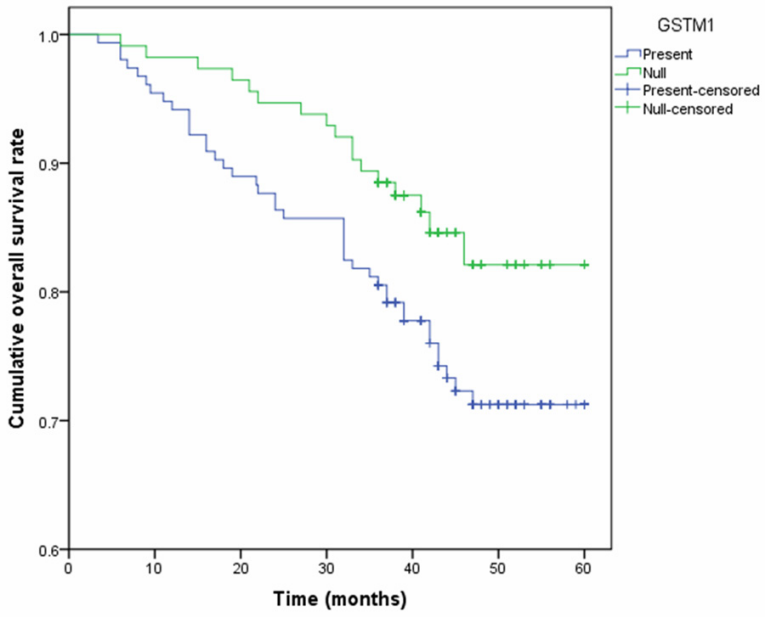

Figure 3. Kaplan-Meier survival curves by *GSTM1* polymorphism in patients with breast cancer.

on cancer [16-24]. Booton et al. conducted a study in a British population, and they reported that *GSTP1* haplotype was associated with response or survival of non-small cell lung cancer [16]. Borst et al. conducted a study in a Danish population and Davies et al. conducted a study in a British population, and they suggested that combined gene dose of *GSTM1* and *GSTT1* may influence outcome in childhood acute lymphoblastic leukemia [17, 24]. Zhang et al. reported that the *GSTP1* gene polymorphism may contribute to the prognosis of osteosarcome patients with chemotherapy [18]. Vreuls et al. reported that the GSTM1 null genotype is an independent risk for metastatic colorectal cancer in a Dutch population [19]. Silva et al. indicated that *GSTT1* deletion may influence the survival rate of patients with malignant glioma under perillyl alcohol-based therapy [20]. Rumiato et al. reported that *GSTM1*, *GSTT1* and *GSTP1* gene polymorphisms did not contribute to the clinical outcome of esophageal cancer patients with cisplatin-based neoadjuvant therapy [21]. Djukic et al. indicated that only *GSTT1* active genotype was associated with survival in muscle invasive bladder cancer patients [22]. Kap et al suggested that *GSTM1* may be a predictive marker for oxaliplatin therapy in colorectal cancer patients [23].

Several previous studies have reported the association between *GSTM1*, *GSTT1* and *GSTP1* gene polymorphisms and clinical outcome of breast cancer, but the results are inconclusive [6-8, 10, 12, 13, 25, 26]. Tulsyan et al. and Oliveira et al. indicated that *GSTT1*, *GSTM1* and *GSTP1* gene polymorphisms were associated with the response to chemotherapy and prognosis of breast cancer [10, 13]. Another three studies reported that GSTP1 gene polymorphism could predict the response to chemotherapy in breast cancer patients [6, 8, 26]. Bai et al. reported that both *GSTM1* and *GSTP1* were

Table 3. Cox regression analysis of *GSTP1*, *GSTT1* deletion and *GSTM1* deletion with overall survival of breast cancer patients

Genotype		Patients	Survival time	*P* for Log-rank test	Events		Alive		Overall survival	
					N=58	%	N=210	%	HR (95% CI)[1]	*P* value
GSTP1	Ile/Ile	102	51.55		25	43.10	77	36.67	1.0 (Ref.)	-
	Ile/Val	112	52.16		23	41.70	89	42.38	0.80 (0.40-1.60)	0.49
	Val/Val	54	53.13	0.14	10	15.20	44	20.95	0.70 (0.27-1.68)	0.39
Allele	Ile	316	51.93		73	62.93	243	115.71	1.0 (Ref.)	-
	Val	220	52.76	0.11	43	37.07	177	84.29	0.81 (0.52-1.26)	0.33
GSTT1	Present	120	51.98		27	46.55	93	44.29	1.0 (Ref.)	-
	Null	148	52.28	0.08	31	53.45	117	55.71	0.91 (0.49-1.71)	0.76
GSTM1	Present	155	50.42		41	70.69	114	54.29	1.0 (Ref.)	-
	Null	113	54.79	0.02	17	29.31	96	45.71	0.49 (0.25-0.96)	0.03

[1]Adjusted for age, menopausal status, tumor size, TNM stage, ER status and PR status.

associated with the prognosis of breast cancer patients with neoadjuvant chemotherapy [7]. However, Mishra et al. and Franco et al. reported that *GSTT1*, *GSTM1* and *GSTP1* gene polymorphisms could not influence the prognosis of breast cancer [12, 25]. In our study, we found that the *GSTM1* gene polymorphism was associated with the response to chemotherapy and overall survival of breast cancer. The discrepancies of the above results may be attributed to the differences in ethnicities and selection of subjects, as well as the disease stages and sample size.

In conclusion, our study reported that the *GSTM1* null genotype was correlated with good response to chemotherapy and improved the overall survival of breast cancer, but the *GSTT1* and *GSTP1* gene polymorphisms did not influence the prognosis of breast cancer. *GSTM1* could help therapeutic decision for individualized therapy in breast cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Junwen Bai, Department of General Surgery, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China. Tel: +86-471-6636914; Fax: +86-471-6636914; E-mail: baijww@sina.com

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